Abstracts

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Obstetrics and gynecology in the crystal ball

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Many years ago surgeons took care of gynecology and midwives obstetrics.
During the last century when obstetrics and gynecology has been a speciality of its own there has been dramatic development with several subspecialities.
Maternal health care will be more and more individualized, especially in the future Swedish society with many different ethnic groups. Family politics will be an important issue for society, and to stimulate increased number of births in Western countries. Safe motherhood is a global question and pregnancy has to be considered of special interest.
Within perinatology academic positions will develop in fetal medicine. The unborn child will be our future patient. Better diagnostic tools will facilitate our contact with the fetus. Intrauterine death (still birth), and abruptio placentae will decrease in number. Obstetrics will be an important discipline to harvest different stem cells and we will learn more about placenta, which is the natural human bio-implantate.
Diagnostic ultrasound is one of the most important tools for both obstetricians and gynecologists. In the future it will be necessary that all gynecologists have both basic and advanced knowledge in theoretic and practical ultrasound.
Gynecological oncology has contributed to more effective cytostatic regimes and better quality of life. However, ovarian cancer is still the major problem, and hopefully there will be possibilities for early diagnosis in the future.
Urinary incontinence has earlier been a hidden problem. Recently, research in this field and development of operative techniques have improved outcome in these patients. Anal incontinence is another hidden problem that must be prevented and treated in a better way.
New areas to be developed in assisted reproduction technology (ART) are selection of the right embryo and to control the mechanisms of implantation. One embryo transfer will be important to avoid problems linked to multiple birth.
In the future several present surgical procedures within gynecology will be replaced by endocrinological therapy. Hormone replacement therapy (HRT) has during the last decades been under great debate. This will continue until a safe replacement therapy can been reached.
The research within obstetrics and gynecology must in the future concentrate on female reproductive health. This means fewer sexually transmitted diseases (STD), safe abortion, variation of contraceptives, decreased incidence of infertility, optimal maternal care, no violence, reduced cancer and safe menopause not accompanied by numerous adverse effects.

Estradiol protects the adult and aging brain against injury: mechanisms of action

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It is clearly established that estradiol is a critical reproductive hormone with multiple actions that insure reproductive success in females. More recently, we have come to appreciate that estrogen also exerts potent protective and trophic actions in the adult and aging brain. Accumulating evidence from both clinical and basic science studies show that it slows cognitive decline associated with normal aging and neurodegenerative disease, decreases the risk and delays the onset of some neurological diseases such as Alzheimers disease, and decreases the risk and extent of injury associated with cerebrovascular stroke and neurotrauma. During the past century, the average life span of women has increased from approximately 50 years to over 80 years of age, while the age of the menopause has remained fixed at approximately 51 years. At the time of the menopause, ovarian estrogen synthesis and secretion decrease dramatically and remain low for the rest of a woman's life. Thus, today a larger fraction and a larger total number of women will live a larger portion of their lives in the post-menopausal, chronic hypoestrogenic state than ever before. In the absence of estrogen, they may suffer from brain dysfunction, neurodegenerative diseases and injury.

Our laboratory has assessed whether physiological levels of estradiol replacement therapy protect against brain injury using in vivo and in vitro models that mimic cerebrovascular stroke in order to understand when estradiol protects and the cellular and molecular mechanisms that underlie these neuroprotective actions. We have shown that physiological levels of estradiol protect the brain against stroke-like injury in both young and middle-aged rats. This neuroprotective effect is accompanied by alterations in the expression of several genes, including estrogen receptor-alpha (ER-alpha), ER-beta, Bcl-2, galanin, and some immediate early genes. We tested whether estrogen receptors play a pivotal role in mediating neuroprotective actions of estradiol by studying the effects of estradiol in ER-alpha knockout (ER-alpha KO) and ER-beta knockout (ER-beta KO) mice. Our results clearly establish that ER-alpha is a critical link that mediates the protective effects of physiological levels of estradiol in brain injury since deletion of ER-alpha completely abolishes the protective actions of estradiol; whereas, the absence of ER-beta has no effect. Our most recent work approaches the question of whether estradiol induces cell proliferation in the face of injury and which receptor mediates this effect. The recognition that ER-alpha mediates estradiol-induced neuroprotection should help in the design of drugs that target this receptor subtype in the treatment and prevention of neural dysfunction associated with normal aging or brain injury.

Non-genetic causes of early miscarriage

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Approximately 15% of all pregnancies between 4-20 weeks will undergo clinically recognised spontaneous abortions most commonly before week 12. The true early miscarriage rate is probably closer to 50% but occurs unrecognised immediately after conception mainly due to chromosomal abnormalities. While most of these women will not have any further problems, a number will have repeated miscarriages. A history of three or more consecutive spontaneous abortions occurs in 0.5-3% of couples who try to conceive. Despite thorough investigation protocols, there is still a limited understanding of recurrent pregnancy loss and the underlying cause remains unexplained in about 50% of cases.

Recurrent spontaneous abortion is a heterogeneous condition which has many possible underlying causes despite parental chromosomal anomalies that occur in about 2.5-3.6%. The non-genetic causes include lupus anticoagulant and antiphospholipid syndrome and other prothrombotic states, structural uterine abnormalities and cervical incompetence. The role played by endocrinological and endometrial factors such as hypersecretion of LH, polycystic ovaries, hyperprolactinemia, luteal phase defect and immunological mechanisms is controversial. Recently endocrinological and endometrial abnormalities has been found to be present in about a quarter of women with unexplained recurrent miscarriage. Increasingly, clinical and experimental data support the proposal that insemination has consequences for the reproductive process beyond delivery of the male gametes. Successful pregnancy requires a state of maternal immune "tolerance" to accommodate antigens expressed by the conceptus. We have recently shown that exposure to seminal plasma initiates a cascade of cytokine and leukocyte mediated events, resembling an inflammatory response in the human cervix. Studies in mouse have shown that TGFbeta in seminal plasma elicits a 20- and 200-fold increase in the synthesis of GM-CSF and IL-6 in uterine secretion, initiating a cascade of cytokine and leukocyte mediated events, during which local antigen presenting cells take up, process and present paternal MHC-antigens associated with sperm or leukocytes in semen. This sensitisation appears to prime the maternal immune system for a state of hyporesponsiveness to paternal antigens. A critical role for semen in normal implantation and pregnancy is further supported by the observation that exposure to semen around the time of embryo transfer in humans increases the likelihood of successful embryo implantation and development. We are now evaluating the post coital inflammatory response in women with unexplained recurrent spontaneous abortion.

Preimplantation genetic diagnosis - from a clinician´s perspective

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This presentation gives the present state of art of preimplantation genetic diagnosis (PGD) in the perspective of a health technology assessment.

PGD is an alternative to prenatal diagnosis in families with some monogenic diseases and structural chromosomal aberrations. Also, it may be used for screening for aneuploid embryos in routine IVF for infertility. PGD presupposes IVF, since the diagnosis is made on one or two blastomeres biopsied from day three embryos. The diagnosis is made by fluorescent in situ hybridisation (FISH) or by polymerase chain reaction (PCR). The technique represents a risk reduction form typically 50 or 25% to around one percent.

The chance of pregnancy following a PGD cycle is at the level of IVF for infertility reaching a cumulative pregnancy rate of 70% following three embryo transfers. World wide more than 200 children have been born following PGD.

Ethically, the advantage of PGD is that abortion is avoided, but aspects of possible risks of the biopsy procedure and the priority of resources in the health care system may give rise to hesitation.
Among potential users of the technique there is an overwhelming wish (>75%) to have PGD introduced as a diagnostic possibility in the public health care system. Nevertheless, more among members in families with cystic fibrosis (50%) than carriers of haemophilia (18%) or haemophiliacs (8%) have PGD as first priority in case of pregnancy planning.

In terms of health economics, PGD seems much more expensive than prenatal diagnosis. However, performing a health economic analysis for cystic fibrosis (CF), the expected health care costs for a couple with a risk of having a child with CF choosing up to three PGD cycles is DKK 112.390 compared with DKK 78.608 for the PND alternative. In this analysis was included the life time health care costs for a child born with CF. If PGD is introduced as an alternative to PND it was estimated that in Denmark around 57 couples per year will choose PGD. For 30 of these couples where the indication for PGD is a translocation, the cost for IVF will be "saved" as they are already eligible to IVF due to infertility. Totally, this means that the extra costs for the Danish health care sector for the treatment of all 57 couples with PGD - using cystic fibrosis as a model - is expected to be in the order of 1.5 million DKK per year.

In conclusion, technologically, PGD can be introduced in Denmark, but not without moderate extra costs for the health care sector. The PGD technique is very much wanted by potential users (families with a risk of having a diseased child), but presumably the method will be employed by a limited group of people only with a risk of having a child with relatively severe diseases. Ethically the method is preferable from a gradualistic point of view. A minor uncertainty concerning the possible long-term risks associated with PGD does not justify a reservation.

Ultrasound appearance of normal and abnormal early pregnancy

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Approximately 12-15% of all pregnancies end in recognizable miscarriages. This number shows the magnitude of a problem faced by the gynecologist, who must recognize the signs of early pregnancy failure (embryonic demise, spontaneous abortion, ectopic pregnancy, hydatiform mole), and identify normal anatomy or detect anomalies in early viable pregnancies. Systematic ultrasound studies have provided extensive knowledge about the development of the living embryo (before10 weeks) and young fetus (from 10 weeks on), with detailed anatomic descriptions of embryonic organs and extraembryonic structures. The characteristics of the early conceptus are its constantly changing anatomical appearance, uniform development, and constant growth. The balanced proportion between the embryo and its extra-embryonic structures is a guiding principle for normality. This knowledge can be used as the basis for the evaluation of the potential abnormal early pregnancy, when significant departures from normal development and measurements are found. Parameters such as the CRL, BPD, heart rate, diameters of the amniotic cavity and yolk sac, can be measured in order to quantify the young conceptus or part of it. High frequency transvaginal transducers have made it possible to disclose structural developmental disorders of the embryo (before 10 weeks) and the young fetus. An increasing number of studies, reviews and case reports describe ultrasound detection of early anomalies1. Nuchal translucency (NT), which may be found at the early 11-14-week scan, is a well-known marker for fetal disorders. Though NT is seen in normal fetuses, it is not only highly associated with chromosomal aberrations, but it may also be found in fetuses with skeletal anomalies, neuro-muscular disorders, rare genetic disorders, heart defects or infections. The likelihood for associated anomalies increases with the thickness of the edema.

Miscarriage - how we should handle it clinically

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Spontaneous abortion occurs in 14-19 per cent of registered pregnancies. For several decades, the universal standard of care for women with missed or incomplete abortion has been curettage of the uterus. There is growing evidence in treating incomplete and missed abortion with expectant management. The consequence of less surgical procedures is a reduced workload in gynaecologic services. Risk of overseeing intrauterine pregnancy or trophoblastic disease, women´s acceptability, future fertility and medical treatment will be discussed.

Adolescent gynecology - Different content in different countries

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In the history of adolescent gynecology, emphasis has varied over the years and in various countries. It was first largely related to anatomical abnormalities and their surgical correction, then endocrinology, and recently more about sexual health. In some countries, such as Hungary, Czech Republic, and certain Latin American countries, pediatric and adolescent gynecology is a separate subspecialty. This is not the case in any Nordic country. Finland is the only Nordic country, with a separate society for pediatric and adolescent gynecology, being a member of FIGIJ.

The cultural strategies to deal with adolescent sexuality has been 1) early marriage, 2) segregation of sexes, 3) repression and 4) acceptance.
Transitions to puberty, sexual activity, marriage and motherhood can be one or four events. In many Asian countries, marriage and childbearing starts at a very early age, and premarital sex is uncommon. Sub-Saharan Africa resembles Asia, but premarital sex is more common. In some villages in Malawi, 58% of females had sex before menarche. In Finland, menarche occurs at the mean age of 13, first intercourse at 17, and first delivery at 28.
In KwaZulu-Natal Province of South Africa, the incidence of HIV, unintended pregnancies and sexual violence against adolescent girls are very high, but the political leadership is still confused. In adolescent gynecology centers in Buenos Aires, colposcopy is done on all adolescent girls coming for contraception, while others are dying of unsafe abortion. In USA, with a high level of teenage deliveries and abortions, the president preaches only abstinence. In that country, an adolescent can see 400 000 sexual intercourses annually on TV, of which 400 of married couples.

The level of sexual health of young people is relatively good in the Nordic countries in international comparison. Indicators of this are the relatively low numbers of unintended pregnancies, abortions and sexually transmitted diseases. Today´s condition has evolved during a long span of time. Fifty-sixty years ago the situation in Finland was quite different: illegal abortions and STD´s were common, sex education was non-existent and attitudes towards sexuality and contraception were negative. The overall development in society - gender equality, equal education opportunities for boys and girls, development of the health care system, positive attitude changes of the state and Church - have all made it possible to reach the present situation through extended provision of sufficient and reliable sexuality education, confidential and high-quality services and wide selection of contraceptive methods. A good adolescence should be considered as a value in itself, in addition to being the foundation for the welfare of adulthood and forthcoming families.

Young people and secrecy

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Within the fields of health and medical care in Sweden, information about patients is subject to secrecy pursuant to the Secrecy Act, the principal rule. The possibility of revealing information without the individual´s consent is very small.

According to the Secrecy Act, secrecy shall be kept into force towards an under aged person´s parents, but only if it can be assumed that the youngster would be seriously harmed if information about him or her should be revealed to the parents. The signification of this special regulation is that parents normally are entitled to information. But to be able to construe this regulation in the right way, one has to be aware of the relation between the Secrecy Act and the Children and Parents Code.

According to the Children and Parents Code, parents have the right and obligation to decide in matters concerning their child. To fulfil the obligations that follows with the parenthood, the parent has to have full information about the child´s personal matters.

However, the Children and Parents Code also states that the parent is obliged, as the child grows older, to take into account the child´s increasing demand to decide in matters concerning the child itself. The right to decide in matters concerning the child is gradually moved over to the child, as the child grows older. This is also valid when it comes to the question: Who is in control over the secrecy? A parent can accordingly not always receive information about a child who has reached a certain maturity and personal development.

When to decide weather information about an under aged person shall be provided to the parents or not, it is important to decide who is in control over the question of secrecy - the parents or the young person himself.

There is no age limit to serve as a guideline in forming this judgement. The answer to the question depends on the young person´s maturity and personal development. However, when forming the decision the young person´s age will often serve as guidance. The problem will accentuate when the question is about a teenager. In these cases the child often can make demands for a certain protection of the integrity towards the parents. When forming the decision one has to take into account also what kind of information that is in question.

If the evaluation leads up to that it is the young person that is in control of the question of secrecy, information can not be given to the parents without the under aged person´s consent. Otherwise "as a main rule" information has to be given.

However, it sometimes is necessary to withhold information from the parents even in the latter case. In such situations the special regulations mentioned above can be applicable. This special provision is cut out for situations where the child really needs a protection against his or her parents in special situations. For instance if the parent would put the information to an improper use, either because the information is especially delicate or the parent is liable to put it into abuse.

Recent trends in adolescent sexual behavior and contraception

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Current trends of adolescent sexual health are unfavourable in many European countries. In Scandinavia, the decrease in teenage abortions levelled off in the mid-1990s, and even a reverse in the trend could be seen in Finland. In Iceland, teenage abortion rate continued to rise since the late 1970s, and was high above other Nordic countries at the end of 1990s. In Great Britain, teenage birth rates are highest in Western Europe, and almost triple compared to Scandinavian. Also STI continue to increase among adolescents in many countries.
Sexual behavior is a major determinant of sexual and reproductive health. In adolescents, the timing of sexual initiation is important, because many risk-behaviors and adverse health effects are associated with early sexual debut. In general, age at first intercourse decreased in the late 1960s and early 1970s, but the downward trend then levelled off. A recent study from Great Britain shows that the proportion of adolescents having experienced their first sexual intercourse before the age of 16 did not change during the 1990s. Similarly, several minor school surveys in Finland did not indicate any significant change between 1986 and 1994.
In Finland, the question of timing of sexual initiation is now topical, because abortions have increased among girls aged 16 or under, in particular. The School Health Promotion Study is a large scale school survey which provides information on adolescent health behaviour. It was carried out in the 8th and 9th grades at comprehensive schools, and in the 2nd grade in upper secondary schools (USS). Data were collected in April 1996, 1998 and 2000 in eastern Finland and in April 1997, 1999 and 2001 in western Finland. Thus, two consecutive years cover the whole country and they were pooled together. Those schools which participated in the survey three times were included in this study, compromising altogether about 80,000 8th grade pupils (mean age 14.8 years), 77,000 9th grade pupils (mean age 15.8 years) in comprehensive schools as well as about 37,000 students in USS (mean age 17.8 years).

The proportion of adolescents who had experienced their first sexual intercourse increased significantly between 1996/1997 and 2000/2001. Among the 9th grade girls the proportion increased from 29% up to 34%, an in boys from 24% up to 28%. The latest figures are higher than in any other Finnish studies since 1986. A similar trend was found among the youngest participants: in 2000/2001 the figures were 19% for girls and 17% for boys.

18-20% of the experienced boys in the 8th and 9th grade and 16-18% of the girls did not use any contraceptive method at their most recent sexual intercourse, this proportion slightly increased among the youngest respondents. In general, a swift from condom use towards oral contraceptive use could be seen, most clearly among the oldest participants. Proportion of girls who had ever used emergency contraception did not change significantly during the study period.

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Sexual problems among adolescents

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The only difference between adolescents and adults are that the young person is less experienced, mentally, socially and emotionally as well as biologically. The sexual reflexes of the young body are swift and brittle.
In a model for sexual response, the sexual response could be seen as a bio-psycho-social phenomenon and arousability the responsiveness of the sexual system. Sexual motivation is the mental process that might lead to sexual responsiveness, and determinants for sexual motivation are among a lot of things; desire for passion, expectations, social control, wish for normality, curiosity and so on.

In the young person the sexual motivation in it's social and learning aspects is growing at the same time as the biological responsiveness and arousability are developing. Both aspects need rehearsal to work perfect and in a predictable way.

In women, the sexual responsiveness consists of congestion of erectile tissue in the external and internal genitals, the vaginal congestion producing the fluid from the vaginal wall and secretion trom the vestibular glands, the lubricate.
In the young person, the erectile reflex is brittle, and can easily be interrupted when disturbed due to performance anxiety, pain or for no reason at all. In the male the erection of the penis disappears, a fearful and embarrassing event for him. In the female, the lack of congestion results in abscense of the mechanisms that protects from pain during the intercourse. She is embarrassed to, and might be appreciate that her male, likewise inexperienced, partner does not notice her situation. She might continue the vaginal intercourse in spite of the fact that it is no longer is comfortable, sometimes though severe pain. The intercourse might leave her with a acing vaginal introitus for days after, and a memory filled with disappointment, inadequacy and pain. In most cases the pain disappears and another try is more successful, but in some cases the next intercourse is even more painful. In those cases there is a risk for the development of chronic vestibular pain, so called vestibulitis.
In Sweden we experience an increased demand for counselling young patients with impotence and dyspareunia. In a recent Swedish study has reported a possible increase in the number of young women who experience longstanding dyspareunia. It is impossible to say whether this reflects a trend in society towards altered expectations and demands on sexual performance among adolescents. It can also be the result of diminished sexual education in the school. It has been claimed that the adolescent's main source for sex instruction is pornographic movies on television and video, produced for the purpose to stimulate sexual fantasies rather than for information about pleasurable sexual technique in real life. The young person's curiosity and urge for knowledge about sex can never be forbidden, but adults are obliged to help them to find information that they can have benefit from in their way to sexual self esteem and pleasure.

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The youth unit - the first Swedish integrated, multidisciplinary unit for youth care, a collaboration between the dep. of obstetrics & gynaecology, pediatrics and adolescent psychiatry

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This is a 3-year project that started in September 2000. Teenagers need a special care beside what the ordinary clinic can offer. Often they are too old for the Pediatric ward and too young for the dep. of Gynecology. The physiologic development of the puberty demands special knowledge of the changes the young patient goes through. Both somatic and psychologically, not to mention the sexual development our young people go through. Contraceptives are sometimes difficult in the chronic diseases with medication and need cooperation. The purpose of the Youth Unit is to improve care of the teenagers, even to create new models for the care. A center of knowledge in this way is not found elsewhere in Sweden. The patients are the young who need professional care, which cannot be met within the primary care, the Local Youth Office or the ordinary clinic. Teenagers with chronic diseases, psychosomatic problems, legal abortion, sexual abuse are the first groups who have come to the Unit. They often need a multidisciplinary care. Immigrants are a growing group in need of cultural competent care. Doctor's letter of introduction is compulsory except for legal abortion consultation and for the teenagers who already are patients at the Unit. The professions at the Unit are gynecologists, pediatricians, and psychiatrist, midwife and nurses, a psychologist, social workers and secretaries. We meet them separately or in different groups after the need. Also they come as day patients for longer contacts. Young patients with chronic diseases needs continuos contact with the hospital and are in the right to be met in an adequate way. A well care-taking program helps them with acceptance of the chronic disease and the well being in their adulthood. An example can be mentioned, the care of girls exposed to sexual abuse. After being taken care of at the emergency ward they are contacted by a social worker or the psychologist for a first meeting in 1 to 4 days. After a couple of meetings it is settled what she needs. The gynecologist is already introduced so a new examine seldom is a problem. Girls with psychosomatic abdominal pain are another group who gets help from the different specialists they need. The Unit is located in a separate ward with outpatient facilities and a couple of day-care beds for those undergoing legal abortion or laser treatment etc. They can have parents or friends with them because of the single room possibilities. The idea is to create a Unit who works on the teenager's needs. We are living in a time where the importance of their development must be paid attention. There must be enough competence in the different areas to support the young patients need. Being sent to different parts of the hospital does not help them. The specialist should go where the young patients are!

Better care or better babies? The contribution of intrapartum management to improving NICU outcomes

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There has been a steady improvement in survival of extremely premature infants. This is widely attributed to improving skill and technology. The longer term morbidities of these new survivors are still under active study, with some studies reporting no improvement in rates of severe sequelae, and some reporting improvement.

Neonatologists and NICUs have taken credit for this improvement in survival, claiming "better care" and pointing to the use of surfactant, ventilators, parenteral nutrition, etc. However, a significant portion of this is likely attributable to "better babies" - due to more skilled obstetric management.

I present evidence for "better babies" versus "better care" in two cohorts of infants, 5 years apart (1990, 1995), delivered in the same two perinatal centers (1). In the later time period, the infants were slightly older, slightly more mature, and in much better physiologic condition. The key to this is the ability to measure the physiologic condition on admission using the Score for Neonatal Acute Physiology (SNAP). Using statistical modeling, I estimate that on third of the improvement is due to "better babies" and two thirds due to "better care". I then review the potential mechanisms for how the obstetrical management that could cause these improvements. The most plausible explanation is a more aggressive approach to delay of delivery, thereby obtaining the critical hours or days to get the most benefit out of the already very high use of antenatal corticosteroids (66% in the earlier period, up to 76% in the latter period). Other contributing factors may be a shifting estimate of viability with earlier and more aggressive management, and more skilled resuscitation. Important factors that did not enter this analysis were changes in outborn deliveries, or greater use of cesarean delivery.

I then review related literature, showing that others have found both similar and differing results. These may depend on structural effects, such as referral patterns, outborn births, policies and attitudes of clinicians.

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Active perinatal management, even for babies born before 25 weeks of gestation?

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Aim: What is the survival rate infants born at 22-27 weeks of gestation in Sweden? Does survival rate vary between different hospitals and level of care?

Method: A population-based study was designed of all children born alive before 28 weeks of gestation in Sweden during 1985-1999. There were 3693 infants born, of total born 1,600 205 (0,23%) children during the period studied, and registered in the Swedish Medical Birth Registry.

Results: It will be presented trends of early neonatal mortality and neonatal- and infant mortality by week of birth week, per 5-years periods and level of care.
For the university hospitals with NICU-units survival will be presented for the period 1990-99 for children born at 23-24 and 25-27 weeks, diagnoses and mode of delivery.

Conclusion: The results shows that a more active perinatal approach is associated with an improved survival of extremely preterm born babies.

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Can optimal obstetrical management be defined at extreme prematurity

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A working group initiated by the Swedish National Board of Health (Socialstyrelsen) is evaluating perinatal outcome in the extreme premature infants. Perinatal outcome is improving. Chorioamnionitis as etiological factor for preterm labour and probably also an important risk factor for perinatal brain damage has influenced diagnostic methods and clinical routines. The first question to be answered is whether it is possible to present national guidelines for clinical management. For obstetrical use the scientific basis for recommendations concerning mode of delivery, antenatal monitoring, treatment with steroids and antibiotics will be discussed. This paper is a report of how the work is proceeding.

Risk factors for cognitive outcome in very preterm infants

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The fetal brain is a jungle with redundant neurons, synapses and pathways formed by innate mechanisms. Environmental stimuli may shape the wiring and the fine tuning of the neuronal circuits by slectionism or neuronal darwinism i.e. promoting survival of the most suitable neural circuits. Preterm infants are exposed to the extrauterine environment too early and furthermore they are transferred from low PO2 (Mount Everest in utero) to a relatively hyperoxic environment. The aim of this study was to investigate whether preterm birth per se can affect the cognitive outcome.

Methods: 182 out of 213 preterm infants (<1500 gram) who were born in Stockholm 1988-93 were examined with Wechsler preschool intelligence test and by a neuropsychological test battery (Nepsy) at the age of 5 1/2 years.
They were compared with 125 term controls.

Results: The preterm infants fell well within the normal range (IQ 95.7), although the control children had significantly higher score. The verbal score was better than the performance score. The executive functions were also better among the controls. Retinopathy of prematurity (ROP) and chronic lung disease were associated with lower scores. Small for gestational (SGA) infants in spite of relativdely higher birth weight had also relatively lower scores. Paternal education was found to be the single most important predictor of IQ for the preterm infants.

Conclusions: Visuo-perception and spatial reasoning seemed to be particularly vulnerable, while verbal development was nearly normal in the preterm infants. Maybe "the language instinct" seems to be fairly robust.SGA infants had lower scores, possible due to lower plasticity. Thus it seems to be better being born too soon than too small

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Short and longterm outcome in very preterm infants

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Neonatal survival of the extremely preterm infant is related to the obstetric team´s perception of the likelihood of survival and their willingness to intervene on behalf of the fetus. Studies have repeatedly shown, however, that obstetricians routinely underestimate the prospects for neonatal survival and survival without handicap. This tendency is related in part to the rapid pace of improvement in perinatal outcomes. The aim of the present paper is therefore to summarize the recent literature on mortality rates and prevalences of major neurodevelopmental disabilities in extremely preterm infants. In summary half of live births at 24 weeks gestation will survive but the survival rate and the rate of severe neonatal morbidity is influenced by the aggressiveness of the perinatal team. Survival of infants at 23 weeks gestation is significantly lower but by no means negligible. Data from the Northern health region in Sweden will also be presented in brief.

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Bedside wet smear examination - a simple test for vaginal ecosystem

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Bedside wet smear is a simple and rapid light microscopic examination of vaginal discharge. The test can be done in office immediately following gynecologic examination, and it only takes a few minutes. No staining is needed. Wet smear provides useful information of the vaginal ecosystem including vaginal bacterial flora, presence of specific infections, and hormonal effect. The equipment required is very simple and easily available. Relatively little training is needed to master the technique. Normal and abnormal findings are easy to recognize. Normal findings include dominant rods consistent with lactobacilli, few white cells, usually less than epithelial cells per 400x microscopic field. Normal wet smear findings rule out most lower and upper genital tract infections (high negative predictive value). Specific infections which can be diagnosed by wet smear examination include yeast infection, bacterial vaginosis (BV), and desquamative inflammatory vaginitis (DIV). Yest can show as mycelia which are relatively easy to detect, or as yeast cells which are not always easy to detect. BV is diagnosed on the basis of pathognomonic clue cells. The diagnostic criteria for DIV include the presence of heavy number of white cells and parabasal cells, and heavy bacterial flora but no clue cells. Increased number of white cells in the absence of obvious vaginitis is always suggestive of cervicitis until proven otherwise, and confirmatory microbiologic tests should be considered (for instance, for Chlamydia trachomatis). The presence of superficial vaginal epithelial cells is consistent with normal estrogen level and normal ovarian function, whereas the presence of parabasal cells is consistent with low estrogen level. Most common technical problems hampering proper wet smear interpretation include the following: too heavy amount of vaginal discharge on the glass slide, dried sample, sample spread all over the glass slide, too much saline added, dirty microscope, inappropriate objective used (should be 40x) or inappropriate light adjustment in the microscope, lack of cover glass, KOH added instead of saline, sample contaminated with cervical mucus or blood, and finally recent use of topical vaginal creams or tablets by the patient. Increasing use of wet smear examination saves time and health care costs, and adds to the efficacy of clinical bedside examination. Basics of the bedside wet smear examination should be included in undergraduate and postgraduate medical education curricula.

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Immunological defense in the vaginal mucosa - influences of steroid hormone contraceptives

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INTRODUCTION:
Studies in monkeys have shown that the susceptibility to simian immunodeficiency virus (SIV) infection through the vaginal epithelium is increased after progesterone administration. Steroid hormone contraceptives may also modify the protective functions of human vaginal epithelium and, as a consequence, women´s susceptibility to sexually transmitted diseases including HIV. The aim of this study is to determine if the use of commonly used steroid hormone contraceptives may affect the immuno-protective functions of the vaginal epithelium negatively. The study was approved by the local Ethics Committee.
METHODS:
Biopsies were taken from the vaginal epithelium of women using either combined oral contraceptives (OC), depo-medroxyprogesterone acetate (DMPA) or Norplant (NP) and compared to biopsies taken from regularly menstruating women (controls) with respect to epithelial thickness as well as the distribution and frequency of immune cells. Fifteen healthy women, aged 20-34 years, were enrolled to each group. Biopsies were taken at two occasions, in the follicular and luteal phase of the menstrual cycle and blood samples were collected for determination of systemic levels of estradiol and progesterone. At each occasion two biopsies were taken for histological and immunomorphometric analysis. In addition the women were interviewed about their medical- and reproductive history. Counting of the frequency of intraepithelial lymphocytes and measurement of epithel thickness were performed using coded samples and a computerized image analysis system.
RESULTS:
In controls, with verified normal menstrual cycle based on their history and verified by their serum levels of estradiol and progesterone, there was no significant difference between the follicular- and luteal phase with respect to epithelial thickness or composition and frequency of immune cells. The vaginal epithelium was significantly thicker in the study groups compared to the control group ($p<0.05$). The number of leukocytes (CD45 positive cells) and T cytotoxic lymphocytes (CD8+ cells) were significantly elevated in the DMPA group compared to controls ($p<0.05$). The ratio of T helper/T cytotoxic cells (CD4/CD8) was significantly decreased in the DMPA group compared to the other study groups and controls ($p<0.05$).
CONCLUSIONS:
The number and composition of intraepithelial lymphocytes in healthy DMPA users are altered compared to controls and OC and NP users suggesting a modified function in the immune-protection. The distended epithelial thickness in the study groups may not be correlated to a superior immune defense.

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Is recurrent vulvovaginal candidiasis an illness of the immunological system?

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Candida albicans is present in the vagina of approximately 15-20% of healthy, asymptomatic, reproductive age women. Conversion of this organism to a pathogen that causes recurrent clinical symptoms depends on changes in vaginal immunity. In most women exposure to C. albicans results in activation of a Th1 pro-inflammatory immune response. Interferon gamma is produced which activates phagocytic cells to engulf Candida and prevent proliferation to levels that can induce pathological reactions. In addition, interferon gamma blocks the conversion of C. albicans yeast forms to the more invasive hyphal form. C. albicans becomes capable of both proliferating to pathologic concentrations and germinating when a Th2 anti-inflammatory immune response is initiated. The Th2 response to C. albicans may be due to genetic factors or may be induced by a local vaginal allergic reaction. The local allergen may be a C. albicans component, an environmental allergen, a component of the sexual partner's seminal fluid or a medication ingested by the women. An allergic reaction results in the release of histamine and prostaglandin E2 (PGE2). The PGE2 blocks a Th1immune response and, therefore, prevents the immune system from limiting Candida growth. The ability of C. albicans to form germ tubes is also stimulated by PGE2. Beta endorphin, a neuropeptide produced by the pituitary gland under conditions of extreme stress or strenuous physical exercise, is also capable of inducing C. albicans germination. Thus, the proliferation and germination of C. albicans in the vagina, in women who harbor the organism at this site, is secondary to local immune system alterations. Treatment with anti-fungal medications which are candidastatic will temporarily alleviate symptoms. However, once the course of treatment is ended, unless the underlying immune system alteration is addressed, the residual Candida will again be free to proliferate and germinate, and vulvovaginal candidiasis will eventually reappear. Treatments aimed at inhibiting the vaginal allergic reaction - identification and avoidance of the offending allergen, use of a condom during sexual intercourse, antihistamines, prostaglandin synthesis inhibitors, mast cell stabilizers- have all been tried with varying degrees of success.

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Signs, symptoms and treatment

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Over the past decade, physicians have become increasingly aware that the vagina is an active "organ", not merely an anatomic passage dedicated for "transport".
A normal ecology of the vaginal secretion is a barrier against infection, but can, on the other hand,easily be disturbed by the intake of antibiotics.
Since the middle of the 2000th century, the incidence of vulvovaginal candida infection (VVC)has increased markedly, especially cases of recurrent infection. Currently, the causes of this increased incidence are not known, but speculations regarding the common use of antibiotics and/or the impact of gestagens on the immunological system in the vaginal wall, have been presented.
Today, effective antibiotics against fungi are available. However, as these compounds are merely fungistatic, VVC has a tendency to recur. With increasing usage of antibiotics against fungi, there is also a risk towards development of resistent bribes. Strict diagnostic criteria concerning VVC are of outmost importance and the patient should be informed that she will recover within four days from the infection; otherwise she has to return for a follow-up cultivation. Depending of the outcome of the cultivation, different scenarios of possible treatments will be presented.

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Hormone replacement therapy: Lessons learned - New Possibilities

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Substitution with female sex-steroids was introduced more than 50 years ago for immediate relief of climacteric symptoms. Today long-term hormone replacement therapy (HRT) is widely prescribed to prevent age-dependent diseases such as osteoporosis and atherosclerosis. The use of HRT has increased markedly worldwide - especially during the last decade with the extension of possible new indications. In the Scandinavian countries every second or third woman will receive HRT after the menopause.

In the beginning oestrogen was prescribed unopposed. When reports of an increased risk of endometrial cancer emerged in the mid-70s, the combined oestrogen-progestogen therapy was recommended. New administration routes were introduced such as the transdermal application and the local vaginal treatment for urogenital complaints. During the 1980s the protective effect of HRT on osteoporosis became evident. Later an increasing amount of observational studies supported the notion of a protective effect on cardiovascular diseases due to favourable changes in cardiovascular risk factors. This has recently been questioned by the first randomised trials of disease outcome. For the last decades the risk of breast cancer has been in focus. The impact of varying doses, type of regimens and length of treatment on cancer risk continues to be discussed.

During all these years enormous advances has been made in understanding how oestrogen works in the female physiologic system and how it affects the health of the aging woman. Lessons have been learned and new possibilities continue to evolve. Certainly HRT provides many health advantages for menopausal women. The crucial question is how we can prescribe safe HRT and still achieve the benefits of the therapy?

Low dose HRT - effects on bleeding patterns and bone density

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In women with an intact uterus estrogens and progestogens as hormone replacement therapy (HRT) are usually prescribed together. Epidemiological studies have shown that most women prefer HRT regimens which do not induce bleeding disturbances. Continuous combined HRT was introduced more than 15 years ago to minimize uterine bleedings and it has been found that such compounds may increase compliance. Lower doses than those commonly prescribed such as transdermal administration of 25 µg estradiol per 24 hours and 1 mg estradiol as well as .3 mg conjugated estrogens orally per day were reported to relieve climacteric symptoms and prevent bone loss. It is prudent to prescribe the lowest effective dose for vasomotor symptoms and osteoporosis prophylaxis.

It is important to individualize treatment in women with regard to age, individual expectations and to modulate dose and route of administration if side effects are perceived. It was reported that about 1/3 of women on high dose HRT discontinue prematurely because of side effects. Clinical studies have shown that more than 90% of women on low dose continuous combined therapy will achieve amenorrhoea - a beneficial effect for most patients. Studies on bone mineral density (BMD) have shown similar positive effects by high and low dose formulations. However, very little data on estrogens and its possible prophylactic effect on fractures have been produced. Long- term studies for the evaluation of effects on fracture risk remains to be conducted.

In conclusion low dose HRT regimens have shown beneficial effects on vasomotor symptoms, bleeding patterns and bone mineral density. Low dose HRT administered as continuous combined regimens may be the treatment of choice for elderly women requesting HRT.

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The cardiovascular protective effect of HRT - myth or reality

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Even though the mortality from coronary heart disease (CHD) has declined since the 1960s, CHD is still the leading cause of death in Western countries. Evidence has accumulated to suggest that postmenopausal hormone replacement therapy (HRT) protects against cardiovascular disease. A primary preventive effect of HRT has been reported by a number of large epidemiological studies supported by experimental biological studies. A risk-reduction as high as 30-60% has been suggested. However, since the epidemiological studies are observational in nature, the results are potentially biased by the fact that women choose themselves whether or not to use HRT as well as the duration of the treatment. Some studies have indicated that women using HRT represent a selected healthier subgroup of women concerning cardiovascular risk factors, "the healthy-user effect", leading to an overestimation of the protecive effect. Even though statistical multivariate analyses are used in observational studies to corrrect for measurable confounders, the ongoing randomized studies such as the Women´s Health Initiative and Wisdom are needed to confirm the cardioprotective effect of HRT. The influence of "the healthy-user effect" can be further elucidated in the Danish Nurse Cohorte Study (n=23.178). In this cohort, the users of HRT were not found to be healthier in lifestyle than non-users.
A secondary preventive role of HRT in women with existing CHD has been suggested in both epidemiological and experimental studies. However, the first randomized studies could not confirm this hypothesis. The Heart Estrogen/progestin Replacement Study (HERS) observed an increased risk during the first year of use, but a reduced risk in the last year of observation. This longterm secondary preventive effect has recently found support in observational studies.

A large number of epidemiological data suggest that HRT has a protective effect on fatal stroke and no influence on the risk of non-fatal stroke. However the latest follow up from The American Nurses´ Health Study questions the neutral effect on ischemic stroke.
Most of the data related to HRT and CVD are based on studies from United States, where conjugated equine estrogen (CEE) is used alone or in combination with medroxyprogesterone acetate (MPA).

Experimental studies indicate that the avaliable progestogens have different cardiovascular profiles. Consequently there is an urgent need for further studies of HRT for the primary or secondary prevention of coronary heart disease as well as the effect on stroke. Crucially, these must include various types of HRT, and different doses to those used so far. This information should be obtained using both randomized clinical trials and epidemiological as well as experimental studies.

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Breast cancer and HRT - Status and size of the problem

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For many years , the major concern associated with HRT has been the impact on the risk of breast cancer. The Collaborative study published in 1997, will for many years still be the key reference on the issue on data such as relative, absolute and cumulated risk. However, limited information was presented on some clinically important issues. Among them are the pattern of distribution of prognostic factors in tumors among users compared to nonusers of HRT. Further, less information is available on the prognosis and mortality of breast cancer among users, but some studies indicate less negative or potentially even paradoxic positive effect. The data on the issue of a possible modulating effect on risk of combined treatment compared to estrogen alone was limited in the study, but more information has been published since than, and will also be adressed and reviewed. Both in vitro and in vivo studies give conflicting results, and is difficult to interpret as a basis for what recommendations should be given in the clinical situation. An inherent problem on the issue is the lack of high quality randomized trials, leaving decision making to be made on the less precise epidemiological studies with their well described limitations. Finally, whether breast cancer patients with climacteric complaints can have HRT for symptomatic relief will be discussed and some information on the ongoing HABITS study on the issue will be presented.

Treatment of urogenital complaints in peri- and postmenopausal women

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Urogenital complaints such as vaginal discomfort, dysuria, dyspareunia, recurrent lower urinary tract infections and urinary incontinence are more common in women after the menopause. Epidemiological studies have demonstrated that more than 50% of postmenopausal women suffer from at least one of these symptoms.

Embryologically the female genital tract and urinary systems develop in close proximity, both arising from the primitive urogenital sinus. Animal and human studies have shown that the urethra is oestrogen sensitive, and oestrogen receptors have been identified in the human female urethra, urinary bladder, the vagina and the pelvic floor muscles.

The histology of the vagina changes extensively after the menopause, when the mucosa often becomes quite thin, and heavily infiltrated with neutrophils. The hormonal changes associated with the menopause have also been shown to induce changes in the bacterial colonisation of the vagina. After the menopause the vagina is colonised with a predominantly fæcal flora in contrast to the dominance with lactobacilli encountered during the fertile period of life. The presence of lactobacilli in fertile women provides protection against vaginal and periurethral colonisation by Gram-neagative bacteria, which have been implicated in the pathogenesis of cystitis and urethritis.

The incidence of urinary tract infections has been shown to increase after the menopause and continues to increase with increasing age. The altered vaginal flora after the menopause has been identified as one of the major causes of the increased incidence of such infections in post-menopausal women. Antibiotic therapy for the treatment of urinary tract infections accounts for a large portion of health care costs in the mananagement of elderly women.

Numerous studies have demonstrated a beneficial effect of oestrogen therapy in the management of urogenital symptoms such as urinary tract infections, vaginal discomfort and urethritis. The treatment of local vaginal symptoms with oral or vaginal application of oestrogens is now well established.

Novofem - clinical experience

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Low-dose 17ß-Estradiol Sequentially Combined with Norethisterone acetate: A new Therapeutic Regimen for Perimenopausal Women

Objectives:

To evaluate the efficacy and safety of Novofem® (first 16 tablets: 1 mg 17ß-Estradiol, following 12 tablets: 1 mg 17ß-Estradiol + 1 mg Norethisterone acetate) in the treatment of perimenopausal women.

Design:

This post marketing surveillance study is a prospective non-interfering systematic collection of data gathered during routine treatment.

Assessments done by gynaecologists include: bleeding profile, climacteric symptom relief, patient´s/doctor´s acceptance and adverse events.

Interim results are presented: 4010 women aged 45.6 years ± 2.9 (28-76) were treated for an average of 180 days with Novofem®.

Results:

91 % of women had regular cycles after treatment and 89 % of the women with an irregular cycle at baseline regained a regular cycle after treatment. Strong menstrual bleedings decreased from 26.3 % to 3.7 % and the frequency of irregular bleedings decreased from 31.1 % to 9.7 %.

Vasomotor symptoms, sleep disorders and nervousness/irritability disappeared or improved in 95 % , 89 % and 89 % resp. from baseline. Less than 1 % of the symptoms worsened.

91 % of the patients and 93 % of the doctors rated the treatment as satisfactory. 1 serious adverse event: generalized exanthema on the whole body was registered. 2 % of the study population reported 1 or more adverse events.

Conclusion:

Novofem® is proven to be effective and safe in routine treatment for climacteric symptoms and cycle irregularities in perimenopausal women.

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A genome-wide scan of endometriosis in a Finnish study sample

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Introduction: Endometriosis is defined as the presence of endometrial epithelium, gland and stroma outside the uterine cavity. It is one of the most prevalent disorders in gynecology, which markedly disrupts physical and emotional well being in many women. The genetic factors, based on several twin and case-control studies play a role in disease etiology. These findings are consistent with endometriosis being inherited as a multifactorial trait with genetic risk ratios similar (2-3) to other complex disorders such as asthma or diabetes. Linkage analysis can be used to trace the susceptibility genes. Identification of the genes and mechanism involved in endometriosis will assist in the development of better methods for early detection, diagnosis and prevention. However, no significant linkage studies have been published so far.
Materials and Methods: A two-stage genome-wide scan was performed. 31 nuclear families comprised with 83 surgically confirmed, definitive (ovarian endometriomas or pelvic endometriotic implants > 5 mm deep or pelvic endometriotic implants with adhesions not attributable to another cause) affected subjects and 95 unaffected (with our best estimates) relatives were analyzed. Unaffected individuals were included in the study only for phase info. In stage I, the whole genome was screened with a total of 320 micro satellite markers. The average marker spacing was 11 cM. In stage II, the regions of interest were covered with denser marker maps and eight additional families with 44 individuals out of which 22 were affected were included in the study.
Results: We retrieved suggestive (lod score > 2) loci on chromosomes 1, 7, 13 and 22 in the primary genome scan. Currently, we are analyzing the more dense marker maps on these areas.
Conclusions: The results provide evidence supporting involvement of multiple loci in the development of endometriosis.

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Therapeutic effect of angiostatin gene transfer in a murine model of endometriosis

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Endometriosis, growth of ectopic endometrial tissue, is a chronic recurrent disease affecting 10% of the female population causing dyspareunia, pelvic pain, dysmenorrhea, and infertility. Suppression of ovarian activity is the cornerstone of medical therapy with limited benefit and severe adverse effects. Angiogenesis plays a major role in the development of endometriosis suggesting that anti-angiogenic therapy would offer a new therapeutic approach. We report successful treatment of endometriosis in estrogen supplemented ovariectomized mice, by transient overexpression of the gene for a natural angiogenesis inhibitor angiostatin, delivered to the peritoneum by a replication deficient adenovirus vector (AdAngiostatin). Established endometriosis was reversed in 14 of 14 AdAngiostatin treated animals, while 11 of 13 control animals showed full disease development. Administered to normal cycling mice, AdAngiostatin caused impaired ovarian function with suppressed corpus luteum development, decreased production of estradiol and progesterone, decreased ovarian and uterine weight and increased body weight. AdAngiostatin treatment lowered the levels of sex steroids but did not induce total castration. Gene therapy with angiogenic inhibitors is a highly effective treatment for endometriosis, even in a host with preserved estrogen levels. However, local or targeted delivery of the gene must be considered to avoid prolonged systemic effects and impaired ovarian function.

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Local immune response in fertile and sterile women with endometriosis

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Introduction: Endometriosis is a common disease, affecting women of reproductive age and is often associated with infertility but pathogenetic mechanisms of endometriosis and endometriosis subfertility are still not clear. Abnormalities in immune function at systemic and especially at local level is shown to be involved in the maintenance and development of ectopic endometrial tissues in peritoneal cavity, but it is unknown whether the same immune disorders are in the background of infertility and endometriosis. The aim of our work was to compare the peculi-arities of functional state of peritoneal lymphocytes in sterile and fertile women with endometriosis to define the mechanisms of infertility in women with endometriosis.

Methods: Peritoneal fluid (PF) of infertile women with endometriosis (1 clinical group), fertile women with endometriosis (2 group) and healthy women without endometriosis (control group) was taken into investigation. The expression of surface CD-markers by peritoneal lympho-cytes was assessed by two-color flow cytometry method.

Results: It was found that the level of CD45+CD14- cells expressing early activation marker (CD25) was increased in PF of infertile women with endometriosis comparing to that in control group but activation did not affect CD3+ or CD4+ cells. Remarkable augmentation of B-cell activity was shown in infertile women at the local level. The amount of lymphocytes with phenotype CD20+HLA-DR+ and of B1 subpopulation (CD20+CD5+) was enhanced in the first group. At the same time the expression of CD40L molecules by peritoneal T-lymphocytes of infertile women with endometriosis was significantly increased. In the 2nd group of patients these parameters did not change and moreover the diminishment of the expression of late stage activation marker upon the surface of CD3+ lymphocytes was observed (CD3+HLA-DR+). Simultaneously the amount of naive T-helpers was evidently higher and of committed T-helpers was lower in the 1 group of patients. In fertile women with endometriosis the level of virgin CTL was on the contrary diminished and the amount of committed CD8+ lymphocytes was increased.

Conclusions: Our results are evidence in favor of the suggestion that the character of immune im-pairments in fertile and infertile women with endometriosis is different. Infertility in women with endometriosis seems to be associated with evident activation of immune reactions of B cell-type and elevation of activity of B1 subpopulation of lymphocytes capable to interact with wild antigens and to facilitate autoimmune reactions.

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In vivo brain uptake of the serotonin precursor [^{11}C]5-HTP during follicular and luteal phase in women with premenstrual dysphoria, studied by positron emission tomography (PET)

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Premenstrual dysphoria is characterized by the cyclical occurrence of negative mood symp-toms during the luteal phase of the menstrual cycle. Cardinal symptoms are irritability, affective lability, depression and impaired impulse control, all symptoms which can be alleviated by drugs increasing serotonergic signaling. Drugs inhibiting serotonin reuptake (the SSRIs) form the most effective pharmacological treatment known today. Thus, lowered serotonergic signaling during the luteal phase might be one symptom provoking factor in premenstrual dysphoria.

We investigated whether serotonergic activity is lower in the luteal compared to the follicular phase of the menstrual cycle in women with disabling premenstrual dysphoria and tested the association with cyclic worsening of VAS scores for irritability. Presynaptic uptake of the serotonin precursor [^{11}C]5-HTP as a measure of serotonergic activity was registered in vivo using positron emission tomography (PET) with both voxel-based and regions-of-interest(ROI)-based assessments. Eight healthy women with regular, ovulatory cycles and prospective VAS ratings indicating premenstrual dysphoria underwent PET registrations during follicular and late luteal phases using [^{11}C]5-HTP as tracer after transmission scan and $^{15}O_2$-water tracer registration for anatomical fit.

Voxel-based subtraction analysis after realignment, spatial normalization and filtering could not detect any significant phase differences in [^{11}C]5-HTP uptake. ROI-based analysis (prefrontal cortex, striatum, mediofrontal cortex, whole-brain) showed lower uptake in the luteal phase in the right prefrontal cortex (4.8%; P = 0.036) and in the right caudate nucleus (3.9%; P = 0.027). Mean 5-HTP uptake was about 5 % lower in the luteal than in the follicular phase for the whole group in the following ROIs: whole brain, left prefrontal cortex, right and left putamen. For 3 subjects with both PET registrations in one menstrual cycle, the corresponding value was 9%. The change in VAS ratings for irritability was negatively associated with the change in 5-HTP uptake in right prefrontal cortex (r_s = -0.81; P<0.014); i.e. the degree of worsening of irritability from follicular to luteal phase was significantly associated with lower 5-HTP uptake in the right prefrontal cortex.

To our knowledge this is the first report of in vivo human PET suggesting a lower uptake of 5-HTP in the luteal phase and an association between menstrual-phase worsening of irritability and lower uptake of brain 5-HTP in women with disabling premenstrual dysphoria.

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Intermittent naratriptan 1mg can alleviate premenstrual irritability in women with premenstrual dysphoria

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BACKGROUND: Anecdotal reports suggested that when naratriptan was used to treat migraines, some women experienced a reduction in pre-menstrual symptoms, mainly irritability and depressed mood. This randomised, double blind, placebo controlled, crossover study was conducted at the University Hospital, Lund, Sweden. The study was approved by the ethic committee at Medical Faculty, Lund University.

OBJECTIVE: To determine the efficacy of intermittent treatment with oral naratriptan 1mg b.i.d. in reducing the irritability experienced during the late luteal phase (day - 5 to day - 1) in women with premenstrual dysphoria.

METHODOLOGY: Potential patients with a history of premenstrual symptoms and regular menstrual cycles, and not using oral contraceptives, were screened for eligibility. This included thyroid function checkouts and utilising the Montgomery Asberg Depression Rating Scale to exclude depressive disorders.
All eligible subjects rated 7 symptoms daily on a visual analogue scale (VAS) during two menstrual cycles (run-in phase). The psychological symptoms rated were irritability, depressed mood, tearfulness and tension. The three physical symptoms rated were food craving, breast tenderness and bloating. Randomised subjects needed to report at least a 50% increase of irritability in the late luteal phase compared to the follicular phase (day 6 to 10).
Randomised subjects were treated with naratriptan 1 mg or placebo twice daily for three menstrual cycles. Treatment was intermittent for ten days, starting from day - 8 to day 2 (day 1 being first of menstrual bleeding). After 3 menstrual cycles, patients were crossed over to receive the alternative treatment for a further three cycles. The primary endpoint was the VAS rating for irritability during day - 5 to day - 1. After each treatment period the subject completed a 'Global Assessment of Treatment Satisfaction' questionnaire.

RESULTS: Thirty-nine randomised subjects completed the study. Compared to placebo, naratriptan 1 mg b.i.d. during the late luteal phase significantly reduced irritability rating by 15 mm (95% confidence interval: 6 mm, 24 mm, p = 0.003) using data from prospective daily symptoms scored on the VAS.
The patient global assessment of the effect of naratriptan was significant. Patients were six times more likely to report improvement with naratriptan compared to placebo, without considering side effects (odds ratio 6.4 [95% CI: 1.7, 24.1]) or with considering side effect (odds ratio 5.9 [95% CI: 1.6, 21.5]).
Thirty-three percent of subjects in the placebo group and 25% in the naratriptan group reported a drug related AE. The most common AE was headache.

CONCLUSION: Oral naratriptan 1mg can alleviate premenstrual irritability in women with premenstrual dysphoria. Naratriptan 1mg was shown to be safe and well tolerated when dosed intermittently twice daily for ten days.

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Influence of menstrual cycle on platelet serotonin uptake site and 5-HT2A receptor binding

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Objective: The neurotransmitter serotonin plays an important role in the pathophysiology of psychiatric conditions such as depression and anxiety and ovarian steroids may profoundly influence the activity of the serotonergic system. As a gender difference in the occurrence of major depression is well recognized, the purpose of this study was to examine whether binding of [3H]paroxetine to the platelet serotonin transporter or binding of [3H]LSD to the platelet 5-HT2A receptor were influenced by the cyclical changes in circulating estradiol and progesterone that occur during the menstrual cycle.
Study design: 28 healthy women, without oral contraceptives and with regular menstrual cycles completed the study. Blood samples for platelet [3H]paroxetine and [3H]LSD binding as well as estradiol and progesterone serum levels were taken at 6 occasions during one menstrual cycle; in the early follicular phase, late follicular phase, ovulatory phase, early luteal phase, mid-luteal phase, and late luteal phase.
Results: In the late follicular phase, Bmax for [3H]paroxetine binding was significantly higher than in the ovulatory ($p < 0.01$), early luteal phase ($p < 0.05$) and mid-luteal phase ($p < 0.01$). Bmax for [3H]LSD binding was significantly higher in the early follicular phase compared to the mid-luteal phase, $p < 0.001$. Also, there was a significant reduction in Bmax for [3H]LSD binding between early luteal and mid-luteal phases, $p < 0.05$. In the luteal phase, significant inverse correlations between progesterone serum concentrations and Bmax and Kd for [3H]LSD binding were found, $p < 0.05$ respectively.
Conclusion: Steroid hormone fluctuations across the menstrual cycle alter binding for the 5-HT2A receptor and the serotonin transporter. Throughout the menstrual cycle, progesterone appears to be the major determinant for these changes.

Long-term, low-dose dexamethasone treatment further reduces androgen levels in metformin-treated PCOS women

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Introduction: In PCOS women both ovarian and adrenal androgen production is increased. The potential of metformin in the treatment of PCOS is well established. Dexamethasone suppresses endogenous adrenal androgen production. We investigate the effect of long-term treatment (26 weeks) with low-dose dexamethasone in metformin treated PCOS women.
Design: Forty PCOS women were included by the following criteria: age 18-40 years, BMI>25 kg/m2, polycystic ovaries by vaginal ultrasonography and at least one of the following; testosterone>2,5 nmol/l, SHBG<30 nmol/l, c-peptide>1,0 nmol/l, oligo-amenorea or hirsutism. All patients received diet- and lifestyle counselling. At week 0 the 40 PCOS women were randomised to dexamethasone 0,25 mg and metformin 850 mg tid or placebo and metformin 850 mg tid. The effect of dexamethasone in addition to metformin, on androgen levels was investigated.
The study was approved by the regional committee for medical research ethics of health region IV, Norway and conducted according to the declaration of Helsinki.
Results: Testosterone, Free Testosterone Index, androstenedione and DHEAS decreased significantly ($p<0,001$) from week 0 to week 26 in the group treated with dexamethasone and metformin compared to the group treated with placebo and metformin. SHBG tended to increase in the dexamethasone group, while we did not observe any differences in body weight and fasting glucose levels between the groups.
Conclusions:
Long-term dexamethasone treatment in addition to metformin further reduces androgen levels in PCOS women. The combined treatment reduces androgens well into levels seen in normal women. Dexamethason (0,25 mg/daily) had no adverse effect on weight or fasting glucose levels.

Perinatal and maternal complications related to post-term delivery. A national register-based study 1978-93.

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Introduction: the objective was to describe the risk of perinatal and maternal complications associated with post-term delivery in a large sample in Denmark in recent decades.
Prolonged pregnancy, defined as a pregnancy with a gestational length of 294 days or more, is a frequent condition occurring in 5-10 % of all births. Perinatal mortality is higher in post-term delivery compared to delivery at term. Prolonged pregnancy has been associated with an increased frequency of perinatal morbidity, such as aspiration, asphyxia and fetal distress. An increased frequency of maternal complications, such as caesarean section and obstetric trauma has also been reported.
Methods: we used data from all women with registered prolonged pregnancy in the period 1978-93 obtained from The Danish Medical Birth Registry (n=78,022) and a 5% random sample of all women who gave birth in the period 1978-93 (n=47,021). These data were linked to The Danish National Discharge Register, where information on discharge diagnoses from all hospitalized patients are recorded. We excluded deliveries with missing gestational ages and multiple births from both samples. Furthermore, we excluded preterm and post-term deliveries, and induced deliveries, from the random control sample in order to establish a term cohort having spontaneous deliveries. We thus had 77,956 singleton births in the post-term cohort and 34,140 in the term cohort. A logistic regression model was used to analyse perinatal and maternal complications as a function of post-term delivery. The odds ratios were adjusted for maternal age group (<19, 20-24, 25-29, 30-34, 35-39, 40+ years), fetal gender (male/female), and prior delivery (yes/no).
Results: the risk of perinatal complications, i.e. aspiration, asphyxia before, during, and after delivery, umbilical cord complications, bone fracture, peripheral nerve injury, pneumonia, and septicaemia was significantly increased in post-term delivery compared to term delivery (adjusted odds ratios between 1.4 and 2.0). The risk of perinatal death was 1.33 (1.05-1.68). There was a significantly increased risk of obstetric complications, i.e. post partum haemorrhage, cephalopelvic disproportion, cervical rupture, dystocia, fetal death during delivery, caesarian section, and puerperal infection (adjusted odds ratios between 1.2 and 3.1).
Conclusion: post-term delivery was associated with significantly increased risks of perinatal and maternal complications in Denmark in the period 1978-93. This could be a causal association or be due to common causes for prolonged pregnancy as well as the recorded complications.

Bishop score and success rate for vaginal delivery after vaginal administration of misoprostol 50 microgram in gellatine capsules

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Bishop score and success rate for vaginal delivery after vaginal administration of misoprostol 50 micrograms in gelatine capsules.

Misoprostol is a highly effective agent for labour induction in women with an unripe cervix (Hofmeyr GJ, 2001, Sanchez-Ramos L and Kaunitz AM, 2000).

Both vaginal and oral administration of misoprostol has been studied in numerous randomised trials. Vaginal administration has been found to be more effective and probably resulting in less tachysystole/ hyperstimulation than after oral administration (Sanchez-Ramos L and Kaunitz AM, 2000).

Since 1999 we have used misoprostol 50 micrograms vaginally every 6 hours for the induction of labour in women with an unripe cervix, according to the protocol used by Belfrage et al (2001). Eighty-eight patients were included in this study. Of these 88 patients 76 were delivered vaginally (86%) and 12 (14 %) by caesarean section.

Eleven patients had a previous caesarean section and, 8 of them were delivered vaginally without complications. Three patients of these 11 cases were delivered by section, and in one case because of rupture of the uterus. After October 2001 Misoprostol has not been used for the induction of labour to patients with previous caesarean section due to our case of a ruptured uterus as well as other reports in the literature regarding the safety of Misoprostol in cases of previously scared uterus.

There were no significant differences in parity between patients delivering vaginally or with a caesarean section. The mean time from induction to delivery differed significantly (P=0,01) between primiparae (22 h 20 min) and multiparae (14 h 48min).

Our result shows a significant higher probability for caesarean section in patients with Bishop score <4 (P=0,001). Only one patient with Bishop score above 3 delivered with a caesarean section. Of 49 patients included with Bishop score < 3, 38 were vaginally delivered and 11 by caesarean section. Analysis of the different components in the Bishop score shows significance only for the effacement of the cervix (P< 0,05). 2 patients of the 76 delivered vaginally showed signs of uterine hyperstimulation and were treated with terbutaline.

Most patients delivered by caesarean section because of foetal distress (7/12) but no newborn, except one case, had an Apgar score below 7 at 5 minutes. In one case there was a foetal death because of uterus rupture in a previous caesarean section combined with anestesiological problems at the caesarean section.

There were 2 cases with Apgar < 7 at 5 minutes and none with Apgar <9 at 10 minutes after a vaginal delivery.

Conclusion: Misoprostol 50 micrograms vaginally every 6 hours according to the protocol used by Belfrage et al (2000) is effective for the induction of labour in patients with an unripe cervix but success rate is lower with a Bishop score < 4.

Mifepristone and misoprostol for induction of midtrimester abortion

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Introduction. Medical termination of pregnancy in the second trimester is a strain and painful process. The aim of the study was to assess the effect of changing the regimen for termination from gemeprost to mifepristone and misoprostol to evaluate quality improvement at our department.

Methods . Included in this retrospective study were 179 women, all had legal abortions due to foetal malformations. In 1994 -96 gemeprost (regime 1, no 77), 1998-199 mifepristone + gemeprost (regime 2, no 40), 1999-2001 mifepristone + misoprostol (regime 3, no 62).

Results. Mean gestational age was 19,5 - 18,4 - 18,8 weeks respectively. Mean induction-to-abortion interval was 22,7 - 9,7 - 9,5 hours. The amount of gemeprost/misoprostol used was 5,5 - 2,9 - 3,3. By regime 1 20% were non-responders, none by regime 2 and 3. The analgesia requirements were less by using regime 3. Morphine doses were 25 - 18 - 15 mg (mean), and petidinhydrochloride 168 - 28 - 16 mg (mean). There were no significant difference in side effects.Vomiting and nausea were the most frequently reported adverse events. Retained placenta was diagnosed in 20 % for all groups. Surgical evacuation of the uterus was performed in 15 - 30 - 13 %.

Conclusions. Our results show that the combination of mifepristone and misoprostol provides a noninvasive and effective regimen for second trimester termination of pregnancy. Introduction of mifepristone was unvaluable. In view of lower cost and ease of storage misoprostol may be a more useful agent than gemeprost. This regimen is preferable also to avoid repeated vaginal administration.

Nitric Oxide Metabolites in Cervical Fluid during Pregnancy: Further Evidence for a Role of Cervical Nitric Oxide in Cervical Ripening

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Introduction: Nitric oxide (NO), a free radical gas with ultra-short half-life, is involved in a variety of physiological processes. Cervical tissue is known to express all the isoentsymes of NO synthase, but the role of NO in cervical physiology is unknown. NO is oxidized to nitrate/nitrite (Nox) the assessment of which reflects the release of NO in vivo.

Material and Methods: We studied the concentrations of Nox in cervical fluid in non-pregnant (n=11) and pregnant women (n=95). Cervical fluid was sucked into Dacron swab and Nox was eluted into physiological saline which was assayed for Nox with Griess reaction; the data were corrected for a dilution factor.

Results: Nox was detectable in 55% of non-pregnant women, but significantly more often ($p<0.05$) in early pregnancy (71%) and in late pregnancy (75%). Cervical fluid Nox in non-pregnant women (33.8 - 56.4 micromol/l, mean -SE) rose to 73.3 - 43.2 micromol/l ($p>0.05$) in the first trimester and to 154.2 - 41.4 micromol/l ($p<0.05$) in the third trimester. Cervical fluid Nox concentration in parous women (251.8 - 53.8 micromol/l) was higher($p<0.05$) than that in nulliparous women (82.3 - 80.7 micromol/l) before the onset of labor. Cervical fluid Nox in women with ripe cervix (Bishop score - 6) (231.2 - 39.5 micromol/l) was higher ($p < 0.001$) than that in women with unripe cervix (80.8 - 28.2 micromol/l) (Bishop score - 6), and there was a significant relationship between cervical fluid Nox and Bishop score($r=0.39$; $p < 0.001$ n=67). Cervical fluid Nox before the initiation of labor (80.8 ? 28.2?mol/l) elevated to 2.9-fold (231.4 - 39.5 micromol/l) after the commencement of uterine contractions. Gentle cervical manipulation (n=11) resulted in 3.9-fold elevation of cervical fluid Nox in one minute. Artificial amniotomy (n=7) reduced the cervical fluid Nox from 624.2 - 462.5 micromol/l to 285.8 - 212.4 micromol/l ($p< 0.005$). The administration of glyceryl trinitrate (0.5mg, NO donor) intracervically (n=5) resulted in 8.3-fold rise in cervical fluid Nox in two minutes, which vanished in 10-12 minutes. There was no correlation between fasting plasma and cervical fluid Nox concentrations (n=41; $r=0.14$, $p>0.05$).
Conclusion: Cervical fluid Nox is unrelated to plasma or amniotic fluid Nox, but it rises following cervical ripening, NO donor administration, or cervical manipulation. These data give further support for a role of NO in cervical ripening.

Economic evaluation of screening and treatment for bacterial vaginosis in early pregnancy among women at low risk for preterm birth

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Introduction
Bacterial vaginosis (BV) is a solid risk factor for preterm birth. Treatment of BV seems to reduce preterm births in high risk populations but the results in low risk populations are conflicting. Thus, we performed an economic analysis of screening and treatment of BV in a low risk population for preterm birth.
Methods
A decision tree model was developed and used for economic evaluation. Altogether 5432 asymptomatic pregnant women were screened in antenatal clinics for BV, and 375 BV-positive women were randomized to treatment with intravaginal clindamycin cream or placebo. Main outcome measures were preterm delivery, postpartum infeactious morbidity and other less common postpartum complications,
Results
The expected costs per capita were 172 USD lower in the screening strategy than in the no-screening strategy. The sensitivity analysis showed that the cost per pregnant woman in the most optimistic scenario would be 797 USD lower in the screening strategy. The decision tree model proved to be robust and insensitive to changes in key probabilities.
Conclusions
Screening and treatment of BV in early pregancy is cost saving and produces better health outcomes. Furthermore, no significant threshold values were identified in the key probabilities used in the model suggesting that BV screening in early pregnancy is beneficial even in the most pessimistic scenario.

Proteoglycans and hyaluronan during term labor in human fetal membranes

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Labor induces increased concentrations of biglycan and hyaluronan in human fetal membranes; Implications of an active remodeling process.

OBJECTIVE: In this study we wanted to establish if a remodeling process exists in the extracellular matrix of human fetal membranes.

STUDY DESIGN: Prelabor samples (N=9) of fetal membranes were obtained from elective cesarean sections at term and regionally sampled from over the cervix (cervical membranes) and midway between this area and the placental edge. Postlabor samples (N=11) were obtained from spontaneous vaginal delivery. Proteoglycan composition and concentration were analyzed using alcian blue precipitation. Hyaluronan was measured using a radioimmunoassay. Collagen was measured by estimating hydroxyproline content. Tissue sections were immunostained for decorin and biglycan, and for hyaluronan by a histo-chemical method using a biotin-labeled hyaluronan-binding protein as a probe.

RESULTS: Vaginal delivered fetal membranes were characterized by a separation of the amnion and chorion due to the occurrence of a gelatinous substance containing a very high concentration of hyaluronan. In addition, a significant increase in the concentration of hyaluronan in postlabor compared with prelabor fetal membranes was found with a concomitant significant increase in biglycan in the chorion. The cervical membrane was characterized by high decorin compared to biglycan; with a significantly lower concentration of biglycan compared with midway samples. The results were confirmed on the mRNA level with high expression of TGF-b in connection high expression of biglycan. During labor the cervical membrane changed into the rupture site with a pronounced separation of the amnion and chorion along with a 2 fold and significant increase in biglycan and a 3 fold increase in hyaluronan. Furthermore, at the rupture site the close association between collagen and decorin was lost in a parallel with a significant decrease in both decorin and collagen in the amnion compared with midway samples.

CONCLUSION: The initiation of labor induces an active remodeling process, which takes place both generalized and locally at the rupture site of the fetal membranes. Formation of the gelatinous substance and the marked increase in hyaluronan and biglycan, which disrupt the well-organized collagen network, leads to a weakening of the fetal membranes. The decrease in both decorin and collagen at the rupture site affect the mechanical properties to an even greater extent and the membranes rupture. The remodeling process could be generated by cytokines such as TGF-b, which were demonstrated in both the amnion and the chorion.

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Preterm delivery predicted by S-relaxin

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This abstract describes results from 3 studies on S-relaxin in term and preterm delivery in either low-risk or high-risk pregnancies.
Study Design: a) A nested case-control study based on serum samples obtained in the 18th week of gestation from 1545 unselected healthy primiparae; 11 delivered before week 32, 42 at 32-36 weeks, and 123 controls were randomly selected in the women delivering at term. b) A nested case-control study based on repeated sampling (one, two or three samples per participant) obtained from 2,846 unselected healthy women: 84 delivered idiopathically before week 37 and 399 controls were randomly selected among the women delivering at term. c) A prospective case-control study based on serum samples obtained from 93 women with threatened preterm delivery (24-33 weeks) of which 46 delivered before 34 weeks gestation.

Results: a) Serum relaxin in the 18th gestational week was 63% higher in very preterm deliveries than in controls (Mann-Whitney: p=0.01). High S-relaxin levels during the 18th gestational week were associated with an increased risk of preterm delivery before 32 week [OR=11, 95% CI=2.1-59]. b) S-relaxin decreased by 0.9% per week in women with preterm deliveries whereas it decreased by 1.9% per week in term deliveries, a statistically significant difference (p=0.004). c) High S-relaxin levels was associated with an increased risk of preterm delivery (crude OR=5, [CI 95%: 1.9-12]). S-relaxin was significantly different (Kruskall-Wallis, p<0.05) in the women with PPROM (316 pg/ml), labour (222 pg/ml), or ripe cervices (203 pg/ml).

Conclusion: Serum relaxin, or the change in S-relaxin, was associated with preterm deliveries in low-risk pregnancies. S-relaxin was a potential predictor of preterm delivery, but due to the number of false positive not a clinically useful predictor if used on its own in low-risk pregnancies. However, in a high-risk population S-relaxin had comparable predictive abilities to fetal fibronectin. Women delivering preterm do not just have upward shifted S-relaxin levels throughout pregnancy, but have initial low but stable S-relaxin levels resulting in elevated S-relaxin levels in the second and the third trimester. One may hypothesize that the deficient corpus luteum or placenta is not capable of the physiological inhibition of relaxin causing stable relaxin levels through pregnancy. Thereby, elevated relaxin levels in late pregnancy will characterize the preterm pregnancies.

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Indications for cesarean section in Norway

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Background: To investigate indications for cesarean sections in Norway, related to type of operation, parity and gestational age.

Methods: Prospective survey using information provided by clinicians at 24 maternity units. The clinicians filled in a specially designed form for each delivery, which included 31 prespecified indications for cesarean sections. If several indications were relevant, the clinician was asked to rank the three most important indications.
2778 cesarean sections were included in the survey from December 1. 1998 to July 1. 1999 and these represent 68.9 % of all cesarean sections and 70.3 % of all births in Norway in the same period.

Results: Data from The Medical Birth Registry of Norway showed that the overall cesarean sections rate in singleton pregnancies was 13.4 %. The cesarean section rate varied by maternal and gestational age, parity and hospital of delivery.
Seven indications for cesarean sections accounted for 76.6 % of the operations and these are fetal distress (21.9%), failure to progress (20.8%), previous cesarean section (8.9%), breech presentation > 34 weeks of gestation (8.3%), maternal request (6.5%), preeclampsia (6.2%) and failed induction (4.0%). 64.3 % were emergency sections. One fourth (n=269)of the emergency sections in active labor (i.e. 3 cm cervical opening or more) took place when the opening was >9 cm.

Conclusions: In this prospective study, representing more than two thirds of all deliveries in Norway in the study period, accurate information about cesarean section has been obtained. More than 60 % of all sections were emergency operations and the most important indications were fetal distress and failure to progress among nulliparous women. In the elective cesarean section group, the two most important indications were previous cesarean section and maternal request among multiparous women. Surprisingly, we found that as much as one fourth of the emergency operations in active delivery were performed with full cervical opening.

The influence of maternal body mass index, age and height, foetal weight and gestational age at the onset of labour, on the caesarean section rate in spontaneously labouring, nulliparous women with a single cephalic presentation at term.

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Background
Spontaneously labouring nulliparous women, with a single cephalic pregnancy at term (SLNSCT) are a large proportion of every obstetric population. As this group of women is also one of the main contributors to the overall caesarean section rate, and the risk of caesarean section is much higher in women with a previous caesarean section as compared to multiparous women without a uterine scar, the management and outcome of SLNSCT is of the utmost importance in every labour ward.

Methods
This study analysed the relationship between maternal body mass index, height and age, foetal weight and gestational age at the onset of labour on the caesarean section rate in 4131 consecutive SLNSCT delivered at Wycombe General Hospital, between January 1, 1995, and December 31, 2000.

Results
In the study period, 312 women (7.19%) were delivered by caesarean section, of which 106 (2.4%) were for suspected foetal distress and 192 (4.4%) were for failure to advance. The variables were analysed by using a multiple logistic regression analysis. A BMI above 25, spontaneous onset of labour after 40 weeks, maternal age above 29, foetal birth-weight >= 4.0 kilograms and maternal height under 1.70 meters were all found to be significantly associated with an increased risk of requiring delivery by caesarean section.

Conclusions
These associations could be causal or just statistical being related to other factors in the management of labour. Further studies in other units are necessary to confirm these relationships.
Nevertheless, the results of this study imply that the influence of these variables should be considered before comparing and interpreting caesarean section rates within or between different labour wards.
Finally, the regression model enables us to estimate the relative and absolute risk of a woman requiring a caesarean section in SLNSCT at High Wycombe. Hopefully this will help women make more informed choices antenatally and in labour.

Complications of cesarean section, rates and risk factors

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Background:
The cesarean section rate (cs) rate has increased over the past decades. It is therefore of main interest to follow the rates and types of complications associated with cs. Furthermore, risk factors of intra- and post-operative complications need to be regularly re-evaluated. In particular, as modern obstetricians tend to choose cs in cases where operative vaginal delivery may be feasible, it is of special interest to consider associations between cervical dilation and complications.
The objective was to determine the overall rates of different types of intra- and post-operative complications and to identify independent risk factors associated with complications in a population- based cohort of pregnancies.

Methods:
During the period from 1.12.98 to 30.6.99 (7 months), a total number of 2751 cs were performed in Norway at 24 hospitals. A questionnaire for each operation was filled inn and centralised to The Medical Birth Registry of Norway (MBRN). The data were subjected to analyses of complication rates, and risk factors were identified.

Results:
Altogether, 588 women (21,4%) had one or several complications. Intra-operative complications and blood loss were the most frequent complications. Unplanned operation, general anaesthesia, low gestational age, fetal macrosomia and cervical dilation were identified as risk factors by chi-square test. In a multivariate analysis general anaesthesia, fetal macrosomia and cervical dilation remained independent risk factors. In particular, the risk of complications increased with increasing cervical dilation, and operations performed at 9-10 cm dilation had a complication rate of 32,6 %.

Conclusion:
Cesarean section remains an operation with a high complication rate: one of five women undergoing cs suffered from one or more complications. General anaesthesia, fetal macrosomia and cervical dilation were identified as independent risk factors. One of three women undergoing operation at 9 or 10 cm dilation had one or more complications.

Short- and long-term maternal complications following elective caesarean delivery for breech at term

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Planned caesarean section in breech presentation at term has been found associated with lower infant mortality and morbidity. The present study was performed in order to determine short and long term consequences for the mother.
Material and Methods:
Population-based study of all primiparous (N=15,441) who delivered singleton breech at term in Denmark 1982-95. According to the National Birth Register mode of delivery was vaginal in 2363 (15.3%), elective caesarean section in 7503 (48.6%) and emergency caesarean section in 5575 (36.1%). By linkage to the national Death Register and Patient Register information on cause of death and subsequent hospitalisations by diagnosis and intervention were obtained.
Results
There were no maternal deaths in the women with elective caesarean section. Elective caesarean section was associated with lower risks of puerperal fever/pelvic infection (OR=0.5 (95% CI: 0.5-0.8)), bleeding/anaemia (OR=0.8 (95% CI: 0.7-0.9)), operation for wound infection (OR=0.4 (95% CI: 0.4-0.7)), bladder damage (OR=0.4 (95% CI: 0.1-1.0)) compared to emergency caesarean section, but to a higher risk of puerperal fever/pelvic infection (OR=2.9 (95%CI: 1.6-5.3)) and laparotomy ($p<0.001$) compared to vaginal delivery.
Mode of delivery did not influence occurrence of fistula, vaginal descensus, urine incontinence, or anal incontinence.
Conclusion
The short term risk at elective caesarean section was lower than at emergency caesarean section and higher than at vaginal delivery. Long term sequelae, however, did not differ by mode of delivery. Subsequent fertility, pregnancies and deliveries need to be studied before the full medical implications of elective caesarean delivery for breech at term can be determined.

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Are health expectations of term breech infants unrealistically high? A nation-wide comparison between outcomes of term infants presenting in breech or vertex born vaginally versus planned caesarean section

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Objective: Comparisons between term breech infants born vaginally or by planned caesarean section (CS) have neglected the fact that vertex vaginal delivery is also associated with neonatal morbidity. This may lead to unrealistically high health expectations of infants born vaginally.

Patients and Methods: We compared the outcome of infants born by breech vaginal (n=1 270) or by vertex vaginal delivery (n=128 683) or through planned caesarean section (CS) in breech (n=1 640) or vertex (n=4 997). The study population was collected from 139 068 non-malformed singleton term infants born after uncomplicated pregnancy between 37 and 42 weeks of gestation and entered into the Finnish Medical Birth Register (MBR) from 1987 to 1989. The MBR is linked to a number of other nation-wide registers such as the birth/death-certificate-register and hospital discharge-register, and this enables a large follow-up study.

Results: One infant perinatal death occurred in the breech vaginal group (1/1270, 0.08%) and 23 deaths in the vertex vaginal group (23/128 683, 0.017%) (P=0.112, NS), but none in either CS group. Breech vaginal delivery was associated with increased risk of Apgar score < 6 at age 1 min (OR 7.65, CI 6.41-9.12) or at age 5 min (OR 6.42, CI 4.36-9.45) as compared to vertex vaginal delivery. These odd rations were also elevated (OR 4.59, CI 3.48-7.04 and OR 7.58, CI 3.09-18.66, respectively) when compared to breech planned CS. Yet the risk for birth trauma of infants in the breech vaginal group was smaller (OR 0.70, CI 0.51-0.96) than that in the vertex vaginal group. No difference existed in the incidence of neonatal intracranial haemorrhage. A number of other neonatal complications (convulsion, respiratory distress, gastrointestinal disease) occurred equally commonly in each group. We followed the infants to the age of 7 years. Breech infants born vaginally needed fewer admissions (OR 0.58, CI 0.47-0.72) to outpatient departments than did breech infants born by planned CS. The cumulative incidence of long-term morbidity in the breech vaginal group was smaller (OR 0.47, CI 0.28-0.80) than that in the breech planned CS. We also studied the maturity for starting school and school performance during the first two school years in one subgroup of children, and these variables showed no dependence on mode of delivery.

Conclusions: Thus, apart from Apgar suppression, elective vaginal delivery of a full-term breech fetus seems not to lead to long-term morbidity. There is therefore, scarcely any need to change the guidelines for the management of full-term breech presentation, at least in Finland or in other countries providing prenatal care similar to that of Finland.

Abnormal glucose tolerance after pregnancy - a long-term follow-up of a danish population

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BACKGROUND AND AIM: Women with previous gestational diabetes mellitus (GDM) are known to have an increased risk of developing overt diabetes mellitus (DM). The incidence of DM and impaired glucose tolerance (IGT) in a Danish population has previously been found to be 34% two to eleven years after pregnancy. The aim of this study was to find the incidence of abnormal glucose tolerance and overweight among women from Eastern Denmark with previous GDM up to 23 year after pregnancy.

MATERIAL AND METHODS: All women with a diagnosis of GDM in the years 1978-1996 from our department were included. Women without known DM at enrollment were classified by a 2-hour 75-g oral glucose toler-ance test (OGTT) according to the WHO criteria (1998). Women treated with insulin were examined by an i.v. glucagon test to evaluate beta-cell function while fasting blood samples were collected from women with known Type 2 DM. Body mass index was used to evaluate the degree of overweight. Overweight was defined as BMI =25 kg/m2 & <30 kg/m2 and obesity as BMI =30 kg/m2.

RESULTS: 520 were investigated with a mean follow-up time of 11 years (range 2-23 years), 88% of the women were treated with diet during index pregnancy. Eight percent had Type 1 diabetes and 17% Type 2 diabetes at enrollment. Among the women not reporting diabetes 23% had a diabetic OGTT and 33% had IFG and/or IGT. Thus, overall 43% had diabetes while 25% had pre-diabetic conditions. Mean BMI was 29 kg/m2, 29% were overweight and 38% obese.

CONCLUSION: The incidence of abnormal glucose tolerance among Danish women with previous GDM was very high, and many of the women were overweight. Women with GDM should be offered counselling to reduce the risk of developing diabetes after pregnancy, and a follow-up program to assure an early diagnosis of diabetes.

Perinatal mortality among immigrants from Africa´s Horn

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This work is an exploration of the possible effects of maternal country of origin on the risk of perinatal mortality (PNM). Increased risk of PNM was found among infants of foreign-born women delivering in a Swedish hospital between 1990-1995. After adjustment for risk factors, however, the finding only held true for a subgroup of women from Ethiopia and Somalia (ES).

In searching for the mechanism behind this observation, an anthropological study of Somali women was undertaken, yielding the hypothesis that experiences and notions of childbirth brought from their country of origin resulted in certain beliefs and pregnancy strategies of which Swedish caregivers were unaware. These factors, combined with miscommunication, may have occasioned sub-optimal care and heightened the risk of PNM.

In order to test this hypothesis, an audit of all perinatal deaths to ES mothers in Sweden was compared to a matched cohort of Swedish women. Sub-optimal factors associated with PNM were noted with significantly greater frequency among the ES mothers. The audit showed that potentially avoidable deaths (e.g., intrapartal and neonatal deaths, as well as SGA stillbirths) could be related to maternal pregnancy strategies (such as avoiding C/S or not seeking perinatal care when needed), deficiencies in medical care (inadequate surveillance of IUGR or intrapartal CTG), and verbal miscommunication.

However, no association was found between female circumcision and PNM. Circumcised women had in fact a lower risk of prolonged labour, and had a significantly shorter second stage of labour, as compared to non-circumcised women.

It was concluded that the higher incidence of PNM appears partly to be due to an unfortunate interaction between certain pregnancy strategies practices by ES women and the sub-optimal performance of Swedish perinatal care services. The pregnancy strategies in question were related to personal experience, rationality, and tradition regarding childbirth in their countries of origin. Lack of awareness of these circumstances could be linked to sub-optimal perinatal care in the many of the instances studied.

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Vulval intraepithelial neoplasia - Diagnosis and management

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Vulval intraepithelial neoplasia (VIN)like cervical intraepithelial neoplasia has grades 1, 2 and 3 representing the degree, in thirds, that the epithelium is atypical. VIN 3 differentiated describes the highly differentiated VIN where the neoplastic cells are well differentiated but often do not extend throughout the full thickness of the epidermis. Older terms such as Bowen´s disease, erythroplasia of Queyrat, bowenoid papulosis and carcinoma in situ are discontinued. The VIN terminology is currently unsatisfactory and changes in the terminology are planned to be in agreement with FIGO and The International Society of Gynecological Pathologists and VIN would be used exclusively for those conditions that are premalignant and would be separated into two distinct types one fully undifferentiated i.e. the old VIN 2 and 3 and associated with HPV, the other type being well differentiated VIN, the old intraepithelial carcinoma of simplex type. i.e. In this latter type the atypia is confined to the basal areas with fairly normal differentiation above it is very uncommon, is not associated with HPV and carries a much greater risk of progressing to invasive disease. It is most frequently found in vulvectomy specimens in women with SCC occurring on a background of LS or LP.

Extra mammary Paget's disease and melanoma in situ would not be included in the squamous intraepithelial neoplasia terminology and would remain as distinct entities.
Clinically the lesions can be unifocal or multifocal. Multifocal disease is strongly associated with the oncogenic papilloma virus HPV 16 and 18 and almost exclusively occurs in smokers. 2/3 of the patients have concurrent or past cervical intraepithelial neoplasia.
Morphologically the lesions are variable some resembling typical warts, others hyperkeratotic papules and plaques which can be white, red or deeply pigmented resembling seborrhoeic keratosis.
There are a number of treatments both surgical and medical but all are limited due to their ineffectiveness and recurrence rate. Management is tailored to suit the patient symptoms and the extent of her disease.

Localised, unifocal lesions should be excised. Extensive multifocal disease is challenging as excision and laser treatment are associated with both physical and psychological morbidity and do not guarantee clearance of the disease. Fortunately risk of invasive disease in the young, immunocompetent patient is low being 4% or less so current management entails limited excisions for histological assessment and debulking the area involved. Large, polypoid lesions should always be removed as they may harbour occult, early invasive disease. Long term regular follow up is mandatory to remove any suspicious areas and to screen for disease at other sites particularly the cervix. The promise in the future may well be in immune modulating therapy with agents such as imiquimod and vaccines for the prevention and or treatment of HPV infection.

Strategy of diagnosis, prevention and therapy of blood transfusion in obstetrics

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Experience with iron sucrose complex in the Department of Obstetrics, Zurich University Hospital (1992-2002)
Iron sucrose was administered as either a bolus (undiluted) or short infusion (in 200 ml of 0.9% NaCl). Maximum cumulative doses were 800 mg postpartum (200 mg daily for 4 days) and 1600 mg in pregnancy (200 mg twice weekly to a target hemoglobin of 11.0 g/dl or for a maximum of 4 weeks), administered via peripheral catheter over 30 minutes for short infusions (inpatients) and over 5-10 minutes for bolus injections (outpatients).
Safety profile
Over a 10 year period (1992 to 2002) a total of 800 patients received a total 4000 ampoules, each containing the equivalent of 100 mg of elemental iron. Side effect rates - all on the first day of treatment - were 1.5% relative to the total number of patients and 0.36% relative to the number of ampoules (Breymann, 1998; Hoigné et al. 1998). No serious side effects or anaphylactoid reactions were observed. In no case did treatment have to be discontinued or blood transfused due to non response to treatment
Pre-Delivery

Pretreatment mean Hb was 9.2 ± 0.6 g/dl (7.9-9.9 g/dl) and gestational age 31.5 weeks (20-38 weeks). Mean treatment duration was 21 days (8-29 days). Both ferritin and transferrin saturation were clearly pathological at a baseline: 7.0 ± 4.0 µg/l and 6.2 ± 3.7%, respectively. Hypochromic red cells levels were markedly elevated: 18.5 ± 9.3%. All parameters improved significantly after 2 weeks. Anaemia was corrected in all patients, with a mean increase in Hb of 1.9 g/dl and significant increases in MCV and MCH. Hypochromic red cells fell by a mean 4.2%. By the end of treatment, transferrin saturation and ferritin were normal.
Postpartum
We present data from studies with iron sucrose with and without rhEPO at cumulative doses of 100-800 mg given as a single dose (100 mg), on two days (2 × 200 mg), and on four days (4 × 200 mg) (Breymann et al., 1996; Breymann et al., 2000). Following mean blood loss of 840 ml (300-3600 ml), postpartum Hb ranged from 7.3 ± 0.9 to 8.8 ± 0.8 g/dl before treatment. Overall response at 14 days showed a dose-dependent increase in Hb (by 2.1-3.2 g/dl) to normal levels in all groups; the maximum mean daily increase in group 4 was 0.23 g/dl.
Parenteral iron sucrose is a safe and effective therapy of progressive peripartal anaemia and has the potential to prevent obstetric patients from peripartal blood transfusion. In severe cases additional rhEPO might be taken into consideration.

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Erythropoietin and intravenous usage of iron while treating post partum anaemia - Swedish experience

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BACKGROUND: During pregnancy there is a high prevalence of maternal anaemia. This is partly due to the physiological adaptation with an expansion of plasma volume, and partly due to a true iron defiency that becomes evident as the demands increase. Patient compliance with iron replacement therapy is reported to be low.
At delivery, the anaemia is compounded by blood loss. In 1996 at the Department of Obstetrics at Södersjukhuset, Stockholm approximately 20% bled more than 600 ml, and around 3% received red cell transfusion.
Post partum anaemia results in prolonged hospital stay and maternal difficulties in coping.
The increased awareness in both patients and physicians about the risks with homologous blood transfusions has cut the number of transfusions and turned the interest towards alternative methods. The availability of recombinant erythropoeitin has opened new fields in treatment of anaemia. Its efficiency in treatment of renal anaemia is well documented.
At the University Hospital of Zurich, they have long experience in treating postpartum anaemic patients with EPO and iron intravenously. The limiting factor for erythropoesis has been suggested to be the availability of iron.
That inspired us to conduct a Swedish study where we doubled the dose iron given. We also choose patients with a more pronounced anaemia- thus accomplishing a better alternative from a clinical view regarding cost-benefit usage of rhEPO.

METHOD: 60 patients with haemoglobin values under 81g/L, where randomised within 72 hours after childbirth to three different treatments. All three groups were given a total dosage of 450 mg intravenous iron. Two groups were given EPO, 10.000 U and 20.000 U. The treatment was given at two occasions with an interval of three days.

RESULTS: There was no differens between the three groups. The mean value of haemoglobin was at treatment initiation 74,3 g/L (SD=4.6,n=49) and after 1 week Hb had raised to 92,2(SD=10.8). After two weeks Hb was 102,5 g/L (SD=10.4) which means a total raise of 28,2 g/L.

CONCLUSION: All regimens were effective and no differences between the groups were found. The use of erythropoeitin did not enhance the increase in this study.

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Term Breech Trial: Cesarean section or vaginal birth for the singleton fetus in breech presentation at term

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Non-randomised studies have found better outcomes for singleton infants presenting breech at term if delivered by planned or elective Caesarean section (CS) vs those delivered by planned vaginal birth (VB), that is either an actual VB or an emergency CS. Non-randomised studies may suffer from selection bias, however, and thus the results may not be true. The Term Breech Trial was a large (N=2088) RCT, undertaken to test the hypothesis that a policy of planned CS would decrease the risk of serious adverse perinatal outcome compared with a policy of planned VB for the singleton fetus in breech presentation at term. A consensus was reached on the selection criteria for the study and on the intrapartum management protocol during a meeting of experts, convened for that purpose. Women having a VB were to have an experienced individual in attendance at the birth. The study was undertaken in 121 centres in 26 countries.

The design and principal results of the Term Breech Trial were published in the Lancet 2000; 356:1375-83; maternal outcomes 3 months after the birth are scheduled for publication in JAMA in April 2002. The presentation will outline the methods and results of the Term Breech Trial and invite discussion on controversial issues.

Breech deliveries in Finland

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The "Term breech trial" (TBT) raised in Finland a lively discussion about the best way to deliver babies in breech. So far, most of the studies had been retrospective, with a small number of patients, and with a short follow-up of as well children as of the future health and pregnancies of the mothers. TBT was a good try to answer this important question but so far the TBT group published the follow up ending at 6 weeks post partum. It is clear that the possible long term maternal complications, the impact of the CS on future pregnancies and reproductive future of the woman, as well as the long term health of the infant were not taken into account.
Another issue of discussion is that babies presenting in breech at term differ from those presenting in cephalic position: the number of IUGR babies, babies with malformations and other problems like imminent hypoxia is significantly higher among those presenting in breech. Therefore, the idea to collect a control group of breech babies delivered by CS is not totally correct: these babies do not experience the normal way of labor through the birth canal. The comparison of such two groups is as wrong as is the comparison of the health of cephalic babies born either vaginally or by CS. In such a comparison, the babies born by CS would certainly have higher Apgar scores than those delivered vaginally. Therefore, to really have a good study on the impact of being born vaginally in breech on the neonatal health, two control groups should be collected. The first control group should consist of breech babies born by CS, and the second control group of cephalic babies born vaginally.

Therefore, in spite of the results of the TBT, willing and compliant multiparous patients should have the possibility to deliver a breech baby vaginally, with continuous CTG, possibility of blood sampling from the fetal buttock if needed, and possibility of emergency CS when necessary. After careful selection, an experienced obstetrician should have the possibility to support such a choice by the patient without fear or risk of being sued of malpractice.
However, this is not a straight forward issue anymore, because 1) the general opinion is for CS when the baby is in breech, and 2) the generation of obstetricians able to regard themselves as experienced in vaginal breech delivery will slowly retire. Thereafter the patient will have no choice: a baby in breech will be born by CS.
However, there will always be nondiagnosed emergency breech deliveries, as well as second twins presenting in breech. Will they urgently experience an emergency CS because of the fact that there is not such an obstetrician available who had ever helped a vaginal breech baby out?

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Scandinavian post-trial panel- the Swedish experience.

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During recent years there has been an intensive discussion regarding how to deliver breech presentation at term in Sweden. There has also been an increasing Caesarean section rate in this group. In September 2000 this topic was discussed at the yearly meeting with the Swedish Association of Obstetrics and Gynecology without reaching consensus. The randomised study (Hannah et al) published in Lancet in October 2000 was questioned in Sweden due to shortcomings especially regarding pelvimetri, estimation of fetal weight and fetal supervision during delivery. As a consequense of the study the Swedish Perinatal Association had an extra meeting in December 2000 to discuss how to deliver breech presentation at term. No consensus was reached even if it was a common experience that the caesarean section rate was inreasing even more The conclusion was that there is further need of data and a case-controlstudy was initiated and is ongoing.
Meanwhile the discussion has calmed a little, a high Caesarean section rate in breech presentation at term is accepted even if the evidence is still questioned.

Delivery of term breech in Denmark 1997-2001

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The Term Breech Trial was published in October 2000. In December 2000 Danish obstetricians arranged a National Consensus Meeting to discuss the findings and their impact on subsequent mode of delivery in term breech pregnancies and in general. In order to describe the consequences we analysed the rates of Caesarean section in Denmark 1997-2001.

Results
In the 5-year period the overall CS-rates increased from 12.9 to 17.1%. From 1998 to 2001 the rates of Caesarean section in breech at term increased from 79.1% to 92.9%, and the increase from 2000 to 2001 was 9.6%.
In "standard primipara" and in multiple pregnancies the average increase was about 6% and in women with previous caesarean section the rate did not change significantly.
The population adjusted annual number of CS in the same time period increased by 1975 (from 8608 to 10583) and out of these 573 (29%) were associated with singleton breech at term.

Conclusion
The publication and discussion of the Term Breech Trial in 2000 was associated with a significant increase in CS for term breech in 2001. In the 5-year period 1997-2001 - before and after the trial - there was a general increase in caesarean section rates in most other groups as well.

Men's experiences of investigation and treatment of infertility

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This presentation is based mainly on literature and on my experiences as a clinical and researching psychologist in the field of human reproduction. Until recently, infertility has been regarded as a problem for the woman. A consequence of this is that we know much more about female than about male experiences of infertility. There are two major reasons for paying more attention to the men in the context of infertility investigation and treatment: 1) The couple is the patient, and 2) The revolution regarding possibilities to treat male infertility via IVF and ICSI. Therefore we need to focus also the man and learn more about his experiences, problems, questions an possibilities.
In the presentation I will focus on men's experiences of the infertility, on his experiences of the relationship with his woman and her reactions and on his experiences of investigations and treatments.

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The male partner involved in legal abortion

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Introduction: Roles and reactions of men in connection with unwanted pregnancy and legal abortion is an unexplored and neglected field. Men are usually invisible in abortion studies and hardly ever considered as a target group in efforts to prevent legal abortions.

Method: Seventy-five men answered a questionnaire concerning psychosocial background, current living conditions partner relationship and attitudes and feelings towards the pregnancy and abortion.

Results: The vast majority were found to be in stable relationships with adequate finances. Half the men had previous children. Most stated that they wanted the woman to have an abortion and 20 of them also added that they submitted themselves to their partner ´s decision. Two men wanted the woman to complete the pregnancy. About half gave motives for abortion, which were related to family planning. Either they wanted to postpone childbirth or they already had all the children they wanted. Apart from wanting children within functioning family units, the motives for abortion revealed that the desire to have children depended on the ability to provide qualitatively good parenting. More than half had discussed with their partner what to do in event of pregnancy and half had then decided to have an abortion if a pregnancy occurred. The majority expressed ambivalent feelings about the coming abortion, using words such as anxiety, responsibility, guilt, relief and grief.

Conclusions: Prevailing expectations concerning lifestyle make abortion an acceptable method in family planning. Abortion is experienced as a relief and a form of taking responsibility simultaneously as many experience the termination of the pregnancy as a painful life event. A deeper understanding of the complexity of legal abortion makes it necessary to be open for paradoxical feelings and attitudes.

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Three men and a woman - the case of donor insemination

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This presentation will be based on a consideration of gender issues in donor insemination(DI) In particular it will focus on the three males--infertile male partner, semen provider and male clinician (where this is the case)--and the interactions between them and the female recipient. These interactions will be explored through the issues of vulnerability, sexuality and secrecy

Postpartum depression - the father´s role

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The average prevalence rate of non-psychotic postpartum depression (PPD) based on a large number of studies is 13% . Depression during the puerperium is a serious health problem for women and its consequences has serious implications for the welfare of the family and the cognitive and emotional development of the child. The strongest predictors of PPD are past history of psychopathology, psychological disturbance during pregnancy , poor marital relationship and low emotional support. Depression and anxiety are also common during pregnancy and some women continue to be depressed postpartum.
The role of the partner relationship and support in depression during pregnancy and postpartum will be discussed from recent international and Swedish studies. Results from a transcultural study of perceptions of postpartum depression in new mothers and fathers, conducted in eight European countries including Sweden, will be presented and clinical implications will be discussed.

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Male partner's role in women with psychosomatic disorders

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The role of the male partner for women´s health and disease has attracted a considerable attention during the last decades. When addressing the psychosomatic aspects, we need the definition of the concept "psychosomatic". Generally accepted is the following statement: the importance of psychological and social factors for health and illness.

Within the field of obstetrics, we have included the male partner in the obstetrical team as a provider of support. However, we have to count with his own emotional reactions in connection with childbirth. His reactions may influence the woman with fear of childbirth, her breast feeding and the use of prenatal diagnosis. He has his own experience of intrauterine fetal death, often not outspoken by himself or realized by the staff. He still is expected to provide emotional support to the woman. On the other side, we have to realize that the male partner may be a dangerous risk for the woman. He may be the perpetrator in cases of violence against pregnant women. This violence is an important reason for maternal death during pregnancy. He is also, in the role of present or previous partner, the man who rape.

Within the gynecological field there is reason for attention towards the male partner. In the cases of chronic pelvic pain he may be a stabilizing factor, but in other cases helplessly trapped in her symptoms and the aggressive struggle for help from the medical care. The role of the relationship with a male partner in cases of severe vulvodynia and vulvar vestibulitis remains to be studied.

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Ovarian folliculogenesis from fetal to adult life

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Primordial germ cells originate from embryonic ectoderm and migrate to the developing gonad during 5th and 6th week after fertilization. The human ovary begins to differentiate morphologically at 11-12 weeks of development, and loose follicular structures begin to form the same time. The number of oogonia increases steadily until they enter first meiosis when they transformate into oocytes. The number of oocytes reaches a maximum of 7 million around 20th week, and by 24th week most oocytes are surrounded by a single layer of flat granulosa and form primordial follicles. Thereafter the number of primordial follicles (oocytes) decreases and is 1-2 million at birth, and the programmed cell death, apoptosis, is the mechanism of this process. The remaining follicles comprise the pool of resting follicles. At puberty there are only 0.2-0.4 million resting follicles left, and finally approximately 400 oocytes from the original 7 million will ovulate during the fertile lifespan. During the reproductive life, continuously a small number of follicles leaves the resting pool and start growing. The exact time for the follicle to attain the preantral stage is unknown, but it may take 200-300 days. The follicular development from preantral stage to ovulation takes about 90 days. When the follicles contain three to six layers of granulosa cells the surrounding connective tissue differentiates into two parts, theca externa and interna. Already at this stage (preantral), a considerable portion of growing follicles undergo atresia i.e. apoptosis, and this process continues for the entire follicular development, and only one of the follicles is selected for ovulation. All the rest are deleted. After the primary follicular stage, gonadotropins and especially FSH are increasingly important in sustaining follicular growth. The essential role of FSH has been demonstrated in women with inactivating mutation of FSH receptor. Ovarian biopsies of these subjects have revealed high number of primordial and primary follicles but only occasional signs of further development. As mentioned already apoptosis is present in the ovaries already from early fetal life. It can be localized both to oocytes and granulosa cells. The key regulators of apoptosis are the members of Bc-2 family. Both the apoptosis promoting factor Bax and the anti-apoptotic factor Bcl-2 are present in the ovaries already from the early stages of fetal development. In the fetal ovary, apoptosis is abundantly present in oocytes while in the adult ovary apoptosis is found mainly in granulosa cells of growing follicles suggesting that depletion of fetal ovarian follicles occurs through intrinsic mechanisms of apoptosis in oocytes, and in adult life the survival of growing follicles is determined by granulosa cell apoptosis. Gonadotropins and estrogens seem to act as a survival factor while testosterone increases follicular apoptosis, but the detailed mechanisms of their action are not well understood.

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Why are not all follicles equal?

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In the human menstrual cycle a single follicle is normally selected during the follicular phase for final maturation and ovulation with release of a fertilizable oocyte. The absolute concentrations of FSH during the follicular phase is responsible for the selective maturation of this single pre-ovulatory follicle. For this final growth of the follicle the FSH concentrations must reach a critical threshold level. During controlled ovarian hyperstimulation for IVF the FSH levels are maintained for a long time above this threshold levels and multiple follicles will grow and mature into the preovulatory stage. The functional quality of the follicles and the fertilizability of the oocytes from the different follicles that are punctured during ovum pick up procedure are not uniform. Thus, the unphysiological situation during controlled ovarian hyperstimulation induce maturation of multiple large follicles which are of low quality. Several biochemical and functional markers may indicate that follicles are of less quality. The factors that have been suggested to be related to follicular quality are follicular blood flow, follicular volume, oxygen tension, follicular inhibin production as well as follicular fluid levels of inflammatory mediators such as eicosanoids and chemo/cyto-kines. The specific changes that may indicate that follicles are of less quality and the roles for this mediators in final maturation and ovulation of the follicle will be discussed.

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Novel ovulation induction regimens

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Ovulation induction may either be to induce a physiological ovulation in women with anovulation, or to induce a controlled ovarian hyperstimulation (COH) in women undergoing ART. In patients with WHO II the first choice is clomiphene citrate and second choice hMG/rec FSH. Commonly hMG/recFSH is combinated with GnRH agonist but there is no concensus on the need for down-regulation. Patients with WHO I need to be stimulated with hMG or rec FSH+rec LH. Ovulation induction with gonadotropins needs careful planning and experience in order to avoid multiple pregnancy and ovarian hyperstimulation (OHSS).
In the majority of cycles, ovulation induction is used in ART to obtain many oocytes for fertilisation. A combination of GnRH agonists and rec FSH is currently the gold standard in ART cycles. The main advantage using the agonists are prevention of premature LH surges, optimal oocyte quality and cycle programming. The long treatment duration and the hypoestrogenic side-effects are drawbacks. Antagonists of GnRH were recently introduced and enable a shorter and softer ovarian stimulation. In young women with normal ovarian function the antagonists seem to offer similar results as the agonists. One drawback is the lack of cycle programming. In most patients rec FSH is sufficient for stimulation. Rec LH was recently introduced, but apart from WHO I, the advantage of rec LH is not yet defined.

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Assessment of the function of the corpus luteum

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The human corpus luteum (CL) is a transiently appearing endocrine gland, functionally active for only about 14 days. It´s principal function is to produce and secrete progesterone, which is necessary for endometrial implantation and to prevent rejection of the developing embryo. In the event of a non-fertile cycle, locally activated functional and structural demise of the CL follows, which is necessary for a new ovulatory cycle to begin.

To further define local regulators of CL function, ovarian biopsies were obtained from 60 fertile women, grouped according to CL-age following occurrence of a preovulatory LH surge. Using cultures of isolated steroidogenic luteal cells it was established that the sensibility towards hCG peaks during the early-mid luteal phase in concordance with elevated numbers of LH/hCG receptor coding mRNAs. These cells, were the bulk of progesterone is produced, are located in the peripheral layer of the CL, and exhibit a relatively high expression of a variety of receptors including luteinizing hormone/human chorionic gonadotropin (LH/hCG) but also prolactin and GnRH, in addition to steroid receptors such as the progesterone receptor (PR) isoforms A and B, estrogen receptor type beta (ER-beta), but interestingly not ER-alpha. During mid LP, hCG-stimulation can be blunted by the PR antagonist mifepristone, suggestive of an auto or paracrine stimulatory action of progesterone within the steroidogenic cells of the human CL.

Increased amounts of PGF_{2alpha} and its corresponding receptor (FP) mRNA are found during the later developmental stages of the CL. However, progesterone output from steroidogenic luteal cells was unchanged to added PGF_{2alpha} until mid-late LP, indicative of an acquisition of sensitivity to the proposed luteolytic signal during this stage. Quantitative real-time RT-PCR measurements indicates a direct effect on gene expression, since the PGF_{2alpha} analog cloprostenol when added together with hCG, dose-dependently decreased numbers of LH/hCG-R mRNA in both luteal cells and IVF-stimulated ovarian follicular cells, while hCG alone increased LH/hCG-R transcripts.

In clinical practice, transvaginal ultrasonography in combination with color Doppler measurements may serve as a useful clinical tool to evaluate CL function. Morphometric evaluation showed that intraluteal vascular density was highest in early LP and dramatically decreased during the course of CL development, a finding which was inversely correlated to resistance blood flow in intraovarian blood vessels supplying the CL. Importantly, a high degree of agreement between ultrasonographical and anatomical measurements of the CL was found.

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Ovarian influence in implantation

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INTRODUCTION: Endometrial function has often been regarded being a passive process depending on ovarian stimulation in IVF treatment. The aim of this lesson is, with background in a clinical study, to review the influence of local, steroid hormone dependent changes in the endometrium in preparation for implantation.
How does progesterone influence on endometrial maturation? During the last 10 years, the presence of several cytokines in the endometrium, like leukaemia inhibitory factor, the interleukin-1 system, integrins and glycodelin have been investigated. These cytokines are under steroid hormone regulation. Both animal studies and human studies have shown that an aberrant expression of one or several cytokines in the endometrium is related to different kinds of infertility.
METHODS: Key note lecture
RESULTS: In a newly finished and yet not published clinical study, a group of fertile controls had significantly higher plasma progesterone levels on cycle day LH+7 than infertile women due to tubal infertility. The infertile group started down regulation on day LH+7, and all had embryos transferred in the following IVF treatment. Women who became pregnant had significantly higher plasma progesterone levels day LH+7 than women who did not conceive.
CONCLUSIONS: Midluteal phase progesterone levels in spontaneous cycles seem to have clinical value in predicting outcome in the following IVF treatment.

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Neuroprogesterone: Nerve/myelin protection and repair, memory, anxiety, neuroplasticity, aging...

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Neurosteroids, including "neuroprogesterone", are synthesized in the nervous system, and act upon nerves and neurotransmission according to several modalities. 1/ There are effects via the classical nuclear receptors of steroid hormones, i.e. progesterone produced in glial cells which can repair damaged myelin in CNS and PNS. 2/ There are membrane effects, acting upon neurotransmitter receptors, of steroidal precursors and metabolites of neuroprogesterone, such as DHEA and pregnenolone sulfates stimulating NMDA receptor and inhibiting GABAA-R function, and allopregnanolone stimulating GABAA receptor. As a consequence, the promnesic action of pregnenolone sulfate in the hippocampus is described, and the decrease of memory with age correlated with pregnenolone sulfate concentration in hippocampus, and corrected by local administration of the steroid. "Normal" memory deficit of ageing thus seems reversible ! Anxiety can be suppressed by allopregnanolone. 3/ A new mechanism of action of steroids, at microtubule associated protein (MAP2) level, is described with increase of tubulin polymerization of microtubule formation by pregnenolone, antagonized by progesterone. This new mode of steroid action, neither at the nucleus nor at the plasma membrane levels, may open new ways to understand neuroplasticity. Thus a novel field is open, with new theoretical background and anti-ageing drugs to come. In addition, some clinical implications related to reproductive medicine and gerontology will be reported.

Review :

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Neuroactive steroids in gynecological and neurological disorders

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Steroid hormones are vital for the cell life and affect a number of neuroendocrine and behavioral functions. In contrast to their endocrine actions, certain steroids have been shown to rapidly alter brain excitability and to produce behavioral effects within seconds to minutes. In this symposium I throw attention on to this issue of neuroactive steroids by outlining several aspects of current interest in the field of steroid research. Recent advances in the neurobiology of neuroactive steroids are described along with the impact of advances on drug design for sex hormone-linked CNS disorders. The theme is selected in association with the clinical aspects and therapeutical potentials of the neuroactive steroids in CNS disorders. A wide range of topics relating to the neuroactive steroids are outlined, including steroid concentrations in the brain, premenstrual syndrome, cognetive disorders, side effect of oral contraceptives, hormone replacement therapy and Catamenial epilepsy. Three different principles of steroid actions in the brain are outlined, namely direct effects of sex steroids on CNS, CNS disorders induced by tolerance to neuroactive steroids and CNS disorders induced by steroid withdrawal.

Brain sensitivity to progesterone metabolites - changes in hormonal status

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Progesterone metabolites, such as pregnanolone and allopregnanolone, have profound effects in the brain through their interaction with the GABAA receptor. The GABA system is the major inhibitory neurotransmitter system in the mammalian brain and the receptor is a pentameric chloride channel, composed of five subunits. Today, 19 different GABAA receptor subunits have been identified, and typically the receptor is composed of two a, two b and one g subunit. The commonly used benzodiazepines and barbiturates exert their actions by binding to the GABAA receptor. Likewise, progesterone metabolites bind to a unique binding site at the receptor and progesterone metabolite effects are consequently similar to the actions of benzodiazepines and barbiturates, i.e. sedative, anxiolytic, anesthetic and anticonvulsive.
Reproductive events can change GABAA receptor function and expression and consequently sensitivity to GABAergic compounds, such as the progesterone metabolites. Certain women, in particular women with premenstrual dysphoric disorder (PMDD), display distinct changes in benzodiazepine, pregnanolone and alcohol sensitivity across the menstrual cycle. Compared to control subject they have a reduced sensitivity to benzodiazepines and pregnanolone, whereas sensitivity to low doses of alcohol is enhanced. The pharmacological changes reported in women with PMDD are likely due to changes in GABAA receptor subunit composition. In particular, a4 and d subunits have been suggested to be involved in the changing sensitivity to GABAergic compounds. During progesterone withdrawal, female rats display increased anxiety and increased susceptibility to seizures together with decreased sensitivity to benzodiazepines as well as progesterone metabolites. These changes in behaviour and pharmacology are accompanied by increased expression of a4 and d subunits in the hippocampus. Similar changes in mood and seizure susceptibility are seen in women with PMDD and in women with partial epilepsy during the late luteal phase of the menstrual cycle.

Progestin effects on learning and memory

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Women might at situations with high levels of progesterone experience negative effects on cognitive functions. This includes impairment of verbal memory during pregnancy. Progesterone effects in the brain are caused by progesterone binding to the progesterone receptor and by CNS active metabolites.
Steroids produced within the brain are called neurosteroids. Neurosteroids affect cognitive processes both positively and negatively. This is not surprising as there are neurosteroids with opposite effects, excitatory as well as inhibitory actions. The A-ring reduced progesterone metabolite allopregnanolone achieve CNS inhibitory effects by GABAA receptor agonistic activity. On the other hand, pregnenolone sulfate acts as a negative modulator of the GABAA receptor and with positive effects on the NMDA receptor, resulting in a stimulatory neuronal effect.
As a standard test of learning and memory in rodents the Morris Water Maze is used. Rodents are natural swimmers that in this test learn to find a platform situated 40 centimetres into the pool and just below the water surface. To learn this spatial task extra-maze cues are used. Necessary for this process is the hippocampal formation.
In rats we explored the acute effect of allopregnanolone on learning in the Morris Water Maze. Adult male Wistar rats were injected i.v. with allopregnanolone (2 mg/kg) 8 or 20 minutes before the start of each training session. Control rats were injected with vehicle, 16.7% 2-hydroxypropyl-beta-cyclodextrin. Allopregnanolone concentrations were analysed in plasma and in nine different brain areas 8 or 20 minutes after injections.
Rats injected with allopregnanolone 8 minutes before swimming did not learn to find the position of the platform as well as control rats. Allopregnanolone administered 20 minutes before the session did not affect the performance. Swim speed did not differ between groups. Thus, the longer time rats in the allopregnanolone 8 minutes group needed to find the platform was not caused by motor impairment. In this group there were several rats that mainly spent the time swimming close to the pool wall. The reason might be increased anxiety or a behavioral abnormality resulting in loss of strategy how to search for the platform.
The allopregnanolone concentrations in the brain areas were at 8 minutes 1.5 to 2.5 times higher than in the allopregnanolone 20 minutes group, while the concentrations after vehicle injection were at normal levels. In plasma, allopregnanolone concentrations increased also after the 8 minutes vehicle injection.
In conclusion, in rats the natural progesterone metabolite allopregnanolone have a major impact on the learning ability of the Morris water maze task. This might be caused by a combination of changed swimming behavior and difficulties in navigation. This indicates that spatial tasks also might be affected in women at situations with high allopregnanolone levels, i.e. at progesterone peaks.

Progestin effects on mood

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The addition of progestins to estrogen in hormone replacement therapy (HRT) seems to affect mood as well as causing physical symptoms. Some women are more sensitive to side effects than others. The type of progestin as well as the dosage seems to be of importance. The symptomes provoked are similar to those experienced by women with premenstrual dysphoric disorder (PMDD).

Neurosteroids with specific effects on transmittor systems in the brain might be responsible for provoking the mental symptoms in PMDD. Some neurosteroids are GABA agonists and therefore produce anxiolytic effects while others act anxiogenic, most likely due to effects mediated by the NMDA-receptor. It is possible that synthetic progestins could use the same enzymatic pathways in the brain as progesterone does, and subsequently produce neuroactive metabolites with properties similar to those of some of the neurosteroids.

A history of PMDD seems to be of importance to the response of negative side effects when treating women with a combination of estrogen and progestins after menopause. The addition of sequential medroxyprogesterone acetate (MPA) or noretisterone acetate (NETA) both cause negative mental effects, but to a greater extent in women with previous PMDD. MPA is however, preferable to NETA with respect to mood symptoms in women without a history of PMDD.

When comparing different doses of MPA during sequential hormone replacement therapy, a higher dose of MPA induce less negative and more positive mood symptoms in women with a history of PMDD, than when using a lower dose. One theory to explain this is that a higher dose of MPA has an anxiolytic effect in the brain whereas a lower dose has an anxiogenic effect.

Progestins have a beneficial effect on the endometrium; since progestins given in a correct way abolish the increased risk of endometrial hyperplasia, atypia and cancer produced by estrogens. However, negative side effects caused by progestins lower compliance to HRT. Our challenge is to find therapies without negative side effects.

Twin epidemiology in Finland in 1987-2001

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Background: The twinning rate has increased due to greater use of advanced infertility treatments (including IVF, ICSI and FET; subsequently referred as IVF). The aim of this study is to describe the secular trends in twinning, the care of twin pregnancies and deliveries, and the perinatal outcome of twins in Finland since 1987.

Methods: Data from the nationwide Medical Birth Register were utilised. In the 1987-2000 period, the register included information on 865 962 deliveries, of which 11 896 were twin, 287 triplet and 7 quadruplet deliveries. Comparisons were made for two time-periods: 1987-1990 (N=2810 twin deliveries) and 1997-2000 (N=3720 twin deliveries).

Results: The incidence of twin deliveries increased from 1.11 per 100 deliveries in the 1987-1990 period to 1.62 per 100 deliveries in the 1997-2000 period. The incidence of non-IVF twin deliveries was 1.22 per 100 deliveries in the latter period; thus IVF contributed up to 79% of the total increase. The incidence of twin deliveries increased by 50% among mothers aged 30-34 years (from 1.3% to 1.9%) and among mothers aged 35-39 years (from 1.5% to 2.2%), but more than doubled for mothers aged 40 years or more (from 0.9% to 1.8%). By parity, the incidence increased most for primiparous women (from 1.0% to 1.9%) and for women with one or two previous deliveries (from 1.2% to 1.5%). In the second time-period, 58% of women giving birth to twins were hospitalised during pregnancy. Half of all twin pregnancies ended in Caesarean section and 36% in iatrogenic delivery, including induced labour and planned Caesarean section. Between the late 1980s and the late 1990s, the proportion of premature twins (< 37 gestation weeks) increased from 43% to 45%, and the proportion of low birth-weight children (< 2500 grams) increased from 36% to 41%, but the proportion of very low birth-weight twins (< 1500 grams) remained at the same level (7.2% and 7.4%, respectively). The perinatal mortality rate for twins decreased from 45 per 1000 newborns to 25 per 1000 newborns. B-children (30/1000 in 1997-2000) still have a higher mortality rate compared to A-children (21/1000). The proportion of twins which were home at the age of seven days increased from 31% in 1987-1990 to 57% in 1997-2000.

Conclusions: The twinning rate has increased mostly due to the more intense use of IVF. The highest increase in the twinning rate was observed among older and primiparous parturients, which challenges health care services during the prenatal period and delivery. Despite the increased proportion of premature and low birth-weight twins, perinatal mortality has decreased substantially. Follow-up studies are needed in order to investigate the long-term health of twins.

Chorionicity and implications for surveillance

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The major prenatal determinant of outcome in twin pregnancies is chorionicity, which can be reliably determined by ultrasonographic examination before 14 weeks of gestation, and can be conveniently carried out at the 11-14 week scan with measurement of fetal nuchal translucency thickness (NT). Monochorionic (MC) twin pregnancies are at 5-fold increased risk for pregnancy loss before 24 weeks´, in addition to twice the risk for perinatal mortality; most of this excess risk is a consequence of twin-to-twin transfusion syndrome (TTTS) due to the presence of feto-fetal placental anastomoses. Early features indicating MC twin pregnancies at increased risk for TTTS are increased fetal NT and abnormal ductus venosus Doppler flow velocity waveforms at 11-14 weeks´, and folding of the intertwin membrane at 15-17 weeks´.

Determination of chorionicity also has implications for screening and invasive fetal testing for fetal chromosomal defects and subsequent management of pregnancies discordant for fetal abnormality, since selective fetocide using traditional techniques is not an option in MC twin pregnancies and novel techniques may be required. Furthermore, management of third trimester pregnancy complications such as intrauterine growth restriction and single fetal death, are critically dependent on prior knowledge of chorionicity.

How to prevent twins in IVF pregnancies

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Introduction. One of the main challenges in assisted reproductive treatment (ART) programmes is to avoid multiple pregnancies without significantly lowering the overall pregnancy rate (PR). In many countries more than 2% of the new-borns are born after ART. Traditionally, ART has been associated with a 20-fold rate of multiple pregnancies compared to spontaneous pregnancies which means that about half of the children born after assisted reproduction originate from multiple gestation pregnancies. The only method of avoiding twins is to transfer one fresh embryo and freeze all other embryos. We started our elective single embryo transfer program (eSET) in 1997. Later, we changed our transfer policy and two embryo transfer was carried out only if there were specific reasons: woman's age > 37 years, two unsuccessful IVF cycles, poor embryo quality, and no medical contraindication for twin pregnancy. The aim of this report is to answer how this policy affects over all pregnancy rate as well as multiple pregnancy rate.

Material and methods. During the years 1997 to 2001 we have performed altogether 1699 IVF/ICSI-ET cycles at our infertility clinic. Out of these 470 (28%)were eSETs and 1024 (60%) two embryo transfers, whereas in 205 (12%) cycles only one embryo was available. During the same time period 1288 frozen embryo transfers were carried out, 507 (39%) of these were single embryo transfers and 781 (61%) two embryo transfers. We have now analysed the clinical ongoing pregnancy rate (PR) and the multiple pregnancy rate in our IVF/ICSI/FET program.

Results. The overall clinical PR per transfer in IVF/ICSI cycles during this time period was 34%, and the multiple pregnancy rate 19%. The number of eSETs increased gradually during the years, representing more than half of the cycles year 2001. The PR in eSET during the five years was 34% (162/470), including two sets of monozygotic twins (1.2%). When two embryos were transferred, PR has been 37% with a multiple pregnancy rate of 28%, including 106 twins and one triplet. The overall clinical PR in FET cycles during the same time period was 26% with a multiple pregnancy rate of 14%. When one embryo was transferred, PR was 21% (106/507), including two sets of monozygotic twins (2%). When two embryos were transferred, PR was 29% with a multiple PR of 20%, including 44 twins and one triplet.

Conclusions. In our hands, single embryo transfer results in very acceptable pregnancy rate with a low risk of twins. This strategy has gradually been implemented to our daily practice, the percentage of eSETs in fresh cycles being 11% in 1997, and 56% during last year. The multiple pregnancy rate has decreased, in 1998 24% of the pregnancies were multiple pregnancies and in 2001 only 8%. Since the cumulative delivery rate per oocyte retrieval after frozen embryo transfer is over 50%, single embryo transfer combined with freezing of extra embryos is highly effective. Two embryo transfer can be considered in specific conditions.

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How to prevent preterm deliveries of twins

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The major complication responsible for the markedly increased perinatal mortality in multiple pregnancies is spontaneous severe preterm delivery. Delivery before 32 weeks of gestation affects about 1% of singleton pregnancies, 5% of dichorionic twins and 10% of monochorionic twins; the excess risk in monochorionic twins is due to development of twin-to-twin transfusion syndrome. Attempts to reduce this preterm delivery rate have generally been unsuccessful with several studies reporting that bedrest and uterine activity monitoring are not beneficial. More recently, there has been increasing interest in the use of transcervical sonographic measurement of cervical length at 23 weeks of gestation to predict those at highest risk of subsequent spontaneous preterm delivery. The rate of spontaneous preterm delivery before 33 weeks? gradually increases with shortening of the cervix, from about 2.5% at 60mm to 12% at 25mm, and exponentially below this length to 17% at 20mm and about 80% at less than 10mm. Cervical length below 20mm is found in about 8% of twin pregnancies and this group contains about 40% of those delivering spontaneously before 33 weeks. The extent to which insertion of cervical sutures in those with a short cervix will reduce the risk of severe preterm delivery remains to be determined. In monochorionic twin pregnancies, early detection and appropriate management of twin-to-twin transfusion syndrome will have the largest impact in reducing severe preterm delivery rates.

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Twin delivery, an obstetric challenge

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Twin delivery is an obstetric challenge, some times an emergency challenge without much time for planning. Twin pregnancy results in increased perinatal morbidity and mortality, and although pregnancy with the risk of preterm birth still is the major problem, there are often problems connected with the delivery itself.

The considerable increase in the frequency of multiples, in Norway twins have more than doubled since 1981, has made twin delivery a frequent procedure in most obstetric units.

Perinatal mortality has decreased, but this could be attributed to several factors. For several reasons the proportion of monozygotic twinning is decreasing and there have been several changes in twin pregnancy care; early diagnosis, planned and to some extent centralized deliveries, improved intrapartum fetal monitoring, an increase in the use of caesarean section (CS) and improved neonatal care.

In our department the CS rate was 0.6% 25-30 years ago, against more than 40% today. There has been a more than 70-fold increase in abdominal delivery for twin pregnancy. There is no international agreement about the indications for CS in twin pregnancy, but the CS rate for twins has increased more than for singletons. Abdominal delivery has been proposed for all twins, for small twins, for non-vertex twins, and in some series the frequency of combined delivery with a CS for twin II has been considerable.

The increased frequency of abdominal delivery has been coincident with the decrease in perinatal mortality, but while the CS rate for twins increased tenfold in Norway, there was less than a threefold decrease in perinatal mortality during the same years.

There is a general lack of prospective, randomized studies, and the appropriate mode of twin delivery is therefore controversial, and practice differ between countries, hospitals and doctors. Some places it is based on local or national consensus.

In the present paper the emphasis is on the intrapartum management, and especially the most challenging part of twin delivery, the delivery of the second twins. What are the implications of an increased frequency of combined delivery in many centers?

Profile of trimegestone

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Trimegestone, a potent new 19 norpregnane progestin with a "natural progesterone-like" hormonal profile, has demonstrated in preclinical models significant differences from current progestins.

Trimegestone has a high affinity and selectivity for the progesterone receptor, low affinity for the androgen and glucocorticoid receptors, a slight affinity for the mineralocorticoid receptor. In animal models trimegestone has a some anti-androgenic and anti-mineralocorticoid effects similar to natural progesterone except for that Trimegestone has no glucocorticoid effects. Trimegestone has ability to block estrogenic activity in the uterus, lack of estrogen effect by it self, and no adverse effect on bone.

In comparative clinical trials to date, a sequential regimen of 2 mg of 17beta-estradiol combined with 500 mcg of trimegestone has demonstrated equivalent vasomotor symptom relief and endometrial
protection, a more favorable bleeding profile, positive effects on HDL and LDL profiles, equivalent bone protection, and few side effects. Further clinical studies will be required to assess whether the preclinical profile will result in a reduction of nuisance side effects such as weight gain and breast tenderness.

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A novel sequential estradiol+trimegestone-combination for treatment of menopause: Comparative clinical data on efficacy, bleeding pattern and safety

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Trimegestone, a novel nonpregnane progestogen with a very high affinity for progesterone receptor and with almost no affinity for androgen receptor, appears to meet many criteria for ideal progestin as a part of HRT. A combination of oral estradiol (E2) (2.0 mg)(days 1-28) and Trimegestone (0.5 mg) (days 15-28) (Totelle Sekvens) has been compared in large clinical trials with E2+norethisterone acetate (NETA) or E2+dydrogestone-combinations. E2+Trimegestone alleviates hot flushes and other climacteric complaints equally effectively as the comparators. The duration of withdrawal bleeding was 16% shorter during E2+Trimegestone-regimen (mean 5.0 days) than during E2+NETA (5.8 days), and its start was more predictable during E2+Trimegestone. This novel combination was safe towards endometrium (= no hyperplasia or carcinoma), caused beneficial changes in a number of vascular surrogates (= e.g. rise in HDL, fall in LDL, fall in homocysteine, rise in fibrinolysis) or bone mineral density. Some progestin-associated side-effects, such as bloating and nausea appeared less frequently during E2+Trimegestone than during E2+NETA. Thus, a novel E2+Trimegestone-combination provides an effective and well tolerated HRT alternative for postmenopausal women.

How to select a progestin in HRT

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While the selection of estrogen for HRT is not very difficult, the selection of progestin is much more complicated. The reason is that the family of progestins is rather extensive, and the different compounds have definitely different properties as to metabolic effects, in particular. Micronized progesterone has, as yet, not been widely used in HRT. Dydrogesterone is very closely related to progesterone, and has shown beneficial effects on lipid metabolism and no effect on carbohydrate metabolism. The most widely used progestin in HRT is, without doubt, 21-C-pregnane medroxyprogesterone acetate (MPA). However, the results of HERS-trial have awakened attention on the metabolic effects of MPA. MPA may counteract some positive effects of estrogen on lipids, and it may have a negative effect on carbohydrate metabolism. Hence, MPA may antagonize the beneficial antiatherosclerotic effects of estradiol, while Norpregnanes like trimegestone, which lacks a methyl group at carbon 17, are devoid of androgenic effects, and may have a more neutral effect on lipids than MPA. Trimegestone decreases the amount of some cellular adhesion molecules, in contrast to dydrogesterone. The 19-C-19-nortestosterone derivatives are also widely used. Norethisterone acetate (NETA) may be more neutral than MPA as to the effect on lipids. Still, NETA and levonorgestrel have clear androgenic properties while in 3-ketodesogestrel and gestodene they are less pronounced. Androgenicity may render negative effects on lipid metabolism in comparison to progestins devoid of androgenic properties. On the other hand, androgenic progestins lower both triglyceride and lipoprotein(a) levels, which may be beneficial.
The common effect of all progestins is the secretory transformation of proliferative endometrium. The purpose of development of new progestins is to minimize the adverse effects. In comparing the new progestins with the older ones we must largely base our assessment on surrogate endpoints as lipid and carbohydrate metabolim, homocysteine levels and probably on adhesion molecule levels. Endpoints as mortality, cardiovascular events or breast cancer would be hard endpoints, yet the data concerning them are hard to produce. Ultimately, they will be available, and progestins may be compared in a more concrete way.

New progestins in HRT: What are the advantages?

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More and more women will present to their health care provider with menopausal symptoms perceived as intruding on life quality. Reliable estimates show that 10% of the global female population is currently either going through menopause or have already gone through it, and at least another 2 % will reach this stage of life in the next decade Solving the problems of rising health costs and population aging requires application of a modern approach to menopausal health evolved in recent years from an improved understanding of the complex changes that occur during this transition in a woman's life.

Estrogen alone or estrogens in combination with a progestin are, however, the only replacement therapies, which are efficient as treatment for both the menopausal syndrome as well as for the prevention of the long-term clinical conditions associated to ovarian deficiency. The current challenge for the physician is, how to optimise prescription of the replacement therapy based upon the selection of hormonal compounds available. Identification of novel estrogen receptors has demonstrated that the biologicial activity of a specific estrogen or estrogen like compound may vary form tissue to tissue. Current theories indicate that estrogen has extraordinarily complex biological effects and clinically, this translates into a variety of actions in diverse tissues such as skeletal, urogenital, digestive, cardiovascular and nervous systems.

Progesterone exerts most of its actions through its specific receptors. However, synthetic progestins and progesterone itself may bind with other steroid receptors, thus producing a variety of effects. The 19-carbon series (estranes) includes all the androgen derived progestins. The removal of carbon 19 from testosterone changes the major hormonal effect from androgenic to progestogenic, but these "19-nor" steroids retain varying degrees of androgenic activity. Some of the 19-nortestosterone are acting as prodrugs and some are active unchanged. . The 21-carbon series (pregnans) includes the corticoids and the true progestogens (e.g., medroxyprogesterone acetate). Newer, orally active, products have been developed through a molecular approach to compound selection. Such transcriptional products e.g, trimegestone are used to further profile new HRT compounds. The expectations from these new nonpregnane progestins are suppression of estrogen-induced endometrial stimulation, antiproliferative activity or no stimulatory effect in the breast, no mineralocorticoid or glucocorticoid activity, and minimal adverse physiologic effects on metabolism.

Thus, HRT with a wider range of progestogens enables individual and refined substitution possibilities and will increase compliance throughout the whole period from the menopausal transition to senescence.

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Epidemiology and standardisation of terminology on nocturia

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Nocturia refers to waking at night to void. However, currently there is no standard definition. The WHO classification of >2 voids per night has been scrutinised for not accounting for bothersomeness for some individuals. The International Continence Society (ICS) is expected to propose a new which probably will define nocturia as waking up to void >1 times per night.

Nocturia has a multifactorial origin. The three main pathophysiological categories are: nocturnal polyuria (where a relatively higher proportion of urine is produced and voided in nighttime compared to daytime); low nocturnal bladder capacity; and mixed nocturia (a combination of nocturnal polyuria and low functional bladder capacity). The majority of patients with nocturia present with a combination of nocturnal polyuria and low bladder capacity.

Nocturia appears to be as common in women as it is in men. The prevalence of nocturia (assuming it represents 2 micturitions per night) shows a linear increase with successive decades of age, occurring in 9% of women aged 19-39 years to 51% of females 80 years old.

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The consequences of nocturia

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Nocturia is commonly percived as a reasonably trivial condition but its healt related consequencies are grossly underestimated.Ostensibly,sleep disturbances are common which markedly influence Quality of life but elderly women with disrupted have 1.5 times higher mortality from cardiac disease stroke and suicide.
Nocturia is also a common cause for falls in elderly women and 10% of hip fractures are estimated to follow from nocturnal desire to void.
The prevalence of nocturia increases with age and more than half of the female poulation above 80 are sufferers.
In the women´s health in Lund area study impaired control of micturition was reported by 33 % of women between 50 - 60 years.
Of women with more pronounced problems true nocturia was found in
27% with a highest frequency in postmenopausal women without HRT.
An interesting finding was the positive association with hysterctomy on benign conditions.

The role of the unstable bladder

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There are three main pathophysiologic categories for nocturia: a. Nocturnal polyuria, in which a relatively high proportion of urine is produced and voided during nighttime (the relative nocturnal volume is >33% of 24-hours urine volume). b. Low bladder capacity, usually due to an unstable bladder and c. Mixed nocturia, a combination of nocturnal polyuria and low functional bladder capacity. The majority of the patients with nocturia have a combination of nocturnal polyuria and low bladder capacity or unstable bladder.

Unstable bladder is a frequent syndrome in women and depends in most cases on involuntary detrusor contractions. If the involuntary bladder contractions are secondary to known neurologic disease, such as stroke, multiple sclerosis, etc, the condition is known as detrusor hyperreflexia. If the involuntary bladder contractions are not due to known neurologic disease, then the condition is known as detrusor instability. The symptoms are urgency, frequency, nocturia and/or urge incontinence. If the patient describes lower urinary tract symptoms, she should be asked to keep voiding diary and pad-test to provide information on the pattern of micturition, leakage, functional bladder capacity, diurnal and nocturnal distribution of voids and volume of urine. Nocturia and the role of the unstable bladder can be diagnosed simply by analysing the events in a voiding diary.

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Nocturia: The role of the kidney (urine production)

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Nocturnal polyuria is defined as an excessive amount of urine produced during night. It is multifactorial and should be separated from 24-h polyuria. The increased diuresis at night can be solute or water driven. The normal range in nocturnal urine volume is wide and nocturnal urine production is known to increase with age, also in the absence of nocturia.

Several definitions for nocturnal polyuria have been suggested in literature, based on different principles:
1.absolute volume, with or without adjustment for night length or bodyweight
2.relative volume; the proportion of 24-hour urine excreted during night
3.functional overproduction; nocturnal urine volume exceeding functional bladder capacity.

Suggested definitions were applied on a patient material of community-dwelling elderly. Nocturnal polyuria was found in 45 to 100% of elderly with 2 or more voids per night and in 28 to 39% of those with one void or less per night. Different definitions chose different subjects. Irrespective of definition, nocturnal polyuria is a frequent finding in nocturia, underlining the need for frequency-volume charts in the assessment of nocturia.

Relevant pharmacological treatment of nocturia

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Nocturia is a urinary disorder of multifactorial origin, which has a significant impact on quality of life. Two main mechanisms have been identified either alone or in combination: nocturnal polyuria and/or low functional bladder capacity. Relevant pharmacological treatment depends on the underlying cause, why an accurate diagnosis is crucial prior to treatment. The aim of the pharmacological treatment is to reduce the nocturnal polyuria and to increase the bladder capacity by counteracting detrusor instability. Therapeutic options for polyuria include antidiuretics (desmopressin) and cautious use of diuretic therapy. Desmopressin has been shown to be effective in the reduction of nocturnal urine volume, frequency and percentage of urine passed during the night among patients with nocturia. Among patients with oedema, diuretics may reduce the number of voids and nocturnal volume of urine, if taken before early evening.

The therapeutic options for increasing bladder capacity include antimuscarinic drugs with and without calcium antagonistic properties. Based on documented effects in randomised, controlled trials (RCTs), the International Consultation on Incontinence (ICI) recommends tolterodine, oxybutynin, trospium and propiverine for treatment of detrusor overactivity. Symptoms of nocturia may also improve after continuous regime of combined hormone replacement therapy in postmenopausal women.

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Results of antidiuretic treatment in women

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Nocturia, defined as waking at night to void, is caused by several factors including an increased nocturnal urine production due to a nocturnal deficiency of antidiuretic hormone (arginine vasopressin (AVP)).

Desmopressin (Minirin®) is a synthetic vasopressin analogue with specific antidiuretic effect that successfully has been used in over 25 years for the treatment of diabetes insipidus and nocturnal enuresis, which also can be caused by an AVP deficiency.

It has been shown that orally administered desmopressin (Minirin®) given to women suffering from nocturia with nocturnal polyuric background (the relative nocturnal volume is >33% of 24-hour urine volume) is an effective and well tolerated treatment.

With dose titration (i.e. 0,1 mg, 0,2 mg or 0,4 mg desmopressin) a majority of the patients can expect a 50% reduction of nocturnal voids.

Desmopressin (Minirin®) not only reduces the number of nocturnal voids and nocturnal urine volume but also improves sleep resulting in an improved quality of life.

The type of reported adverse events with desmopressin (Minirin®) in nocturia treatment seems comparable to previous experience with desmopressin in other indications. The elderly (over 65 years), in particular, seem to be more susceptible to developing hyponatraemia.

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Glomerular endotheliosis found in antepartum renal biopsies in both normal and hypertensive pregnancies

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INTRODUCTION. Glomerular endotheliosis has been considered pathognomonic for preeclampsia. This lesion comprises endothelial cell swelling and vacuolisation, obliteration of endothelial fenestrae and encroachment of the capillary space area. Renal biopsy studies have previously shown, that in as many as 20-40% of cases, proteinuric hypertension in pregnancy was instead caused by clinically undetected renal disease such as glomerulonephritis. The aim of this study was
-to estimate the proportion of patients, presenting with hypertension in pregnancy, that could be diagnosed by the aid of renal biopsy as preeclampsia as opposed to renal disease
-to specify the morphological changes in hypertensive diseases in pregnancy compared to the findings in normal pregnancy
METHODS. Antepartum renal biopsies were performed on 36 patients presenting with hypertension in pregnancy, recruited from our perinatal ward as well as on 12 healthy controls, recruited from our maternal health care centres. Patients with previous renal disease, chronic hypertension, diabetes or autoimmune disease were excluded from the study. The diastolic blood pressure was required to be less than 105 mm Hg, the blood platelet count > 100 x 109 and APTT < 45 s to be eligible for renal biopsy. The study was approved by the Ethics committee at the University of Lund.
RESULTS. All patients in the hypertensive group showed characteristic signs of preeclampsia whether proteinuria was present or not. Glomerular endotheliosis was also present in 7 of the 12 normal healthy controls. No underlying renal disease was detected in any of these patients. Complications were few, but in the severest case of preeclampsia a retroperitoneal haematoma developed requiring treatment.
CONCLUSION. Glomerular endotheliosis was found in normal, as well as in hypertensive pregnancies and is not, as earlier believed pathognomonic for preeclampsia. Underlying renal disease seems to be a rare cause of hypertension in pregnancy in our population.

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Eclampsia in Scandinavia

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OBJECTIVES: This study was designed to describe the incidence of eclampsia in the Scandinavian countries, and to study the clinical outcome after eclampsia for both the mother and child.

STUDY DESIGN: For a period of two years (1998-2000), eclamptic cases have been registered prospectively in Denmark, Sweden and Norway. Requests for notification of any case of possible eclampsia antenatally, intrapartum, or in the first 10 days postpartum were sent to all the maternity units every third month. We received photocopies of the prehospital and hospital case records. We also obtained information about the infants.

RESULTS (preliminary): Two hundred and one cases of eclampsia were found in the three Scandinavian countries during the two years study period. The incidence in Sweden and Norway was 1 per 2000 deliveries. The incidence in Denmark was lower, one per 3000 deliveries. Seventy-six percent of the patients had a classical eclampsia with both hypertension and proteinuria. Forty-one percent of the patients had antepartum eclampsia, 28% intrapartum and 30% postpartum eclampsia. Antepartum eclampsia occurred mainly preterm, and intrapartum eclampsia at term.
In almost 90% of the cases, the first fit occurred in the hospital. The mean number of days in hospital before the eclampsia was 2.8 (0- 39). Eighty percent of the patients had one or more subjective symptoms before the first eclamptic fit, and the most prominent symptom was headache (73%). Seventy-four percent had one seizure, 18% had 2 seizures, and 8% had multiple seizures.
The perinatal mortality was 1.4%. The perinatal morbidity was mainly due to prematurity. Fifty-six percent of the children were born before the 37th gestational week and 20% before the 32nd gestational week. Nineteen percent were small for gestational age (birthweight less than 10th centile). There was one maternal death (0.5%), and 35% had maternal complications related to eclampsia (16% HELLP/DIC, 6% renal failure, 3% cerebrovascular events).

CONCLUSION: The incidence of eclampsia in the Scandinavian countries is comparable to that reported from other western countries. Major headache is an important antecedent symptom. In hospital, one fourth have repeated seizures. The rate of prematurity is high amongst women with eclampsia. Eclampsia is still associated with significant maternal and perinatal complications.

Linkage disequilibrium to chromosome region 2p13 in Finnish patients with preeclampsia and obstetric cholestasis suggests a common risk locus

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Background: The pathophysiology of preeclampsia is incompletely understood, but the familial nature of the disease has long been recognized. Recent genome-scan studies have reported associations in the p23 region of the chromosome 2. We have previously reported linkage disequilibrium to chromosome region 2p13 in patients with obstetric cholestasis.
Methods: We conducted population-based linkage disequilibrium (LD) screening to find potential preeclampsia-associated loci on chromosome 2 and to test whether preeclampsia and obstetric cholestasis share a single risk locus. The study was carried out in 115 unrelated control women, in 133 preeclmaptic women and in 57 cholestatic women.
Results: Additional screening with microsatellite markers at the 2p13 region revealed that the D2S286 marker was significantly associated with obstetric cholestasis in the overall LD analysis (P = 0.03) while it revealed only borderline association with preeclampsia (P = 0.08). However, single allele association analysis indicated that both preeclampsia and obstetric cholestasis showed a statistically significant association with a common allele (P <0.05), which was overpresented in both obstetric cholestasis (0.42) and preeclamaptic (0.37) groups when compared to control group (0.28).
Conclusions: These findings suggest a possible genetic link between the chromosome region 2p13 and preeclampsia and obstetric cholestasis. More specifically, these data suggest that there may be a common risk locus associated with both obstetric complications located in the vicinity of the 2p13 LD region.

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Two exonic biallelic SNP:s in the microsomal epoxide hydrolase gene are jointly associated with preeclampsia

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Two exonic biallelic SNP:s in the microsomal epoxide hydrolase gene are jointly associated with preeclampsia

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Purpose: We determined whether genetic variability in the gene encoding for microsomal epoxide hydrolase (EPHX) contributes to individual differences in susceptibility to the development of preeclampsia.

Methods: The study involved 133 preeclamptic and 115 healthy control pregnant women who were genotyped for two single nucleotide polymorphisms (SNPs), 113Tyr-His in exon 3 and 139His-Arg in exon 4, in the EPHX gene. Chi-square analysis was used to assess genotype and allele frequency differences between preeclamptic and control groups In addition, single point analysis was expanded to two-locus haplotype analysis to examine the estimated haplotype frequencies of the two SNPs with unknown phase among the preeclamptic and control groups. Estimated haplotype frequencies were assessed using the Arlequin software.

Results: Single-point allele and genotype distributions of the exon 3 and exon 4 of EPHX gene were not statistically different between the groups. However, according to the haplotype estimation analysis, we observed a significant overpresentation of haplotype 113Tyr-139His among pre-eclampsia group when compared to control group (P=0.010). The odds ratio for preeclampsia associated with the high-activity haplotype 113Tyr-139His was 1.61 (95% CI: 1.12-2.32).

Conclusions: The use of two intragenic SNPs jointly in the haplotype analysis of association demonstrated that the genetically determined high-activity haplotype 113Tyr-139Hisis significantly associated with preeclampsia.

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The Copenhagen First Trimester Study screening for Down´s Syndrome in 9,468 women

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Objective: To evaluate a prospective ultrasound screening for Downs Syndrome in week 11-14 in an unselected Danish cohort and estimate the combination of ultrasound and maternal biochemical markers.

Material and Methods: An unselected cohort of Danish-speaking women referred to the three maternity units in central Copenhagen from March 1998 to June 2001 was studied. Using ultrasound the crown rump length was measured for gestational dating, and the Nuchal Translucency (NT) for Down´s Syndrome (DS) risk calculation. A combined risk using NT and maternal age was given to the women, and an invasive test offered at a risk cut-off of 1:250. Blood was sampled for free beta human chorion gonadotrophin (b-hCG) and Pregnancy associated plasma protein A (PAPP-A) analysis. The biochemical markers were analysed prospectively without konwledge of clinical data, but were not acted upon. The performance of the NT-screening was evaluated by follow up of the pregnancies and a cross check with all chromosomal analyses during the study period. A combined performance of NT and biochemical screening in the first trimester will be calculated using the identified marker values supplemented with historical distributions of DS marker values. The quality of the NT measurements was assessed throughout the study by following the distribution of the NT-MoMs (multiple of the medians) based on our own medians.

Results: We included 10,045 women who had an ultrasound examination including malformation screening before 14 weeks +6. Among these women 9,468 had a Nuchal Translucency measurement in week 11 +1 to 13 +6. Abdominal and transvaginal ultrasound was performed in 82% of the cases, and an abdominal scan only in 18 %. Blood was sampled and analysed in approximately 70% of the women.

We detected 9 out of 12 Down´s Syndrome pregnancies in week 11 +2 - 13 +6 by the NT screening. The expected false positive rate was 5%, but the observed rate of screen positive pregnancies throughout the study was 2%.

When combining NT and the biochemical markers b-hCG and PAPP-A in the first 3000 pregnancies the expected detection rate for a 5% false positive rate was 81%. Results from the whole population will be presented at the congress.

Conclusion: Prospective NT screening in this unselected cohort combining maternal age dependent risk with NT resulted in a high detection rate and a remarkably low false positive rate. Further benefit can be achieved by adding maternal biochemical markers in the first trimester to the screening.

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Combined first and second trimester serological and ultrasound screening for Down's syndrome

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Introduction:
During the last two decades the possibilities of non-invasive screening for fetal chromosomal disorders have changed from using maternal age alone as a risk marker to the use of various biochemical and ultrasound markers in combination with maternal age. Thus, the triple test (alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG) and unconjugated estriol (uE3)) in the second trimester, nuchal translucency (NT) screening in the first trimester, and first trimester serological screening (pregnancy associated plasma protein A (PAPP-A) and free b-form of hCG (b-hCG)) are offered to pregnant women. Combinations of different markers have been suggested as the optimal screening strategy. Our aim was to examine the detection rate (DR) of different marker combinations for a 5% false-positive rate (FPR).

Material and methods:
We selected a subpopulation (n = 196) of women with a NT measurement from the Copenhagen First Trimester Study where information and serum samples from both the first and the second trimester were available. Gestational age of the first trimester NT-measurements and serum samples ranged from 10+5 to 13+4 weeks. Gestational age of the second trimester serum samples ranged from 14+0 to 20+2 weeks. All women had normal live birth outcome. We examined the relation between different serological and ultrasound markers. The screening performance of different marker-combinations was estimated using Monte Carlo simulation involving the distributions of LogMoM markers and their correlations.

Results:
Using a fixed FPR of 5% the DR of combined PAPP-A, b-hCG and NT was estimated to be 78%. The triple test yielded an estimated 61% DR, whereas adding Inhibin A to the triple test increased the DR to 68%. The combination of PAPP-A and NT with the triple test yielded a DR of 83% for the 5% FPR whereas the addition of Inhibin A (the integrated test) increased the DR to 86%.

Conclusion:
The first trimester combined test (PAPP-A, b-hCG and NT) and the integrated test perform markedly better than the presently used screening methods (maternal age and/or triple test). This result is in accordance with the recently published international results on combined and integrated screening and supports an implementation of combined screening in the Nordic countries. However, our knowledge is still based on a small number of Down's syndrome cases and therefore such a screening should be carefully controlled and preferably conducted as a prospective trial.

Bilateral notching of uterine arteries at 12-14 weeks of gestation for prediction of PIH and IUGR in high risk pregnancies

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INTRODUCTION
The purpose of this study was to asses the value of transvaginal Doppler ultrasound of uterine and umbilical arteries in predicting pregnancy-induced hypertension(PIH)or intrauterine growth retardation(IUGR)in high risk women at 12-14 weeks of gestation.
METHODS
120 pregnant women with at least one anamnestic risk factor for PIH or IUGR(chronic hypertension, familiar risk for pre-eclampsia, gestational diabetes, age under 20 or over 40 years, previous pre-eclampsia, previous IUGR, or previous intrauterine death) underwent transvaginal Doppler ultrasound investigtion at 12-14 weeks of gestation. The presence or absence of bilateral notches, resistance and pulsatility index, mean and maximum velocity of uterine arteries and resistance and pulsatility index of umbilical arteries were registered. 90 women with bilateral notching of uterine arteries were randomised to receive acetylsalicylic acid or placebo. 43 were followed up succesfully in both groups. These women(n=86)were followed up twice at 24-26 and 32-34 weeks of gestation and Doppler ultrasound measures were repeated.Outcome data were obtained on 29 of those 30 women without bilateral notching. In this study we compared women with bilateral notches receiving placebo(n=43)to women who were not randomised and didn´t have bilateral notches(n=29).
RESULTS
PIH developed to 16 (37.2%) women with bilateral notches receiving placebo and to four (13.8%) women without bilateral notches (p=0.030). Bilateral notching was associated with an increased risk of PIH (relative risk, RR 2.70[95%CI 1.00-7.25]) and proteinuric pre-eclampsia (RR 6.74 [95% CI 0.91-49.9]).In the incidence of IUGR there was no statistically significant difference between groups. In other flow measurements of uterine or umbilical arteries there were no differences between normal or adverse outcome of pregnancy.
Sensitivity, specificity, positive and negative predictive values of bilateral notching for predicting PIH at 12-14 weeks of gestation were 80, 48, 28 and 91% and for predicting IUGR 75, 41, 24 and 87%, respectively.
Specificity and positive predictive value of bilateral notching increased and sensitivity decreased as the gestational age advanced. The rate of adverse outcome was 64.3% in the women with bilateral notching at 32-34 weeks of gestation and 18.5% in the women without bilateral notching (p<0.001).
CONCLUSION
The results of this study suggests that uterine artery Doppler and bilateral notching of uterine arteries at 12-14 weeks of gestation may be a useful screening method for prediction of PIH in high risk women, but other methods are needed to integrate with Doppler flow velocimetry to improve the specificity of the method.

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Is recruitment of specialists a problem? What is the situation in the Nordic countries?

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The balance between recruitment of specialists vs. turnover and loss through retirement or death has recently been studied both in Denmark, Norway, Sweden and Finland. A total of 3.6% of the doctors in the Nordic countries are specialists in obstetrics and gynecology, ranging from 2.9 % in Denmark and Norway to 4.3 % in Sweden.
One conclusion from the presented surveys is that obstetrics and gynecology remains a popular specialty among junior doctors, the number of applicants to vacant positions is sufficient. Another common aspect emphasized in reports from Sweden and Norway, is that the projected loss due to retirement and death will be relatively large from now on and 10-15 years ahead in time, because of the age distribution of specialists. The cohort of individuals of 50 (+) years is large in the group of specialists as well as in the general population, and the large increase in the number of elderly individuals in the Nordic populations will also lead to an increase in the need for medical services.
In Sweden, the prognosis until 2015 indicates a substantial and cumulating deficit of specialists. In Norway the projected supply of specialists is believed to match the loss, but the manpower situation will probably not give room for any expansion. In Denmark, the number of trainee positions is presently considered the limiting factor. In Finland concern is caused by a substantial proportion of hospital based specialists stating that they plan to leave public health and take up work in the private health care system.
The national reports will be briefly summarized and discussed.

How to challenge the gendered choice of specialty within the medical profession?

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The proportion of women doctors in the Nordic countries was insignificant until the middle of the last century. Now, the rate of women doctors ranges from 22 percent (Iceland) to 51 percent (Finland). At the same time, the medical profession has undergone profound structural and organisational changes in all the Nordic countries, from a small male-dominated power elite to a large group of health workers with working conditions more similar to other health occupations. However, the shift in the gender composition of the medical profession as a whole has not levelled out gender differences, as might be expected. On the contrary, the increasing number of women in the medical profession has resulted in a profound gender segregation within the profession, with a highly gendered pattern in the choice of medical specialty. While men choose highly prestigious specialties such as surgery and certain fields within internal medicine, women end up in less prestigious medical fields such as general medicine, geriatrics and psychiatry. This pattern is a part of the internal differentiation within the profession, where some specialties have difficulties in recruiting new members, while others have been popular but hard to manage because of harder working conditions. Gynechology and obstetrics is a very interesting field in this respect. The clientele is exclusively women and from the very beginning gynechology has attracted many women. At the turn of the last century it was the main field of female doctors in many countries. It is a specialty with a large element of surgery (even though it is not classified as such), which shows that women are attracted to surgical fields as well as men. In the paper it is argued that the gender differentiation of the medical profession is the result of various closure mechanisms, which are socially constructed and reproduced. It is important for the medical profession to unravel these mechanisms in order to create balanced and positive working conditions for all doctors.

Important elements in our education of specialists

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The increasing subspecialisation challenges the traditional concept of the OB/GYN specialist as an omnibus professional, capable of performing all tasks in the department. However, the biggest challenge of modern specialist training lies not in ensuring the necessary medical expertise, but rather in empowering the specialist to fill the multitude of roles required in present-day healthcare: the doctor as medical expert, as well as communicator, leader, teacher, co-worker etc. To attain these skills we need to introduce new ways of teaching (ie. use of simulators or problem based learning), and we need new instruments of assessing acquired skills. We also need to focus on the training of the trainers; many of the senior doctors acting as tutors have not themselves been formally trained in the skills, they are now required to teach.

How to find pleasure in our daily work?

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Essential to our enjoyment of work is the possibility to be the kind of doctor we want to be. I will focus on things we as individuals need to consider to make this happen rather than structural changes that are also needed. The individual level and the structural level are interdependent, on the individual level we can all contribute in the way we think about and perform our daily work.
I have never met a doctor who does not want to be a good doctor. What is a good doctor? I will introduce the concept of the good-enough doctor rather than some imaginary "ideal" doctor and stress the importance of diversity. Happiness at work is related to goals and how well they are fulfilled. Are we working with unrealistic, unachievable goals? Do patients want doctors who are gods or will they accept mere human beings with special knowledge who do their best in cooperation with the patients? Do we as doctors accept our fallibility? The fear of making mistakes and the fear of being reported or sued need to be faced and diminished since fear is rarely helpful in making us perform well. How can we make the best of the mistakes that will inevitably happen? Learning from our mistakes and from the things that go well presupposes acknowledging them. Accepting our imperfections also opens the possibility of constant growth and learning (something already perfect can not be improved). Increased understanding is a source of pleasure. Some form of (personal) monitoring is helpful in letting us know if things go the way we want them.
Our work as gynaecologists and obstetricians gives uncountable opportunities for close contact with the most important events in life and possibilities to something worthwhile every day.

Obstetrics towards the American situation?

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The process of becoming an obstetrician in the US is long and arduous. Physicians intending to practice obstetrics have to fulfill these requirements before they can work:
1)Education and training: After completing basic medical training a physician should complete a four year residency program in OB/GYN at an approved Medical Institution.
2)Licensing: Each state has its own Board of Registration in Medicine. The Board verifies the credentials of the physician and issues a license to practice medicine in that state.
3)Certification: This process consists of a written and an oral examination administered by the American Board of Obstetrics and Gynecology.
4)Types of OB/GYN practices:
a)academic faculty position
b)hospital employment
c)employment by a Health Maintenance Organization
d)private practice - group or solo
5) Hospital credentialing: Every hospital has to independently verify the physician's credentials before it grants admitting privileges.
6)Medical Malpractice Insurance Coverage: This is essential in order to practice Medicine in the US.OB/GYN's pay one of the highest premiums for this coverage ($35,000 to 70,000).

The practice of OB/GYN is also confounded by a complex payment system. Patients can have either private insurance, state funded insurance, Medicare or may choose to pay out of pocket. Some patients dont have any insurance and are treated free of charge. Each insurance company pays differently for the same service and the paper work is enormously frustrating.

Due to increases in malpractice premiums and decreasing reimbursements from insurance companies the OB/GYN's have seen their income shrink on a yearly basis. According to ACOG, this has forced many doctors to increase their clinical hours to 52/week and increase the number of patient visits by 25% in order to maintain their income at standard levels.

Unfortunately the US has the maximum number of lawyers in the world. Suing doctors is a four billion-dollar industry. A recent survey by ACOG reveals that an average OB/GYN can expect 2.53 medical malpractice suits to be filed against them during the course of their career. The survey also reveals that 76% of the OB/GYN's have already been sued aleast once. Obstetric claims continue to result in higher damage awards with an average payment of $459,324. This has forced changes in practice patterns by OB/GYN's:
a) by decreasing the level of high risk obstetric care
b) by giving up obstetrical practice
c) decreasing the number of deliveries per physician.

In order to avoid malpractice suits obstetricians care for their patients in a defensive manner. All obstetrical and gynecological procedures are performed only after obtaining a very detailed, multi-paged informed consent.

Supervision of laboring patients is very intense with continuous fetal monitoring and with in-house physician coverage. Fear of lawsuits has also led to an increase in cesarean section rate and a decrease in assisted vaginal births.

As a result, practicing obstetrics is widely believed to be very stressful and most obstetricians give up obstetrics in their prime and devote their time to office gynecology.

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The use of embryonic stem cells in research and therapy

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Stem cells are responsible for the growth and renewal of tissues, and reparation of tissue injuries. In adult organism, about 20 different types of stem cells have been identified. These adult stem cells have recently been shown to be more flexible than had been thought. Some of them can back in their development, and transdifferentiate to other types of stem cells. Stem cells can also be isolated from cord blood and fetal tissues after termination of pregnancy. The most potent stem cells, embryonic stem (ES) cells can now be grown from the inner cell mass of 5-6-day-old embryos, which result from in vitro fertilisation. These cells have been grown on feeder cell layers, which keep them undifferentiated. Removing the feeders causes spontaneous differentiation to various cells and tissues. Feeder-free cultures on extracellular matrix using feeder-cell-conditioned culture media have also been successful. Insulin-producing cells, neurons, cardiomyocytes and blood cells have been seen in cultures. In vitro cultured or transplantated hES cells to animals in vivo have been shown to give rise to cells of all three embryonic layers.
Severe degenerative diseases can be treated using stem cells. There is large experience from using blood stem cells from bone marrow or peripheral blood in the treatment of malignant, autoimmune and certain blood diseases. The limitation of adult and fetal stem cells is the very small number of such cells in tissues, and the difficulty in increasing their amount in culture. Donated cells will always be needed in hereditary disorders and in urgent situations. Embryonic stem cells can divide endlessly, and large amounts of cells can be grown and stored. Banks with a large variation of genetically different ES cell lines would provide cells for different types of cell transplantation in the future. Among others, diabetes, severe nervous system disorders, sever liver damage, heart failure and malignant diseases could be treated using such transplantation.

Mouse ES cells have been cultured from early eighties. Human ES cells were cultured for the first time in 1986 by Robert Edwards, the inventor of IVF, but permanent cell lines were reported in 1998 by James Thompson in Wisconsin, and at the same time by a group in Singapore and Melbourne, with (Alan Trounson). In summer 2001, the government of USA (NIH) collected information regarding the existing hES lines worldwide, and the number was 65. We have been culturing hES cells after obtaining an ethics approval in April 2000. ES cells derived from six embryos are on the NIH list, and the work with new cells is ongoing.

The challenges for today´s research are feeder-free cultures with no non-human materials, all carried out in GMP conditions to obtain cells, which can be used in transplantation. Much basic research is needed to identify the factors which specifically guide these cells to certain cell types and tissues. A big challenge for infertility clinics is to develop a large amount of genotypically different cell lines, which could be used for transplantation and research.

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Molecular genetics in reproductive medicine

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The mutations identified to date that result in female reproductive dysfunction have been predominantly subpituitary in origin and are manifested primarily at puberty. The majority are rare autosomal recessive mutations that result in a loss of function. The frequence of detection of these mutations may increase as more prospective studies are performed and as a genetic basis is sought in more women with reproductive dysfunction.

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Violence during pregnancy epidemiology, consequences for the woman and the child

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During the last decades, studies from all over the world have documented that women are subjected to physical, sexual and emotional abuse by their partner. The proportion of women who report to ever have been subjected to violence inflicted by their partner varies between countries and regions. In Western countries the proportion typically is reported around 10 %. Violence is shown to continue also during pregnancy. It may even increase. The reported proportion of pregnant women documenting violence varies from less than 1 % to 20%. The variation is related to population sampled, differences in measuring violence and definition of abuse. Violence against women during pregnancy is potentially lethal both for the woman and the child. Maternal mortality attributed to spouse inflicted violence is documented, but might be overlooked and underestimated. Direct violence is shown to causes injuries and even death of the foetus. However, even when the direct physical trauma is less severe, other health consequences might be the result. These include complications in pregnancy and general somatic and emotional complaints and disorders. Violence is also considered to be a risk factor for adverse perinatal outcomes as delivery of a low birth weight baby and prematurity.

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Violence against women during pregnancy: Preliminary results from the WHO multi-country study on women's health and domestic violence

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Background
Increasingly, violence against women during pregnancy is recognized as a significant health problem, leading to a variety of adverse pregnancy outcomes, including bleeding, low birth weight, miscarriages, inadequate weight gain, etc. To date, there is a dearth of reliable information, particularly from developing countries, on the prevalence of violence against women during pregnancy. The WHO multi-country study has been conducted in 8 culturally diverse countries (Bangladesh, Brazil, Japan, Namibia, Peru, Tanzania, Thailand, and Samoa), with the aim of collecting data on the prevalence of physical and sexual violence by partners; the prevalence and characteristics of violence during pregnancy, the health consequences of VAW, and to explore strategies that women use in violent relationships to minimise and end violence.

Methods
Following careful preparation and in-depth interviewer training, in each country a cross-sectional survey of 3,000 women of reproductive age in the capital city and one rural area was conducted. Women were asked directly about their experiences of different violent and abusive acts (including whether they have been forced to have sex against their will by their partner). Follow-up support was provided to women requesting assistance.

Conclusions
Data collection is ongoing and/or has been completed in eight countries. An analysis of the prevalence of the prevalence of physical and sexual violence has been conducted in Brazil, Peru and Thailand. The findings provide minimum estimates of the prevalence of physical and sexual violence during pregnancy. These results will provide critical inputs for the development of interventions to address violence in the context of reproductive health services.

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Physical partner abuse during pregnancy a risk factor for low birth weight in Nicaragua

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Abstract:
The main aims of this research were to assess whether physical partner abuse during pregnancy increases the risk for low birth weight (LBW), to determine the population atributable proportion of this among other risk factor, and to identify the relationship between physical partner abuse during pregnancy and the type of LBW (preterm or small for gestational age)found.

Methods: A hospital based case-referent study was performed in León, Nicaragua. Cases were 101 newborns with a birth weight <2500 grams, and for each case two referents were randomly selected among infants born the same day with a birth weight > 2500 grams. Crude and adjusted odds ratios (OR) with 95% confidence intervals and population attributable proportions for the main factors leading to LBW were calculated. Multivariate logistic regression analyse was used for controlling of potentially confounding variables.

Results: Seventy five percent of LBW newborns (cases) were small for gestational age and forty percent were preterm. Twenty-two per cent of the mothers of LBW infants had experienced physical abuse during pregnancy by their intimate partners as compared to 5% among referents. LBW was associated with physical partner abuse even after adjusting for age, parity, smoking and socio-economic status {OR 3.9 (95% CI 1.7-9.3)}. Given a causal interpretation of the association about 16% of the LBW in the population could be attributed to physical partner abuse in pregnancy.

Main conclusion: Physical partner abuse during pregnancy is an independent risk factor for LBW in Nicaragua.

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The pregnant woman and domestic violence: The importance of personal skills, techniques, and evaluated methods

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It is estimated that one out of every five women has experienced violence in an intimate relationship at some point in her life. Recent research conducted in USA, Australia, Canada and Europe on abuse during pregnancy demonstrates prevalence rates between 1% and 20%. Woman abuse is linked to attitudinal, structural and systemic inequalities that are gender-related. It affects women in different social relationships and contexts. Woman abuse occurs regardless of age, race, ethnicity, education, cultural identity, socio-economic status, occupation, religion, sexual orientation or personality. Abuse has serious consequences for women, their children, their families, their communities and their abusers. Physical injury, mental health problems and complications of pregnancy are some of the health consequences that results from violence inflicted on women by their present or former partner. Domestic violence can be physical, psychological or sexual and takes place through interpersonal behavior. It is therefore of great importance that women with experience of abuse meet healthcare providers who are aware of the cycle of power and control in the abusive relationship. Most women experience pregnancy which is one of the few times when healthy women interact with the medical setting on a routine basis. Since the prevalence of abuse is greater than the prevalence of toxemia for which the pregnant woman's blood pressure is measured at each antenatal visit, enquiry about a history of violence should be included routinely in any social history taking. A systematic questioning by trained and sensitive personnel leads to high levels of disclosures of woman abuse.

The minimum requirement of health care professionals who asks about abuse are:

To be educated about the prevalence, seriousness, dynamics and health effects of woman abuse; To set as a priority the safety and autonomy of the abused woman; To be aware of the impact of cultural attitudes on the issue of abuse and practice cultural competency; To be trained in how to ask about abuse; To be trained in providing abused women with medical assessments and interventions; To be authorized to record findings; To be familiar with and respectful of the services and professionals in other sectors; To be prepared to refer disclosing women to community specialists who offer justice, support, counseling and advocacy services; To be prepared to offer follow-up to disclosing women to ensure continuity of care.

It is well documented that routine screening is both acceptable and welcomed by most women involved. However, it is of outmost importance that trained professionals perform the questioning. Education and training about domestic violence should be integrated into the curriculum for all health professionals. Working in conjunction with other professionals and domestic violence advocates, health care professionals are in a unique position to respond to domestic violence.

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Antenatal screening for men's violence against women

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Introduction: The prevalence of reported physical abuse during pregnancy ranges between 1 and 20%. In most previous investigations, separate homogeneous clinical samples have been studied. When random samples were investigated, prevalence rates were in the lower part of the interval. Within the Swedish public health service, all pregnant women have equal access to antenatal care and virtually every pregnant woman visits her clinic regularly. Swedish antenatal care therefore facilitates the study of almost all pregnant women within a specific district. Shame and guilt prevent women from raising the issue of abuse themselves and fear of offending deters carers from enquiring about violence.
Methods: All women registered for antenatal care in Uppsala, a Swedish university town, during a 6-month period were assessed regarding acts of violence and feelings about being asked about violence. The Abuse Assessment Screen (AAS) was used on two occasions during pregnancy and once between 4 and 20 weeks after delivery. On the last occasion the women were asked to respond to an open-ended written question worded: Please describe how you felt about being questioned by your midwife at the antenatal clinic concerning violence? The efficacy of repeated interviews was investigated and characteristics of abused and non-abused women were compared. The Ethics Committee of the Medical Faculty at Uppsala University approved the study.
Results: The AAS questions were answered by 93% (1,038) of the eligible subjects. Physical abuse by a close acquaintance or relative during or shortly after pregnancy was reported by 1.3% and by 2.8% when the year preceding pregnancy was included. Lifetime prevalence of emotional, physical or sexual abuse was 19.4%. Repeated questioning increased the detection of abuse. Women abused during pregnancy reported more preceding ill-health and more elective abortions than non-abused women and gave birth to infants of somewhat shorter gestational age.
When 879 women were presented with the open-ended question 80% found it entirely acceptable, 12% neither acceptable nor unacceptable/disagreeable, 5% both acceptable and unacceptable/disagreeable and 3% only unacceptable/disagreeable. There was no significant difference regarding disinclination to answer questions about exposure to violence between those who reported abuse and those who did not.
Conclusions: Physical abuse is a risk factor in pregnancy comparable in frequency to obstetric complications such as gestational diabetes and pre-eclampsia. Routines need to be established to make questioning about violence an integral part of the standardized screening for risk factors during pregnancy. This requires knowledge among care providers of the nature of intimate partner violence and an awareness of appropriate referral and intervention strategies.

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Mucosal immunity in uterus during normal pregnancy

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Ever since the recognition of transplant rejection as an immunologic phenomenon due to genetically determined histoincompatibility between graft and recipient, the development of an embryo in the uterine cavity is a challenging paradox of nature. The immune compromise in decidua allows a semiallogeneic fetus to survive without significantly impairing the ability of the maternal immune system to fight infections. What cells and mechanisms are responsible for the local immunologic privilege of the fetus in the pregnant uterus?
Several cellular and humoral mechanisms are suggested to be involved in preventing the maternal immune system from rejecting the fetus. The trophoblast lacks polymorphic MHC class I and II antigens, which prevents direct stimulation of maternal cytotoxic cells. Maternal T lymphocytes may acquire a transient state of immune tolerance toward paternal antigens which contributes to maintain pregnancy.
The pregnant uterine mucosa - the decidua - is rich in immune cells. Morphometric studies have shown that 10-15% of all cells in decidua belongs to the lymphoid lineage. They are dispersed near the endometrial glands, between the stromal cells or organized in lymphoid cell clusters. The most abundant lymphoid cell type are the CD56+bright/CD16- large granular lymphocytes followed by the second largest population, the T cells, expressing either alpha/beta- or gamma/delta-T-cell receptor. The alpha/ beta T cells are a heterogeneous population of activated cells consisting of NK-T cells and cells with regulatory cytokine profile. The gamma/delta T cells in decidua are of particular interest since several studies have shown that the systemic, MHC-restricted, maternal T cell-mediated response to paternal alloantigens is downregulated by different, but overlapping, mechanisms. The suppression of the specific T-cell response may be compensated by the non-specific innate immune system in order to meet the particular requirements at the feto-maternal border, i.e., protection against microbial infections, control of trophoblast invasion, and creation of local transient allotolerance.
The gamma/delta T cells in decidua utilize Vdelta1, are CD4- and CD8- and can be subdivided into TCR gamma/delta+ /CD56+and TCR gamma/delta+ /CD56-. Immunohistology and immunoelectron microscopy of human decidua in situ show that they exert intimate contact with epithelial and stromal cells and with other lymphocytes through long processes. Decidual gamma/deltaT cells proliferate in situ and have cytotoxic granules, containing the cytolytic molecules perforin, granzyme A and B, granulysin and FasL. The cytokine profile of these cells exhibits strong expression of IL-10 and TGF-beta in a pattern characteristic for suppressor/regulatory cells.
Extrathymic T-cell differentiation, cytotoxic potency and regulatory cytokine profile are all mechanisms working in concert in the pregnant uterine mucosa, contributing to the creation of the maternal immunotolerance towards the fetus.

Lymphocyte populations and cytokine profile in peripheral blood in normal pregnancy

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The fetus is partly foreign to the maternal immune system. Therefore, the maternal immune system undergoes adaptive changes during pregnancy in order to avoid rejection of the fetus. Although this adaptation primarily takes place locally, it is clear that the maternal immune system is affected also at a systemic level. Clinical observations in support of this include the altered clinical course of some immune mediated diseases, increased susceptibility to some infections, and the observation that the risk of preeclampsia increases in successive pregnancies with the same partner.

The original idea of immunosuppression during pregnancy was that of a general suppression of the maternal immune system. A lot of data support this notion, including our own observations of decreased proliferative capacity of lymphocytes after in-vitro stimulation with mitogens. Furthermore, T-cells showed signs of suppression like lower proportions of activated HLA-DR expressing T-cells, of IL-2 receptor expressing T-cells, and of activated cytolytic CD8 cells. However, about 10 years ago it was proposed that instead of a general suppression, there was a polarization of the maternal immune cytokine response towards an increase in the fetus-protecting T-helper 2 (Th2) type cytokine pattern (e.g. IL-4) and a decrease of the abortion promoting Th1 cytokine pattern (e.g. IFN-gamma). This altered balance could explain why Th1-mediated diseases like multiple sclerosis and rheumatoid arthritis tend to improve during pregnancy. Studies of circulating cytokines in part have confirmed the Th2 polarization, however data are controversial. Our studies, at the protein level as well as at the mRNA level, showed an up-regulation of both Th1 and Th2 cytokines. We interpret this finding as a functional Th2 situation still allowing Th1 reactions that are important in the defense against several infections. Definitely our data show that pregnancy represents an active immune suppression, also supported by our previous findings of increased proportions of memory T-cells during pregnancy.

While T-cell immunity thus seems suppressed and deviated, the maternal immune system still must have strength to fight infections. One mechanism for this is a compensatory upregulation of the innate immune system such as monocytes/macrophages and granulocytes. Another way to ensure a strong immune response is that the major suppression of T-cells is not general, but selective against paternal antigens. In order to study the maternal immune response against fetal antigens we mixed blood mononuclear cells from the mother with inactivated paternal cells, representing fetal antigens. This stimulation induced increase of IL-4 secreting maternal cells that was not seen after stimulation with cells from unrelated donors, suggesting that this Th2 response was mainly directed against fetal/paternal antigens.

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Progesterone as an immunomodulatory molecule

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There is evidence now that pregnancy is recognized by the immune system, and the maternal immune system might not only recognize pregnancy, but also react in a differential way resulting in success or failure.
The immunological relationship between the mother and the fetus is bi-directional, determined -on one hand - by fetal antigen presentation and on the other hand - by recognition and reaction to these antigens by the maternal immune system.
Progesterone is a hormone endowed with immunological properties and is essential for the maintenance of pregnancy in humans. Due to chronic allogeneic stimulation by fetal antigens, lymphocytes of pregnant women develop progesterone receptors (PRs). The regulation of lymphocyte PR expression is hormone-independent, and is related to lymphocyte activation. The percentage of PR positive lymphocytes increases throughout gestation. Recurrent abortion, spontaneous abortion and pre-term labour are associated with a decreased number of PR positive cells. The immunologic effects of progesterone are mediated by a 34 kDa protein, named the progesterone Induced Blocking Factor (PIBF). PIBF affects various phases of the immune response, inhibits the release of arachidonic acid and exerts an anti-abortive effect in mice. The immunological effects of progesterone are mediated by cytokines. Immunoglobulin synthesis in pregnant women is increased, whereas cell mediated responses are decreased. PIBF induces a significant increase in production of Th2 type cytokines, thus it might stimulate antibody synthesis by B cells. There is a population of antibodies which owing to the presence of a mannose rich oligosaccharide residue on one of the Fab arms of the molecule, posses an asymmetric structure. Due to the asymmetric structure these molecules do not exert effector functions, thus prevent cytotoxic responses to fetal antigens. We found a positive relationship between asymmetric antibody content of pregnancy sera and PIBF expression on lymphocytes of the same women. Blocking of progesterone receptors by RU486, or neutralising endogenous PIBF activity by specific antibody significantly reduces the production of asymmetric antibodies in pregnant mice.
In vitro data suggest a correlation between the rate of progesterone receptor expression and the success or failure of pregnancy, but provide no direct evidence for their role in maintaining gestation. To test the biological significance of our findings, we used animal systems. In vivo studies revealed that: a) The anti-abortive effect of the PIBF in vivo is manifested via blocking the NK activity: b) A proper stimulation of the maternal immune system is required for the operation of the progesterone-dependent immunomodulatory pathway: c) Neutralization of endogenous PIBF results in pregnancy termination. These data allow the conclusion that the operation of progesterone-dependent immunomodulation is indispensable for the maintenance of normal gestation in mice.

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Immunological aspects of pre-eclampsia

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Pre-eclampsia is a heterogeneous pregnancy-associated syndrome, caused by a wide variety of etiologies. The presence of placental tissue is a prerequisite for the syndrome to develop. Inadequate uteroplacental circulation with placental hypoxia and oxidative stress are central elements in the pathogenesis. Different causes may underly the inadequate uteroplacental circulation, and the hypothesis has been raised that pre-eclampsia may either be of "placental" or "maternal" origin. Superficial trophoblast invasion and poor placentation may occur due to abnormal expression of adhesion molecules throughout
implantation. In these cases, the development of pre-eclampsia should be ascribed to a limited blood supply due to a primary placental disease.
The pre-eclamptic condition is associated with diffuse maternal endothelial cell activation. Women who develop pre-eclampsia of "maternal" origin seem to be sensitive to, or predisposed to,endothelial cell activation. This dysfunction will also be associated increased risk for diseases such as hypertension, arterosclerosis and type II diabetes. Pre-eclampsia of maternal origin may also develop due to endothelial cell activation caused by a generalised systemic maternal inflammatory response evoked by pregnancy. A maternal inflammatory response is observed in normal pregnancy, but it is weaker.Different reasons may underly the stronger response; a larger placenta, an abnormal stimulus from a microfragments have been detected. In accordance with this, raised apoptosis rate has been reported in the syncytiotrophoblast layer of placentas from pre-eclamptic pregnancies. It is not known whether apoptosis is increased due to the pre-eclampsia associated placental
hypoxia, oxidative stress, increased levels of cytokines and/or high concentrations of death receptors/ligands. In a recent study we observed that increased syncytiotrophoblast apoptosis was only present in pre-eclampsia cases with restricted fetal growth,suggesting that apoptosis is not influenced by pre-eclampsia pathogenesis per se. The increased syncytiotrophoblast apoptosis observed in cases with fetal growth restriction should probably be considered as a manifestation of an established syncytiotrophoblast
layer damage, causing reduced transport between mother and fetus and insufficient fetal growth. Fetal growth restriction due to pre-eclampsia appears to be confined to cases with a primary placental disease.
In conclusion, pre-eclampsia is a heterogeneous disease. A number of immune mechanisms may be involved in the pathogenesis of the condition.

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Control of HIV-1 transmission across the placenta: Immunological, virological and genetic aspects.

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Introduction : Early in utero transmission of HIV-1 seems to be a rare event despite a close contact between infected maternal cells and the placenta. We are investigating the main factors of the placental environment which are involved in the control of in utero transmission.
Methods : In vitro and ex vivo approaches are developed in parallel. In vitro : 1) BeWo choriocarcinoma cells are used as a model for early trophoblast cells (placental cells in direct contact with maternal blood); 2) Primary trophoblast cells from early and term placentae are purified; 3) Histocultures of early and term placentae are being established. Ex vivo, the placental cytokine/chemokine profils from HIV-1- and HIV-1+ mothers under different preventive treatment regimens are under analysis.
Results : Results from pseudotypes and cell-free virus infection suggest a major restriction at the level of HIV-1 entry in BeWo cells. CD4+, CXCR4+, CCR5+ BeWo cells, as well as primary trophoblast cells, do not produce detectable level of virus after in vitro infection with cell free virus. However, BeWo cells can support HIV-1 replication after transfection or after contact with infected PBMC and selected maternal viral sequences are detected in placental cells from HIV-1+ mothers. Our study on the expression of HIV-1 coreceptors on primary trophoblast cells indicates variations according to their maturation but a predominant intracellular expression of the CXCR4 molecule in trophoblast cells from first trimester and term human placentae.
The placental environment is involved in the maintenance of pregnancy as well as in the protection of the fetus against in utero infections, most probably through soluble factors such as some cytokines (inflammatory, Th1 and Th2 types) and chemokines (beta and SDF-1). We are currently studying the impact of these soluble factors involved in the natural protection against in utero transmission.
Conclusions : Altogether our data indicate that, in vivo, multiple mechanisms are involved in the control of HIV-1 in utero transmission. The role of cytokines and chemokines as well as other immunological aspects of the placental environment will be discussed as potential regulatory mechanisms.

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Who has an increased risk of ovarian cancer? Genetic aspects

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Predisposition to ovarian cancer can be inherited, and family history of ovarian cancer is the most important risk factor of the disease. Women who are first-degree relatives of epithelial ovarian cancer patients have a 3 to 4 times increased risk of ovarian cancer. This increase is probably largely due to mutations in the BRCA1 and BRCA2 genes. BRCA mutations predispose to both breast and ovarian cancer. Individual risks vary, but the cumulative risk by the age of 70 is estimated to be about 40-87 % for breast cancer and 16-66 % for ovarian cancer in BRCA1 mutation carriers and 28-84 % for breast cancer and 10-27 % for ovarian cancer in BRCA2 mutation carriers. Carriers of DNA mismatch repair gene mutations, which cause HNPCC (hereditary nonpolyposis colorectal cancer) may also have an increased risk of ovarian cancer: the lifetime risk is estimated to be about 9 percent. Both BRCA and HNPCC-related gene mutations are highly penetrant, dominantly inherited and clinically often detectable from the family history. These mutations constitute high individual risks, but are rare in the population and their contribution to overall ovarian cancer incidence is small. It is possible, that low penetrance genes, which might modify ovarian cancer risk, exist. Although the effect of these polymorphic gene variants on individual risks most likely is of small magnitude, because of their prevalence in the population their contribution to overall cancer incidence could be bigger than the contribution of rare, high penetrance genes. Finding such gene variants is, however, difficult, as these do not manifest as cancer families. The most used study approach is an association study using cases and controls, and so far examined candidate genes include genes which participate in steroid metabolism and DNA repair. The role of low penetrance genes in ovarian cancer predisposition remains to be seen. In conclusion, women at an increased risk of ovarian cancer include BRCA1, BRCA2 and HNPCC-related gene mutation carriers and women with a family history of both breast and ovarian cancer. In these women, the risks are high enough to warrant special consideration. For women with only one first-degree relative affected with ovarian cancer, with no other cancers in the family, the cumulative risk of ovarian cancer by the age of 70 is approximately 5 percent.

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Steroids and ovarian cancer

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Ovarian cancer is the most deadly malignancy of the female reproductive tract. The ovarian epithelial tumours are considered to be endocrine related, however the actions of sex steroids on the genesis and progression of the disease remains unclear. The presence of sex steroid receptors in epithelial ovarian tumors and response to endocrine therapy has been observed. It has further been reported that expression of progesterone receptors (PR) is associated with a better outcome of the disease. To further investigate the effects of sex steroids studies on tumor cell survival, autonomous steroid secretion and estrogen receptor (ER) and PR expression were performed. The studies were performed in primary cell cultures derived from patients suffering from ovarian tumors. Emphasis was placed on obtaining pure tumor cell cultures and the effects of an environment with low levels of the steroid hormones 17 ß-estradiol, testosterone or progesterone on cell survival were studied. To study the cell survival the fluorometric microculture cytotoxicity assay (FMCA) was used and the steroid secretion was measured by an immunofluorometric assay (IFMA) - the time-resolved fluoroimmunoassay technique (Delfia). Immunocytochemistry was used to study ER and PR expression.
Tumor cells cultured in 17 ß-estradiol and testosterone showed a reduced cell survival (-10.3±2.3% and -15.6±2.7% minimum survival respectively). This reduction was inversely proportional to hormone concentrations within the range studied. No similar effect was observed in the progesterone cultures. It was found that 17 ß-estradiol was secreted from the primary cell cultures and, interestingly, the amount of 17 ß-estradiol secreted increased with increasing levels of 17 ß-estradiol in the environment. Neither progesterone nor testosterone production was observed in any of the cultures studied.
In the study where receptor expression in the ovarian epithelial tumor cells was analyzed the majority of the cells isolated expressed ER and PR and the combination ER+PR+ was the most abundant. Both ER and PR expression was decreased after 72 h culture, however the expression of these receptors before and after culture corresponded well. A trend was observed that the cultures with lower cell survival, when cultured in progesterone had a higher PR expression than the high survival cultures. The same trend was not observed for 17 ß-estradiol and ER. Except for ER it appears that other factors are involved in the process leading to a reduced cell survival in the 17 ß-estradiol cultures. It is believed that 17 ß-estradiol has an antiapoptotic effect on ovarian surface epithelial (OSE) cells. Reduction of 17 ß-estradiol in the environment may inhibit this effect, resulting in reduced cell survival. The ovarian epithelial tumour cell's ability to secrete 17 ß-estradiol suggests that epithelial ovarian tumours play an active role in altering their own hormonal environment, promoting tumor progression.

Proliferation, apoptosis and locally acting ovarian steroids

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A relationship between ovarian epithelial cancer and gonadal steroids has been established through epidemiological and biomedical experimental research. The present investigation was undertaken to further characterize the possible role of gonadal steroids and their proposed local action on the origin, development and prognosis of ovarian epithelial cancer.

The mechanism of action of gonadal steroid hormones is mediated via ligand-specific receptors. Estrogen receptor alpha (ERalpha), estrogen receptor beta (ERbeta) and progesterone receptor A/B isoforms (PR) were immunolocalized using mono- or poly-clonal antibodies in the nuclei of epithelial cells in normal ovaries and in benign, borderline and malignant ovarian tumors of different histopathological types in both pre- and post-menopausal women. The expression of ERbeta and PR was found decreased in epithelial cells in tumorous as compared with normal ovaries, based on mean indices of immunoreactivity scoring. All types of mucinous tumors (benign, borderline and malignant) retained ERbeta expression, albeit a lower level, a finding in sharp contrast to the loss of expression of ERalpha and PR in the same tumors.

The development of epithelial ovarian cancer is dependent upon the balance between cell proliferation (tumor growth) and cell death. Immunolocalization of the proliferation marker, Ki67, and morphologic evaluation of programmed cell death (apoptosis) in women with poorly differentiated ovarian epithelial tumors demonstrated a relationship between high ERalpha expression, increased proliferation and decreased apoptosis.
In primary ovarian epithelial tumor cell cultures, treatment with 17beta-estradiol resulted in a reduced cell survival which were inversely proportional to hormone concentrations. Moreover, findings were suggestive of an autocrine and/or paracrine stimulation of 17beta-estradiol release by epithelial tumor cells in culture. Ovarian tissue concentrations of 17beta-estradiol and progesterone were hundred-fold higher than peripheral serum. Increased synthesis of gonadal steroids by ovarian cancer tumors is suggested by earlier studies. In the present series, it was found that malignant ovarian tumors, when compared to benign ovarian tumors, contained decreased amounts of 17beta-estradiol in both ovarian tissue and cyst fluid and decreased amounts of progesterone in ovarian tissue. Furthermore, in women with elevated serum progesterone levels, treated for poorly differentiated ovarian epithelial cancer, an improved 5-year survival was seen, possibly further enhanced in combination with PR expression.

Taken together, it is suggested that estrogens exert a facilitative role in ovarian epithelial carcinogenesis, an effect which may be counteracted by the local action of progesterone.

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Matrix metalloproteinases in ovarian cancer

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Matrix metalloproteinases (MMPs) are involved in the degradation of the extracellular matrix. MMPs are classified according to substrate specificity. Gelatinises (MMP-2, MMP-9) are those responsible for the disruption of basement membranes, the critical elements in invasion and metastases. The connections of MMP-2, MMP-9 and the proteinase inhibitors TIMP-2 and TIMP-1 in ovarian cancer invasion, metastases and prognosis are rewieved.

Ovarian cancer tissue analyses: Significant relationship between activated MMP-2 and invasiveness, metastasis and disease progression has been observed in epithelial ovarian cancers (Wu at al). ProMMP-9 activity has shown to serve as a statistically significant independent prognostic factor in advanced (FIGO III) ovarian cancers (Lengyel et al). The intense mRNA signal for TIMP-2 in primary ovarian tumors has been shown to be associated with fatal outcome. Coincidental TIMP-2 and MMP-9 in tumor cells correlate with poor clinical outcome. In metastatic lesions mRNA levels of TIMP-2 in stromal cells and MMP-2 in tumor cells have been found to be markes of short survival (Davidson). The positive expression for MMP-2, MT1-MMP and TIMP-2 is more common in advanced and high grade ovarian cancers than in early-stage and low grade ones. Additionally MMP-9 has been shown to be positive more often in ovarian cancers with lymph node metastases (Sakata et al).

Metalloproteinases in ovarian cancer cyst fluids and effusions: The unique spread of ovarian cancer by dissemination of tumor cells and migration into the peritoneal cavity has raised the question about the role of the metalloproteinases in cystic fluids and effusions in ovarian cancer invasion and metastases. MMP-2 and MMP-9 concentrations in ovarian cancer cyst fluids seems to be clearly higher than in benign ones. Increased MMP-2 and degreased TIMP-2 levels in ovarian cancer effusions are suggested to indicate metastatic potential of the tumor cells (Davidson et al).

The regulation and ligands for the metastatic behaviour of ovarian cancer via MMPs has been investigated eagerily. E-cadherin, endothelin-1, TGFbeta1, EGFR, trypsin and lysophophatidic acid are some of the potential signalling factors in MMP mediated tumor invasion and metastasis.

Drug resistance in ovarian cancer

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The majority of patients with ovarian cancer are diagnosed in advanced stages of the disease. Paradoxically, although the large majority of patients initially will respond to chemotherapy, most will relapse and in the end die of their disease, which by that time is resistant to all relevant drugs. Drug resistance can be primary or intrinsic when a tumor fails to respond to first-line chemotherapy, or secondary (acquired) if it develops during treatment.
The main message of the presentation will be that clinical resistance to chemotherapy is a multifactorial phenomenon. An overview of different mechanisms and their relevance for ovarian cancer treatment will be given. Generally, mechanisms can be divided into three categories according to the level at which they occur in relation to the target. Data will be presented of our own research on the possible significance of classical MDR (Multidrug Resistance), that is defined as an acquired or intrinsic resistance to a broad range of structurally and functionally unrelated compounds. It is associated with the expression of P-glycoprotein (Pgp), a 170 kD transmembrane glycoprotein, functioning as an active efflux pump and leading to a reduction of intracellular drug concentration.
Results will also be presented of our research on apoptosis-related proteins and their possible role in the biology of advanced ovarian cancer and drug resistance. It appears that all known cytostatic drugs kill cancer cells predominantly through apoptosis, a mechanistically driven form of cell death that is distinct from necrosis. P53, Mdm2, Bcl-2, Bax, Bcl-XL and Mcl-1 are known regulators of the apoptotic process, and a study was undertaken to investigate the possible prognostic and predictive relevance of the expression of these proteins in advanced ovarian cancer.
Patients and methods: Tumor biopsies from 185 consecutive and homogeneously treated patients with FIGO stage 3 ovarian cancer were examined immunohistochemically for expression of p53, Mdm2, Bcl-2, Bax, Bcl-XL and Mcl-1 proteins. Pgp expression was examined in a subgroup of these patients. Both uni- and multivariate analysis of prognostic factors was performed, and correlations with classical clinicopathological parameters and response to chemotherapy were examined.
Results: In multivariate analysis histological type, degree of differentiation, residual disease and p53 expression alone or combined with Bcl-2 and Bax expression were found to be associated with overall survival. A clear pattern of prognostic significance was found with lack of p53 expression and presence of Bcl-2 and Bax expression as good risk factors. This allowed patients to be separated into 3 clearly distinct risk groups. None of the proteins was predictive for the efficacy of platinum/anthracyclin chemotherapy. Pgp was found to be of both independent prognostic and predictive significance.
Conclusions: Drug resistance is a multifactorial problem. Single molecular biological parameters are unlikely to be of benefit in guiding treatment decisions. Methods (e.g. micro-array based) taking into account the complexity of the phenomenon are needed.

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The search for PCOS genes

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PCOS is a common disorder of unknown etiology. However, several lines of evidence suggest that there is an underlying genetic cause for PCOS. Studies of first degree relatives of women diagnosed with PCOS reveal familial clustering of the disease. A prospective study of first degree female relatives of PCOS women found that 46% of ascertainable sisters of PCOS women were hyperandrogenemic. The serum bioavailable testosterone in the cohort of sisters showed a bi-modal distribution. These observations suggest a dominantly inherited trait controlling androgen levels. Studies on cultures of human theca cells derived from thecal shells from follicles isolated from the ovaries of PCOS and normal women demonstrated that PCOS theca cells produce greater amounts of testosterone, 17a-hydroxyprogesterone and progesterone than normal theca cells, despite the fact that cells were cultured under identical conditions for multiple population doublings. Examination of the metabolism of radiolabeled steroid hormone precursors and steady state levels of mRNAs encoding steroidogenic enzymes revealed that there are multiple alterations in the steroidogenic machinery of PCOS theca cells including elevated expression of CYP11A, 3b-HSD, and CYP17. The increased mRNA levels are the result, in least in part, of increased gene transcription. Interestingly, the StAR gene is not expressed at a higher level in PCOS theca cells. The stable up-regulation of steroidogenesis in PCOS thecal cells indicates either a genetic abnormality in these cells or a persistent metabolic imprint established in vivo. Several strategies including suppression subtractive hybridization and DNA microarrays are being pursued to identify the full repertoire of genes whose expression is altered in PCOS cells. These studies have already discovered genes whose expression is altered in multiple cell types (theca, skeletal muscle, adipocytes and fibroblasts) from PCOS women compared to normal cycling females. Linkage and association studies conducted by the National Cooperative Program in Infertility Research using affected sib pair analysis and the transmission disequilibrium test to explore candidate genes point a finger at a region 2 MB centromeric to the insulin receptor gene. The putative PCOS gene lying in this region has yet to be identified. However, existing data suggest that it is probably involved in signal transduction mechanisms leading to altered expression of a suite of genes that affect theca cell steroidogenic activity as well as the metabolic phenotype of other cell types including muscle and fat.

Insulin resistance in PCOS - primary cause or secondary event?

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During the last decades knowledge of the enigmatic polycystic ovary syndrome (PCOS) has increased vastly. Largely, this is depending on the introduction of high resolution ultrasound in the diagnostic procedure. By this non-invasive method, easily displaying the major morphologic features of the polycystic ovary, the heterogenous clinical and biochemical picture has been fully shown for the first time. A spectrum from slight to severe aberrations is displayed in the large group of women with polycystic ovaries and, importantly, all the major features of the PCOS may vary and change within the individual, depending on factors like age, nutrition, physical exercise and the present body weight. Also the metabolic aberrations in PCOS are highly variable with life style factors. Insulin resistance, the key factor in the metabolic syndrome also containing dyslipidiaemia and hypertension, seems closely linked to the amount of truncal-abdominal fat in both women with PCOS and women with normal ovaries. The tendency to accumulate fat on the upper body is more prevalent in women with PCOS than in women with normal ovaries, and therefore there is an increasing difference in insulin sensitivity between these groups at increasing body weight. However, this difference disappears with weight loss and reduction of the truncal-abdominal fat in the women with PCOS. The PCOS constitution seems closely linked to, and overlaps that leading to diabetes type 2. Thus, obese women with PCOS have a high prevalence of diabetes type 2. Women who previously had gestational diabetes contain a large proportion of women with polycystic ovaries, and again these women exhibit reduced insulin sensitivity associated with increased truncal-abdominal fat. Beta-cell dysfunction is common in women with PCOS, as are reduced hepatic clearance of insulin, and these aberrations are also found frequently in normal-weight women with PCOS, suggesting that the search for primary metabolic abnormalities should be focusing on these areas. Also of interest are new findings in lipolysis regulation in abdominal fat tissue from lean women with PCOS, and suggestions of disturbed regulation of appetite and satiety in PCOS.
The high prevalence of the PCOS constitution in various ethnic populations with a traditional nomad life style suggests it may have provided evolutionary advantages in times and circumstances of restricted nutrition supplies, given the energy conserving characteristics of moderate abdominal obesity and diminished insulin sensitivity. Together with a tendency to increased muscular strength, this may have been a female phenotype with favours in survival terms, thus preserving a high prevalence of the constitution. It seems reasonable to assume that such a favourable constitution could instead turn into a disadvantage when confronted with last decades of less limited nutrition supplies and changes in Western dietary and physical activity habits. Thus, it is likely that we in parallel with the increase in obesity and diabetes in the society will see more women with fully developed insulin-resistant, high-androgen, anovulatory PCOS. Conversely, many of these women would be less androgenic, ovulating, normal-weight and exhibit normal insulin sensitivity if adapting to a less sedentary life style with normal-calory dietary habits.

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Medical risks and long term sequels in PCOS, and benefits and side effects of antiandrogen and steroid hormonal treatment

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PCOS is the most common endocrinopathi in women in reproductive years presenting a varying pattern of the well known symtoms: irregular menstrual periods, oligo-anovulation, obesity, hirsutism and acne. In the latest decade the information on long term effects has increased and today PCOS is not only a challange to specialists in Reproductive Medicine but also to specialists handling the Metabolic Syndrome. Many women with PCOS show varying degrees of insulin resistance, which deteriorates with increasing obesity.
A review of the prevalence of hypertension, NIDDM, calculated risk for and reported fatal heart infarction will be presented.
The PCOS has in younger women a hyperandrogenic hormonal profile whereas the estrogen levels vary from subnormal to supernormal. Also many women with PCOS have been subject to hormonal treatment due to irregular bleedings, oligo-anovulation and infertility and there has been concern about a possible negative impact on the reproductive system and the bone metabolism. A review on the prevalence of neoplasia of the endometrium, ovaries and breasts, as well as data on bone mineral density will be presented.
Hirsutism is a frequent and embarassing symtom in PCOS. Since long we have treated affected women with oral contraceptives and antiandrogen drugs during several years. There has been concern about the impact of long term treatment on metabolic variables. A review of the current knowledge on this matter will be presented.

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Treatment with metformin and insulin-sensitizing drugs

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Hyperinsulinemia and insulin resistance play a central role in the pathogenesis of polycystic ovary syndrome (PCOS). Hyperinsulinemia is associated with several endocrine and metabolic alterations in PCOS patients; e.g. increased ovarian androgen synthesis and decreased serum SHBG concentration.

Metformin is an antihyperglycaemic drug used to treat non-insulin dependent diabetes mellitus. Recent studies have indicated that metformin ameliorates the endocrine and metabolic alterations in women with PCOS. Furthermore, metformin administration has resulted in an improvement in menstrual pattern and ovulatory function. Similar beneficial effects have been achieved also by other insulin-sensitizing drugs, e.g. troglitazone and rosiglitazone. This treatment mode has been shown to increase the responsiveness to ovulation induction therapy.

In our own studies menstrual cyclicity improved in more than half of the obese PCOS women, and several patients conceived during therapy. Those who responded to metformin tended to be more obese and hyperandrogenic than nonresponders, but no significant difference was observed in insulin sensitivity or carbohydrate tolerance. Ovarian androgen response to gonadotropin stimulation was shown to be decreased during metformin but no significant increase took place in the circulating SHBG level. Despite the slight alleviation of hyperandrogenism, the hirsutism score did not improve significantly. The clamp studies performed in these subjects suggested that the effect of metformin in improved glucose utilization is mediated through its effect on adipose tissue mainly by decreasing central obesity. In obese PCOS women the serum lipid profile improved after 6 months of therapy. Also in non-obese PCOS women similar endocrine and metabolic changes were recorded during metformin treatment.

Metformin therapy is tolerated quite well; and about 5 to 10 % of cases stop the treatment because of side effects (mostly gastrointestinal symptoms). In all the studies published so far the duration of therapy has been less than 12 months, and hence, the possible effect of metformin on the long-term consequences of PCOS; e.g. type 2 diabetes and cardiovascular diseases, is still unknown.

In recent studies, metformin has been shown to decrease the serum plasminogen activator inhibitor (PAI) activity and the rate of miscarriage. Although, there is no evidence of any adverse effects on the fetus, more data is needed of the safety of metformin administration during pregnancy .

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Effects of estradiol on angiogenesis and immuno gene therapy in experimental breast cancer

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The majority of breast cancers are estrogen dependent and although current treatment strategies have improved the survival rate, approximately 50% of women with breast cancer will develop metastasis. New treatments such as immune gene therapy that result in long-term systemic immunity aimed at prevention of metastatic disease are therefore being developed. Estrogen has the ability to stimulate both breast epithelial cell growth and angiogenesis, and a well-characterized in vivo cancer model where these functional interactions can be studied is lacking. We demonstrate estrogen dependent angiogenesis, growth in vivo, and proliferation in vitro, in explants from polyoma middle T transgenic (PyMT) mouse mammary tumors. Thus, in addition to genetic similarities, this model also exerts a sex hormone, and angiogenic phenotype similar to human breast cancer.
This immune-competent animal model offers the opportunity to study molecular events in estrogen dependent breast cancer and effects of estrogen on various treatment modalities. In this tumor model we have previously shown that intratumoral adenoviral gene transfer of B7-1/IL-2 to murine breast cancer, in normal cycling female mice, induces a high rate of complete tumor regression and systemic immunity. Since estrogens not only affect breast cancer but also been shown to modulate immune function and secretion of immune-regulatory cytokines, we explored whether estradiol altered the immune response induced by intratumoral injection of an adenoviral vector expressing B7-1/IL-2.
PyMT breast cancer tumors were induced subcutaneously in ovariectomized mice, supplemented either with a physiologic level of estradiol or placebo. We report the somewhat unexpected finding that intratumoral injection of adenovirus expressing B7-1/IL-2 induce complete tumor regression in 76% of estradiol supplemented mice while only 18% of the tumors regressed in the estrogen depleted group. Cured mice in both groups exhibited a similar cytotoxic T-cell response against the tumor antigen. However, intratumoral IFN-g levels, two days after B7-1/IL-2 injection, were significantly higher in mice treated with estradiol compared to estrogen depleted animals. This may be one mechanism explaining the higher response rate of tumors in estradiol replenished mice.

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HRT-use and breast cancer

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In a large cohort investigation in South Sweden the risk of breast cancer after HRT use has been investigated. In 1990-92 40000 randomnly selected women were invited to participate in the investigation. Women were between the ages of 25-65 and had no past history of malignancy. An interview included among other things reproductive factors, family history of breast cancer and past and present history of hormone use. The cohort has now been followed between 8-10 years. Results: After more than 4 years the risk of breast cancer was increased 1.8 times compared to never users. The risk was independent of other risk factors of breast cancer and family history and HRT use did not interact. After 5 years of non use the risk returned to base line. The over-all cancer incidence was not increased and for some tumour types as colon cancer there was a reduction in cancer incidence after HRT use. A past history of oral contraceptive use did not interact with the risk. There was a clear difference in risk between different types of HRT use. Preparations containing progestins and continously used gave the highest risk while estrogen only preparation did
not substantially increased the risk. A previous investigation by our group has found that the survival of HRT users are better than nonusers adding to data suggesting that the tumour biology in HRT users are more favourable. The overall data suggest that there is now a possibility to use HRT in a way that minimize the risk for breast cancer.

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The breast in treatment of climacteric women

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Hormone replacement therapy (HRT) has been given to postmenopausal women for more than 30 years.
A therapy boom took place in the beginning of the 1990´s .
The gynecologists have been very aware of the gynecological positive and negative effects of HRT, but only in recent years they have realised that HRT also affects the breast tissue.
The mammography radiologists on the other hand have for more than a decade seen the increase in mammographic breast density caused by HRT, especially in the breast screening cohort in which women in the age group 40 to 74 are invited every other year to a mammography check up in the search for breast cancer.

The Swedish Breast Cancer screening program initiated by the Swedish Board of Health and Welfare has reduced the breast cancer mortality by in general 20 - 30%. 80 - 150 women are invited every weekday per screening unit and 1 - 2 mammograms are taken of each breast. The only purpose of the screening program is to find breast cancers in an early stage and in a cost effective way.

Breast density is the third strongest risk factor for breast cancer after sex and age. Various HRT regimes effect the breast density in different ways. Continuous combined HRT increase mammographic density in more than 50 %. Cyclic continuous combination HRT and oral estrogen-only therapy will increase the breast density in 20 % of the patients, while tibolone-only treatment only will increase the density in 5 %. The increase in mammographic density is apparent rapidly after only a few weeks use. It has been shown that continuous combined HRT not only results in a density increase but also increase the risk of breast cancer with almost 25 % increase in risk for each 5 year period of use.

Several authors claim that the use of HRT leads to a decrease in the sensitivity of breast screening (64 - 65% compared to 77 - 80 % according to Kavanagh et al) and that HRT-users have more false positive and more false negative screening results than non-users.
The false negative results in more interval breast cancers.

In my presentation I will show the impact of different HRT on the mammographic breast density and the difficulties that the mammography radiologists will have in interpretation when the breast density increases

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Effects of Tibolone and conventional HRT on breast cell proliferation and mammographic density

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In vitro and uncontrolled clinical studies have indicated that the effects of tibolone on breast tissue are different from those with conventional HRT. A total of 166 postmenopausal women were included in a prospective, double-blind trial and randomized to receive either 2.5 mg of tibolone, estradiol 2 mg/noretisterone acetate 1 mg of placebo for 6 months. Mammograms and fine needle aspiration biopsies from the upper, outer quadrant of the left breast were performed at the baseline and after 6 months of treatment. Mammographic breast density was quantified both as the percentage of the breast area with a dense pattern in classes of 20 % and by means of the Wolfe score classification. Proliferation was assessed by immunocytochemical staining using the Ki67/MIB-1 antibody. An increase in mammographic density was found to be much more common among women receiving estrogen/progestogen HRT (46 - 50%) than among those receiving tibolone (2 - 6%) and placebo (0%) treatment. During continous combined E"/NETA the percentage of MIB-1 positive cells displayed a near threefold increase whereas the effect of tibolone did not differ from that of placebo. From a clinical perspective an increase in mammographic density and breast cell proliferation should be regarded as an unwanted side-effect during HRT. Efforts should be made to define tratment regimens for postmenopausal women which have a minimum of effects on the breast but still maintain the many advantages of replacement therapy. Data suggest that tibolone may be such an alternative.

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Going South: The Canadian Experience

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The Society of Obstetrician-Gynecologists of Canada has integrated International Women´s Health as one of the five pillars of our Strategic Plan, and has made a commitment to doing as much as possible to help decrease global maternal mortality. This has led to successful projects such as our FIGO partnership project in Uganda, as well as numerous other initiatives. I will discuss both the successes and difficulties encountered in these projects, as well as our plans for the future.

The development of the International ALARM (Advanced Labour and Risk Management) course, and its recent delivery in numerous countries will be discussed. In doing so, I will discuss content development, as well as logistical considerations.

In all international work done by our society, the principle of partnership is central, and one of our goals is always to strengthen ties between our Canadian society and our sister organizations in other countries. Underlying all our efforts is a deeply held belief in the importance of integrating women´s empowerment and reproductive rights principles into the work of all health care professionals. In International Women´s Health, as at home, this means identifying the barriers to improving women's health, and includes an analysis of social, economic, and cultural factors. We believe that Safe Motherhood is the right, and should be the expectation, of all women everywhere, and that we all share a global responsibility for moving toward that goal.

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The FIGO Save the Mothers Initiative, an Ethio-Swedish project

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Background. At the Copenhagen conference 1997 a FIGO initiative invited societies for obstetrics and gynaecology of developing and developed countries to apply for participation and formulation of projects to significantly reduce maternal mortality. Four projects with "twinned" societies were subsequently launched by FIGO, one of which with the Ethiopian (ESOG) and Swedish (SFOG) societies.
Aim. Co-operation of the Ob/Gyn societies in improving maternity services. The project focused on improving emergency obstetric services in Ambo district, a rural area 120 km west of Addis Ababa with a population of 2.5 million and well over 100,000 deliveries annually and an estimated maternal mortality of 1000.
Design. Major project components included training of staff of Ambo hospital and two health centres, provision of equipment, establishing an outpatient pharmacy and blood services, strengthening of documentation and reporting, and regular supervision. The FIGO secretariat under a Steering Committee monitored the project. Outcome was given in proxy indicators of maternal mortality, such as admissions with life-threatening complications and number of life-saving procedures, notably numbers of caesarean sections.
Implementation. Communication between the two participating societies was difficult throughout the project. Provision of equipment was late and Ambo staff turnover necessitated repeated batches to be trained. The war with Eritrea adversely affected the project as Ethiopia's national priorities shifted.
Results. From 1998 to 2000 Ambo hospital deliveries increased from 700 to 850 in 2000, complicated deliveries from 260 to 320 and the number of caesarean sections from 30 to 120. Referral of patients to Addis Ababa for caesarean sections virtually stopped. Serious limitations were uncontrolled and high turn-over of staff, hardly any increase of facility use and total patient load, lack of drugs and supplies, absence of hospital management autonomy, limited improvement of documentation and unsatisfactory blood services.
Conclusion. This experience may be used for future projects. To affect maternal mortality, emphasis needs to be placed on emergency obstetrical care and issues relating to hospital/service management, drugs and supplies, staffing and training, must be dealt with. Regional and community involvement in order to increase utilization of health services need to be addressed. The success of a project must be judged by relating outside input to the resources available for health care in the country. Overall health expenditure per capita in Ambo (1994/95) was US$ 0.5. The Ambo project added a budget of US$ 241 000.
There is a desperate need for a wise use of funds to improve reproductive health care and obstetric services. Societies for obstetrics and gynecology have an obligation to find ways to promote reproductive health at home and abroad.

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The NFOG and Baltic collaboration

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Slightly older delegates at this meeting will remember the NFOG congress in Helsinki 1984 when the social program included an evening boat trip to Tallinn. We had anticipated a short visit to the old city and were very disappointed when we could not go ashore but were only allowed to see the Tallinn sky line from the boat, carefully watched by Estonian cost guards. My memory of that visit is the perception of a country so close geographically and, yet, so very distant. Since the independence of Estonia, Latvia and Lithuania in the early 1990s the borders have opened and so much has happened also within collaboration in obstetrics and gynaecology. In part, this is a result of a demand for professional exchange, in part it has become a necessity, since increased travelling also means that we share patients and problems. In 1997, the board of NFOG decided to make improved collaboration with our Baltic colleagues one of our areas of priority. This has resulted in meetings with board members of the Baltic societies where several areas of professional collaboration have been discussed and outlined and in a fellowship program for young Baltic colleagues to visit departments in all Nordic countries in connection with NFOG congresses. The NFOG scientific journal Acta Obstet Gynecol Scand is being distributed to larger departments in the three Baltic states. There are obstacles still to be overcome, for example language barriers, but there is a dynamic development going on with increasing exchange in all areas of obstetrics and gynaecology, closing the cultural and political gap that once existed between the Baltic and the other Nordic countries. It seems a reasonable scenario in the not so distant future that the Estonian, Latvian and Lithuanian Societies of Obstetrics and Gynaecology be invited into the family to become full and active members of the Nordic Federation of Societies of Obstetrics and Gynaecology.

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Safe motherhood initiatives by the WHO, World Bank and other major development partners (DPs)

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What role do the major DPs partners play in improving maternal-newborn health, what and challenges do they face?

WHO works with policy issues; monitoring; research; advocacy; and tools development. It has a limited role at the country program level. WHOs Making Pregnancy Safer (MPS) initiative promises to address systems issues of maternal health. It targets 10 pilot countries. MPS includes a set of technical guides, Integrated Management of Pregnancy and Childbirth (IMPAC). How WHO really will prioritize the initiative remains to be seen. UNFPA is devoted to RH, and has an important presence in many countries. UNICEF is close to the operational level in countries, and draws on technical knowledge of other partners in SM/RH. Its mandate in health is currently under internal review.

The World Bank (WB) lends money as hard or soft loans. Its overarching objective is to reduce poverty, but staff incentives are still tied to placing loans. The national Poverty Reduction Strategy Papers (PRSPs) have recently become a requirement for all soft loans, and for debt relief. PRSPs can become a common planning framework for all DPs in a country. WB has a key role in the national policy dialogue, due to its intersectorial perspective, due to its links with macroeconmic issues, and due to its lending. In its big portfolio, keeping sight of priority areas such as SM/RH remains a challenge. WHO, UNICEF, UNFPA and WB attempt to use the same indicators and goals, tied to the Millenium Development Goals.

In the intersection between these multilateral organizations, agencies such as Sida, Norad, and Danida (bilaterals) play an important role, as well as international and national NGOs, including professional societies such as those of ob-gyns or midwives. This requires committment to the common cause. NGOs that have coherent programs, and persist in their efforts, have good chances to get sustained funding. NGOs tend to be more rapid and flexible than multilaterals - their challenge is "going to scale".

How research could contribute to reproductive health in resource-poor countries

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The historical legacy of research collaboration with low-income countries in the field of reproductive health is not impressive. In the early 1970s Sweden was in the forefront of supporting alleged needs in some of these countries through its involvement in the special programme of the World Health Organization (HRP). In a historical perspective there was no distinction between "alleged needs" (assumed on the donor side) and "perceived needs" (felt on the recipient side) in the process of priority-setting. Vested interests in the north prescribed simplistic solutions to alleged needs in the south and - in retrospect - we can note the very late appearance of safe motherhood-oriented research and research on determinants for maternal mortality and perinatal mortality on the research agenda.

The principal lesson learnt from the last three decades is that the concept of "unmet needs" in reproductive health should be in focus and that initiatives to work in close collaboration with health staff (doctors, midwives and other staff) in resource-poor countries should emanate from community level experiences of clinical and community health work among scientists coming from the north. The disrespect for this principle might imply not only absence of progress but also obvious and direct damage due to misdirected efforts and malplaced research investments. Still today there are glaring examples of such investments in high tech laboratory research, while crucially important community-based studies of operational character have been left in the background.

The critical review of events preceding severe morbidity and mortality should be given highest possible priority in order to enhance sensitisation among clinicians of a need to carry out audit on a regular basis and at various levels of health care and among various levels of health staff. Several successful examples of this audit approach can be quoted, which concern above all basic expressions of reproductive ill-health, like "near-miss cases" in severe maternal morbidity, case fatality rates for eclampsia, postpartum haemorrhage, malaria and other major killers among pregnant and puerperal women.

Regional research collaboration in the poorest, low-income countries implies a possibility of exchange of important research experiences and how to enhance low-cost initiatives directed to correspond to "unmet needs". Such an attitude requires long-time practical collaboration in the field in low-income countries.

Research initiatives can contribute to reproductive health in resource-poor countries and can also generate spin-off activities by creating a critical mass of researchers in such countries. This is best done by leaving behind us the previous recipient/donor perspective and stick to a more respectful partnership agreement, in which mutual benefits are duly recognised and perceived and unmet research needs acknowledged with a high degree of sensitivity from the partner representing the more affluent setting.

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Doctors in projects and programs

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Many doctors dream about travelling out to save lives of people that are more in danger and ill-health than people at home. For the more adventurous, there are organizations like "Medicine sans frontiers", but most development work is not as dramatic as demonstrated in mass media. Development aid agencies have very different policies regarding placing so called experts into working positions in hospitals or communities. Medical students and young doctors do benefit from exposure to health in poor settings. Quality improvement, skills training and systematic research and data analysis are the three main issues of technology transfer that seem apropriate. In the presentation, I will give examples of research in a field seting in the Gambia, University collaborations in South Africa and Botswana, and operations research in a development program in Mozambique, where doctors and students have been involved.

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How to preserve ovarian function during chemotherapy

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Survival rates for young cancer patients continue to improve and protection against infertility caused by the necessary chemotherapy treatment with or without radiotherapy, has gained a higher priority during recent years. The aggressive chemotherapy has become increasing successful in curing the cancer, but as a side effect an increased risk of gonadal failure exist, which in women may impose permanent damage to fertility due to the lack of ovarian follicular replenishment. Treatment may eliminate the pool of primordial follicles leading to infertility and lack of menstrual cycles, and even if ovarian failure does not occur immediately, the risk of premature menopause is substantial.

As a consequence, strategies for preserving fertility in women has now gained considerable interest, and several different strategies has been attempted:

1) Inducing ovarian quiescence by the administration of GnRH-agonists in parallel with chemotherapy has been reported to minimize the gonadotoxic effect of chemotherapy. However, convincing evidence for the beneficial effect of GnRH-a in women is still lacking.

2) During recent years protocols for cryopreservation of ovarian tissue before onset of chemotherapy has successfully been developed. The pool of primodial follicles is almost exclusively found in the ovarian cortex and they survive cryopreservation in high numbers and re-implantation of frozen/thawed cortex-tissue result in folliculogenesis and steroidogenic active follicles. This method allows the woman to regain her menstrual cycles and it may allow her to gain fertility again, although no children has yet been born as a result of re-implantation of cryopreserved ovarian tissue. However, studies in animals have shown good fertility and normal offspring as a result of implanted cryopreserved ovarian tissue.

A widespread use of this method is currently hampered by the risk of reintroducing the cancer in connection with reimplantation of the ovarian tissue and it should be emphasised that the procedure is still experimental.

3)Cryopreservation of embryos resulting from IVF treatment before chemotherapy is a clinically available option already now. However, IVF treatment including ovarian stimulation with exogenous gonadotropins postpones initiation of chemotherapy, which often is undesirable. In addition, the increase in oestradiol concentrations as a result of ovarian stimulation may aggravate the clinical situation of patients with oestrogen sensitive tumours. In addition, the woman needs to have a partner, whereas young women or girls without a partner are unable to benefit from this method. This is further highlighted by the fact that cryopreservation of unfertilised oocytes from fully mature follicles is still not feasible, although the possibility exists that methods to cryopreserve such oocytes may be developed in the coming years.

This presentation will focus on cryopreservation of ovarian tissue, but the other strategies will also be critically presented.

STAN-new evidence based obstetrics

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The aim of intrapartum fetal surveillance is to identify fetuses at risk of hypoxia, thus enabling timely intervention to avoid an adverse outcome. However, electronic fetal heart rate (FHR) monitoring may show changes also in cases without significant fetal hypoxia, leading to unnecessary interventions. On the other hand, misinterpretation of ominous cardiotocographic (CTG) traces may delay intervention and contribute to the development of asphyxia. These problems have motivated development of alternative and complementary methods for fetal assessment.

In the fetal ECG, hypoxia typically causes an elevation of the ST segment and T wave, changes that are explained by a catecholamine surge, beta-adrenoceptor activation, and myocardial glycogenolysis. Fetuses exposed to hypoxia stress may also show ST segment depression (biphasic ST). Automatic ST analysis (STAN®) of the fetal ECG provides continuous information that, in combination with CTG, increases the ability to identify cases of significant hypoxia. Two randomized controlled trials (RCT), comparing intrapartum monitoring with CTG alone and CTG combined with ST analysis have been performed. In first study Westgate and coll showed a significant reduction of operative deliveries for fetal distress (ODFD) in the combined monitoring (CTG+ST) arm of the study. The recently published Swedish RCT, including 4966 parturients, showed significant reduction of both the rates of ODFD and of metabolic acidosis at birth. The risk of being born with umbilical cord arterial metabolic acidosis was reduced from 1.44% in the CTG group to 0.57% in the CTG+ST group in adequately monitored cases.

In addition, the neonatal outcome has been related to the ST information made available in both arms of the trial. In 29 cases there was a probable intrapartum asphyxia, defined as metabolic acidosis, neonatal encephalopathy, or perinatal death; 19 in the CTG group and 10 in the CTG+ST group. Of 29 newborns, 25 had pathological CTG patterns, and 21 had CTG+ST changes that indicated a need for intervention according to protocol, used in the randomized study. In the CTG+ST group there were two neonatal deaths, and three cases of moderate encephalopathy.

The presenting data allows us to conclude that CTG + ST analysis provides accurate information on intrapartum hypoxia, and may prevent intrapartum asphyxia by alerting the staff in charge.

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Randomized clinical trial of total versus subtotal hysterectomy: Results after one year of follow-up

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Introduction. The incidence of total abdominal hysterectomy (TAH) for benign uterus diseases has decreased and that of subtotal abdominal hysterectomy (SAH) has increased without evidence from randomized clinical trials supporting this change.
Methods. Our aim was to compare TAH and SAH regarding urinary incontinence, postoperative complications, quality of life (SF-36), constipation, descensus of the vaginal top/cervical stump, satisfaction with sexual life, and pelvic pain. In this Danish multi-centre trial women suffering from benign uterus diseases were randomized via a central, computer-generated procedure. Data were collected via validated, self-administered, postal questionnaires and via case record forms filled out by the gynecologists, confirmed by patient records. The results after one year follow-up were analysed through chi-squared tests, multivariate logistic regression analyses, and Wilcoxon tests. The conclusions were based on the intention-to-treat analyses.
Results. 319 women were randomized to TAH (n=158) or SAH (n=161). Recruitment rate was 15.1%. Response rate of the one year follow-up questionnaires was 86.8%. A significantly (p=0.036) smaller proportion of women were urinary incontinent one year after TAH compared to SAH (8.6% versus 16.7%, odds ratio: 0.46, 95% CI: 0.22-0.94). Thirty women (22%) from the SAH group had vaginal bleeding and two of these had their cervix removed. No other clinically important differences were found between the two hysterectomy methods after one year.
Conclusion. A smaller proportion of women suffers from urinary incontinence after TAH than after SAH one year postoperatively. This study does not support the increasing use of SAH.

Comparison of TVT and Laparoscopic Colposuspension in the Treatment of Stress Urinary Incontinence

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The purpose of this on-going, randomized, multicenter clinical trial is to compare laparoscopic extraperitoneal mesh-staples colposuspension (LC) and TVT in the treatment of SUI. The study is carried out in four University and two Central Hospital Clinics in Finland.
Materials and Methods
128 women with urodynamically proven SUI, positive stress test, no previous incontinence surgery, BMI under 32, closure pressure >20 cmH2O, residual urine < 100 ml were randomized into TVT or LC operation. 121 patients have been operated and evaluated at their six-week post-operative visit: 70 in TVT group and 51 in LC group. The main outcome measures were: intraoperative and immediate post-operative complications, operation theatre time, operation time and hospital stay. 38 patients in TVT group and 26 in LC group have been evaluated after one-year.
Results
The operation theatre and the operation time were shorter in TVT group (60 vs 91 min; p< 0,001 / 29 vs 47 min; p<0,001). Return to normal voiding (residual urine volume < 100 ml) was faster in TVT group (9.2 vs 24.4 hours; p=0.004). The use of analgesics was less in TVT group (opioid doses 0,2 vs 1,8;p<0,001 / anti-inflammatory doses 1,8 vs 3,4;p<0,001). The hospital stay was shorter in TVT group (0,7 vs 1,8 days;p<0,001). The sick leave was shorter after TVT (15 vs 24 days; p<0,001). Blood loss during the operation was similar (34 vs 30 ml; p=0,537). One bladder perforation occurred in each group. Two patients in each group had prolonged retention (residual volume > 100 ml). One port infection occurred in the LC group and there was one wound infection in both groups. In LC group one patient had pain in trocar port and one had a hematoma, which was evacuated. Three patients in TVT group and one in LC group got urinary tract infection. After TVT one patient with bladder perforation was rehospitalised because of urinary retention and urinary tract infection; in LC group one patient got pneumonia and sepsis postoperatively.
At one year control there is statistically significant difference in Urinary Incontinence Severity Score, UISS (0.7 vs 2.5; p<0.05), in VAS (0.6 vs 2.2;p<0.05) and in 48 hour PAD test (1.8g vs 12.1g;p=0.05) in favour to TVT.
Conclusions
The immediate post-operative results of these procedures are similar. Complication rates were similar. The operation theatre time and the operating time were significantly shorter with the TVT. The need of postoperative analgesics was less and the recovery time shorter in the TVT group. TVT requires less hospital resources than LC. After one year there is a trend that both subjectively and objectively TVT gives better results than LC.

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Prevalence and risk factors of adenomyosis at hysterectomy.

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Adenomyosis uteri is a pathological entity characterized by the presence of endometrial glands and stroma embedded within the myometrium without apparent contact with the myometrial junction. It is often seen in perimenopausal women and it is suggested to be related to bleeding disorders, dysmenorrhoea and parity.
The present study was performed to evaluate the prevalence and possible associated risk factors for adenomyosis. Medical records were retrieved and histo-pathological material re-examined for 549 consecutive women undergoing hysterectomy in a 2 year period from 1990-1991.
The results of the study showed a prevalence of adenomyosis varying from 10.0-18,2 %, depending on different diagnostic criteria.The presence of endometrial hyperplasia at the time of hysterectomy was the only variable significantly associated with adenomyosis(OR = 3,0;95 %;CI:1,2-8.3).
No statistically significant association was found between adenomyosis and previous caesarean section, endometrial curretage or evacuation of the uterus.Furthermore, we did not see any significant association between adenomyosis and painrelated symptoms, indication for hysterectomy, age, parity or number of myometrial samples.
Our study stresses the need for precise diagnostic criteria for adenomyosis and furthermore indicates that endometrial hyperplasia and adenomyosis may have a common aetiology.

Limiting factors for a 24-hour stay after abdominal hysterectomy

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INTRODUCTION
Recent advances in our understanding of the multiple factors that may control postoperative outcome suggest that a revision of the perioperative program with optimised patient information, use of refined anaesthetic techniques, multimodal analgesia, antiemetics and early mobilisation and oral nutrition leads to shortened hospitalisation and convalescence. The hypothesis was that an accelerated stay program could be designed to allow abdominally hysterectomised women the same quick recovery as is generally accepted after laparoscopic and vaginal hysterectomy.

METHODS
Eighty patients in three consecutive series of patients undergoing abdominal hysterectomy were studied in a fast track setting with three different regimens to control postoperative pain. The planned length of stay was one day. The patients registered pain, nausea, dizziness, fatigue and hours spent out of bed during the first postoperative week. The following recommendations were given for the convalescence period: light or sedentary work and leisure activity could be resumed after two weeks, and physically strenuous work and sports after three weeks; Lifting of more than 10 kg should be postponed until two weeks and sexual intercourse for 3 weeks after surgery. Data on resumption of defined common activities, work, leisure activities and sexual intercourse were collected from questionnaires.

RESULTS
Median postoperative hospital stay was 2 days, and the main reasons for staying hospitalised more than one day was pain, nausea or complications. From the second postoperative day the patients spent median 12 hours out of bed. Within the first four days, 50% of the women felt able to clean, shop and cook. Median sick leave was 25 days (range: 2-81) and median time to resumption of leisure activities was 14 days (range: 2-83). 70% had an active sex life, which they resumed after median 28 days (range: 5-77).

CONCLUSIONS
This study suggests that it is possible to accelerate return to normal activities following abdominal hysterectomy to levels similar to what is achieved with minimally invasive surgery - with a revision of traditions and recommendations and with standardised care regimens for the postoperative period. We found that 34 of the 80 women were discharged on the day after an abdominal hysterectomy irrespective of the immediate postoperative treatment in the three different regimens tested. Nausea and pain were common complaints in the immediate postoperative period although these complaints seemed to have little effect on the return to normal activities. Since only properly conducted randomised studies can provide the exact answer to the question of whether to prefer laparoscopic or abdominal techniques, an accelerated stay program with a revision of traditional care regimens should be used in such a trial of abdominal versus laparoscopically assisted hysterectomy.

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High Expression of Cyclooxygenase-2 (Cox-2) Predicts Poor Outcome in Serous Ovarian Cancer

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Human trials and animal studies indicate that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a reduced risk of cancer, especially in the gastrointestinal tract. The best-known targets of NSAIDs are the cyclooxygenase (Cox) enzymes. The Cox-2 isoform is overexpressed in a variety of malignancies, for instance cancers of gastrointestinal tract, lung, pancreas, uterine cervix as well as corpus and in some ovarian tumors. And often the stronger the expression of Cox-2 has been the worse has been the prognosis of cancer. However no large scale data exist on the prognostic significance of Cox-2 expression in various ovarian malignancies. Therefore we get up to study the expression of Cox-2 in serous ovarian cancer and to explore in a large patient population if this expression could serve as a prognostic factor also in ovarian malignancy.

We analyzed the expression of Cox-2 protein in human serous (n= 458) ovarian carcinomas by immunohistochemistry using micro tissue arrays. The Cox-2 staining intensity was compared to clinicopathological parametres (age, preoperative CA125, stage, grade, tumor size, lymph node positivity and radicality of first operation). Strong Cox-2 immunoreactivity was detected in malignant epithelial cells in 70% of serous tumors. The staining was cytoplasmic or perinuclear. Elevated expression of Cox-2 protein was associated with poor differentation ($p=0.001$), large residual tumor size ($p=0.019$) and so with reduced survival of patients ($p< 0.0001$). There was no statistically significant correlation with any other previous mentioned clinical parametres.

These findings open up possibilities to study the Cox-2 selective inhibitors as an adjuvant chemotherapeutic modality in ovarian adenocarsinoma.

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Ectopic pregnancy 1970-1999 in the county of Sør-Trøndelag, Norway - decreasing incidence in the younger cohorts

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Objective: to study cumulative incidence of ectopic pregnancy by birth-cohort over a 30-year time-period, 1970-1999.
Material and methods: In- and outpatient cases with a diagnosis of ectopic pregnancy have been identified in the discharge registry and registry for outpatient treatments at the two hospitals; St. Olavs Hospital and Orkdal Hospital in the county of Sør-Trøndelag, Norway. Eligible for analyses were residents of the county who all had a histologically verified diagnoses. Units for analyses were five-year time-periods, 1970-74 etc., five-year age-groups 15-19 etc., five-year birth-cohorts 1950-54 etc. Separate analyses were done for 1st ectopic pregnancy.
Results: Overall the general incidence (15-44 years) increased linearly from 0.4 to 1.6 during the time-period 1970-74 to 1990-94 ($p<0.01$). Over the last 10-year period the overall incidence decreased from 1.6 to 1.2 (1990-94 to 1995-99) ($p<0.01$). The age-specific incidence increased by increasing age during the years 1970-74 to 1990-94. The age-specific incidence decreased more in the age-groups 34 or less over the last 10-year period (1990-94 to 1995-99).
By birth-cohort the cumulative incidence of ectopic pregnancy increased by age for all birth-cohorts from 1950-54 to 1960-64. However, the birth-cohort of 1965-69 had a 30% lower cumulative incidence by age 30 compared with the older cohorts. The major part of this decrease could be attributed to women who had their 1st ectopic pregnancy.
Conclusion: The decreasing trend of ectopic pregnancy observed over the years 1995-1999 can be explained by decreasing incidence of ectopic pregnancy in the birth-cohort of 1965-69. The 1965-69 birth-cohort was 17 years of age in 1982 when extensive screening for C trachomatis started in the county of Sør-Trøndelag.

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Hormone Replacement Therapy (HRT) and risk of stroke. Analyses based on the Danish Nurse Cohort Study

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INTRODUCTION

Epidemiological data suggest an overall neutral effect of HRT on stroke. The definition of exposure and outcome vary in the literature. Consequently we have investigated association between HRT (current, past and never use) and strokes with focus on type of HRT (unopposed oestrogen and combined oestrogen-progestin therapy) and ischemic strokes.

METHODS

All Danish nurses aged 44 and above were sent a detailed questionnaire on lifestyle and HRT-use in 1993. Subsequently they were followed in national registers of hospital discharges and death until the end of 1998. Strokes were defined according to ICD-8 as 430-434 and 436, and I60-65 according to ICD-10. Data were analysed in multivariate cox-survival models.

RESULTS

In total 19,898 (86%) nurses replied the questionnaire in 1993. Of them 13,122 were postmenopausal and free from previous major cardio- or cerebrovascular disease.
At baseline 28,0% used HRT currently and 14,3% had previously used HRT.
During 6-years follow-up 144 strokes occurred, of which 99 strokes were categorised as ischemic, of them 77 were non-fatal.
For all strokes, fatal as well as non-fatal current HRT-users had a hazard ratio (HR) of 1.26 (0.82-1.92) as compared to never HRT-users, while in an analysis looking at type of HRT current users of combined HRT had HR of 1.56 (0.94-1.57). For ischemic strokes (fatal and non-fatal), current users of all types of HRT had a HR of 1.64 (0.99-2.72) and current users of combined HRT a HR of 1.99 (1.09-3.63) compared to never HRT-users. When considering only non-fatal ischemic strokes the HR was higher for current users of all types of HRT 1.83 (1.07-3.13) and augmented further with a HR of 2.49 (1.36-4.58) for current users of combined oestrogen-progestin therapy as compared to women who had never used HRT at baseline. After extending the analyses with additional follow-up for the non-fatal ischemic stroke 19 more cases were added and the HRs were respectively 1.82 (1.13-2.93) for current users of all types and 2.14 (1.22-3.74) for current users of combined therapy as compared to never users.

CONCLUSION

In a prospective nurse cohort study we found that current use of HRT had a neutral effect on all strokes, whereas a significantly increased risk of ischemic stroke was found among current users of HRT especially when HRT contained both oestrogen and progestin.

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Long-term use of contraceptive depot medroxyprogesterone acetate is associated with impaired endothelial function

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INTRODUCTION

Depot medroxyprogesterone acetate (DMPA) inhibits proliferation of ovarian follicles resulting in anovulation and a decrease in circulating estrogen; the latter action is potentially disadvantageous to cardiovascular health. We investigated the vascular effects of long-term contraceptive DMPA in healthy young women.

METHODS

Endothelium-dependent (flow-mediated dilatation - FMD) and -independent (glyceryl trinitrate - GTN) changes in brachial artery area (Figure, arrows) were measured using Cardiovascular Magnetic Resonance (CMR) in 13 amenorrheic DMPA users (> 1 year use; mean age 29±4 years), and in 10 controls (mean age 30±4 years) with regular menstrual cycles, all without excess risk of coronary disease. FMD and GTN responses were measured just prior to repeat MPA injection and 48 hours later in DMPA users, and during the menstrual and follicular phases of the menstrual cycle in controls.

RESULTS

Estradiol levels and FMD were reduced in DMPA users compared to controls (58 pmol/l vs. 96 pmol/l, $p<0.01$ and 1.1% vs. 8.0%, $p<0.01$ respectively) without difference in GTN responses. Acute elevation of MPA levels was not linked to a further impairment of FMD (2.0% vs. 3.1%, $p=0.23$). Estradiol levels were significantly correlated to FMD ($r=0.43$, $p<0.01$).

CONCLUSIONs

Endothelium-dependent arterial function is reduced in chronic users of DMPA with hypoestrogenism as a likely causative factor. High circulating levels of MPA did not acutely cause further endothelial dysfunction. Endothelial effects of long term DMPA use is of concern especially in younger women at cardiovascular risk.

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Prevalence of chlamydia trachomatis antibodies and DNA in infertile couples

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Introduction: Pelvic infections with C. trachomatis is a well known cause of tubal damage and infertility in affected women. It is still not fully known whether modern diagnostic tests can be a useful predictor for silent ongoing infections in couples seeking help for infertility, and its relation to treatment success and pregnancy outcome. In a prospective cohort study the prevalence of IgG antibodies and C. trachomatis DNA in infertile couples and their possible relation to investigation diagnoses was analyzed.

Methods: The study was approved of by the Human Ethics Committee, Umeå University. Blood samples from each consecutive couple (n=244) attending the gynecology outpatient clinic at the Umeå University Hospital because of infertility, were collected at the start of investigation during the period of Jan 1998 through Sep 2000. Serum was analyzed by the microimmunofluorescence test for IgG antibodies against C. trachomatis. IgM and IgA antibodies were also analyzed in 143 and 133 cases respectively. If IgG-testing showed antibodies (cut-off level 1/20) in either the man or the woman, a second blood sample was drawn and a urine sample for C. trachomatis DNA analyzes, by mainly PCR, was collected. Tubal patency was assessed either by hysterosalpingosonography (HSS) and/or laparoscopy in the routine infertility investigation. Medical records of all couples were analyzed with respect to C. trachomatis serology results, PCR results, findings in HSS and laparoscopy, diagnoses, treatments and pregnancies.

Results: Mean age of the women was 31.1±4.7 (mean ± SD) years and of the men 34.0±5.4 years. The principal diagnoses were distributed as follows: anovulation 17.6%, not specified 31.1%, anomalies of the uterus 0.4%, male factor 14.8%, unexplained infertility 11.5%, endometriosis 10.7% and tubal factor infertility (TFI) 13.9%. Sixteen percent had TFI as one of three diagnoses. Samples for IgG-testing were available in all 244 women and 236 of the men. None of the patients complained of symptoms indicating ongoing STD. IgG was found in 59 (24.4%) of the women, 45 (18.4%) of the men and in 78 (32.0%) of the couples (where either one or both were positive). Seven out of 75 (8.0%) of the women were positive in DNA-testing, 5/66 (7.6%) of the men and 10/77 (13%) of the couples. Thus, the prevalence of a silent C. trachomatis infection was calculated to 4.1% of all couples where one or both had a positive DNA test. IgM was positive in 17.9% and IgA in 20.9% of tested couples. A significant correlation ($r=0.3$, $p<0.001$) was found between IgG in the woman and TFI. Such a relationship was not found between IgM or IgA and TFI.

Conclusion: Among infertile patients a high proportion of couples with elevated IgG antibody levels against C. trachomatis was found, which was also correlated to TFI. The high prevalence of C.trachomatis suggests that screening of both men and women should be included in routine infertility workup.

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Female reproduction rate after intensive care (critical illness).

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Introduction

Outcome after intensive care can be evaluated in several ways, the most usual being survival and quality of life (QOL). However, other endpoints may also be of interest. We wanted to investigate another measure of outcome in the female ICU population using reproduction rate (child birth) as an indicator.

Materials and methods

Female ICU patients in their reproductive age (16 to 42) at the general ICU at Haukeland University Hospital of Bergen between 1994 and 1999 were investigated. Patients were followed after hospital discharge, and for those surviving more than 1,5 years all childbirth before and after the ICU stay was registered. For this purpose data from the Norwegian Birth Registry was used. Then an age matched sample with regard to normal birth frequency was created from the Norwegian female population using available data about birth rates in Norway published by Statistics Norway. The expected birth rate could then be compared with our female ICU population before and after the ICU stay.

Results

During these six years 146 patients met the inclusion criteria and 110 survived. Mean age was 28.7 years and mean ICU stay was 3.4 days. Four patients (non-Norwegians) were lost to follow up. The total observation time in the remaining 106 patients was 1772 years, 1336 before and 436 years after ICU stay. In the normal female control group the number of births was expected to be 107.2 before ICU stay and 29.9 after (birth rate of $80/10^4$ and $69/10^4$. The observed numbers of births was 128 and 10 respectively (birth rate $96/10^4$ and $23/10^4$). The difference and the 95% CI (ICU group vs control group) was 16% before (-6 to 37%)and -46% (-18 to -73%) after the ICU stay.

Discussion/conclusion

We have found a significant reduction in female reproduction in long-term survivors after intensive care. The reason or reasons for this observation remains unknown at present but could be related to medical condition after ICU, a voluntary constraint or both.

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The gynecological examinations - with focus on sexual abuse victims

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Introduction: History of sexual abuse is associated to a broad range of health problems. Studies have shown that diseases such as chronic pelvic pain, pelvic inflammation and premenstrual syndrome are associated to a history of sexual abuse. Victims of sexual abuse report more visits to health care services than do non-abused.However studies have shown that women with a history of sexual abuse are less likely to attend gynecological services, such as cervical cancer screening, out of fear of the examination. The aim of this study was to describe womens experience of the gynecological examination and to assess possible risk factors including a history of sexual abuse, as to the reporting of severe discomfort.

Study methods: The study was the Danish part of a multi country study on abuse conducted in five Nordic countries. Consecutive patients visiting the Department of obstetrics and gynecology at Glostrup County Hospital, Denmark, were invited to participate in the study. Of the 1.156 patients asked, 1.011 accepted to participate. The participants received a postal questionnaire which included questions about the index visit to the department, obstetric and gynecological history and four types of abuse history including sexual abuse both in childhood and as adults.
Results: The level of discomfort during the gynecological examination was rated as severe by 18 % among all participants. Among sexually abused this figure was 29 % and for the non-abused 15 %. Other risk factors of reporting of severe discomfort were young age, a negative emotional contact with the examiner, prior negative or abusive experiences with a gynecologist, sexual dysfunction, and reporting of mental health problems as depression, anxiety and insomnia. Adjusting for these factors, the association between history of sexual abuse and reporting of severe discomfort during the gynecological examination remained statistically significant. Gender of the examiner did not influence the reporting of severe discomfort, neither among sexually abused women nor among non-abused.
Conclusion: Generally a small proportion of women reported severe discomfort during the gynecological examination. However women with a history of sexual abuse and women with mental health problems are at risk of reporting adverse experience when undergoing gynecological examination.
This study emphasizes the importance of identifying patients with a history of sexual abuse in the gynecological setting in order to adjust to the patients needs. This might reduce the risk of severe discomfort during the examination.

Prevalence rates of earlier abuse in relation to present suffering

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Objectives
The aim of the study was to estimate the prevalence of abuse among patients visiting gynaecological clinics in the five Nordic countries.

Study Methods
All in- and out- patients attending the department of gynaecology in the five study sites, one in each country, Denmark, Finland, Iceland, Norway and Sweden were consecutively invited (n=4718). One-two weeks after their visit, the participants received the NorVold Abuse Questionnaire (NorAQ) addressing emotional, sexual, physical abuse, and abuse within the health care. NorAQ has three to four questions including several examples for each kind of abuse. The examples classify different degrees of severity of the abusive act. The women were also asked to estimate how much they presently suffered from their experience of abuse on a scale from 0-10, were 10 meant that they suffered enormously.
NorAQ has been validated against an interview in a separate population based study, and was found to have good test-retest reliability and concurrent validity.

Results
The study period started fall 1999 and was completed summer 2001. The response rate varied from 69 to 85 % between countries. Preliminary analysis demonstrated differences between countries as to the proportion of women reporting abuse, demography and reasons for encounter. Most women had not told the gynaecologist about their history of abuse at the latest consultation, and only very few were asked.
High prevalence rates were found for all kinds of abuse in all countries. Prevalence rates dropped considerably when the "suffering" variable was dichotomised into suffering/no suffering (0 = no suffering and 1-10 = suffering), and only women presently suffering were counted. In Sweden for example, the prevalence of emotional abuse dropped from 18.7 to 15.4%, abuse in the health care from 19.7 to 13.0, physical abuse from 37.5 to 20.1%, and sexual abuse dropped from 16.6 to 10.0%.

Conclusion
Prevalence rates of abuse dropped considerably when a criterion of present suffering was added to raw data concerning occurrence. It may be argued that prevalence rates combined with present suffering are of greater clinical relevance, while raw data concerning occurrence more describe the context in which abuse occurs.

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Background of abuse in the health care among gynaecologic patients

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OBJECTIVES
To estimate the prevalence of a background of abuse in the health care among patients visiting gynaecology clinics in 5 Nordic countries.
METHODS
We invited consequtively all in- and outpatients attending the departments of gynaecology in 5 study sites in Denmark, Finland, Iceland, Norway and Sweden to the study (n=4718). After their visit to the clinic, the participants received the NorVold Abuse Questionnaire (NorAQ). It addresses emotional, sexual, physical abuse, and abuse within the health care. For each kind of abuse three to four questions are asked, including examples which classify different degrees of severity of the abusive act. In NorAQ, the women are also asked to estimate how much they presently suffer from their experiences of each kind of abuse on a scale from 0-10.
NorAQ has been validated against an interview in a separate population based study, and was found to have good test-retest reliability and concurrent validity.

Abuse in the health care was operationalized in NorAQ as follows:
MILD: Have you ever felt offended or grossly degraded while visiting health services, felt that someone exercised blackmail against you or did not show respect for your opinion ? in such a way that you were later disturbed by or suffered from the experience?

MODERATE: Have you ever experienced that a "normal" event, while visiting health services, suddenly became a really terrible and insulting experience, without you fully knowing how this could happen?

SEVERE: Have you experienced anybody in health service purposely - as you understood - hurting you physically or mentally, grossly violating you or using your body to your disadvantage for his/her own purpose?

RESULTS
Data collection took place fall 1999 - summer 2001. The response rate varied from 67 to 84% between countries. Preliminary analysis demonstrated differences between countries as to the proportion of women reporting abuse, demography, and reasons for encounter. High lifetime prevalence rates were found for all kinds of abuse in all the countries.
Lifetime prevalence rates for abuse in the health care (all three degrees of intensity) was 21% (13-28) between the Nordic countries. Moderate and/or severe abuse in the health care service was reported by 14% (9-18).
Fifteen percent of the Nordic population suffered 1 or more from abuse in the health care on the NorAQ scale of suffering, with a range of 8-20% between countries.
For women with a background of any abuse, the odds ratio for also having experienced abuse in the health care were significantly increased and varied from 2.6 to 6.2 between countries.
The violations experienced will be analysed in relation to the ethical principles guiding the health care.

CONCLUSION
A background of any abuse increases the risk that the patient also will have experienced abuse in the health care system.

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Prevalence and incidence of prolonged and severe dyspareunia: results from a population study

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INTRODUCTION: An increasing incidence of dyspareunia in women has been suggested but is not confirmed. In fact very little is known about the prevalence and nothing about the incidence. What is known is that it is a very common complaint when specifically asked for at gynecological clinics.
The principle aim of this study was to investigate the prevalence and incidence of prolonged (6 months or more) and severe dyspareunia in a non-patient population of women, and to explore the rate of recovery as well as the inclination to seek medical care. Another aim was to compare the use of oral contraceptives among women who had ever had dyspareunia and those who had not.
METHODS: A total of 3,017 women aged 20-60 participating in a screening program for cervical cancer answered a questionnaire about possible painful coitus.
RESULT: The prevalence was 9.3 % for the whole group and 13% for women aged 20-29 and 6.5% for the women aged 50-60, with a risk ratio of 2.0 (95% CI interval 1.4- 2.8) for the youngest age group compared to the oldest. The incidence risk ratio was 9.3 (95% CI interval 2.8-30.9) for the youngest age group compared to the oldest. Using age-specific incidence rates, a rising incidence of dyspareunia in young women was demonstrated. Twenty-eight percent had consulted a physician for their symptoms. Twenty percent recovered after treatment, while 31% recovered spontaneously. No differences were found in the use of oral contraceptives between the women who had had dyspareunia and those who had not.
CONCLUSIONS: Prolonged and severe dyspareunia is a great health problem among all women and especially for young women, for which a rising incidence of dyspareunia is suggested and discussed. Surprisingly few women have consulted a physician, raising the question of why this is the case and what can be done about it.

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Quality assessment of gynecological operations commonly performed

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WHY ASSESS QUALITY? Patients and health authorities demand quality assessments. The effectiveness and results of the health care system are questioned. The physician and the department´s policy have great influence over when and how to treat the patient, which raises concern that the medical outcome may differ considerably depending on both the physician and the department.

WHAT TO ASSESS? Objective measurements and assessments by parties other than the treating physician are needed. The physician is biased. In treatment of symptoms of benign conditions, objective parameters are few; however, data collection pre- and posttreatment can often be done by the patient herself. This will make evaluation of indications possible as well as reduce the physician´s work in terms of data collection.

A few simple yet reliable indices are wanted by physicians and the departments to make quality assessment easy, with minimal or no extra work. In the analysis, an adequate number of preoperative parameters concerning health and symptoms are essential to avoid confounding analyses due to patient selection. A dilemma in quality assessment is to set enough parameters without creating too much extra work for the participants. No quality assessment, however, exists without extra work. The parameters will also change over time due to patients´ and (physicians´) experiences and results.

WHO CAN DO IT? Either the medical profession takes the initiative in making quality assessments or someone else will enforce them. In order to make analyses and comparisons possible, comparable data collected in a uniform manner are needed. These have to be organized, which calls for a register, which will also serve as resource for statistical analyses. The register will identify areas where improvements can be made, and, equally important, where quality is adequate. It is up to the department to analyze whether the results are valid and whether they should or should not influence its routines. Due to the large number of patients, rare medical events, which are unsuitable for randomized trials, can also be described.

IN WHOSE INTERESTS? Today, the Swedish National Register of Gynecological Surgery demonstrate that participating departments have good results with low complication rates and high patient satisfaction. Patients can be confident of receiving good health care. In terms of future quality assessment, patients will benefit since efforts for improvement will be based on measurements of past experience. Health authorities will gain knowledge from the results of allocated resources. Moreover, the reputation of the departments will grow as they can present a record of good results; besides which, the quality assessment will help in spotting, and correction, of any flaws in a department´s system. A valid, transparent quality assessment register will show up the high quality of health services and help to further improve them.

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The Norwegian register for incontinence operations

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In 1996 only 16% of Norwegian dept of Gynaecology and Obstetric had a controlled outcome of their incontinence surgery. A committee of five uro gynaecologists were set up, and all departments were invited to a meeting in order to discuss how to design a national follow up procedure. It was agreed that a symptom specific questionnaire and simple objective outcome values were acceptable. Most of the existing psychometrically tested, disease specific questionnaires, were found too extensive for our purpose. Ubersax et al. found that a short form questionnaire was as useful as their long form version. We decided to develop a short form questionnaire not exceeding 2 A4 pages. The questionnaire was designed on the basis of a short form questionnaire created by Black et al. Due to experiences during the recording, some new variables have later been introduced to our questionnaire. The participants in one of the half yearly meetings have always approved the introduction of these variables. The recording started in September 1998. Today 30 of 38 departments performing incontinence surgery are reporting to the database. Twice a year reports are generated comparing local data to the mean of all departments? data. We believe that the success is partly due to an organised follow up, partly to the limited number of variables and finally due to an increased interest in uro gynaecology. The semi annual NUGG meetings and the yearly NUGA meetings have contributed substantially to this increased interest. Not having resources to construct a data application for all participants, a solution was chosen in 1998 where the paper questionnaire was scanned to a database. The scanning has been taken care of by a secretary. All the technical problems during scanning and quality assurance of the data had to be taken care of by me. Grants from the Norwegian health authorities financed the development of the database, the report generator and the secretary salary. The development and the validation of the questionnaire, and the organisation of the database were exiting for me the first 2 years, but with increasing number of questionnaires the workload became too heavy and last year the situation became unbearable. The NUGG meeting 2001 decided that we should develop a data application for local use. Our programmer and I develop the application using Microsoft Access. It is the intention that quality assurance is taken care of by the local user and that correct data are transferred via Internet to the central database. Experiences gained during the scanning process are used to avoid misunderstandings and faults in the new application. Users may analyse their own data. We are planning to charge all users with a licence fee. In order to satisfy the user´s demand for new reports, a user group has to be organised by NUGG for prioritising. Swedish colleagues, using the same questionnaire opens up for exiting collaboration and comparison of data. The NUGG data application and report examples will be demonstrated.

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Patient accept questionnaires integrated in clinical routine, a study by the Swedish National Register for Gynecological Surgery

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Background: In 1996, the Swedish National Register for Gynecological Surgery started to collect pre- and postoperative information on patients by means of questionnaires given out as part of routine medical care. The information is used in providing clinical care to the patient and for quality assessment.
Aims: To evaluate patients´ acceptance of questionnaires as a means of collecting information, and to investigate whether the questionnaire is a suitable tool for follow-up of patients.
Methods: In 1998, evaluations of the ordinary questionnaires were done by an evaluation questionnaire mailed to 80 patients´ recently hysterectomized. The results were triangulated with results from the register´s database and data from interviews with physicians and secretaries.
Results: The majority of the patients appreciated the questionnaires. Patients did not report any major problems in filling in the questionnaires. Most problems were due to administrative errors of the departments. Up to 36% of the patients missed the scheduled follow-up visit 2 months after the operation. Two out of 4 departments regarded the follow-up visit necessary and requested by the patients. Out of 1226 patients followed up postoperatively by questionnaire, 75% stated that they did not need any medical care. Among physicians, some distrust of questionnaires was noted.
Conclusions: The patients in this study preoperatively, and for short- and long-term follow-up, accepted the questionnaire as an instrument of data collection. Questionnaires provide a more complete collection of post-treatment information than follow-up visits do. A large number of unnecessary follow-up visits can be avoided through use of a questionnaire.

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What is the incidence of complications after hysterectomy and how can a register lower them?

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Introduction: In Finland, there are no ongoing registers for gynaecological surgery. For quality assessment complications after hysterectomy were evaluated.

Method: We have started two registers to study complications after hysterectomy. Laparoscopic hysterectomy (LH)-register collected data prospectively in 1993-1994 from every Finnish hospital. Finhyst-register studied morbidity after all types of hysterectomies in 1996 also from every department. Finally, we have analysed data retrospectively from The Finnish Hospital Discharge Register and The Patient Insurance Association to follow up major complications after laparoscopic hysterectomy.

Results: A total of 10 110 hysterectomies were analysed in Finhyst-study. The overall complication rate was 17.2%, 23.3%, 10.9%, infection rate was 10.5%, 13.0%, 9.0%, haemorrhagic events occurred in 4.0%, 4.6%, 4.7% and injuries to adjacent organs took place in 0.8%, 0.7%, 2.8% after abdominal, vaginal and laparoscopic hysterectomy, respectively. Urinary tract and bowel injuries were the most severe complications after hysterectomy. Ureteral injury occurred in 0.2%, 0%, 1.1%, bladder injury in 0.5%, 0.2%, 1.3% and bowel injury in 0.2%, 0.5%, 0.4% after abdominal, vaginal and laparoscopic hysterectomy. However, surgeon´s increased experience decreased the rate of urinary tract injuries (from 4.2% to 1.3%) in laparoscopic and bowel injuries (from 1.3% to 0.3%)in vaginal hysterectomies. In abdominal hysterectomies, the most difficult operations are done by experienced surgeon and the rate of severe complications did not decrease with increasing experience.

As laparoscopic hysterectomies were the main source of urinary tract injuries, these procedures were followed up with LH-register and by analysing data from two reliable Finnish registers. Major complications, which consisted of injuries to the gastrointestinal tract, urinary tract and large vessels, as well as nerve paresis, deep venous thrombosis and unintended procedures, decreased from 4.9% in 1993 to 0.7% in 1999. The rates of urinary and gastrointestinal tract injuries decreased significantly during these years. Ureteral injuries decreased from 1.9% to 0.4%, bladder injuries from 1.4% to 0.1%, vesicovaginal fistulas from 0.6% to 0.03% and intestinal injuries from 0.6% to 0.06% during seven years. Ureteral injuries seemed to be more common in local hospitals, where the expertise was not as extensive as in university hospitals.

Conclusions: It is essential to follow up the morbidity after gynaecological surgery and without registers we will not find out the complications related to our procedures. With the help of registers we may realize which procedure or which hospital is causing problems and we may overcome these problems with training.

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NFOG Quality Guidelines for Gynecological Surgery.
A Questionnaire Study of all Nordic Departments.

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Background: The NFOG Board established The Nordic Quality Group for Gynaecological Surgery in benign diseases with one member from each of the Nordic countries. Its mandate was to make guidelines for quality assessment for such surgery.

Design: A questionnaire concerning the quality of surgery was sent to all gynecological departments in the Nordic countries to evaluate their opinion on quality assessment by registers. Based upon the results of the questionnaire Nordic guidelines for quality assessments were elaborated.

Results: Of the departments that responded (83%), 92% expressed interest in participating in a quality register.
Using a Visual Analogue Scale (VAS) the majority of responders agreed that registers: 1) are necessary for comparison of treatment results between departments (bench marking). 2) improve quality by itself and act as a checklist for essential data to be collected. 3) detect areas were quality improvement may be needed, as well as areas where quality is adequate. (VAS: 0 = total agreement, 10 = total disagreement, range of means 2.0-2.6). However, several departments did hesitate to join a register when the financial costs were not specified, and the data collection meant extra work.

The responders were then asked to answer yes or no on each item if monitoring of uterine, adnexal, incontinence and prolapse surgery with abdominal, vaginal laparoscopic and hysteroscopic procedures should be done. The proportion of yes answers was between 73% - 95%. In addition, the departments agreed to include the following parameters: patients´ general health and gynecologic status, preoperative treatments, indication of surgery, operative procedures, postoperative diagnosis, medical and surgical complications, recovery after discharge, and patients´ satisfaction with treatment. (VAS: 0 = yes, 10 = No, range of means 1.2-2.3)

The results listed above were incorporated into common general guidelines for quality assessment of gynecological surgery in the Nordic countries. By co-operation within a special NFOG body, sub-specialists of the Nordic countries will elaborate more detailed guidelines for specific groups of diseases. No parameter without importance for the treatment should be registered. All data collected must be analyzed regularly and made available for all the departments.
Conclusion: The gynecological departments in the Nordic countries agree upon the necessity and the main content of registers for quality assessment. In accordance with the results of the Nordic questionnaire, common general quality guidelines for gynecological surgery are suggested.

The results of combined treatment of invasive cervical cancer (1991- 1995) at Tartu University Clinics of Hematology and Oncology

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Aim
To analyze the survival rate of patients with invasive cervical cancer, who had undergone combined treatment modality (surgery+radiotherapy/brachytherapy).
Material and Methods
Retrospective analyses, based on case histories and medical records during 1991 - 1995 with main attention to risk factors (abortions, smoking), treatment methods and survival rate.
Results
67 patients underwent combined treatment. Mean age was 48,9. The youngest patients were 26 (2), oldest one was 76 years old. 35 patients with cervical cancer had some relatives with cancer, 17 of them had gynecological malignancies and breast cancer, 18 patients had non-gynecological cancer. 51 patients had had abortions before, which was 76,1%. 28 patients had undergone 1 - 3 abortions, 23 patients had more then 4 abortions. 24 from 67 patients were cigarette smokers, it was 35,8%, less then 5 cigarettes was smoked by 6 patients and more then 5 cigarettes by 16 patients. Cervical cancer was found in 18 patients during prophylactic examination, 11 patients had only leukorrhoea. 44 patients had squamous cell carcinoma, 6 patients had adenocarcinoma, 4 patients had clear - cell carcinoma, mesonephroid carcinoma or leiomyosarcoma of cervix. By stages the patients were divided: IB - 35; II - 12; III - 15; IV - 5 patients, 67 patients altogether. 55 patients are since alive, 12 patients died of cervical carcinoma and 1 of them died malignant melanoma. 35 patients got preoperative brachytherapy 20 -30 Gy, external beam radiotherapy was applied to 9 patients and combined treatment modality to 11 patients. These patients underwent operation due to a residual tumor. Postoperative radiation therapy was applied according to indications. All 67 patients underwent Wertheim operation, patients being in IV stage applied combined operations: anterior pelvic exenteration with continent urinary reservoir. The overall five-years survival rate was 82%. Survival rate by stages was: IB - 97,1%(35), II - 75%(12), III - 66,7(15), IV - 40%(5).
Conclusion
1.Our group of patients was too small to compare it with the results of other big clinics and studies. 2.Combined treatment modality seems to be more effective than radiotherapy and brachytherapy alone. 3.Locally advanced cervical cancer is safely and successfully operable with combined operations.

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Expression of matrix metalloproteinase-2 (MMP-2) in endometrial carcinoma

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Introduction: Endometrial carcinoma is the most frequent malignancy of female genitals in Western countries. Most of the cases are diagnosed in stage I and have favorable prognosis. The traditional prognostic factors of endometrial carcinoma include the clinical stage, histologic subtype, grade of differentation, depth of myometrial invasion and lymph node spread. More accurate prognostic factors are needed to define the high risk patients, the adjuvant treatment and follow-up schema. Local invasiveness is an important prognostic factor in endometrial carcinoma. Matrix metalloproteinase-2 (MMP-2) belongs to a family of zinc-dependent metalloendopeptidases which can degrade type IV collagen and other extracellular macromoleculars and it´s linked in cancer invasion and metastasis. The aim of the study was to evaluate whether the expression of MMP-2 correlates with the conventional prognostic indicators and survival of patients with endometrial carcinoma.
Materials and methods: The series consisted of 127 patients who had undergone surgery at the Department of Obstetrics and Gynecology, University Hospital of Oulu, during the years 1993-1997. Expression of MMP-2 was studied in paraffin-embedded endometrial tissue samples from the primary tumors by using a specific monoclonal antibody for MMP-2 in a avidin-biotin-peroxidase immunohistochemical staining.
Results: Expression of MMP-2 immunoreactive protein was found in 81% of the primary tumors. A statistical correlation was found between grade ($p<0.05$), stage ($p<0.01$) and MMP-2 immunostaining. All grade 3 tumors were MMP-2 positive. In survival analysis only 1 of 24 patients presenting MMP-2 negative immunostaining died during the 5-year follow-up.
Conclusion: Our results suggest that the increased expression of MMP-2 in endometrial carcinoma with the consequent disruption of collagen architecture may be a prerequisite for neoplastic cell invasion and dissemination.

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Concurrent paclitaxel and cisplatin in vulvar squamous cell carcinoma in vitro

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Background: The combination of paclitaxel and cisplatin has proven to be effective in the treatment of ovarian cancer, but it has proven efficacy also in head and neck and cervical squamous cell carcinomas.

Material and methods: The effect of concurrent paclitaxel and cisplatin was tested in five vulvar squamous cell carcinoma, (SCC), cell lines (UM-SCV-1A,-2,-4,-7 and UT-SCV-3) in vitro. Chemosensitivity was tested using the 96-well plate clonogenic assay. Paclitaxel concentrations used varied between 0.4 and 1.6 nM and cisplatin concentrations between 0.1 and 0.9 ug/ml. These drug concentrations are clinically achievable. Survival data was fitted to the LQ-model, and area under the curve (AUC) value was obtained with numerical integration. The type of interaction was determined by comparing the area under the curve -ratio (AUC-ratio) of the two drugs to survival fraction (SF) of paclitaxel alone.

Results: With all cell lines tested the growth inhibitory effect of simultaneous paclitaxel and cisplatin was at least additive. The effect of the tested combination on the UM-SCV-1A and UT-SCV-3 cell lines was clearly supra-additive with all paclitaxel concentrations tested, and the UM-SCV-4 and UM-SCV-7 cell lines showed a supra-additive effect with increasing paclitaxel concentrations. The degree of supra-additivity was dose dependent in the UM-SCV-7 cell line with increasing synergy with higher paclitaxel dose.

Conclusions: The combination of paclitaxel and cisplatin had a clear additive or supra-additive cytotoxic effect on the vulvar SCC cell lines and it has been successfully used in other gynecolog-cal malignancies; therefore concurrent paclitaxel and cisplatin also deserves further testing in clinical settings in advanced stage vulvar carcinoma, which otherwise has a poor prognosis.

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Kinetics of an ultrasound contrast agent in benign and malignant adnexal tumors

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PURPOSE: To evaluate the effects of a microbubble contrast agent on the power Doppler ultrasonographic (US) examination of adnexal tumors specially focusing on timing of the transit of the microbubble bolus.
MATERIALS AND METHODS: Seventy patients with suspected ovarian tumors were examined preoperatively using contrast-enhanced ultrasonography. A-five-minute examination was stored digitally and the behavior of the contrast agent was evaluated objectively by measuring the time-dependent image intensity at the region of interest with a computer program. A time-intensity curve of each case was derived and analyzed.
RESULTS: Both the baseline and maximum power Doppler intensities as well as the absolute and relative (%) rise in intensity were significantly higher ($P<=0.0005$) in malignant as compared to benign tumors. The arrival time shorter (17.5 s vs 22.5 s; $P=0.005$) and the duration of contrast effect longer (190 s vs 104 s; $P=0.00006$) in malignant than in benign tumors. The area under the time-intensity curve was significantly greater in malignant compared to benign tumors ($P<=0.00001$).
CONCLUSIONS: After microbubble contrast agent injection, malignant and benign adnexal lesions behave differently in degree, onset, and the duration of Doppler US enhancement.

Motor evoked potentials from the pelvic floor muscles

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BACKGROUND:
Motor evoked potentials can be used in the diagnosis of central or peripheral demyelinating neuropathies. As lower urinary tract dysfunctions often accompany these diseases we wanted to study the application of the method as a test of pelvic floor innervation. However, transcutaneous magnetic stimulation is broadly focused and the specificity of the method therefore depends on the precision of the recording of action potentials from the target muscle. Stronger signals from larger, surrounding muscles (i.e. levator ani and gluteals) might contaminate results if surface electrodes are used to record sphincter potentials.

METHODS:
A group of 30 healthy women without evidence of neurological or lower urinary tract disease volunteered for the study. They had a mean age of 52 years. Transcutaneous magnetic stimulation was performed over the vertex, the upper lumbar spine and the sacrum. Compound motor action potentials were recorded with concentric needle electrodes placed in the striated urethral sphincter and in the levator ani muscle, and with two different surface electrodes (intra-vaginal and intra-urethral). Stimulations were performed with the pelvic floor resting and with tonic contraction (facilitated responses). At least three responses were recorded for each modality and latencies of potentials were calculated. Success-rates of the different electrodes were calculated as the ratio between acceptable curves and expected responses. Stepwise multiple regression analysis was performed to test for the effect of age, height, body mass index, vaginal parity and menopause. Bland-Altman plots were used to compare responses from the various electrodes and muscles. Pearson´s chi-square test was used to compare success-rates.

RESULTS:
After multiple regression analysis only height had an independent effect and only on sacral latencies. There were no significant differences between the latencies recorded with the various electrodes from either muscle, but the limits of agreement were wide. The concentric needle electrodes had a higher success-rate.

CONCLUSIONS:
Our data can serve as reference values in future studies of demyelinating neuropathy with sphincter dysfunction. However, the wide confidence intervals might limit the diagnostic potential of this method. For sacral latencies the height of the patient should be taken into account. We advocate the use of concentric needle electrodes in further studies.

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Care of urinary incontinence, treatment needs and construction of treatment scheme

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The estimates of the prevalence of urinary incontinence (UI) vary due to the subjective nature and tendency to accommodate to the symptom. It is said to be an embarrassing symptom not discussed with the general practitioner. The evidence-based treatment of UI includes pelvic muscle training, bladder drills and anticholinergics, which suit well to the primary health care and can often be initiated basing the diagnosis on clinical examination.
The aim of the study was to evaluate the presence of UI, subjective need for treatment and current treatment status in a sample of 30-60 years old women in a rural area. The factors preventing optimal treatment were evaluated and a treatment scheme involving primary health care was constructed and implemented.
A questionnaire on presence, frequency and type of UI symptoms and the need for treatment was sent to 689 women who participated in pap screening. The questionnaire included Urge Score to differentiate types of incontinence. 464 women responded. 205 (44%) had experienced UI during the last year, 31 (4,4 % of all women) had daily incontinence and 59 (8,6 % of all) wanted treatment. 80 % of women with incontinence had symptoms of stress and 20 % had mixed or urge UI. Respectively 21,5 % and 60 % of them expressed need of treatment.
136 women with incontinence were later interviewed to explore previous incontinence treatments, the subjective benefit of the treatment and the obstacles perceived in getting help. The interview included Urinary Incontinence Severity Score validated to measure the degree of incontinence. 90 % of women not needing treatment had mild incontinence based on UISS. 84 (61,8 %) of the interviewed women had previously some form of treatment, mostly written instructions for pelvic floor training. Only one had individual physiotherapy, 2 had bladder drill instructions, 7 had tried anticholinergics and 11 had undergone surgery. 44 % of women having pelvic floor training instructions had at least moderate help. The main obstacles for treatment reported were finding incontinence as a normal phenomenon, finding UI as a sensitive issue and distrust towards health care personnel.
A multiprofessional group of primary and specialised health care personnel evaluated the gaps in the service system preventing optimal UI treatment. The analysis pointed to lacks in training and recognition of available resources, lack of formal treatment chain and easily available treatment algorithm and lacking information to the public as main weaknesses. Based on the analysis a treatment scheme was constructed empowering the district nurses as the first step in recognition and treatment of UI. The construction of the chain included training of the nurses by incontinence physiotherapist construction of evidence based treatment algorithm and training of the GPs to use the algorithm. The impact of the intervention will be analysed after two years implementation.

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Tension-free Vaginal Tape Procedure - An effective minimal invasive operation for the treatment of recurrent stress urinary incontinence?

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INTRODUCTION: The short (Ulmsten et al., 1998, Nilsson CG, 1998, Wang et al., 1998, Ulmsten et al., 1999, Schiøtz, 2000, Nilsson et al., 2001) and long term success rates (Nilsson et al., 2001) as well as the safety (Kuuva et al., 2001) of the new minimal invasive, ambulatory Tension-freeVaginal Tape procedure [TVT] (Ulmsten et al., 1996) have in recent reports assessed to be good. There is limited amount of information concerning recurrent stress urinary incontinence [SUI] patients undergoing the TVT operation (Rezapour et al., 2001, Nilsson et al., 2001, Rufford et al., 2001), and the effectiveness of the procedure as a secondary surgery method needs additional surveys. Our study will further examine the results of TVT procedures in women with recurrent SUI.

PATIENTS AND METHODS: In a prospective study 51 women with urodynamically proven recurrent genuine stress incontinence were treated with TVT and followed for a minimum of 24 months according to a protocol. Included were patients with no need for additional concomitant surgery, no existing urogenital prolapse protruding beyond the vaginal introitus and no severe cystocele with residual urine. Mixed incontinence was included if the urge component was not dominating. The patient was regarded as objectively cured, if she had a negative stress test result and a negative 24-hour pad test result [<10 g/24 h]. To be regarded as subjectively cured the patient had to score $\leq$10 on the visual analoque scale [VAS]. To be regarded as objectively improved the patient had to have a negative stress test result and >50% reduction in urine leakage as measured by the 24-hour pad test or a pad test result <15 g/24 h. To be considered as subjectively improved the patient had to score $\leq$25 on the VAS. All other patients who did not meet the above requirements for cure or improvement were classified as failures.

RESULTS: Twenty percent of the women had undergone two previous continence procedures and 80% one respectively.The mean follow-up time was 25.3 months. Objective cure rate was 89.6% and subjective 80.4%. Bladder perforations, postoperative voiding difficulties, urinary tract infections and de novo urge symptoms were all registered at a rate of 5.9%. No serious complications occurred. The majority of patients were discharged on the afternoon of the operation day. No significant difference was observed between the pre- and postoperative residual urine, maximal urethral closure pressure, total and maximum voided urine volume values, whereas, the changes in urinary frequency, minimum voided volume, pad test result and VAS scores were highly significant.

CONCLUSION: TVT is a safe and suitable treatment for recurrent stress urinary incontinence.

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Urinary incontinence and depression

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INTRODUCTION: Recent experimental data in experimental animals has led to a new hypothesis suggesting that lowering monoamines such as serotonin and noradrenaline in the central nervous system leads to depression and bladder hyperactivity. Accordingly patients with altered central nervous system monoamines may manifest both depression and an overactive bladder.
We had two aims for the present study: firstly to assess the rate of depression and anxiety of the urinary incontinent women and secondly to investigate the influence of: anamnestic details, the objective parameters of urinary incontinence severity (pad test), depression and anxiety on the women´s self-perception of urinary incontinence severity.
METHODS: In the prospective study 82 incontinent women, referred to a urogynaecological clinic, we estimated the severity of urinary incontinence using the visual analogue scale (VAS) and a validated disease-specific quality of life instrument Urinary Incontinence Severity Score (UISS). The psychiatrist evaluated the women´s depression and anxiety using a structured interview of Hamilton Depression Scales (HDS) and Hamilton Anxiety Scales (HAS). Urodynamic and clinical investigation including pad test were done. Patients were classified on the basis of history and urodynamic evaluation in two diagnostic groups: stress urinary incontinence (n=57) and urge incontinence with or without stress incontinence (n=25).
RESULTS: Major depression (HDS³16) occurred in 44.0% of women with urge (±stress) incontinence and in 17.5% women with stress incontinence (odds ratio [OR] 3.69, 95% confidence interval [95% CI] 1.30 -10.49). Major anxiety occurred equally in these two groups. 22 patients had severe incontinence defined as UISS >14 points (upper quartile) and 23 patients defined as visual analogue scale >9 (upper quartile). In logistic regression analysis, major depression (OR 5.57; CI 1.19 - 26.11), urge incontinence diagnosis (OR 23.13;CI 1.90, 282.11), parity (OR 2.33; CI 1.16 - 4.60) predicted UISS in upper quartile. Neither the age, duration of urinary incontinence, amount of urine lost or major anxiety predicted the patients? self-perception of urinary incontinence severity. Only pad test (OR 1.01; CI 1.00 - 1.02) predicted VAS in upper quartile.
CONCLUSIONS: There is a strong indication that depression is an important factor, in the aetiology of urge incontinence and that it has also an effect on the patients´ assessment of the severity of urinary incontinence.

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Experience of hysteroscopic surgeries in the Riga city hospital No.1

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Hysteroscopic surgery in Latvia is performed since 1998.
Objective: To analyse frequency, indications of hysteroscopies and specificity and sensitivity of US examination before hysteroscopic surgeries.
Methods: Retrospective analysis of case histories of hospitalized patients in the Riga City Hospital No.1 from 1998 till 2001. In this period of time 129 patients were hospitalized for hysteroscopic surgery.
Results: 50% of patients were less then 45 years of age; 38 % - in the age group 45-55; 12% - over 55 years. 19% of patients were nulliparous. 16% of patients were postmenopausal women. Main complaints were: abnormal uterine bleeding in women of fertile age - 69%, abnormal uterine bleeding in postmenopausal women - 15%, pain in lower abdomen - 2%, infertility - 1%, no complaints - 13% of cases. The analyses of the history have shown that 46% of patients have gone through D&C, 3% - hysteroscopic surgery and 1% - conservative myomectomy. 29% of patients have received hormonal treatment in length 2 months to 3 years, including 3% - therapy with GnRH agonists because of submucose myoma. US examination was performed for all patients before surgery. There were 14% of US misdiagnose comparing with data of pathohystological examination mainly the cases when endometrial polyps were covered by endometrial hyperplasia. The following pathology was diagnosed: 36% of patients - endometrial polyp, 42% - submucose myoma, 21% - endometrial hyperplasia, 1% - syndrome of Asherman. There were no postoperative complications observed.
Conclusions: Hysteroscopic surgery is modern minimally invasive method of treatment for intrauterine pathology, which is highly effective, with low complication rate and short stay in hospital. It holds away from necessity of radical surgery and preserves women reproductive function for patients in fertile age. US is good first step screening technique in the evaluation of patients with abnormal uterine bleeding and helps to avoid ineffective procedures. It is the leading method to diagnose and choose the management in cases of submucose uterine myoma. It's even more important in the countries with developing economy to preserve patients from expensive medical treatment and invasive procedures.

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Persistent ectopic pregnancy following linear salpingotomy
Can serum hCG be used to predict patients at risk?

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Objective:
The drawback of conservative surgery for ectopic pregnancy is the risk of persistent trophoblast with an occurrence reported from 5 to 29%. The purpose of this study was to investigate whether serum hCG can be used to predict persistent ectopic pregnancy (PEP) after linear salpingotomy for tubal pregnancy.

Materials and methods:
Medical records of 417 patients treated with linear salpingotomy for tubal ectopic pregnancy were reviewed. PEP was defined as the continued growth of trophoblastic tissue resulting in additional surgical or medical treatment after initial salpingotomy as a consequence of either insufficient decline in serum hCG and/or clinical symptoms. Forty-eight (11.5%) patients were diagnosed with PEP.
Cases fulfilling the following criteria were identified: A preoperative hCG value within 3 days prior to the operation, a hCG measurement within the first 9 postoperative days and not yet treated for PEP. Three-hundred-and-seventeen (86%) of the uncomplicated cases and 38 (79%) cases with PEP fulfilled these criteria. For the interval of the first 12 days postoperatively, the corresponding figures were 324 (88%) and 33 (69%), respectively. Data were analysed with Mann Whitney U test or Fischer´s exact test.

Results:
Preoperative serum hCG levels were significantly higher in patients who developed PEP compared to patients treated successfully (2.100 IU/L versus 893 IU/L, $P < 0.01$). A preoperative serum hCG > 2500 IU/L was associated with a significantly higher risk of PEP (21 / 112 patients = 19%) than lower values (26 / 282 patients = 9%), ($P = 0.015$).
Preoperative serum hCG had a low diagnostic value. The specificity of predicting PEP ranged from 0.74 to 0.77 using threshold levels of 2500 or 3000, while the sensitivity ranged from only 0.38 to 0.45.
Within 9 days postoperatively, 25 of 38 cases subsequently treated for PEP compared to 72 of 317 successful cases had serum hCG´s ³ 10% of preoperative values ([OR] = 6.54; $P < 0.0001$). Before day twelve, 22 of 33 cases subsequently treated for PEP had serum hCG´s ³ 7% of initial values compared to 80 of 324 cases treated successfully ([OR] = 6.1; $P < 0.0001$). The sensitivity and specificity of predicting PEP were 0.66 - 0.67 and 0.77 - 0.75, respectively, by using these two cut-off levels.
Conclusions:
PEP is associated with a higher preoperative serum hCG and a slower decline in early postoperative hCG. However, PEP cannot be predicted from single preoperative or postoperative measurements of hCG with an accuracy sufficient for clinical use.

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Improved fertility following conservative surgical treatment of ectopic pregnancy

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Objectives: To evaluate fertility after salpingectomy or tubotomy for ectopic pregnancy (EP).
Design: Retrospective cohort study.
Setting: Clinical University Center, Hvidovre Hospital, Copenhagen.
Participants: 276 women undergoing salpingectomy or tubotomy for their first EP between January 1992 and January 1999 and who actively attempted to conceive, were followed for a minimum of 18 months.
Main outcome measures: Intrauterine pregnancy rates and recurrence rates of EP after surgery for ectopic pregnancy.
Results: The cumulative intrauterine pregnancy rate was significantly higher after tubotomy (88%) than after salpingectomy (66%) (Log Rank $p<0.05$) after correction for confounding factors. No difference was found in the recurrence rate of EP between the treatments (16% vs. 17%). In patients with contralateral tubal pathology the chance of pregnancy was poor (Hazard ratio 0.463) and the risk of recurrence high (Hazard ratio 2.25), assessed with Cox regression. The rate of persistent ectopic pregnancy was 8%.
Conclusion: Conservative surgery is superior to radical surgery at preserving fertility. Conservative surgery is not followed by an increased risk of REP, but the risk of persistent ectopic pregnancy, which should be taken into account when deciding on operative procedure. Management in case of contralateral tubal pathology is disputed and should ideally be addressed in a randomised clinical trial.

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Three-dimensional ultrasound volumetry in the management of missed miscarriage

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Purpose:
To investigate whether the volume of the gestational sac as measured by transvaginal three-dimensional ultrasonography can predict the outcome of missed miscarriage managed expectantly.

Methods:
This was a prospective observational study. Ninety patients with a first trimester missed miscarriage who chose to have an expectant management were recruited to the study. A single investigator performed all ultrasound scans and volume measurements. The main outcome measure was a complete spontaneous miscarriage within 4 weeks of initial diagnosis. The miscarriage was considered to be complete if the maximum antero-posterior diameter of endometrium was <15 mm on transvaginal scanning and there was no persistent heavy vaginal bleeding. The patients had the option of requesting surgery at any time but those who had not expelled the products of conception within four weeks were advised to have surgical uterine evacuation.

Results:
A total of 86 patients completed the study. The mean gestational sac volume (GSV) as measured by three-dimensional scanning was 9.69 ± 8.9 ml and the mean sac diameter (MSD) was 24.5 ± 8.0 mm. There was a significant ($r = .8$; $p < .0001$) exponential correlation between the MSD and the GSV. Forty-six (53.5%) patients had a complete miscarriage within four weeks of diagnosis, five had an incomplete miscarriage, and 35 did not expel the products of conception. The volume of the gestational sac as measured by three-dimensional ultrasonography was also not significantly different ($p = .821$) in both groups and did not show significant correlation with the outcome of missed miscarriages managed expectantly ($p = .924$).

Conclusion
The gestational sac volume as measured by three-dimensional transvaginal ultrasonography does not predict the outcome of expectant management of missed miscarriage within four weeks of diagnosis.

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Postoperative hospitalisation, morbidity and readmission after hysterectomy in Denmark

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INTRODUCTION
The national consequences of the increased focus on minimally invasive surgery and optimised postoperative regimens in Denmark are unknown. The aim of this study was to demonstrate the incidence of standard hysterectomy in Denmark, including surgical route, postoperative hospitalisation, morbidity, mortality and readmission rate within 30 days.

METHODS
We analysed data from the Danish National Patient Register from a two-year period (1998-2000) concerning hysterectomies for benign indications, carcinoma in situ cervicis uteri and cancer corporis uteri stadium 1. The term standard hysterectomy describes the removal of uterus performed on benign indication or because of carcinoma in situ cervicis uteri and cancer corporis uteri stage 1, in which cases the immediate postoperative courses are presumed to be comparable. A stratified sample of 821 discharge résumés was reviewed for detection of reasons for prolonged hospitalisation, readmission and death within 30 days postoperatively. Prolonged hospitalisation was defined as postoperative length of stay of more than 4 days, which equals the median length of stay in this period. The response rate was 99,9%.

RESULTS
In the two years, 10.171 women had stardard hysterectomies followed by a median postoperative hospitalisation of 4 days. In departments performing more than 100 operations per year, the median hospital stay varied from 3 to 5,5 days. 80% of the hysterectomies were abdominal, 6% laparoscopically assisted and 14% vaginal with marked regional variation in the choice of surgical approach. The number of vaginal hysterectomies varied from 0-67% in departments with a surgical activity of more than 100 operations per year. 8% were readmitted within 30 days after the operation and the mortality rate was 0,06%. If allowing extrapolation from the random sample of discharge résumés to the entire population, the complication rate was estimated to minimum 18%.

CONCLUSIONS
Standard hysterectomy in Denmark is associated with considerable morbidity and marked regional variation in choice of surgical approach. The results argue for a closer monitoring of the gynaecological operations with establishment of a national hysterectomy database in order to evaluate surgical activity, morbidity rates and to develop homogeneous guidelines for the perioperative care.

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Danish gynecologists' opinion about hysterectomy on benign indication - results of a survey

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Aims: To survey Danish gynecologists` recommendations concerning hysterectomy and hysterectomy methods for benign diseases.
Methods: A questionnaire of seven clinical cases was sent to all gynecologists in Denmark (n=450). The gynecologists were asked to recommend one of fourteen possible treatments as the most appropriate for each case. In case of hysterectomy the gynecologists were asked to rate the appropriateness of oophorectomy. Questions about age, employment, geographic area, sex of the gynecologist and preference of the hysterectomy method for themselves/their wives were included.
Results: Response: 73%. Age above 50 years, meno-metrorrhagia and symptomatic fibroids seemed to be important for the recommendation of a hysterectomy and age below 50 years, asymptomatic fibroids and unexplained pelvic pain for the recommendation of other treatments. Employment, gender and geographic area influenced the recommendation of hysterectomy. Employment and geographic area influenced the recommended method of hysterectomy. The abdominal route was the recommended method of hysterectomy by most gynecologists, and the subtotal hysterectomy was the preferred method. The gynecologists agreed on the recommendation concerning oophorectomy in cases of women under 46 years and over 55 years. Disagreement was found in cases of perimenopausal women. The gynecologists' preferences of the hysterectomy methods did not differ from their recommendation for the cases.
Conclusions: Agreement regarding the recommendation of hysterectomy was found in cases of postmenopausal metrorrhagia, while disagreement was found in cases of asymptomatic leiomyomas and unexplained pelvic pain. Certain attributes of the gynecologists were found to be important to the recommendation of hysterectomy and method of hysterectomy.

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Tubo-ovarian abscess. Treatment and recovery

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Tubo-ovarian abscess complicates a large percentage of patients admitted to hospital for acute salpingitis. Independent of treatment modality, tubo-ovarian abscess causes long-term admission and sickleave to the patients.
The Purpose of this study was retrospectively to register the causes and treatment of tubo-ovarian abscess, correlate length of admission, sickleave afterwards, and time to recovery, to treatment modality.
Material and Method. All files from 1996 until 2001 in a University Hospital in Denmark categorized with the diagnosis tubo-ovarian abscess and/or the operative diagnoses of transvaginal puncture of Cul-de-Sac were studied. Twenty-two patients with ultrasonographically verified pelvic abscess were included, 4 of these patients were lost for follow-up. Patients with abscess after operative procedures, perisigmoiditis or appendicitis were excluded from this study.

Results. The median age of the 22 patients were 41 years (23-55). Eleven patients had an IUD. In 8 patients the direct cause was unknown, 1 patient had a hydro-sonography of the uterus performed 1 day prior to the debut of her symptoms, one patient had given birth 23 days prior to her admission, and 1 patient had a positive specimen for Chlamydia Thrachomatis 1 week prior to her admission.
Different bacteria were found by culture from cervix or abscess; In 17 patients specimen were negative. In the remaining 5 patients, specimen showed different low-pathogenic bacteria.
All patients were treated with antibiotics. Ten patients had a transvaginal drainage of the abscess, 4 of these proceeded to laparotomy at a later stage. One patient had a laparascopic drainage, solely. Six patients went directly to laparotomy.
The admission time differed between 1 and 15 days with a tendency of longer admission time for laparotomy patients. The sickleave was from 1 to 10 weeks, showing the same tendency. The time until the patients felt fully recovered was 1 to 40 weeks, large diversities were seen in both groups.

Conclusion. Tubo-ovarian abscess is treated differently in the same department. Culture rarely revealed a cause, nevertheless, all patients had antibiotics.
The length of admission, sickleave, and time until full recovery were generally longer in patients treated by laparotomy, perhaps reflecting these patients suffering from more severe infection

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Complicated case of cervical pregnancy - successful management

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Cervical pregnancy is an uncommon form of ectopic gestation which is frequently associated with extensive hemorrhage. The aetiology is obscure. Treatment options vary from conservative treatment including systemic methotrexate administration and angiographic uterine artery embolization to surgical interventions including evacuation of products of conception with subsequent cervical cerlage and total abdominal hysterectomy with internal iliac artery ligation.

A 21-year-old woman, gravida 1, para 0, was admitted to our department with heavy bleeding at 10 weeks and 5 days of gestation. Previously, she had had minor vaginal bleeding for three weeks. Ultrasound examination indicated distended cervical canal with hemorrhagic material bursting out. No vital fetus was found. She underwent curettage and very heavy bleeding occurred. To control hemorrhage, tamponade preceded by placement of cervical sutures was performed. Cervical pregnancy was considered to be the diagnosis. Tampon was removed on next day without any further bleeding. Serum human choriongonadotropin (HCG) level decreased from 1850 to 474. The patient was discharged three days after admission in good condition.

Before follow-up appointment patient returned on the 18th day of surgical intervention with infection which was treated with antibiotics. By ultrasound was found dilatated cervix (dimension: 60 x 70mm). There was seen a heterogenic mass with increased vascularity on the surface. Serum HCG was 197 and methotrexate-folic acid treatment with 8-day protocol was administred. 25 days later patient returned with heavy bleeding that resolved spontaneously before any further interventions. Serum HCG was < 5 but cervical status had not altered and selective single uterine artery branch embolization was performed.

One week later, the patient returned again with extensive bleeding and hypovolemic shock. Prostaglandin was injected into the cervix without any response. Cervical tamponade was performed again. Arteriovenous (av-) malformation of the right uterine artery was considered to cause recurrent bleeding and large uterine artery embolization was performed. Eleven days after this procedure dimensions of the cervix were 34 x 29 x 47 mm. Only minimal bleeding had occurred.

Three months after first intervention the cervical anatomy had normalised, patient had recovered and her menstruation had started.

Conclusion: If in a case of cervical pregnancy recurrent bleeding occures after uterine artery embolization an av-malformation should be excluded with re-angiography.

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Well-being in postmenopausal women at the onset of two different continuous combined therapies

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Aims
of the study were to investigate the changes on well-being at the onset of hormone replacement therapy (HRT) from an untreated state or switch from an earlier HRT and to investigate differences in effect on well-being between two continuous combined therapies, 0.625 mg, conjugated estrogen (CE)+ 5mg, medroxyprogesterone acetate (MPA) and 2mg, 17 ß-estradiol (E2)+ 1mg, norethisterone acetate (NETA).
Methods
One-year prospective, double-blind randomized study with 249 postmenopausal women stratified into, "Starters" who had not received HRT during the last two months preceding the study and "Switchers" already using HRT. Validated daily symptom scales were used to register severity and changes of symptoms. Symptoms in the scales were physical symptoms: swelling, breast tenderness, positive symptoms: cheerful, energetic, negative symptoms: depression, tension, irritability, and fatigue. In addition following symptoms sweating, effects on daily life, insomnia and headache.
Results

During the first treatment week starters improved in negative mood symptoms ($p<0.001$) but deteriorated in breast tenderness ($p<0.001$). During first month of treatment starters showed an improvement in sweating ($p<0.001$), insomnia ($p<0.001$) and effect on daily life ($p<0.005$) but deteriorated in breast tension ($p<0.001$) and swelling ($p< 0.039$).
Switchers improved in sweating ($p<0.030$) but deteriorated in breast tension and swelling ($p<0.001$) positive wellbeing ($p<0.001$), depression ($p<0.050$) and effects on daily life ($p<0.001$).
In starters physical symptoms deteriorated more on E2+NETA than on CE+MPA ($p<0.02$) and cheerfulness reported got worse on E2+NETA ($p<0.025$).
Switchers deteriorated more on E2+NETA than CE+MPA for breast tension ($p<0.012$). Positive symptoms and negative mood changed negative on E2+NETA $p<0.039$, $p<0.034$) compared to CE+MPA and insomnia and sweating ($p<0.025$ and $p<0.011$) improved more on CE+MPA than on E2+NETA.

Conclusions
Starters and switchers react differently at the onset of HRT. Sweating disappears during one month's treatment while the side effects develop rapidly already during the first treatment week. Already from the start of treatment with continuous combined HRT both starters and switchers appear to better tolerate CE+MPA than E2+NETA.

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Progesterone effects during hormone replacement therapy

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Objective: To investigate the effect on mood and the physical symptoms of two dosages of natural progesterone and placebo in postmenopausal women with and without a history of premenstrual syndrome (PMS).

Study design: Postmenopausal women (n = 36) with climacteric symptoms were randomized in a placebo-controlled, double-blind, crossover study. They received 2 mg estradiol continuously during three 28-day cycles. Vaginal progesterone suppositories with 800 mg/day, 400 mg/day, or placebo were added sequentially for 14 days per cycle. Daily symptom ratings using a validated rating scale were kept.
Results: Women without PMS history showed cyclicity in both negative mood and physical symptoms while on 400 mg/day of progesterone but not on the higher dose or placebo. Women without a history of PMS had more physical symptoms on progesterone treatment compared to placebo. Women with prior PMS reported no progesterone-induced symptom cyclicity.

Conclusion: In women without prior PMS progesterone causes negative mood effects similar to those induced by progestogens.

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CRP, E-selectin and SHBG in elderly osteoporotic and non-osteoporotic women: Effects of continuous combined oral HRT, alendronate or HRT plus alendronate

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Background
The release of C-reactive protein (CRP) in liver is induced by different cytokines. Recent data have shown that high levels of CRP, as assessed by highly sensitive assay, precede subsequnt myocardial infarction. This supports a role of inflammation in the detachment of atherosclerotic plaque which leads to the final occlusion of artery. In this process monocytes, trapped from blood stream to vascular endothelium by adhesion molecules (such as E-selectin) are of importance. We compared the effects of continuous combined hormone replacement therapy(HRT) and alendronate, alone or in combination, on CRP and E-selectin levels in elderly women with osteoporosis, because these regimens have been connected to the reduced risk of cardiovascular disorders.
Patients and methods: 90 osteoporotic women (BMD less than the mean -2.5 SD in fertile age group) and 50 non-osteoporotic controls were studied. The age ranged from 65 to 80 years at baseline. Osteoporotic women were randomized to receive HRT (2mg of estradiol plus 1mg norethisterone acetate (NETA) Kliogest®;Novo Nordisk,n=30), alendronate (10 mg Fosamax®,Merck & Co,n=30) or HRT and alendronate concomitantly (n=30). Each medication was used for one year. Serum samples collected after overnight fast were assessed for CRP, E-selectin and sex hormone binding globulin (SHBG) at recruitment and at 6 and 12 months of treatment.
Results: At baseline CRP and E-selectin showed no difference between the study groups, but SHBG in non-osteoporotic group was lower (p=0.002) than in osteoporotic groups. CRP increased at 6 and at 12 months in HRT group (76.5%,p=0.001 and 47.1%,p=0.078) and in HRT plus alendronate group (50.0%,p=0.031 and 52.9%,p=0.019) from the baseline, and there was no significant difference between the groups (p=0.936 and p=0.957). In contrast, E-selectin decreased in HRT group and HRT plus alendronate group significantly at 6 and 12 months (p<0.001)(HRT -24.3% and -30.0% and HRT plus alendronate -21.4% and -22.5%,respectively). Alendronate alone did not change either CRP (-11.6%,p=0.84 and 0.6%,p=0.68) or E-selectin (2.8%,p=0.56 and -4.5%,p=0.15) levels. No treatment affected SHBG.
Conclusions:Osteoporosis is not associated with changes in CRP or E-selectin, but SHBG was higher in the osteoporosis group. HRT induced rises in CRP reflect most likely the stimulatory effect of estrogen on CRP synthesis in liver rather than an effect on vascular wall CRP. Falls in E-selectin during HRT may imply a reduced trapping of monocytes to the endothelium during HRT and therefore, this effect may be beneficial. Alendronate, although known to be bound to vascular wall, failed to affect CRP or E-selectin. These data may be seen as evidence of vascular safety of HRT and alendronate, in elderly osteoporotic women.

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17beta-estradiol changes the inotropic response in isolated cardiac myocytes: Significant differences between species

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INTRODUCTION

The putative primary protective effect of Hormone Replacement Therapy (HRT) against cardiovascular disease (CVD) raises the possibility that 17beta-estradiol (E2) may have direct effects on cardiac tissue. In guinea pig cardiomyocytes it has been demonstrated that E2 in a concentration of 10^{-5} M reduces the inotropic response by approximately 25 %, probably by blocking the Ca^{++} channels. But our knowledge on the effect of E2 on the function of cardiac myocytes in other species, including human, is still limited.

METHODS

Cardiomyocytes were enzymatically isolated from rat, rabbit and human heart biopsies. Animals and patients were all male. Contraction of warmed (37 degrees C) and electrically stimulated (0.2 or 0.5 Hz) myocytes was induced by Ca^{++} 2 mM (2-8 mM for human cells). The effects of vehicle (alcohol 0.1 %) followed by washout and E2 10^{-5} M followed by washout were recorded using a video-edge detection system. The studies were approved by the local Ethics Committee and all patients gave informed consent.

RESULTS

Contractile myocytes were obtained from the ventricles of 9 rabbits, 6 rats and 6 human patients. The effect of E2 in rabbit was similar to guinea pig, with a reduction in amplitude of 29 +/- 5 % (percentage of the contraction amplitude before addition +/- SEM). However, the result in human was even more dramatic, with a decrease in amplitude of 60 +/- 5 %. In contrast, in rat cardiomyocytes E2 increased contraction with 12 +/- 6 %. The changes induced by E2 were significantly different between all the species (ANOVA, $p<0.0001$). Vehicle alone induced no changes in the contraction amplitude and the effects of E2 and vehicle were reversible following washout in all the species. The time to maximum effect of E2 was significantly higher for the human cardiomyocytes (8.1 +/- 1.2 minutes +/- SEM) compared to the rabbit (4.2 +/- 0.3) and rat (3.4 +/- 0.4) cardiomyocytes (ANOVA, $p<0.001$).

CONCLUSIONS

The results indicate that E2 acutely changes the inotropic response of cardiac myocytes. This effect is reversible and significantly differs between the examined species: The decreasing effect in guinea pig extends to human and rabbit cardiomyocytes, but in rat, E2 induces an opposite increasing effect. These findings may be part of the mechanisms behind the putative primary protective effect of HRT against CVD in postmenopausal women, as well as the lack of a secondary protective effect of HRT in women with established CVD.

No effect of long-term HRT on blood pressure and body weight of postmenopausal women with special reference to compliance

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Despite the well known benefits of HRT, the compliance has often been unsatisfactory partly because of withdrawal bleeding. In addition, it has been suggested that HRT will result in weight gain and it may elevate blood-pressure (BP). The aim of the present study was to evaluate in a prospective, population-based, randomized, placebo-controlled trial the effects of a sequential HRT on body weight, blood pressure (BP), compliance and bleeding pattern, among 464 women in a 5-year trial. A total of 464 early postmenopausal (last menstruation 6-24 months ago) women (mean age 52.8 years) of Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE, n=13100) were randomized to four groups: I) HRT, a sequential combination of 2 mg estradiol valerate + 1 mg cyproterone acetate (Climen ®, Schering AG, Germany), II) Vitamin D (D-Calsor ®, Orion Ltd., Finland), III) HRT + Vit D and IV) placebo. Body weight was measured at the baseline and at the 2.5- and 5-year appointments. BP was measured once a year at the outpatient visit at sitting position with standard manometer.
At the baseline, there were no significant differences in behavioral or laboratory values between the groups (Kruskall-Wallis-test). The drop-out rate was 36 %, 26 %, 11 % and 9 % in treatment groups I, II, III, IV, respectively. The main reason for discontinuation was disorders of bleeding (21-27 %) and headache (13-17 %). At the baseline there were 63 women with medicated hypertension: 16 both in groups I and II, 19 in group III and 12 in group IV. There were no significant changes in systolic and diastolic BP between the four study groups in time or between the women in different treatment groups with (n=63) or without hypertension medication.The body weight increased by three kilograms in 5 years in all study groups. However, there was no significant difference between the four groups in weight gain (p=0.415). After six-months treatment there was regular scheduled bleedings in 82 % and 77 % in groups I and III, and unscheduled bleedings in 22 % and 25 % of women in groups I and III, respectively. Unscheduled bleedings reduced in time: after five years 11 % and 17 % of women reported unscheduled bleedings in groups I and III, respectively. In addition, 34 % and 40 % of women in the group I and group III had amenorrhea after five years.
This prospective, randomized trial shows that long-term HRT has no adverse effects on BP or body weight. The sequential combination of estradiol valerate and cyproterone acetate provides a good cycle control and good long-term compliance among early postmenopausal women.

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Influence of postmenopausal hormone replacement therapy on platelet serotonin uptake site and 5-HT_{2A} receptor binding

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Objective: To examine whether binding of [^{3}H]paroxetine to the platelet serotonin transporter or binding of [^{3}H]LSD to the platelet 5-HT_{2A} receptor are influenced by postmenopausal estrogen/progestagen treatment.
Methods: Twenty-three postmenopausal women with climacteric symptoms completed this double masked, randomized, cross-over study. The women received 2 mg estradiol (E2) continuously during four 28-day cycles. A sequential addition of 10 mg medroxyprogesterone acetate, 1 mg noretisterone acetate or placebo was given the last 14 days of each cycle. Before treatment, as well as once during the last week of each treatment blood samples were collected for the analysis of [^{3}H]LSD and [^{3}H]paroxetine binding. The power of the study setup was 81%.
Results: B_{max} or K_d for [^{3}H]paroxetine binding did not change during estrogen or estrogen/progestagen treatment, nor did B_{max} or K_d for the [^{3}H]LSD binding change during the different treatments. However, in a subgroup of depressed patients, the decrease in B_{max} for [^{3}H]LSD binding during treatment was significantly more pronounced than in the nondepressed subgroup, $P < .05$.
Conclusion: Estrogen treatment with or without the addition of progestagen does not affect the binding to the serotonin transporter or to the serotonergic 5-HT_{2A} receptor in healthy postmenopausal women.

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Increase of estrogen dose deteriorates mood during progestin phase in sequential hormonal therapy

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Estrogen is known to increase well-being and quality of life in postmenopausal women with climacteric problems. However, the addition of progestins provoces fysical symptoms, increases negative mood symptoms and decreases well-being.
In this study we have investigated wether different doses of estrogen during sequential hormone replacement therapy affect mood and physical symptoms.
28 women completed a randomized double-blind cross over multi-center study. The participants of the study were recruited at three centers in northern Sweden. The women received either 2 or 3 mg estradiol continously during three 28 day cycles with an addition of 10 mg medroxyprogesterone acetate on day 17-28. There after a crossover to the other estrogen dose was made for two more 28-day cycles. The women kept daily records of 12 symptoms on a Lickert scale. The symptoms rated were bloating, breast tenderness, depressed mood, irritability, tension, fatigue, friendliness and cheerfulness. Menstrual bleeding, hot flushes, libido and influence on daily life were also monitored on the scales.
With the higher estrogen dose, negative mood symptoms increased significantly, but only during progestin phase. Tension, irritability and depressed mood were all sigificantly augmented during cycles with estradiol 3 mg ($p<0.001$). Likewise, with the higher estrogen dose physical symptoms increased during progestin phase ($p<0.001$).
Postive mood symptoms were less affected, but friendliness decreased significantly ($p<0.015$) during progestin phase with the higher estrogen dose.
Our conclusion is that an increase of the estrogen dose accentuates negative mood and physical symptoms during progestin phase in sequential hormonal therapy.

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Endothelial function is impaired in women with polycystic ovary syndrome

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INTRODUCTION
Polycystic ovary syndrome (PCOS) is associated with atherogenic metabolic abnormalities and has been linked to coronary atheroma formation. However data are inconsistent both with regard to cardiac morbidity but also with regard to endothelial function in women with PCOS. Intrinsic oestrogen levels, which often are high in PCOS, could be a protective factor.

METHODS
We assessed arterial function and oestradiol levels in women with PCOS and in healthy controls with a regular menstrual cycle. Endothelium-dependent (flow-mediated dilatation - FMD) and -independent (glyceryl trinitrate - GTN) changes in brachial artery area were measured using cardiovascular magnetic resonance in 14 women with PCOS and irregular menstrual cycles (mean age 33±4 years) and in 11 controls with regular menstrual cycle (mean age 31±6 years). Arterial function was assessed twice in both women with PCOS (during menses and 14 days later) and controls (during menses and at calculated day of subsequent ovulation). Oestradiol levels were measured by RIA at each visit.

RESULTS
FMD was greatly reduced in women with PCOS compared to controls both during the menstrual phase (-1.4% vs 8.0%, $p<0.01$) and at mid-cycle (2.5% vs 12.5%, $p<0.01$) without differences in GTN responses. Between visits, significant differences were observed in oestradiol levels in controls (79pM vs. 624pM, $p<0.01$) but not in women with PCOS (117pM vs. 236pM, NS). Total cholesterol was not different between women with PCOS and controls (4.9mM and 5.1mM, NS).

CONCLUSIONS
PCOS is linked to reduced endothelial function, which might transform into increased cardiovascular risk in later life. Lack of cyclical changes in circulating oestrogen with PCOS might be linked to adverse effects on the endothelium.

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The association of self-reported symptoms with biochemical findings typical of PCOS

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INTRODUCTION

Oligomenorrhea and hirsutism are typical symptoms of PCOS, a common disorder associated with infertility, NIDDM and cardiovascular diseases. Earlier studies are based on hospital populations and no general population based studies on markers and predictors typical of PCOS exist. The aim of this study was to investigate the value of self-reported symptoms of oligomenorrhea and hirsutism in distinguishing women with a typical endocrine profile of PCOS.

METHODS

This was a nested case-control study and the population derives from 1966 Northern Finland birth cohort where the subjects were followed since 6th month of their mothers pregnancy until the age of 31 years. The study population included 508 cases who had reported symptoms of oligomenorrhea and/or hirsutism and 1031 randomised controls. The serum levels of testosterone, SHBG, LH, cortisol, insulin and glucose were investigated. The results of the cases and controls were also compared in three BMI categories.

RESULTS

The testosterone, LH and insulin levels were significantly higher while SHBG levels were significantly lower in the case group. Insulin and cortisol levels did not differ significantly between the groups. The testosterone levels increased with increasing BMI, the levels being higher for cases in all BMI categories. SHBG levels decreased with increasing BMI, but the levels were significantly lower for cases in all BMI categories.

CONCLUSIONS

These results show that simple questions are meaningful in finding women at risk of PCOS and its consequences. The self-reported symptoms were associated with biochemical findings typical of PCOS and should further lead to metabolic investigations and possible treatment of the subjects to reduce their risk for NIDDM and cardiovascular diseases.

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Persisting polycystic ovary syndrome is associated with high prevalence of autoantibodies

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Introduction: The polycystic ovary syndrome(PCOS) is a heterogeneous clinical condition characterized by hyperandrogenemia and chronic anovulation. Likely more than one pathophysiologcal mechanism is involved in development of clinical signs and symptoms of PCOS. We hypothesized that autoimmunity may have impact to clinical course of PCOS.
The aim of our study was to analyze hormonal characteristics and the prevalence of organ-nonspecific autoantibodies in patients with suspicion of PCOS having different clinical outcome.
Material and methods: 50 patients with oligomenorrhoa and clinical symptoms of hyperandrogenemia visiting the ambulatory department of Tartu Women?s Clinic between 1997 and 1998 were included to the study. On admission ultrasound examination, clinical and hormonal assessment (FSH, LH, testosterone, estradiol, progesterone, prolactin, SHBG, DHEAS) was done, and blood serum for autoantibodies were taken simultaneously. Nuclear (ANA), cardiolipin (ACA), smooth muscle (SMA), thyroid microsomal (TMA) autoantibodies were tested by immunofluorescence method; antibodies against beta-2-glycoprotein I and carbonic anhydrase were analysed by enzyme-linked immonosorbent assay. The persistence of the clinical symptoms and if necessary hormonal parameters were estimated after three-years follow-up period.
Results: The patients were divided into three groups: I - no PCOS on admission (13 patients, mean age 23,1±4,3 years) II - PCOS on admission, no later confirmation in three years (13 patients, 22,5±3,8 years), III persisting of PCOS (24 patients, 24,5±4,4 years). The prevalence of nonspecific autoantibodies was significantly higher in the group of persisting PCOS as compared to both other groups ($p<0,005$). Mean body-mass index (BMI) and mean waist-hip-ratio (WHR) were also the highest in the III group (25,0 versus 21,3 and 20,3; 0,81 versus 0,74 and 0,71; $p<0,005$).
Testosterone and LH/FSH ratio were higher in both PCOS groups compared with the "no PCOS group" (3,6 and 4,0 versus 2,6; 2,4 and 2,5 versus 1,3; $p<0,05$). There was no statistically significant difference in other hormonal parameters between three groups.
Conclusions: The elevated values of testosterone and LH/FSH ratio are specific for diagnosis of PCOS, the higher values of BMI and WHR as well the prevalence of non-specific autoantibodies are associated with higher rate of persisting PCOS.

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Body size from birth to adulthood as a predictor of self-reported polycystic ovary syndrome symptoms

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Objective: To study the association between body size from birth to adulthood and self-reported symptoms of polycystic ovary syndrome (PCOS), particularly hirsutism and menstrual disturbances.
Design: Longitudinal, population based study of a cohort of women born in 1966 in northern Finland. The study population included 2007 women who were not pregnant and did not use hormonal contraception. Of these 528 (26%) had self-reported symptoms of PCOS.
Results: Weight at birth, gestational age or being small for gestational age were not associated with PCOS symptoms at 31 y. An increased risk of PCOS symptoms was observed among women with abdominal obesity at 31 y who had normal weight in adolescence but subsequently gained weight and were overweight or obese at 31y (relative risk (95% CI) 1.44(1.10-1.89)), and among women with abdominal obesity who were overweight or obese at both 14 and 31 y (1.71 (1.30-2.24)). Respectively, 30% and 41% of the women with PCOS symptoms in these groups could be attributed to overweight, obesity and abdominal obesity at 31y.
Conclusions: These results suggest that obesity in adolescence and in adulthood, and also weight gain after adolescence, particularly in the presence of abdominal obesity, are associated with self-reported PCOS symptoms in adulthood. Thus, based on the results from intervention studies treating PCOS and the results of this study, the prevention of obesity and abdominal obesity is important among young women.

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Unique alcohol sensitivity of alfa4beta2delta $GABA_A$ receptors

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Direct effects of low dose alcohol on $GABA_A$ receptors have remained elusive despite reports of an alcohol binding site and altered $GABA_A$ receptors following alcohol withdrawal. Here we show that low (1 mM) concentrations of alcohol increase by 40-50% currents gated by a novel recombinant $GABA_A$ receptor, alfa4beta2delta. We also show increased expression of this receptor in hippocampus using a rodent model of premenstrual and stress syndromes, in which 1 mM alcohol also preferentially enhanced GABA-gated currents. The alcohol sensitivity of this receptor may underlie the reinforcing effects of alcohol during premenstrual syndrome and chronic stress, when responses to low doses of alcohol are increased.

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Recent developments in structure-activity relationships for steroid modulator of GABAA receptors: 3 beta-hydroxypregnane steroids are pregnenolone sulfate-like $GABA_A$-receptor antagonists

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In contrast to their endocrine actions, certain steroid hormones have been shown to rapidly alter brain excitability and to produce behavioural effects within seconds to minutes. Steroids can both positively and negatively modulate GABAergic neurotransmission. The steroid effects are thought to be mediated by binding of steroids to specific sites on $GABA_A$- receptors ($GABA_AR$). Endogenous neurosteroids have rapid actions on ion channels, particularly $GABA_AR$, which are potentiated by nanomolar concentrations of 3 alpha-hydroxypregnane steroids (ex, allopregnanolone and pregnanolone). Previous evidence suggests that 3 beta-hydroxypregnane steroids may competitively antagonize potentiation induced by their 3 alpha-diastereomers. Because of the potential importance of antagonists as experimental and clinical tools, we characterized the functional effect of 3 beta-hydroxypregnane steroids. Although 3 beta-hydroxypregnane steroids reduced the potentiation induced by 3 alplha-hydroxypregnane steroids, 3 beta-hydroxypregnane steroids acted non-competitively with respect to potentiating steroids and inhibited the largest degrees of potentiation most effectively. 3 beta-hydroxypregnane steroids also reduced potentiation by high concentrations of barbiturates. 3 beta-hydroxypregnane steroids are also direct, non-competitive $GABA_AR$ antagonists. 3 beta-hydroxypregnane steroids co-applied with GABA alone significantly inhibited responses to > 15 μM GABA. The profile of block was similar to that exhibited by pregnenolone sulphate, known blockers of $GABA_AR$. This direct, non-competitive effect of 3 beta-hydroxypregnane steroids was sufficient to account for the apparent antagonism of potentiating steroids. Mutated receptors exhibiting decreased sensitivity to pregnenolone sulphate block were insensitive to both the direct effects of 3 beta-hydroxypregnane steroids on $GABA_AR$ and to the reduction of potentiating steroid effects. At concentrations that had little effect on GABAergic synaptic currents, 3 beta-hydroxypregnane steroids and low concentrations of pregnenolone sulphate significantly reversed the potentiation of synaptic currents induced by 3 alpha-hydroxypregnane steroids. We conclude that 3 beta-hydroxypregnane steroids are not direct antagonists of potentiating steroids but rather are non-competitive, likely state-dependent, blockers of $GABA_AR$. Nevertheless, these steroids may be useful functional blockers of potentiating steroids when used at concentrations that do not affect baseline neurotransmission.

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Metabolites of sex-steroids are neuroprotective and may be used in stroke treatment

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Stroke is either occlusive (due to closure of a blood vessel) or hemorrhagic (due to bleeding from a vessel). Insufficiency of blood supply is termed ischemia. Under severe ischemia, neurons die causing infarction. GABA and glutamate are the major fast inhibitory and excitatory neurotransmitters in the mammalian CNS. Agents that affect these systems have potential clinical utility as anesthetics, anxiolytics, cognitive enhancers and neuroprotectants. Excitotoxicity refers to the ability of glutamate and related compounds to destroy neurons by prolonged excitatory synaptic transmission. Extracellular accumulation of glutamate during ischemia activates glutamate receptor (GluR) excessively, thus triggers a chain of events that leads to neuronal death. Understanding excitotoxicity has important implications for treating neurological disorders. Blocking GluR could protect neurons from injury due to stroke, trauma and seizures. Unfortunately, clinical trials of GluR blockers have not led to much improvement in the outcome of stroke since excitotoxicity is only one of several mechanisms by which ischemia damages neurons. Therefore, neuroprotective agents that negatively modulate glutamate neurotransmission and simultaneously augment GABA neurotransmission are of great value in treating stroke. We report that the antiepileptic drug riluzole belongs to the family of use-dependent Na+ channel blockers that selectively inhibits glutamate release. In addition to its presynaptic effect, riluzole also potentiates postsynaptic GABA current in both Xenopus oocyte expressing recombinant ·1·2·2L $GABA_A$ -receptor($GABA_AR$) and cultured rat hippocampal neurons.

Sex steroids and their metabolites have fundamental effects in the CNS and can be called neuroactive steroids. Novel neuroactive steroid analogues, 3·-hydroxypregnane-3-carboxylic acids (3·PCs), are characterized with both NMDA receptor (a subclass of GluR) antagonists and $GABA_AR$ potentiating actions. Carboxylated steroids are synthesized as non-hydrolyzable analogue of 3·-hydroxypregnan-20-one hemisuccinate. Like the hemisuccinate, at physiological pH (7.4) the carboxylic acid group should be largely deprotonated, making 3·PCs as NMDA receptor blockers as pregnenolone sulphate. However, like GABA potentiating steroids, which contain a 3·-hydroxyl group as a hydrogen bond donor, the -COOH of unionized 3·PCs at lower pH(5.8) is a similarly located hydrogen bond donating group, and therefore unionized 3·PCs are shown to augment potentiation at $GABA_AR$. The unique attribute of the neuroactive steroids 3·PCs and neuroprotectant riluzole are their ability to potentiate $GABA_AR$ function and inhibit GluR function. This combination of cellular effects may enhance the clinical profile over previously characterized anti-glutamate drugs in stroke treatment.

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Progesterone metabolites interact with the GABA-mediated chloride flux in opposite directions

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The progesterone metabolite 3alpha-hydroxy-5alpha-pregnan-20-one or allopregnanolone increases gamma amino butyric acid (GABA)-mediated chloride conductance by $GABA_A$ receptors in a similar fashion as sedative drugs such as benzodiazepines and barbiturates. GABA is the major inhibitory transmitter in the central nervous system (CNS). Altered GABAergic function is associated with neurological and psychiatric disorders of humans, including Huntington´s chorea, epilepsy, alcoholism, schizophrenia, sleep disorders, and Parkinson´s disease. The GABA-system is also associated with premenstrual syndrome (PMS) by progesterone metabolites. The steroid effects are thought to be mediated by binding of steroids to specific sites on $GABA_A$ receptors. This alteration of GABA conductance might be an explanation for the mood variations during the female menstrual cycle. The 3beta isomer, 3beta-hydroxy-5alpha-pregnan-20-on (isoallopregnanolone) does not have these effects on $GABA_A$ receptors.

Therefore we have studied the interaction between allopregnanolone and isoallopregnanolone in cortical homogenates from adult male Whistar rats. We measured the chloride uptake into micro sacs in presence of 10 µM GABA and various concentrations of the steroids.

Isoallopregnanolone decreased the allopregnanolone and GABA mediated chloride uptake in a dose dependent manner.

These results indicate a possible role for isoallopregnanolone and structurally related compounds in the control of not desired GABAergic inhibition caused by high levels of allopregnanolone.

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Acute allopregnanolone tolerance

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Systemic administration of progesterone or its metabolites, like allopregnanolone (3alpha-hydroxy-5alpha-pregnan-20-one), induces anxiolytic, hypnotic and anticonvulsant effects. In women there are situations when tolerance to prolonged progesterone exposure can occur (e.g., pregnancy). In rodents tolerance to the anticonvulsant activity of allopregnanolone can be seen by repeated administration. Allopregnanolone acts as a positive modulator of the GABA-A receptor, similar to the benzodiazepines action. This enhancement of GABA mediated Cl- current results in an inhibitory effect on neuronal functions. During chronic treatment with benzodiazepines tolerance gradually develops, resulting in hypofunction of the brain GABA system.

To detect acute tolerance to GABA-A receptor active substances the EEG-threshold method can be used. By continuous EEG recording the amount of substance needed to reach the criterion "silent second" (SS - burst suppression of 1 second or more) can be identified. The substance infusion is then stopped and for longer anesthesia the infusion is started again when there have been no SS for a period of 1 min.

To detect if acute tolerance develops to allopregnanolone and if changed expression of any GABA-A receptor subunits is involved in tolerance development male Sprague-Dawley rats were used. Allopregnanolone (3 mg/ml in 10% 2hydroxypropyl-beta-cyclodextrin) was infused intravenously 4 mg/kg/min. After different time intervals (first SS, 30 min or 90 min of anesthesia) the last infusion period to SS was followed by decapitation and samples from blood, different brain regions, muscle and fat tissue were analyzed for allopregnanolone content. Half the brain was used for GABA-A receptor subunit mRNA detection in different brain regions using in situ hybridization.

The dose of allopregnanolone needed to maintain anesthesia was significantly ($p<0.001$) higher in the time period 65-85 min (0.98±0.04 mg/kg/min) compared with the period 10-30 min (0.67±0.03 mg/kg/min), meaning development of acute tolerance. We will present results from the elucidation of the possibility that the tolerance is caused by changes in GABA-A receptor subunit expression due to the prolonged allopregnanolone treatment.

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Patients with premenstrual dysphoric disorder have a decreased sensitivity to alcohol in the luteal phase

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Objective: Women with premenstrual dysphoric disorder (PMDD) have previously been shown to have a reduced sensitivity to GABAergic compounds such as benzodiazepines and pregnanolone, a progesterone metabolite. We have evaluated the functional sensitivity to alcohol in thirteen women with and twelve women without premenstrual dysphoric disorder (PMDD) at two stages of the menstrual cycle, by comparing the effects of an intravenous alcohol infusion on saccadic eye velocity (SEV) and self-rated sedation.
Results: The alcohol infusion produced significant changes in SEV, saccade deceleration and self-rated alcohol intoxication compared to placebo infusion. PMDD patients responded with a decreased SEV and saccade deceleration response to alcohol infusion in the luteal phase compared with the follicular phase ($F(1,12) = 5.42$; $p < 0.05$ and $F(1,12) = 6.15$; $p < 0.05$, respectively), whereas alcohol sensitivity in control subjects remained unaltered across the menstrual cycle. Self-rated sedation and alcohol intoxication scores did not differ between phases in either group.
Conclusion: These findings are compatible with decreased alcohol sensitivity in brain areas controlling saccadic eye movements among PMDD patients in the late luteal phase.

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Gynecologic status of patient in adolescence with Diabetes Mellitus

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The Introduction

The Gynecologic problems of patients group with Diabetes Mellitus have never been analyzed in Latvia before.
The goal of research is to evaluate the incidence and risk of gynecological pathologies for all cases of adolescent girls with Diabetes Mellitus, living in Latvia, and compare it with control group as well as to investigate management of pathologies.

Methods

The data were obtained, using retrospective analysis of hospital and outpatient?s case histories in girls of pubertal age (age 10-17) with Diabetes Mellitus. Special questionnaire was designed and approved by the local Ethics Committee.
The results were calculated using SPSS package.

Results

109 girls with Diabetes mellitus and 109 healthy adolescent girls as control group were analyzed.
To 20 (18.4%) of patient we did not have any information about gynecological status at all.
Among other encountered gynecological pathologies were delayed sexual development (21.35%), dysmenorhea (4.5%), ovarial dysfunction (10.1%) and Candida caused vulvitis (5.62%). While girls from control group mentioned only dysmenorhea (6.4%) and ovarial dysfunction (20.2%).
There is significant correlation between mentioned pathologies and age of Diabetes Mellitus onset and middle HBA1C ($p<0.01$).
Diagnoses were established by complaints, physical examination, ultrasonography, laboratory findings - hormonal rate evaluation, karyotype analysis.
Therapy was indicated in 52.6% to patient with delayed sexual development 33.3% with ovarial dysfunction, 75% with dysmenorhea and 60% with Candida caused vulvitis.

Conclusion

There is a difference in age of sexual development between girls suffering with Diabetes mellitus and healthy girls. Manifestation of pathologies like ovarial dysfunction and dysmenorhea are not leaded by Diabetes Mellitus.

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Contraceptives used before and after induced abortion and correlated to the women´s attitude

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The aim of the study was to evaluate the women´s attitude to use different types of contraceptives before and after an induced abortion. This was correlated to the women´s motive to ask for induced abortion.

DESIGN: A Prospective study was carried out at Kolding Hospital among all women referred to induced abortion within the first trimester. All the participants got specific questions to describe their motives for the induced abortion. We asked about their use of contraceptives before this pregnancy and to the plans about contraceptives in the future.

RESULTS: 854 women were referred to Kolding Hospital during 3½ year, and 831 (97,3%) participated in the study and answered the questions. The women´s motive for abortion had following percentages: Never any babies 32%, babies later on, but not now 20%, education has priority 19%, occupation has priority 19%, delivery recently 7%, the father to the pregnancy deserted the girl 7%, and various reasons 4%.
All the pregnant women in our study told they had used contraceptives with following percentages: Condoms 40%, contraceptive pills 18%, IUD 5%, and various reasons 5%. Surprisingly we found, that 32% of the pregnancy were cases where the couple never had used any kind of contraceptives.

CONCLUSION:
Presentation of ideas and stratifications to debate, how to give optimal information about the use af contraceptives in specific groups.

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Knowledge of oral contraceptives by provider

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Objective: to study whether contraceptive consultations with public health nurses (PHN)or generalpractitioners (GP) are associated with improved knowledge about oral contraceptives (OCs) among Norwegian teenagers.
Methods: 1789 female high school students (responserate 76%)answered a questionnaire about communication on contraception and knowledge about OCs. Eligible for analyses were 688 OC users. Knowledge about OCs was assessed through 15 questions comprising three separate indices and a total knowledge index. Logistic regression analyses were used to predict high scores on the knowledge indices by provider.
Results: most females (87%) discussed contraception at least monthly with friends. Few subjects discussed contraception with parents or health workers. Logistic regression analyses yielded that high scores of knowledge about physical changes during OC use (index 1), the pill's relative efficacy compared with other methods (index II), risk of cancer and tromboembolism (index III)and about OCs in general(total index) was not related to provider.
Conclusion: information conveyed during consultations contribute little to adolescents knowledge about OCs. More information is disseminated through frequent discussions about contraception with peers or through school education and written information (packet information, brochures, magazines etc.).

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Why women switch oral contraceptive pills

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OBJECTIVES: To investigate how often and why women switch OC-s.

METHODS: Five hundred questionnaires were distributed among women applying for OC refill prescription in January - March 2001. 462 completed questionnaires were returned (92,4%). Statistical analysis was performed using Microsoft Excel and EpiInfo2000 program (Dean AG et al. Centers for Disease Control and Prevention, Atlanta, Georgia, USA, 2000).

RESULTS:142 women (30,7%) switched OC at least once. In 95 cases (45,8%) women themselves initiated switching. The main reasons for switching were irregular bleedings (32-22,5%), weight gain (26-18,3%) and headaches (15-10,6%). Depression, increased vaginal discharge, nausea, breast tenderness, acne, loss of libido, frequent vaginal candidiasis and other reasons were mentioned too. Providers initiated the switching in 47 cases (33,1%). The most popular OC were the ones containing 20 microgr etinylestradiol (EE) (299 users - 64,7). Of gestagens, gestoden (273 - 59,1%) and desogestrel (115 - 24,9%) were the favourites. Trifasic preparations were used relatively seldom (41 - 8,9%), OC-s containing 50 microgr EE were not used. The average duration of OC, use was significantly higher among switchers than among women who have used only one preparation: 30.2±18,9 vs. 18,9±14,6 months ($p<0,001$).

CONCLUSIONS: Nearly one third of OC users switched the brand at least once. Providers´ active attitude helps women to choose a satisfactory OC preparation in most cases. When counselling women on OC it is important to stress that trying different components is possible to reduce side effects and improve adherence.

Oral contraceptives and compliance among Norwegian adolescents

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Obective: to study compliance and consequences of low compliance when using oral contraceptives (OCs) in a cohort of Norwegian adolescents.
Methods: from August 31, 1998 to December 31, 1999
1152 teenagers were recruited to a study evaluating how public health nurses and midwifes performed as OC-prescribers. The study was run as a clinical trial with scheduled visits at 3-6 months interval. Compliance was measured along three outcomes: continuation rates, forgotten pills and starting a new cycle on a wrong day. All analyses were done in SPSS using survival analyses and logistic regression.

Results: during the 1st year of use 428 of 1152 (37%) participants discontinued use. The probability of continuation through Mo-03, Mo-06 and Mo-11 were 0,81; 0,73 and 0,59, respectively.
The cumulative probability of forgetting at least one pill in at least one cycle over the first six cycles were 0,45, and 0,13 for forgetting at least two pills. The cumulative probility of starting at least one cycle on a wrong day over the 1st six months were 0,07. Six pregnancies were diagnosed over the 1st 11 months of use, whcih translates into a cumulative probability of OC-failure (overall) to 0,01. Low BMI were the only significant predictor of forgetting pills and starting a new cycle on a wrong day. The study did not have power to pursue consequences of "low" compliance.
Conclusion: Compared with results from international published studies (very few) we may consider compliance as reported among Norwegian teenagers as good.

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Why women apply for abortion and why they use no contraception

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OBJECTIVES
To determine, why women apply for first trimester pregnancy termination,
and why they used no contraception prior to subsequent pregnancy.
METHOD
Semi-structured interview of all women applying elective first trimester abortion at Tallinn Central Hospital in February - April 2001.128 women were interviewed
RESULTS
The leading reasons for pregnancy termination were poor economic condition (32,0%) and already achieved desired number of children (21,9%).
Neglected contraception accounted for 1/3 of unwanted pregnancy terminations. The proportion of unsafe method use is high (rhythm, withdrawal and vaginal douching ? 21,9% of applicants). No one of applicants used postcoital contraception. The proportion of repeated abortions among applicants was 68,6%.
CONCLUSION
If the economical situation in the country will improve, the rate of pregnancy terminations will diminish. Better and wider counseling on conception physiology, safe and postcoital contraception would lower the abortion rate. Post abortion counseling needs immediate improvement.

Norlevo, the first over-the counter emergency contraceptive: Lessons learned from non-prescription users in Norway

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INTRODUCTION

Norlevo (levonorgestrel 0,75 mg x 2) was made available on a non-prescription basis in October 2000. In order to obtain further information on women's knowledge, attitudes and experience with non-prescription access to EC, the Population Council coordinated a multi-centre study in four European countries where Norlevo is sold over the counter (OTC) in pharmacies (Norway, France, Sweden and Portugal). This report concerns the Norwegian arm of the study.

METHODS

Recruitment of study participants took place either via pharmacies in Oslo, which distributed a recruitment letter with each sale of Norlevo or via a mention of the study in the student newspaper.
In November 2001 to February 2002 we conducted five focus groups interviews with 27 women.
The study was approved by the regional research ethics committee.

RESULTS

Age range was 19-45 years (median 24). Four of the women worked, the majority were students. Two were married, eight living with a partner and the remaining single.
The study demonstrates that the level of general awareness of the existence of the method is good, but that specific knowledge is lacking. It varied if the women knew about the OTC-status before they needed it themselves. Most had heard about Norlevo from media and friends. Most of the women didn't get any oral information in the pharmacy. They were satisfied to get written information. Mostly they thought that the pharmacy's lack of privacy did not make it the right place to get information on a sensitive topic. They felt safe about using the method because they read the package insert, the product was easy to use, and they experienced minimal side effects.
The women felt that it is positive to be able to buy EC on a non-prescription basis. They mentioned that it is important to start the treatment soon after an unprotected intercourse, and that the need for the product often arises in weekends and holidays. OTC sale makes the product more available, especially where there are pharmacies with extended opening time. The women appreciate that they don't have to wait for an appointment by the doctor to get a prescription, and also that they don't have to tell their doctor about the need. Some women say that they would have been too embarrassed to visit a doctor to get EC, and would rather have waited until the next menstrual period hopefully came.
Almost all felt shameful. The feeling was expressed that it was morally inferior to use contraception after intercourse instead of having shown foresight.

CONCLUSION

The results confirm that non-prescription delivery of EC permits women to obtain EC in a timely, affordable manner. Users are able to diagnose their need for Norlevo and understand how to use it. Most participants said they would not want to use EC repeatedly. Norlevo use did not cause them to abandon their regular contraceptive method and in some cases motivated the adoption of a regular method.

Comparing success rates in two regimens for early medical abortion

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Introduction

Early medical abortion is traditionally performed with 600 mg mifepristone followed by vaginal gemeprost. Recent studies have shown that the short-term efficacy of the regimen can be maintained after reduction of the mifepristone dose and replacement of gemeprost by misoprostol (1). At our department we changed the regimen for medical abortion from mifepristone 600 mg followed two days later by gemeprost 1 mg vaginally to mifepristone 200 mg followed two days later by misopristol 800 microgram vaginally. The new regimen is much cheeper, the saving is about 900 Dkr for each woman treated. The purpose of the present study was to compare the long-term success rates of medical abortion before and after changing the regimen.

Material and Methods

During one year 266 consecutive women with gestational age =<63 days received a medical abortion at H:S Hvidovre Hospital. From December 2000 through May 2001 152 women received mifepristone 600 mg followed two days later by gemeprost 1 mg vaginally (group 1). From June 2001 through November 2001 114 women received mifepristone 200 mg followed two days later by misopristol 800 microgram vaginally (group 2). Serum-hCG measured day 1 and day 8 were used to identify ongoing pregnancies. All admissions during 3 months following the abortion were identified, and surgical interventions due to abortion related complications were recognized. Success was defined as no surgical intervention. The groups were compared with Fishers exact test and Mann-Whitney test, significance limits are $p < 0,05$.

Results

The success rates were similar in group 1 and 2 after two weeks (99,3% versus 98,2%), after four weeks (96,1% versus 98,2%) and after 3 months (95,4% versus 94,7%). The median time from treatment with mifepristone to surgical intervention was 23 days with no significant difference between the two groups.
Totally 13 women underwent surgical intervention, the majority due to prolonged bleeding and incomplete abortion. There was one case of ongoing pregnancy in group 1 and one cases of missed abortion in group 2. In three cases (one from group 1 and two from group 2) acute heavy bleeding caused surgical intervention and one of these required blood transfusion.

Conclusion

The efficacy of a medical abortion regimen with 200 mg mifepristone followed by 800 microgram misoprostol vaginally is comparable to a regimen with 600 mg mifepristone followed by 1 mg gemeprost vaginally at gestational age =< 63 days. The success rates were similar. The low dose mifepristone/misoprostol regimen can reduce the estimated expenses directly related to medication for each patient by 900 Dkr. There will be a lot of money to save for the hospitals by changing the regimen for early medical abortion.

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Medical abortion - defining success and optimizing follow-up

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Introduction

The success rates of medical abortion regimens vary from 92% to 98%. Comparison of succes rates is complicated by a lack of consensus on criteria for success. The purpose of the present study was to compare the short and long-term success rates of medical abortion, and to determine the diagnostic value of serum-hCG (human chorionic gonadotropin) and ultrasonography in predicting failures.

Material and Methods

Four hundred sixty-one consecutive women with gestational age < 63 days received mifepristone 600 mg followed two days later by gemeprost 1 mg vaginally. Serum-hCG was measured day 1, 8 and 15, and the endometrial thickness was measured by vaginal ultrasonography day 15. All readmissions during 15 weeks after the abortion were identified, and surgical interventions due to abortion related complications were recognised. Success was defined as no subsequent surgical intervention. The study was approved by the local Ethics Committee. Groups were compared with Mann-Whitney test.

Results

The success rate declined from 98,7% after two weeks to 94,6% after 15 weeks. In total 25 out of 461 women underwent curettage, one due to ongoing pregnancy, four because of acute bleeding, 15 because of prolonged bleeding and five because of retained tissue on ultrasound day 15. The mean time interval from mifepristone treatment until surgical intervention was 31,5 days (95% CI 22 - 41, range 5-103). The majority (76%) of failures were diagnosed after the two weeks follow-up visit and forty percent after one month.
The initial se-hCG was higher in the failure group than in the success group (median 123.721, range 27.722-200.000 vs. 88.252, range 1.992-271.000, $p < 0,05$). Both the absolute and the relative se-hCG after two weeks were higher in the failure than in the success group (1.287, range 315-13.949 vs. 301, range 9-10.170, $p<0,01$, and 1,4% vs. 0,4%, $p<0,01$). Though the negative predictive values of these parameters exceeded 0,97, the diagnostic value was low, with positive predictive values ranging from 0,09 to 0,33 - at different cut-off levels.
In 435 women the width of the endometrium after two weeks was significantly wider in the failure than in the success group (16 vs. 10 mm, $p< 0,01$). Again the positive predictive values were low.

Conclusion

Determining success of medical abortion after two weeks results in an overestimation of success. The majority of surgical interventions occur after two weeks and most are due to prolonged bleeding. Absolute and relative se-hCG values at follow-up are higher for failures than successes, but because of low positive predictive values, they are not useful as diagnostic tests. In order to compare success rates of different regimens we suggest, that the criteria for success are stated, and the reasons for secondary intervention are categorized.

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How to retrieve a " missing" implanon implant

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Implanon is a new progestin only contraceptive method with a duration of 3 years. It consists of a single subdermal implant which is inserted in the inside of the upper arm. It releases around 60 ug/day of etonogestrel.

The best thing to avoid problems at removal is to insert the implant correctly, i.e. subdermally so it is easy to palpate. Should it however be difficult to find the best way to visualize it is with ultrasonography. As the implant is quite small the degree of resolution is important. A transducer with a frequency of > 10 MHz should preferebly be used. The implant can also be seen with MRT. The implant is not radioopaque and can therefore not be seen with neither x-ray nor CT-scan. In special cases when the implant is difficult to find, the serum level of etonorgestrel can be measured in order to determine if the implant really was inserted.

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Attitudes among semen donors in 1992 and 2002

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Objective: To investigate attitudes of semen donors toward anonymity, motivations for becoming a donor, and considerations about donor offspring.
Method: I 1992 and again in 2002 semen donors at the same sperm bank were asked to fill out an almost identical questionnaire. In 1992 43 of 47 donors answered the questionnaire (87%); in 2002 the figures were 93 out of 102 (91%).
Results: In 2002 only 15% of semen donors accepted that their identity could be revealed to the offspring. 68% accepted a more detailed donor profile than the existing one only giving the following information: ethnicity, height, weight, colour of hair and eyes. These figures were almost unchanged since 1992.
The most frequent reasons for becoming a semen donor were the economical compensation and the wish to help childless couples.
Information about offspring was wanted by 40% of the donors, nearly all of these were only interested in the number of children born.These answers were identical with the ones in the 1992 survey.
If a child was born with a hereditable disease 42% wished to be informed.
In cases of insemination of lesbian couples 49% stated a positive attitude, 19% were against, and 29% were undecided. In cases of insemination of singles the figures were 37%, 23, and 39%. Again we found a good correlation with the answers from the 1992 questionnaire.
Conclusion: Attitudes among semen donors have not changed significantly during the last decade. Anonymity is crucial to a majority of semen donors. This gives reason to believe that fertility tourism will become even more frequent if anonymity is abandoned.

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Vulvar vestibulitis: a multifactorial condition

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INTRODUCTION: Vulvar vestibulitis is suspected to be increasingly prevalent among young women, but the etiology is still unclear. A wide range of factors has been suggested as causative, even if most of the evidence is derived from clinical reports rather than controlled studies. Psychological or psychosexual factors have been discussed in some papers, but most studies lack a control group, which is true also for the studies that have reported that women with vulvar vestibulitis have many other somatic symptoms.
OBJECTIVE: To study differences in somatic symptoms, personality dimensions, medical, psychosocial, and psychosexual background factors in women with vulvar vestibulitis and a non-symptomatic aged matched control group.
METHODS: Thirty-eight women, 18-25 years, suffering from vulvar vestibulitis, were recruited from two different clinics in the northern part of Sweden as well as 71 healthy aged matched controls. Three questionnaires were used: the Temperament and Character Inventory (TCI), to study personality aspects, the Giessen Subjective Complaints List (GSCL) which is a checklist of subjective bodily complaints and a structured questionnaire about medical, gynecological and psychosexual background factors.
RESULTS: Regarding personality aspects women with vulvar vestibulitis scored significantly higher on exclusively one out of seven subscales of the TCI. This particular trait is regarded to be partly inherited and to give the person a tendency to react to problems with pessimistic thoughts, increased anxiety and fatigue. On the GSCL the women with vestibulitis reported significantly higher number of somatic complaints in all areas, which was in accordance with the results from the third questionnaire where significant differences were noted for several symptoms. Very few differences were seen between the groups in psychosocial and psychosexual background factors.
CONCLUSIONS: There are no indications of a primary sexual disturbance, but it is obvious that these women suffer from many other somatic symptoms more often than their controls. This is interpreted as an indication of a psychosomatic element in their illness. The etiology of vulvar vestibulitis is still unclear but is most probably multi-factorial with different physical and psychological causes and often a combination.

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Acupuncture for the treatment of vulvar vestibulitis: A pilot study

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INTRODUCTION: Being both painful and psychologically distressing for the women involved, vulvar vestibulitis is a therapeutic challenge to physicians. Several authors have argued that vulvar vestibulitis should be regarded as a chronic pain syndrome and that treatments used for other pain conditions could be tried. Acupuncture has been suggested but no studies have been published so far.
The aim of the study was to obtain a preliminary indication of the effectiveness of acupuncture in the treatment of vulvar vestibulitis but also to obtain information how well the women tolerate the treatment.
METHODS: Fourteen young women with vulvar vestibulitis according to Friedrich´s criteria were enrolled in the study and 13 fulfilled the acupuncture treatment of a total of 10 times. For evaluation quality of life (QOL) assessments were made before starting the treatment and then at one week and at three months after it was completed.
RESULTS: The treatment was well tolerated and the QOL measurements were all significantly higher after both the last acupuncture and three months later, compared to before treatment was started.
CONCLUSION: The results seem promising, but a larger controlled randomized study should be carried out before the treatment can be recommended for use in clinical practice.

Victims of sexual assault and sexually transmitted infections in Denmark. Indications for examination and prophylactic treatment

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Introduction

The Danish National Board of Health has at intervals updated their guidelines on how to diagnose and treat sexually transmitted infections (STIs). These guidelines have however never included a section related to the risk of STIs in victims of sexual assault. Until now doctors examining rape victims has therefore been left alone as to the indication of examination for these infections, as well as the indication for prophylactic treatment. Furthermore victims undergoing forensic examination has neither as a routine been examined or treated for STIs. A national centre for adult victims of sexual assault was opened in March 2000 as an integrated part of the department of gynaecology, Rigshospitalet, Copenhagen. This centre is a multidisciplinary centre, where victims seeking help after sexual assault are offered care, medical and legal examination, medical treatment and psychosocial support irrespectively of reporting or not reporting the assault to the police. Among the objectives of the national centre is the task of collecting national data and give recommendations for a standardized handling of the initial examination and follow up of STI.

Method

STIs are most prevalent in the age group 15-25 years, thus similar to the age groups of women most frequent exposed to sexual assaults. The risk of a pre-existing STI may therefore be significant higher than the risk of acquiring STI as a result of the rape. This situation should however not eclipse the fact that sexual assault victims have a potential risk of acquiring STIs and that it is of major concern for many victims, whether they have been infected. The initial examination should therefore include relevant blood tests as well as sampling for STIs from any sites of penetration or attempted penetration. At the first examination at the national centre in Copenhagen victims are as a routine screened for Neisseria gonorrhoea, Chlamydia trachomatis, Hepatitis B virus (HBV), HIV and, if found indicated by the examining doctor, also for bacterial vaginosis . Those screened are offered prophylactic treatment for Chlamydia trachomatis without awaiting the test result. Prophylactic immunization against HBV and post-exposure prophylaxis for HIV are however considered on a case-to-case basis and so is a prophylactic treatment against other STIs.

Results

In 2001 a total of 250 cases of female sexual assault victims attended the national centre in Copenhagen. More than 50% of the victims were under the age of 25 years. Approximately 90% of the women were screened for STIs. Screening results related to the day of attendance after the sexual assault, follow up rate, indications of and number that received any sort of STI treatment will be presented. Draft national guidelines will be discussed in the light of a literature review on STIs in sexual assault victims.

Redesigning care for improved access using the breakthrough model: Experiences from a university hospital outpatient gynaecological setting

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Context: Gynaecological outpatient department of a university hospital. On a daily basis, the staff consists of 2 gynaecologists, 2 residents, 11 nurses and 12 secretaries. Approximately 10500 visits per year are accomplished.

Problem: Due to increasing waiting time, the need to improve the efficiency of the department with focus on increasing access and shortening or abolishing waiting was evident.

Key measures for improvement: Waiting time as measured by the number of patients waiting for consultation. The demand for consultations each day was measured and matched in relation to the total capacity for such consultations.

Methods: Patients waiting for admission were either scheduled by the gynaecologist, referred by letter from a primary care consultant or scheduled for an appointment by telephone consultation. Waiting time and number of patients waiting were counted on a monthly basis.

Strategy for change: Using the breakthrough model with Plan-Do-Study-Act cycles for guidance, the team decided to increase access by increasing staff during the most busy hours of the day. The list of patients waiting for visits was scrutinised critically by a senior nurse together with a gynaecologist. Extra information was gathered by telephone contact with the patient, when necessary. The list was optimised with regard to the actual need of consultation for each patient. Extra office time for drop-in visits during evenings was offered during a limited period. These steps were not allowed to increase costs, and were obtained by using existing resources. The length of each consultation and time for admitting patients were optimised. The competence and capabilities of each staff member were continuously taken into account to maximise efficiency. Nurses were e.g. allowed to treat uncomplicated vaginal candidiasis.

Effects of change: The staff was able to concentrate on other duties after the waiting time had been reduced through increased access during parts of the day. Thus, the working environment was improved radically for the staff. Before the present quality improvement project in January 2000, 2500 patients were scheduled for visits. In June 2001, 522 patients were on this list, a reduction by 79%.

Conclusion: The radical improvement was not thought possible before the project started. For the patient, waiting time and access were the immediate benefits. Secondary effects on the staff were both unexpected and very important. Staff such as nurses and secretaries was taking active part in redesigning care, tasks that these groups never had been offered previously. The present work is an ongoing project with an open-access office as a final goal.

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Systemic and local mechanisms of immunoregulation in normal pregnancy

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Introduction:
The immune paradox of pregnancy is still not elucidated and immune mechanisms facilitating it´s success are of great interest. The main hypothesis of Tom Wegman about the shift to the potentially less harmful Th2 type of immune response does not explain all facts. The aim of the study was to define the peculiarities of maternal immune response at systemic and local level in depend-ence to the stage of normal gestation.

Methods:
Peripheral and decidual lymphocyte populations and their activation parameters were estimated by flow cytometry method. Cytokine profile was assessed in 24-hour unstimulated lymphocytes culture supernatants by ELISA.

Results:
Early pregnancy at systemic level was characterized by the enhanced expression of activation markers, pronounced increase of the amount of virgin, especially CD4+ cells, and decrease of committed lymphocytes, predominantly among T-helpers, augmented level of spontaneous synthesis of IL-2 and of proinflammatory cytokines except IL-1beta. On the contrary, in late pregnancy the decrease of the amount of naïve and increase of committed lymphocytes more pronounced in the pool of CTL, enhanced spontaneous synthesis of both IL-2 and IFN gamma and diminished production of proinflammatory cytokines was shown. At the local level the onset of pregnancy was characterized by the increase of CD16-CD56+ NK and cell activation. At the end of gestation there was shift in NK subpopulations and CD16+ cells became dominating. Early decidua contained lowered amount of naive lymphocytes, especially among CTL but the amount of committed CD4+ and CD8+ lymphocytes was sharply decreased. Towards the end of gestation the level of naïve cell increased due to CD4+ and CD8+ lymphocytes, the quantity of committed T-helpers and CTL did not differ from that in the 1 trimester. At the local level in early pregnancy the production of IFN gamma and IL-2 was practically the same as in nonpregnant women and proinflammatory cytokines have dramatically fallen, but towards the end of pregnancy the sharp rise in IFN gamma synthesis and marked increase in proinflammatory cytokine production was observed but the level of IL-2 and TNF-alpha synthesis di-minished.

Conclusions:
It seems that regulation of maternal immune response at early and late stages of ges-tation at systemic and local level is different. There is no precise evidence in favor of local Th2 shift in early normal pregnancy but late pregnancy can be characterized by local Th1 shift. Activation of innate system seems to be essential in the first trimester of pregnancy at systemic level and in the end of pregnancy at the local level.

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Diagnostic criteria and procedures for pre-eclampsia currently used in obstetrical departments in Denmark

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Background:
Our aims were to identify the diagnostic procedures and criteria for pre-eclampsia used in Danish departments of gynecology and obstetrics, and to identify the level of obstetrical training of persons responsible for coding of records submitted to the National Patient Registry. In Denmark we have two obstetric guidelines with different cut-off limits regarding pre-eclampsia.

Methods:
A structured questionnaire was sent to all obstetrical departments with questions about the qualifications of persons doing the coding work, and about the department´s criteria for pre-eclampsia. Furthermore a diagnosis was requested for three case stories.

Results:
Thirty-three out of 34 departments (97%) returned the questionnaire.
The reporters of pregnancy diagnoses to the National Patient Registry differed widely in training. Concerning the pathological cases the range in the different departments was from only specialists with a long experience in obstetrics to secretaries reporting up to 50% of the cases. In 27% of the departments specialists reported all pregnancies. Answers regarding the cut off limits of blood pressure and protein loss used to diagnose pre-eclampsia showed large differences. Only nine percent of the departments seemed to follow one of the two Danish guidelines on obstetric coding. Regarding the reported criteria from each department, there was little correlation with the diagnoses the departments gave the three case stories.

Conclusion:
Even in a small country like Denmark with only 34 obstetric departments, there was little consensus on the diagnostic criteria for pre-eclampsia. The findings have implications on how to interpret data regarding pre-eclampsia reported to the National Patient Registry.

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Uterine artery blood flow in hypertensive disorders of pregnancy

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The aim of the study: To compare the uterine Doppler velocimetry parameters and pregnancy outcomes in the groups of pregnancies complicated with primary and pregnancy induced hypertension or pre-eclampsia.
The methods: Doppler velocimetry was performed in pregnancies complicated with primary (PH) and pregnancy induced hypertension (PIH) or pre-eclampsia (P) for the patients of High-risk pregnancy unit of Kaunas University of Medicine Hospital. In cases when the velocimetry indices were higher than normal values for the gestation or the early diastolic notch was present, the uterine blood flow was evaluated as abnormal.
The results: Since the June of 2000 06 until the August of 2001 Doppler velocimetry was performed for 67 women with PIH, 21 with mild P and 25 with severe P. During the same period the blood flow of the uterine arteries was evaluated for 44 women with PH, 9 of them developed superimposed pregnancy induced hypertension or pre-eclampsia.

	Bil.abn.BFVW	Monolat.abn.BFVW	Norm.BFVW
PIH	7,46% (5)	35,72% (26)	56,82% (36)
PH	27,27% (12)	31,81% (14)	40,91% (18)
Mild P	28,57% (6)	38,1% (8)	33,33% (7)
Sev. P	40,0% (10)	36,0% (8)	24,0 % (6)

The difference in proportion of bilaterally abnormal and bilaterally normal velocimetric indices in uterine arteries is statistically significant comparing P and PIH groups. The bilateral changes are significantly more common in P group and bilaterally normal indices are significantly more common in PIH group ($p<0,05$).
In the cases with bilateral increase of impedance to blood flow in uterine arteries the mean birth weight of the new-borns (2285± 142,8) differ significantly from the cases with bilaterally normal indices (3676±412,7g.), $p<0.05$.
In the group of pregnant women with the PH 46,67% of cases the RI of placental site uterine artery was higher than non-placental site, 40% RI of placental site uterine artery was lower, 13% the RI values were equal on both sides. After reduction of the pregnancies when superimposed PIH or P occurred, RI of the placental site was higher 67,86%, lower 21,43% and equal in both sides 10,71% of cases.
The higher RI of the placental site uterine artery was found much more frequently in the group of PH than in PIH group ($p<0,05$, PPV-76%, NPV-94%, sensitivity-76%, specificity-94%). In cases of PH superimposed with P or PIH, RI of the uterine artery of placental site was lower than in non-placental site, like in cases of pure PIH or P.
Conclusions: 1. The higher RI index in placental site uterine artery was found the specific for primary hypertension. 2. The bilaterally abnormal velocimetric indices were found more rarely and in contrary bilaterally normal indices were more common in pregnancy induced hypertension group comparing with the cases of pre-eclampsia ($p<0,05$). 3. The birth weight of the new-borns was lower in the group of women with the bilateral abnormal RI indices ($p<0,05$) comparing with bilaterally normal impedance in uterine arteries.

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Using fetal nuchal translucency measurement in a high-risk population

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Objectives To determine the value of fetal nuchal translucency (NT) measurement for the detection of fetal malformations and aneuploidies in a high-risk population.
Design Population based cohort study.
Setting Vilnius University Women Clinic.
Methods The fetal NT was measured with a transvaginal transuder. These women were at a high risk of genetic pathology: were 35 years old or more at the time of delivery, had a first trimester bleeding, had had a previous Down syndrome or other genetic disorder pregnancy. Fetal genotype was not determined antenatally. The newborns were examined to reveal any possibility of genetic syndrome. The fetal nuchal translucency norm we accepted was less than 3 mm.
Results 113 women with a high risk of genetic pathology, who booked in Vilnius University Women Clinic for delivery were examined between tenth and thirteenth week of gestation. The study was carried out prospectively between October 1999 and March 2001. The mean value of NT was 1,853 mm (0,9-2,5 mm). There were no cases of nuchal translucency measurement of more than 3 mm. All babies were born in term and healthy.
Conclusions The normal NT value at 10-13th weeks of gestation in a population with a high risk of genetic disorders provides a good prognostic outcome to the newborn.

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Development and characterization of an Eliza method for ADAM 12-S in serum from pregnant women

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Introduction:
ADAM 12 (A Disintegrin And Metalloprotease) exists in two alternatively spliced forms:the classical membranebound ADAM 12-L (long) and the shorter secreted ADAM 12-S (short)(Gilpin et al J BIOL Chem 273:157, 1998). ADAM 12 has cell adhesion, protease, and signalling properties. One important substrate for the ADAM 12-S protease is IGFBP-3 and -5. Since ADAM 12 is present in pregnancy serum but not in non-pregnancy serum, ADAM 12-S has been implicated as one of the proteases degrading IGFBP-3 in pregnancy serum (Shi et al J Biol Chem 275:18574-18580, 2000, Loechel et al Biochem Biophys Res Commun 278:51, 2000).
Method:
We have developed an ELISA for measuring serum concentrations of ADAM 12-S. Purified recombinant ADAM 12-S was used for standardization. Coating and detection steps were made using two different monoclonal antibodies addressing different epitopes on ADAM 12-S.
Results:
The concentration of ADAM 12-S can be quantitated in serum from women at different times of pregnancy.
Discussion:
Normal range values of ADAM 12-S throughout pregnancy and potential clinical use are under investigation.

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Insulin receptor substrate (IRS) -1, IRS-2, insulin receptor (IR), insulin like growth factor-I receptor(IGF-IR) and PI3-kinase expression in placenta from normal and gestational diabetes pregnancy

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Normal pregnancy is associated with hyperinsulinemia and decline in insulin sensitivity. The insulin resistance is more pronounced in GDM. Placental glucose metabolism is known to differ from other organs. The major role of insulin in the placenta is to stimulate mitogenic rather than metabolic signals. In GDM the number of IR decreases in human placenta. PI 3-kinase is one of the key signal transducers in insulin-stimulated glucose uptake. The activation of the mitogen activated protein (MAP)-kinase pathway is more associated with gene expression and cell growth. In NIDDM IRS-2 becomes the main docking protein in adipocytes. Binding of PI3-kinase to IRS-2 requires a higher insulin concentration than that needed for binding to IRS-1 In the present study expression of IR, IGF-IR, IRS-1 and -2 and PI-3 kinase was studied from normal pregnancies and GDM to find out if the balance between PI 3-kinase and MAP kinase signal pathways is altered in the cells in the placenta. The Institutional Review Board at the University of Turku approved the study design. All patients gave informed consent. Pieces of placenta were taken from 11 patients with GDM and from 8 controls. Immunostaining was performed to frozen sections by the avidin-biotin complex method. Western blot was made to confirm the molecular weights and intensities. There was no statistically significant difference with Fishers exact test in the localisation of the antigens between normal and GDM pregnancy. All the antibodies stained positive in the trophoblastic specialisations, trophoblast islets containing fibrinoid material and the Nitabuch´s striae as well as in the amniotic membrane. IRS-1 antibody stained positive in the stroma of the villi and the vascular walls. IR: in the syncytiotrofoblast, syncytial knots. IRS-2: in the stroma of the villi, in the endothelium of the villous capillaries and in the muscle layers in larger veins. IGF-IR: in the stroma of the villi, all the large veins and some of the capillaries. PI-3 kinase: in the villous stroma and large veins. The present results show that IRS-1 expression is decreased and IRS-2 expression is enhanced in the placenta of patients with GDM, also the number of insulin receptors decreases in placenta leading to hyperinsulinemia. Thus our results agree with earlier reports that in the placenta the glucose metabolism is significantly altered in gestational diabetes. It remains to be studied, how this change in balance between IRS-1 and IRS-2 affects the direction of signals from the insulin receptor in regard to the PI-3 kinase and the MAP kinase pathways.

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Maternal obstetric neuropathies in lower extremities: Incidence, localization,etiology and prognosis

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OBJECTIVES: To determine the frequency, etiology, clinical and diagnostic features of maternal neuropathies in the lower extremities in a general obstetric population, presenting during childbirth.

SUBJECTS AND METHOD: The cases were identified by reviewing all neurological consultations from the department of Obstetrics and Gynecology in Iceland University Hospital during a 25 month period. A further analysis included a careful assessment of patient charts, and when necessary further information was obtained by an interview and physical examination. During the study period there were 5902 deliveries in this hospital, approximately 75% of all deliveries in the country.

RESULTS: A total of 11 women with a peripheral neuropathy were identified or 1.8/1000 deliveries. Motor and sensory deficits were in 8/11 cases consistent with a unilateral L5 radiculopathy, in 4 cases combined with S1 symptomatology. The most distinguishing symptoms of the 2 cases related to anesthesia were unpleasant paresthesia, in those cases the prognosis was worse. The cause was determined as a compression of the lumbosacral plexus during labour in 4 cases, in 2 cases compression of other peripheral nerves, in 2 cases epidural/spinal anesthesia, in 1 case a herniated intervertebral disc, and in 2 cases the cause was left undetermined. The causal frequency of neuropathies related to labour was thus 4/5902 (0.7/1000) and to anesthesia 2/2645 (0.8/1000).

CONCLUSION: Maternal neurological deficits in the lower extremities are uncommon but important complications of labour and delivery. Compression during labour seems to be a more common cause than spinal/epidural anesthesia but we discuss difficulties, especially during prologned labour, in determining their specific causal significance.

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Alcohol in pregnancy: Attitudes and knowledge among pregnant danish women 1998 and 2000

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Introduction: During the 1990s most countries in the Western world officially recommended pregnant women to abstain from alcohol. In Denmark, the recommendation was described in an official leaflet from the Danish National Board of Health (DNBH), and the DNBH guidelines for antenatal care mention alcohol as an item that should be addressed by both doctors and midwives. In 1999 the recommendation was adjusted: Avoid alcohol in pregnancy if possible; If you drink, drink no more than 1 drink per day; and do not drink every day. However, information about the potential harmful effects of alcohol in pregnancy does not necessarily equate to understanding, and information and knowledge may not be associated with pregnant women´s own attitudes towards drinking.
Methods: From October till December 1998 we interviewed 439 (92%) Danish speaking pregnant women, and from March till August 2000 we interviewed 1895 (92%) pregnant women referred for routine antenatal care at their first visit at 15 to 16 weeks of gestation. The women were interviewed about their attitudes towards, beliefs and knowledge about drinking in pregnancy. Questions were also asked about information on alcohol provided to the women.
Results: In 1998, 76% of the women considered some alcohol intake in pregnancy acceptable, mostly on a weekly level. Binge drinking, on the other hand, was considered harmful by 85%. These attitudes were not associated with knowledge about the official recommendation, or whether the woman had talked to a doctor or midwife about alcohol in pregnancy. Only 21% were aware of the official recommendation from the DNBH. Most of the women had received information on alcohol from the mass media or relatives, but most women believed that information about alcohol in pregnancy could best be communicated to them by health personnel. Still, only one third had discussed alcohol with a doctor or a midwife, but these women had mostly been advised that some alcohol intake was all right. Similar proportions and associations were found in 2000.
Conclusions: Most of the women considered some alcohol intake in pregnancy acceptable, mostly on a weekly level, and their attitudes were independent of their knowledge about the subject. Most of the women had not been informed about alcohol in pregnancy. It seems that the mere existence of an official recommendation concerning alcohol in pregnancy, and the production of an official leaflet from the DNBH as well as DNBH guidelines for antenatal care mentioning alcohol as an item that should be addressed by both doctors and midwives, has not been enough to get the information across to the pregnant women.

Use of alcohol among pregnant danish women 1998

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Introduction: During the 1990s most countries in the Western world officially recommended pregnant women to abstain from alcohol. We describe the frequency and pattern of alcohol consumption during early pregnancy among pregnant Danish women.
Methods: From October till December 1998 we interviewed 432 (90%) Danish speaking pregnant women referred to the Midwife Centre in Aarhus, Denmark, for routine antenatal care at their first visit at 15 to 16 weeks of gestation. The women were interviewed about average alcohol intake before pregnancy, binge drinking (intake of 5 or more drinks on a single occasion). They subsequently filled in a two week diary on current alcohol intake.
Results: Nearly 90% of the women reduced their alcohol intake, when they became pregnant. Ninety two percent of women reported a maximum intake of three drinks/week, and only 1% exceeded the recommendations of average alcohol intake of six drinks/week. Nevertheless, 25% exceeded the recommended maximum daily intake of one drink in the second trimester. The proportion of women reporting 1 or more binge episodes was highest during the early weeks of pregnancy. The cumulative proportion of women reporting 1 or more binge episodes in early pregnancy was 50%, if calculated from the last menstrual period, and 40% if calculated from the time of ovulation. Median and mean alcohol intake before and during pregnancy increased with increasing number of binge episodes during pregnancy. Binge drinkers tended to be smokers and primiparous women.
Conclusions: Consumption peaks were a major problem in the first and second trimester. Midwives and doctors should pay special attention to binge drinking, when inquiring about alcohol consumption and providing information on alcohol to pregnant women. Since binge drinkers were more likely to be primiparous, information on the potentially harmful effects of binge drinking should be included in information material and campaigns on alcohol intake in general.

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Violence against pregnant women will remain hidden as long as no direct questions are asked

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OBJECTIVES: the aims of this study were to assess the experience, knowledge, attitudes and routines regarding violence against pregnant women among midwives working at antenatal clinics in the county of Västerbotten, northern Sweden.

DESIGN: five qualitative research interviews with midwives were conducted. In addition, questionnaires were sent out to all midwives at the antenatal clinics in the county.

FINDINGS: the midwives had knowledge and sensitive ears for pregnant women and their needs, but still the midwives rarely disclosed the occurrence of violence. Symptoms and signals of abuse may vary and are not easily discovered by an outsider. Among registered pregnant women at the antenatal clinic, the midwives themselves roughly estimated the frequency of known cases of physical and sexual abuse before and during the current pregnancy to 2.3 and 0.6 % respectively for the preceding calendar year. The local antenatal care program provided no guidelines regarding response to violence, no instruments for disclosure and no directions about support when confronted with an abused pregnant woman. The midwife mostly did not ask any questions if she was merely suspicious and lacked any strong supporting evidence. Referring to the inquiry, the midwives were however positive towards asking every pregnant woman about abuse in about the same way as other public health issues already incorporated in the records.

CONCLUSION: the midwives in this study were probably disclosing only a fraction of the abused women. Violence against pregnant women will most likely remain undisclosed as long as the issue of violence is not included in the national recommendations or in the local antenatal care program.

IMPLICATIONS FOR PRACTICE: there should be specific written recommendations in the national antenatal care program to guide and support the midwives in asking all pregnant women questions about violence. To obtain an adequate and optimal assessment and intervention at the antenatal clinic, the midwives need education and training together with a supportive professional network for both themselves and the abused women.

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Prevalence of psychiatric disorders among pregnant women. A population-based study

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Objective:
This study was undertaken to determine the point prevalence of psychiatric disorders in a population-based sample of pregnant women.
Study design:
Participants were pregnant women attending ultrasound screening at two obstetric clinics in Northern Sweden between October 1st, 2000 and September 30th, 2001. The Primary Care Evaluation of Mood Disorders (PRIME-MD) was used as diagnostic tool for evaluating mood, anxiety, and eating disorders.
Results:
Overall 1734 pregnant women filled in the PRIME-MD patient questionnaire. Psychiatric disorders were present in 14.1% of the women. Mood disorders were most common; major depression was prevalent in 3.3% of women and minor depression in 6.9% of women. Anxiety disorders were also common and were encountered in 6.6% of pregnant women. Compared with undiagnosed women, pregnant women with any psychiatric disorder reported significantly more somatic symptoms such as back pain, abdominal pain, nausea, fatigue and insomnia.
Conclusions:
Depression and anxiety disorders are common among pregnant women and are often accompanied by somatic symptoms.

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Synthesis of small proteoglycans and hyaluronan in human fetal membranes

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Aims:
The aim of this study was to evaluate the synthesis of small proteoglycans and hyaluronan in human fetal membranes.
Methods:
Human fetal membranes were obtained from elective caesarean section from week 38 to 39 of gestational age. Biopsies were taken from the mid-zone and from the cervical membrane, which is the membrane overlaying the internal os of the cervix. The samples were incubated in Earles medium in the presence of 35sulphate and 3H-glucosamine for various periods of time. The biopsies were divided in the amnion and the chorion, homogenized and extracted in 4 M guanidinium chloride, pH 5.8. Newly synthesized proteoglycans and hyaluronan were isolated by ion-exhange chromatography and quantified (CPM). The distribution of decorin and biglycan were evaluated by SDS-PAGE (4-12%) and analysed with a molecular phosphor imager system.
Results: In the amnion and the chorion a linear increase in the incorporation of 35sulphate and 3H-glucosamine were observed during 6 hours of incubation. No signs of degradated proteoglycans were seen. In the chorion a 10- to 15-fold increase in the 35S-labelling per mg wet weight was seen as compared with that of the amnion corresponding to a higher turnover or synthesis of proteoglycans in the chorion. In addition, a massive synthesis of hyaluronan was found in the chorion. However, a tendency towards a decreased turnover or synthesis of both proteoglycans and hyaluronan was noted at the cervical membrane compared with the midzone samples. In the amnion the dominating proteoglycan synthesized was decorin whereas the chorion was dominated by biglycan.

Conclusions:
The distribution of the synthesized proteoglycans in the fetal membranes corresponds to the biomechanical properties of the amnion and the chorion. The amnion is the strengh-bearing component of the fetal membranes dominated by decorin and collagen. The decreased turnover of both hyaluronan and proteoglycans at the cervical membrane confirm that the extracellular matrix in this area is compact and stable during pregnancy maintaining the integrity of the fetal membrane right until labor protecting the fetus in uterus. Further studies are in progress and will be presented at the meeting.

Matrix metalloproteinases and their inhibitors in the cervical mucus plug - an in vitro study

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Introduction: The cervical mucus plug is a dynamic antibacterial structure, as by a functional closure of the cervical canal during pregnancy, is regarded as a part of the competent local defense mechanism, that protects the feto-maternal unit from ascending infections. There exists strong evidence for the association between intrauterine infection and preterm labor and delivery. The matrix metalloproteinases and their inhibitors (TIMPs) are found in the fetal membranes and the amniotic fluid, where they have different functions. The metalloproteases remodel the collagen in the cervix and soften it, and they are implicated in the mechanisms of normal labor, rupture of the membranes and intrauterine infection.
To evaluate the presence of matrix metalloproteinases and their inhibitors in the cervical mucus plug (CMP) of pregnant women.
Methods: Cervical mucus plugs from 17 healthy women at delivery were analyzed by five different assays: A; zymography to detect gelatinases (MMP-2 and MMP-9) and caseinolytic activity (MMP-1, MMP-8), B; reverse zymography for detection of TIMP-activity (TIMP-1, 2, 3 and 4), C; Immunoblot for specific identification of TIMP-1-4, MMP-8 and MMP-9, D; triple-helical collagen degradation to reveal collagenase activity (MMP-1, MMP-8), and finally, E; enzyme-linked immunosorbent assay (ELISA) for quantification of the total amounts of the specific enzymes and their inhibitors.
Results: Gelatin zymography proved the presence of large amounts of MMP-2 and MMP-9. Reverse zymography showed that TIMPs are detectable in the cervical mucus plug, and immunoblotting supported these findings. Triple-helical collagen degradation demonstrated collagenase activity persistent with the finding of MMP-8 by immunoblot. Quantification by ELISA confirmed that MMP-2, MMP-8 MMP-9 and TIMP-1 are present in the cervical mucus plug.
Conclusion: Matrix metalloproteinases and their inhibitors were detected in 17 cervical mucus plugs using five different assays. Our results showed no significant difference between plugs obtained before and after rupture of the membranes, and this observation rules out the possibility that components of the plug should arise from contamination with amniotic fluid. The cervical mucus plug itself proved to contain large amounts of metalloproteinases (MMP-2, MMP-8, MMP-9) and their inhibitors (TIMP-1, 2, 3, 4) with a high degree of inter-patient variation, indicating a potential to degrade fibrous and basement membrane collagen.

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The cervical mucus plug during pregnancy

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Introduction: The majority of pregnancies continue until 37-42 weeks of gestation despite the presence of potentially harmful bacteria in the vagina. This suggests the existence of competent local defence mechanisms, which may include effects of mucosal immune factors, the fetal membranes, and the amniotic fluid.
A presumably important element of the local defence is the cervical mucus plug, which provides a functional closure of the cervical canal during pregnancy. This structure, being shed at the onset of active labor, is known better to midwives than to obstetricians. Whereas other defence elements of the female reproductive tract, including cervical mucous secretions, have been the subject of considerable research, studies of the exact functions of the cervical mucus plug are few. Here we present results of 1) -quantitative analyses of innate and adaptive molecular defence factors and the occurrence of immune cells in cervical mucus plugs collected during natural delivery at term, 2) studies of antimicrobial activity of cervical mucus plugs and plug molecular components in vitro.
Methods: Anti-microbial activity was analysed on agar plate cultures of a broad spectrum of Gram positive and negative bacteria and yeast, using overlay and radial diffusion assays. Levels of anti-microbial peptides were estimated by either semi-quantitative western blotting, lysoplate assay (for lysozyme), or, upon gel electrophoresis, gel overlay assay. Immunoglobulin isotypes (IgA, IgG, and IgM) were quantified by calibrated ELISA. Cells and molecular components of cervical mucus plugs were identified by immunohistochemical.
Results: Donor-dependent inhibition by plugs was observed against several bacteria. In the case of group B streptococci, cervical mucus plugs were inhibitory more than a sample of non-pregnant cervical mucus ($p=0.02$). By semi-quantitative western blotting the following antimicrobial polypeptides were detected in the cervical mucus plug [median (interquartile range)]: lysozyme 660 mg/gram cervical mucus plug (566-940), SLPI 750 mg/g (250-2000), lactoferrin 100 mg/g (30-110), calprotectin 38 mg/g (18-125), neutrophil a-defensins HNP 1-3 12 mg/g (4-20), and epithelial b-defensin HBD-1 1 mg/g (0.63-2.5). Immunoglobulin levels [median (interquartile range)] in mucus plugs were estimated as follows: IgA, 536 mg/ml (343-1,320); IgG, 3270mg/ml (1,285-5,228); IgM, 31 mg/ml (16-53), compared to non-pregnant cervical mucus: IgA, 88 mg/ml (42-232); IgG, 200 mg/ml (31-852); IgM, 13 mg/ml (5.5-62). Histological examination showed infiltration by inflammatory cells (mainly PMN and macrophages) and bacteria in the part facing the vagina, whereas antimicrobial peptides were more evenly distributed.
Conclusions: The cervical mucus plug appears to offer protection of the feto-maternal unit by multiple mechanisms of innate and adaptive immunity.
The antibacterial properties of the cervical mucus plug seem to be augmented compared to those of non-pregnant cervical mucus and could play an important role in host defense against ascending infections during pregnancy.

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Simultaneous bacterial vaginosis and periodontitis among women planning pregnancy

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INTRODUCTON: Multiple infections of the female reproductive tract are associated with preterm birth. Several studies have linked bacterial vaginosis (BV) and preterm birth.
MATERIAL and METHODS: In an ongoing prospective study, women planning pregnancy were examined for BV and periodontitis. We plan to enroll a total of 628 women, including 314 BV+ and 314 BV- women. BV+ women will be randomized to a double-blind placebo-controlled treatment trial with metronidazole. The occurrence of preterm birth will be compared in relation to prepregnancy BV or oral infection. Presently, 186 women (mean age 28.9, SD 5.0 yrs) have been screened. Vaginal smear samples and salivary and serum samples have been obtained and microbiological and immunological analyses have been performed.
RESULTS: BV was diagnosed in 28 (15%) women. Periodontitis was found in 13% of the women, more frequently ($P<0.01$) in BV+ (32%) than in BV- (10%) women. The mean (SD) number of affected tooth surfaces in BV+ and BV- women were 9.4 (22.4) and 8.1 (14.1), respectively. Loss of periodontal attachment occurred at the most coronal part of the root surfaces. As compared to BV- women, BV+ women had significantly higher proportions of deep periodontal pockets (mean (SD): 12.2 (23.9) vs. 7.0 (10.5), $P<0.05$), more frequently had allergies (36% vs. 17%, $P<0.05$), and more often were smokers (29% vs. 15%, $P<0.05$). Age correlated positively with the presence of periodontal disease ($P<0.05$), but not with the presence of BV. Between BV+ and BV- women, no differences were found in the occurrence of caries, susceptibility to infections (2 infections/year), C-reactive protein levels, or salivary antibody levels (IgA and IgG) against periodontal pathogens (Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis).
CONCLUSIONS: Vaginal and oral infections occurred simultaneously in at least 5% of women planning pregnancy. Periodontal disease seem to be overrepresented in women with BV. The preliminary results justify continuation of our prospective study of the causes of preterm birth.

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Chorioamnionitis in preterm delivery is associated with a degradation of proteoglycans and very low hyaluronan concentrations in fetal membranes.

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OBJECTIVE: To determine the concentrations and the integrity of proteoglycans, collagen and hyaluronan, in fetal membranes concerning gestational age, preterm labor, PPROM and chorioamnionitis.
STUDY DESIGN: Human fetal membranes were obtained after delivery at 24 to 33 completed weeks gestation (N=28) and after elective cesarean deliveries in week 34 (N = 4). Severe, histologic chorioamnionitis was identified in 8 patients. Proteoglycan composition and concentration were analyzed using alcian blue precipitation, and SDS-PAGE. The concentration of hyaluronan was estimated by a radioimmunoassay and collagen concentration by determination of the hydroxyproline content.
RESULTS: Increasing gestational age was associated with an increase in the concentration of biglycan in the amnion and a decrease in decorin in both the amnion and the chorion. 1 Preterm delivery complicated by massive chorioamnionitis differed from patients without chorioamnionitis as it was associated with a pronounced degradation of the proteoglycans and an 8-fold decrease in the concentration of hyaluronan. The extracellular matrix of fetal membranes of preterm labor initiated by contractions resembled vaginal delivered fetal membranes at term with high contents of biglycan and hyaluronan and a lower content of decorin. In contrast, the presence of PPROM was associated with a high content of decorin and lower concentrations of biglycan and hyaluronan which was similar to the preterm membranes from elective cesarean deliveries.
CONCLUSION: With increasing gestational age a slow ripening process takes place in the fetal membranes. Massive chorioamnionitis in preterm deliveries induce dramatic changes in the proteoglycans and hyaluronan, which implicates a different labor mechanism in this entity. Two divergent molecular pathways may be of importance in preterm labor and PPROM.

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Perineal ultrasound - an appropriate method for evaluation of cervix during pregnancy

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Design: A blinded crossover study with two examiners performing perineal ultrasounds that measured six distances on the cervix (i.e., proximal width, distal width, functional length, closed length, depth of internal os, width of internal os).
Subjects: 15 women in their second trimester of a single uncomplicated pregnancy.
Objectives: To evaluate the reliability of the perineal ultrasound examination.
Methods: Descriptive statistics and intra- and inter-class correlations.
Results: The cervix could be properly sonographed in the majority of examinations. The interclass coefficient, comparing the results of the two examiners, for proximal diameter was 0.78 and 0.62. The intraclass correlation coefficient, comparing the results of the same examiner, were 0.037 and 0.663, 0.488 and 0.844 respectively
Conclusions: Perineal ultrasound during pregnancy has an acceptable reliability and should be viewed not only as a second best method, but also as a primary alternative for evaluation of the cervix during pregnancy.

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Randomized comparison of nitroglycerine/terbutaline and terbutaline - a pilot study

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Aim: To study the efficacy and safety of nitroglycerine combined with terbutaline for preterm labor.
Subjects and methods: The design was a randomized double-blind control trial. One group received a adhesive bandage containing nitroglycerine (10 mg/24 h), and the other group received a placebo bandage over 48 hours. Both groups received terbutaline iv (5 mg/1000 mL glucose) over 8 hours, with a maximum of 25 mg/min. Inclusion criteria was preterm labor at 23-33 weeks of pregnancy in women who had received 0.25 mg terbutaline subcutaneously and undergone bed rest without effect. Exclusion criteria were membrane rupture: hemorrhage; amnionitis; anemia; heart, pulmonary, or cerebrovascular disease; hypersensitivity to terbutaline; known hypokalemia; and ongoing treatment with NSAIDs. Patients were recruited from September 1998 to December 2000 from the hospitals in the Northern Health Region of Sweden (Sundsvall, Sollefteå, Örnsköldsvik, Östersund, Lycksele, Umeå, Skellefteå, Piteå, Boden/Luleå, and Gällivare). In addition, the hospital of Falun was enrolled for the last year of the study.
Results: Forty-one patients, 0.23% of 17,586 parturients in the catchment area, were recruited for the study. Nineteen received nitroglycerine/terbutaline and 21 received only terbutaline. On very rare occasions during the first year potential study patients were lost for recruitment. The pace of recruitment decreased over time, first year every 5th of those giving birth before 34th pregnancy week had been recruited, second year every 13th Side effects for nitroglycerine/terbutaline and terbutaline, respectively, were headache (8 and 4); heart palpitation (6 and 5); vomiting and nausea (1 and 2); drop in blood pressure (1 and 0). Treatment was discontinued due to side effects for 2 patients in each group. Overall, 2 in each group delivered within 24 hours from the start of treatment, and a further 3 in each group delivered within 48 hours. No statistical significant differences were observed for either side effects or prolongation of gestation.
Conclusion: No advantage to combining nitroglycerine and terbutaline was observed within this sample. The majority receiving nitroglycerine tolerated the drug. Only a minority of women with threatening preterm birth need tocolytic treatment beyond one injection of terbutaline and bed rest.

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Why is the cesarean sectio rate increasing?

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Background: Cesarean sectio (C/S) rates have increased in many countries during the last few years. At Söder hospital, a large clinical service, the cesarean sectio rate increased with 4% between 1994 and 1999.
Objective: To investigate reasons for the increasing cesarean sectio rate.
Material and Method: All case notes from cesarean sectio cases in our hospital during 1994 and 1999 have been scrutinized, focusing on whether they were elective or emergencies and also the indications for the intervention.
Results: In 1994 C/S were carried out in 479 out of 3.663 deliveries (13.1%), and the rate increased to 17.1% (788/4.608) in 1999 ($p<0.001$). Out of these 311 (8.5%) were emergencies in 1994, which incerased to (10.3%) in 1999 ($p=0.006$). Corresponding figures for elective ones were 168 (4.6%) and 314 (6.8%) ($p<0.001$), respectively. The four largest groups of indications were fetal distress, which was present in 23.0% and 26.2% during the two years ($p=0.22$), dystocia 18.7% and 17.9% ($p=0.78$), abnormal pelvis/abnormal presentation 28.8% and 17.7% ($p<0.001$) and psychosocial 8.3% and 16.2% ($p=0.0001$), respectively.
Conclusion: Between 1994 and 1999 a 4% increase in C/S rate was found in our institution. There were significant increases both for elective and emergency ones. A significant increase was found for psychosocial indication and a decrease when abnormal pelvis/presentation was the indication. It seems likely elective ones have contributed more to the increase, but that the trend is pushing towards a "lower threshold" for all C/S indications.

Danish obstetricians and gynaecologists personal preference and general attitude to elective caesarean section for maternal request.A nation-wide postal survey.

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When originally introduced, caesarean section was only performed when medical or obstetrical complications occurred. But throughout the last decade, the number of indications has gradually increased. This is primarily as a result of the increasing safety of the procedure. Maternal request for elective caesarean section without any medical or obstetrical indication has been added to the list of indications. It has been presented in the public as well as the medical literature as a basic maternal right, as long as the women was fully informed about the risk.

The present nation wide study assess Danish Obstetricians and Gynaecologists personal preference and general attitude towards elective caesarean section for maternal request in uncomplicated single cephalic pregnancies at term. 455 Obstetricians and Gynaecologists identified in the records of the Danish Society of Obstetrics and Gynaecology as of January 2000, were send an anonymous postal questionnaire asking about personal preference on the mode of delivery, and their general attitude towards elective caesarean section for maternal request. Respondent rate was 88,1%. One-point-four percent of Danish specialists in Obstetric and Gynaecology would prefer and elective caesarean section with foetal weight estimation of 3.0 kilograms at 37 gestation weeks. This rose to 22.5% when the foetal weight estimation was 4.5 kilograms at 37 weeks. The main reasons given for preferring abdominal deliveries were the risk to the foetus, risks of perineal injury and urinary and anal incontinence. Thirty-seven-point-six percent of Danish specialists in Obstetrics and Gynaecology agreed with a woman's right to have an elective caesarean section for maternal request without any medical indication. Obstetricians and Gynaecologists who had experienced a non-instrumental vaginal delivery themselves or practised as private Gynaecologist only were less likely to agree with the woman's right to elective caesarean section for maternal request. The vast majority of Danish Obstetricians and Gynaecologists would personally prefer vaginal delivery in uncomplicated pregnancies, but nearly 40 % agree with the woman's right to request a caesarean section. Obstetricians and Gynaecologists who had a personal experience of non-instrumental vaginal delivery are less likely to agree with a request for caesarean section, but a personal history of either a previous operative vaginal delivery, elective or emergency caesarean section does not affect their agreement with a request.

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The outcome of the 5th to 9th caesarean section

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Introduction Little is known about clinical conditions before and after operations and operative outcome in patients with caesarean sections (CS) repeated several times. The aim of this study was to evaluate the complication rate and operative findings in patients who have had at least five CSs.

Methods Over a period of 26 years, 150 CS were performed in 23 women (median 6/woman). The outcome of the 5th - 9th CS was compared with ordinary caesarean sections in the clinic.

Results No differences in perinatal outcome, major perioperative complications or postoperative complications existed between the groups. The majority of the 5th to 9th CSs were performed electively. The gestational length in this group was slightly shorter than that in the control patients. A thin or fenestrated isthmic myometrial layer was observed in 48 % of women with five or more previous CSs. The majority of these women had abdominal pains at late pregnancy. The incidence of placental complications did not increase with an increasing number of CSs.

Conclusion The outcome of a multiply repeated CS does not differ from that of an ordinary CS, if the operation is performed electively before the onset of labour contractions. No definitive upper limit for the number of CSs per individual woman can be given.

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Postoperative cesarean delivery infection morbidity in TUH, years 1995 and 2000 -before and during the routine use of profylactic antibiotics

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In year 2000, in order to reduce postoperative infections, we started to use intraoperative i.v. kefuroxime 1,5 mg as a profylaxis in cesarean sections in all cases where fetal membranes were ruptured or the labor was ongoing before the operation. Formerly antibiotics were given only in selected cases of increased risk of infection.

The wide use of large spectrum antibiotics carries well known risks, causes extra work and increases economic load. Thus, suspecting that the routine profylactic use of antibiotics is not necessarily beneficious, we did the following study.

As material we looked through all cesarean sections in single pregnancies in the year 1995 and 2000 (N 936)and noticed that infection morbidity in emergency cesarean deliveries reduced: wound infections from 4,4 to 2,5 %, urinary infections from 2 to 0,4 %, endometritis from 2,0 to 1,6 %, but in 1995 there were no septic infections as oppose to two cases in 2000.

At the same time, however, infection morbidity reduced in elective operations, in which no antibiotics were used: wound infections from 5 to 3,6 %, septic infections from 0,5 to 0,4%. Urinary infections increased from 2,3 to 2,7% and the incidence of endometritis stayed the same 0,9%.

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My difficulties during delivery will mark me for life
A case - referent study of prolonged labour

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Background: Prolonged labour, or dystocia, is a common delivery complication and causing very often a negative birth experience.
This study aimed to analyse and describe differences between women's experiences and perceptions of childbirth following prolonged labour or normal.

Method: Using a case -referent design, eighty-four women who had prolonged labour with assisted vaginal or abdominal delivery were included, as well as 171 controls who delivered following normal labour at three hospitals in northern Sweden.
All participants had given singleton live birth to their first child with spontaneous labour after or more than 37 completed weeks' pregnancy.
Participants completed a questionnaire-included question on the participants' background, their experience of childbirth, support and pain alleviation during labour, as well as previous family relationships, and childhood experiences.

Results: Women with prolonged labour had a negative experience of birthing more often (34%), than did women who had a normal labour (4%), ($P<0.05$).
Cases agreed significantly more than the referents with the statements, "I almost went into a panic because I didn't know what was happening" (OR 3.7, 95% CI 1.1-13.3), "Pain relief during the delivery saved me" (OR 4.5, 95% CI 1.9-11.1) and "My difficulties during the delivery will mark me for life" (OR 12.4, 95% CI 4.4-35.9), but there were no differences between the cases and referents regarding experiences of support from the midwife or the child's father.
Conclusions: Prolonged labour poses a hazard of negative birth experience and a challenge for care and treatment of the women concerned, both intra-partum and post-partum.

Traumatic experience with vacuum extraction delivery is associated with insufficient patient support

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INTRODUCTION:
Operative delivery with either emergency cesarean section (CS) or vacuum extraction (VE) maybe a traumatic experience for some parturients. VE in the first delivery is among those factors leading to an increased demand of elective CS. Except the labor itself, there are many predisposing psychosocial factors during antenatal training that can influence the experience of birth.
The aims of this study were to find out how many of the women delivering with VE experienced birthgiving as traumatic, and disclose factors before or during labor associated with traumatic experience.

METHODS:
A questionary was filled by 204 women 5 days after giving birth. All of them had a VE delivery for different reasons.
We asked for obstetrical history, previous hospital experiences and training for labor during pregnancy. Experiences of pain relief and sufficiency of information and support given by the delivery ward staff were asked for, separately at different stages of labor and after delivery.
The study was approved by the local ethical committee.
The delivery was considered as traumatic if at least one of the following statements was true:
1)"I´m afraid I can´t get my bad delivery experience out of my mind"
2)"If I shall deliver again the only choice for me is CS"
3)"I´m deeply shocked and disappointed with my delivery".
Associations of different backround and intrapartum factors with a traumatic experience were sought by chi square -test.

RESULTS:
21% of our study population had a traumatic delivery experience, as defined as above. However, only 6% of the women felt that CS would appear the only choice for them in the possible next pregnancy.
The factor most strongly associated with a traumatic experience and a positive answer to all three questions was the feeling of not being heard during delivery. Other factors strongly associated with a negative experience ($p<0.001$) were insufficient support by the midwife during the second stage of labor, insufficient support by the obstetrician both during the first and second stages of labor and insufficient patient support immediately and later after the delivery.
The proportions of epidural and paracervical blockades didn´t differ within the groups, but the parturients with a negative experience reported somewhat more insufficient pain relief. Of prelabor factors, previous negative hospital experience, insufficient or unrealistic prelabor class training or previous temporary wishes for CS were somewhat ($p<0.05$) associated with a negative experience.

CONCLUSIONS:
It´s very important to support the mother during labor, especially during the second stage, both by the doctor and the midwife. This is especially true if the mother has previously expressed bad experiences with hospitals or wishes for CS. The mother needs to be an active participient in delivery. Immediate and later discussions after VE birth are useful in order to prevent or reduce traumatic delivery experiences.

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Maternal health care - improving access in Maputo

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Until 2000, there was only one referral maternity hospital in Maputo, Mozambique, despite having a catchment area of more than 1.5 millon people. Hospital Geral Jose macamo was chosen to be upgraded as a second emergency and comprehensive maternity hospital, aided by UNFPA and NORAD. Major investments were installation of spesifically assigned operating theatres, renovation of wards, institutionalization of ward routines, employment of nurse-midwives and a few senior OB/GYN specialists, and procurement of consumables. On April 1, 2000, 24 hour emergency obstetric services were launched. An operations research project has demonstrated considerable quality improvements in services given, but due to increased activities, the number of complications seen also went up considerably. The admision rate went up from 400/month to more than 1000/month during a few months only. The added cost of each delivery in this hospital amounts to ca. 10 US dollars per delivery. The hospital does now also train service providers and students. The main reason for the large increase in admissions are, according to patients, that they recieve technically good services and believe they will survive delivery. The presentation will show indicators of the rapid changes in maternity access in the hospital and the province, and demonstrate some major challenges in delivering good maternity services in a very poor country.

Pregnancy and hereditary angio-oedema - Case report

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INTRODUCTION

Hereditary angio-oedema is due to a deficiency of C1 esterase inhibitor. Inheritance follows a dominant autosomal pattern. Lack of sufficient quantities of functional protein results in episodic attacks of oedema, which characteristically last between 12 and 24 hour, are not itchy, and are not associated with urticaria. These episodes usually affect the subcutaneous tissues but may involve the bowel, resulting in abdominal pain, or rarely produce a potentially fatal laryngeal oedema. Though some attacks are triggered by a known factor, such as dental extraction or trauma, many have no obvious predisposing cause.

CASE DESCRIPTION

A 17-year-old patient was referred by her family doctor for her first pregnancy and hereditary angio-oedema at gestation 17 weeks. Her father has a severe form of disease with relatively frequent episodes including repeated laryngeal oedema. Her younger sister did not experience episodes until now. She has had episodes of moderate swelling on her limbs 2-3 times per year from age of 14. The C1 esterase inhibitor activity was determined one year prior to current pregnancy; it was 35% (normal over 67%).
A C1 esterase inhibitor preparation, Cetor ® (Sanquin, CLB, Amsterdam) was ordered via Finnish Red Cross for the case if any emergency occurs. The pregnancy was uneventful. As pain and trauma can trigger oedema attack, the mode of delivery was discussed. Spontaneous delivery was chosen. On admission, she got infusion of C1 esterase inhibitor - 1000 units. She delivered a healthy term baby without any adverse event.

CONCLUSION

It appears to be safe to let patients with hereditary angio-oedema deliver spontaneously when sufficient C1 esterase inhibitor replacement is administered at the beginning of the labour.

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Fatal pneumococcal meningitis during pregnancy, a case report

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The patient, a 40-year-old gravida 2, para 1, was admitted at 24 weeks of pregnancy to The Central Hospital of Lappland because of severe neck-shoulder and low back pain. She was febrile and the level of consciousness was altered. Lumbar puncture was done in midatsolam-sedation and the culture was positive for streptococcus pneumoniae as was the blood culture. She developed septic shock. Infection and the septic shock were treated with broad spectrum iv. antibiotics, noradrenalin, dopamine and hydrocortisone. Two days later computer tomography of the head showed local parenchymal damage and edema. Sedation was discontinued but consciousness did not recover. Ventilation was supported mechanically. On follow up, the next 2-4 weeks, the therapy was intensified: the patient received insulin, desmopressin, thyroxin and cortisone once more. The next 5-9 weeks recurrent respiratory infections were also treated. The pregnancy, monitored intensively with ultrasound and CTG, progressed normaly. At 32 weeks of pregnancy bethametason 24 mg im. was administrated for fetal lung maturation. At 34 weeks of pregnancy the blood pressure became unstabil, the oxygen saturation worsened and fetal cardiotocography became monotonic. An emergency caesarean section was performed. A 2380-gm female infant with Apgar score 9 was delivered. The arterial cord pH was 7.33. On follow up examination at 6 months of age, she was found to have normal growth and development. The next day after the caesarean section computer tomography of the patients head showed extensive intracranial damage and edema. Chest x-ray showed pneumonia. Maternal ventilatory support was stopped and cardiac activity ceased shortly thereafter.

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Obstetric outcome among women with unexplained infertility after in-vitro fertilization

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Introduction: As women with unexplained infertility in earlier studies are reported to be at an increased risk of intra-uterine growth restriction during pregnancy after assisted reproductive treatment, we wanted to study the obstetric outcome of pregnancies among these women after in-vitro fertilization (IVF) treatment.

Methods: A matched case-control study was performed on care during pregnancy and delivery, obstetric complications and infant perinatal outcomes of 107 women with unexplained infertility, with 118 clinical pregnancies after IVF treatment. These resulted in 90 deliveries, of these 69 were singleton, 20 twin and one triplet delivery. Two control groups were chosen from the Finnish Medical Birth Register; one group for spontaneous pregnancies leading to birth (including 445 women and 545 children), matched according to maternal age, parity, year of birth, mothers residence and number of children at birth, and the other group for all pregnancies after IVF leading to birth during the study period (including 2377 women and 2853 children).

Results: The mean birthweight among singletons in the study group was 3425 ± 621 g and the mean gestational duration was 39 ± 2.1 weeks. No difference was found in the mean birth weight or gestational duration when comparing these to the results of the control groups. The incidence of low birth weight (<2500g) and very low birthweight (<1500g) was comparable to that of the control groups. Among twins in the study group the mean birthweight was 2540g ± 662g and the mean gestational duration was 36.5 ± 2.8 weeks, these were comparable to the results of the control groups. No differences were found in the mean Apgar scores, mean umbilical artery pH, incidence of major congenital malformations or perinatal mortality among the groups studied. Among singletons in the study group, there were more term breech presentations (10.1%) compared to both spontaneously conceiving women and all IVF women ($p<0.01$). The rate of pregnancy induced hypertension was significantly lower among singletons in the study group ($p< 0.05$) compared to other IVF singletons. The rate of cesarean section in the study group was comparable to the control groups both for singletons and twins. The multiple pregnancy rate was 23.3% in the study group. The obstetric outcome of the twins in the study group was similar to both control groups.

Conclusions: The overall obstetric outcome among couples with unexplained infertility treated with IVF was good, with similar outcome compared to spontaneous pregnancies and IVF pregnancies generally. The only factor increasing obstetric risk and adverse perinatal outcome in assisted reproductive treatment programmes is the high rate of multiple pregnancies.

Twin ratio and perinatal mortality

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Aim:
To study the impact of the increasing twin ratio on perinatal mortality

Methods:
Data from the perinatal audit in Vejle County Denmark. The study included all fetal and neonatal deaths from 22 weeks of gestation to 28 days after births. The study period was 1995-2000. Total number of births covered were 30.138. A total of 252 pregnancies and 268 fetuses/infants were evaluated in the perinatal audit

Results:
Overall perinatal mortality was 8,9 pr 1000 births ranging from 9,5 pr 1000 births for the first 3 years to 8,3 pr 1000 births for the last 3 years. The difference is not significant. Overall rate of multiple pregnancies was 1,94% ranging from 1,81% during the first 3 years to 2,06% for the last 3 years. The difference is not significant ($p = 0,26$). The twin ratio was 1,88%.
Fetuses and infants from multiple pregnancies contributed with 18% of the overall perinatal mortality. For single births overall perinatal mortality was 7,5 pr 1000 single births and for multiple births overall perinatal mortality was 42,2 pr 1000 infant/fetuses from multiple births ($p<0,0001$).
For 67% of multiple pregnancies with fetal or neonatal death GA was less than 28 weeks compared to 26% of single pregnancies ($p < 0,01$).
The importance of taking the twin ratio into consideration when interpreting overall perinatal morality is demonstrated from the data.

Conclusions
Infants and fetuses from multiple pregnancies have a 5-6 fold higher risk of dying in the period from 22 weeks of gestation to 28 days after births. The gestational age for the majority of deaths from multiple pregnancies is less than 28 weeks. The very high rate of multiple pregnancies must be a result of assisted conception. The increasing rate of multiple pregnancies makes it important to take the twin ratio into consideration when evaluating changes in statistics of perinatal mortality.

Obstetric outcome of multiple pregnancies

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Background: During last half decade the number of multiple pregnancies has markably increased due to the introduction of extracorporal fertilization, at the same time the rate of cesarean section (CS) has increased in Estonia as well.
Objective: The aim of this study was to determine the outcome of multiple pregnancies during last years.
Subjects and methods: All multiple deliveries at Tartu University Women`s Clinic over the 2 years from 1999 to 2000 were reviewed retrospectively.
Results: During the study period, there were 3693 deliveries of which one was triple and 46 were twin gestations (1,3%). 36% of all multiple deliveries were term, 64% were preterm, 1/5 of which were delivered before 32nd week of gestation. There were 4 perinatal death cases of 95 newborns delivered in the group, perinatal mortality rate occurred to be almost ten times higher as among all newborns. The total multiple CS rate, including CS for the second twin, was 44%, which is threefold higher of the general CS rate in the university hospital. CS for the second twin after vaginal delivery of the first twin occurred only in two cases, the triplets were delivered by elective CS. ½ of prematures below 32 weeks of gestation were delivered by vaginal delivery. Nonelective cesarean section (n=36) characterized by the highest rate of neonatal asphyxia, Apgar score <7 at 1 min occurred in ¼ of the newborns. Those delivered by vaginal delivery (n= 42) and by elective cesarean section (n=17) had markably lower incidence of neonatal asphyxia.
Conclusions: CS rate among multiple pregnancies was threefold higher than the general CS rate. There was no major difference in neonatal outcome of those delivered by vaginal delivery and by elective CS. We conclude the need for revision of the delivery mode of the second twin.

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Fetal Macrosomia and Perinatal Outcome

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BACKGROUND:Fetal macrosomia is defined as birth weight over +2SD of the mean birthweight by gestational age. It is associated with increased risk of birth trauma and neonatal morbidity. The aim of the study was to assess perinatal outcome of term macrosomic infants and to determine relationship between fetal macrosomia and gestational diabetes in this group.
METHODS:Case reports of 338 mothers and their term macrosomic newborns were analysed retrospectively during two consecutive years 1999-2000 in Tartu University Woman´s Clinic. Subjects of investigation were divided into 4 groups: GDM risk group(n=124),GDM group(n=9),IDDM group(n=4),unexpected macrosomia group(n=201).
RESULTS:Macrosomia occured in 9% of all deliveries. There was no cases of perinatal death in the group. 1/4 pregnant women had risk factors for GDM, which were assessed retrospectively. As none of these mothers had passed glucose tolerance testing we suppose some undiagnosed GDM cases in this group. The Caesarean Section rate was higher in GDM group and IDDM group (respectively 44% and 75%) than in GDM risk group and in unexpected macrosomia group (respectively 24% and 12%). Shoulder dystocia in vaginally delivered infants occurred only among newbors of GDM risk group and unexpected macrosomia group (respectively 4% and 3,5%). There were 7,5% of birth trauma in unexpected macrosomia group, 2,5% in GDM group and 2 cases in GDM group.The incidence of asphyxia was moderately higher as compared with the total population of newborns in the groups of unexpected macrosomia and GDM. Metabolic disorders occured more often in the newborns of GDM risk group.
CONCLUSIONS:Term macrosomic infants were characterised by higher rate of birth trauma, shoulder dystocia and asphyxia compared with normal weight babies. The morbidity of the newborns in treated GDM mothers group was less than in unexamined GDM risk group and in unexpected macrosomia group. This study is expected to lead to universal acceptance of GDM screening in the area.

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Female genital mutilation - revaluating obstetrical complications

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Background: Several authors associate female genital circumcision with obstructed labour and perinatal death. The comparatively higher perinatal mortality, which has recently been observed among immigrant women from the Horn of Africa in Sweden, raised the question whether there is an association between genital circumcision, prolonged labour, and perinatal death in a community of high standard of obstetric care. The objective was also to compare the duration of the second stage of labour between circumcised and non-circumcised women in Sweden.
Methods: 83 circumcised nulliparae women from the Horn of Africa were compared to 2.779 non-circumcised nulliparae giving birth at University Hospital in Malmö, Sweden, between 1990-96. Also a perinatal audit was performed covering a total cohort of 63 perinatal death infants to circumcised women giving birth in Sweden.
Results: Circumcised women were found to have second stage labour, which was statistical shorter by significant amount (34/53 minutes respectively) and a lower risk of prolonged labour than the non-circumcised group. No evidence could be find to confirm that hypotheses that female genital circumcision was related to perinatal death, nor that obstructed labour was found to have any impact on the numbers of perinatal death.
Conclusion: Assertions made in past linking genital circumcision to prolonged labour and perinatal mortality are questionable, since they do not appear to be the case in a fluent society with high standard of obstetric care. The results are in agreement with recent findings by WHO, which announce that no documented evidence has been found to confirm a relationship between obstructed labour and circumcision.

Successful EXIT (Ex Utero Intrapartum Treatment) procedures in neonates with antenatally detected airway obstruction - the Stockholm experience.

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INTRODUCTION: Congenital malformations causing airway obstruction in neonates can be successfully treated if detected prenatally. The EXIT procedure establishes free airway in the fetus while maintaining placental circulation. Since 1998 three fetuses have been successfully treated with EXIT procedures at the Karolinska Hospital. SUBJECTS: Case 1. The fetus of a healthy 28-year old primigravida presented at 16 weeks with ascites and later with enlarged hyperechogenic lungs with inverted diaphragm, an expanded trachea and a single umbilical artery. Laryngeal atresia was suspected and an EXIT procedure was applied at 35 weeks of gestation. Laryngoscopy confirmed the diagnosis of atresia and a tracheostomy was performed. The child has developed normally and, still tracheotomized, awaits final reconstructive surgery at the age of five. Case 2. A 29-year old multipara had a normal fetal midtrimester ultrasound scan except for a single umbilical artery. A repeat scan at 32 weeks revealed a 3.5 cm oro-pharyngeal cyst. Magnetic resonance imaging (MRI) could not rule out compression of the upper airway. Abdominal delivery with an EXIT procedure was carried out at 36 weeks. The cyst was drained from 25 ml of fluid followed by intubation. No further respiratory or feeding problems occurred. Histological examination identified a benign dermoid cyst originating from the sublingual area. Final excision of the cyst is planned at the age of three months. Case 3. A 37-year old woman with a history of lymphoma, was referred from Norway during her third pregnancy due to a prenatally diagnosed neck tumor of the fetus. MRI demonstrated an 11 cm multicystic tumor surrounding the fetal neck and dislocating the pharynx and trachea. At 36 gestational weeks a surgical delivery with EXIT procedure was performed and the fetal airway was secured through tracheostomy. The tumor was cytologically diagnosed as a lymphangioma. The treatment plan is to reduce the tumor volume with sclerotizing agents at the age of one, aiming at future radical surgery. METHOD: The EXIT procedures have comprised: 1) Deep maternal and fetal anesthesia with profound uterine relaxation. 2) Placental localization and fetal monitoring with ultrasound. 3) Delivery of the fetal head, right arm and shoulder. 4) Supplementary intramuscular analgesia to the fetus. 5) Fetal monitoring using intraoperative ultrasound and pulse oximetry. 6) Immediate diagnostic laryngoscopy followed by intubation. 7) Tracheostomy as well as administration of surfactant when necessary. 8) Clamping and dividing of the cord when satisfactory ventilation has been achieved. SUMMARY: A multidisciplinary fetal therapy team consisting of obstetricians, sonographers, pediatric surgeons, anesthesiologists, radiologists, neonatologists and oto-rhino-laryngologists has provided life-saving therapy of congenital airway obstruction syndromes.

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The role of parents in the transmission of HPV to the newborn

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Background: Human papillomavirus (HPV) infection is a mostly sexually transmitted disease. Men have been considered to be the most common transmitters of HPV although clinical infections of HPV are more common in women. HPV DNA and RNA have been previously detected both in seminal plasma and in sperm cells, and certain HPV genes are expressed actively in infected sperm cells. HPV DNA has also been detected from spontane-ously aborted products. Therefore, it is possible that sperm cell acts as a vector of HPV DNA to fertilized egg and the father is a vertical transmitter of HPV DNA to the neonate. The aim of this study was to evaluate the potential role of the parents as transmitters of HPV to the newborns.
Methods: A subgroup of 70 consecutive families from 257 mothers, 111 fathers and 258 neonates participating in the ongoing Turku HPV Family Study was analyzed for the pres-ence of HPV DNA. Cervical and oral samples from the mother were taken before delivery and two months thereafter. Urethral, oral and semen samples were taken from the father before delivery. Oral and genital samples from the neonate were taken after delivery, 2-3 days and one month later. HPV DNA was detected be nested PCR (MY09/11 and GP05+/06+) and confirmed by Southern blot hybridization with 12 high risk HPV oligo-probes.
Results: In fathers 19.3% (12/62) of urethral and 17.1% (12/70) of semen samples were high risk HPV DNA positive. In mothers 15.9% (11/69) and 17.2% (11/64) of cervical samples taken before and two months after delivery were high risk HPV DNA positive. Before delivery fathers had 17.1% (12/70) and mothers had 13.0% (6/46) of oral samples high risk HPV DNA positive. In neonates high risk HPV DNA was detected in 11.8% (8/68), 9.9% (7/71) and 12.7% (8/63) of oral and in 14.3% (9/63), 20.0% (14/70) and 14.7% (10/68) of genital samples taken during delivery, 2-3 days and 1 months after delivery.
In 13 families (18.3%) father (urethral and/or semen sample) and neonate (any oral and/or genital samples) were HPV DNA positive. In 6 cases only the semen sample was positive. In 12 (16.9%) families mother (any of the cervical samples) and neonate (any oral and/or genital samples) were HPV DNA positive.
When farher´s semen and/or urethral sample and semen sample were high-risk HPV DNA positive OR for neonate to acquire HPV DNA was 1.6 (95% CI 0.772-3.200) and 1.2 (95% CI 0.411-3.229), respectively. When mother had any of the two cervical samples positive for high risk HPV, OR for neonate was 2.2 (95% CI 0.919-5.155).
Conclusions: Detection of HPV DNA in the genital and oral mucosa seems to be more common than expected in parents and the newborn. Detection of high-risk HPV in parents is a risk for the neonate to contract a high-risk type HPV infection.

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Fetal exposure, heredity and risk indicators for cardiovascular disease in a Swedish welfare cohort.

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Background: The overall aim of the study was to test whether low birth weight (LBW) in newborns is associated with the risk indicators for cardiovascular disease in early middle age, even in a welfare society. Further, a possible interaction of LBW and heredity for myocardial infarction or stroke was investigated.

Methods: Common subjects were identified as newborns in a local birth register and as adult participants in the Västerbotten Intervention Program (n = 7876). Outcome measures such as systolic (SBP) and diastolic blood pressures (DBP), body mass index (BMI), cholesterol, triglycerides and anthropometrics were investigated (at the age of 29-41 years) in relation to LBW.

Results: LBW was associated with increased SBP and DBP. Triglycerides were elevated among women with LBW and total cholesterol was elevated in men with LBW. Heredity for myocardial infarction or stroke interacted with LBW, and indicated a synergistic effect on the level of SBP. BMI did not differ between LBW and NBW subjects.
Conclusions: Our interpretation is that the "fetal origins- hypothesis" is valid for middle-age subjects who grow up in a welfare society. The population attributable proportions that result from different exposures to LBW were relatively small overall; from a public health perspective, heredity was more important than LBW for elevated SBP.

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Rhu EPO (Erythropoeitin) - an alternative for treatment of anemia post partum?

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According to the WHO definition 110 g/l, 20-40 % of pregnant women are anemic. During delivery this condition aggravates due to blood loss. 20 % of the women have a blood loss of more than 600 ml and about 3 % are transfused. Recombinant human EPO is used for treatment of anemia due to kidney failure.

Method: 60 women with a hemoglobin value of less than 80 g/l after delivery were randomized to three different regimens :
1.10 000 U EPO s.c + 200 mg Venoferrum i.v day 1 and day 3
2. 20 000 U EPO s.c + 200 mg Venoferrum i.v day 1 and day 3.
3. 200 mg Venoferum i.v day 1 and day 3.

Results: Mean Hb at randomization was 74.0 g/l (sd=4.6) and after one week of treatment it has increased to 92.2g/l (sd=10.8). After two weeks mean Hb was 102.5 g/l (sd=10.4) giving a mean increase of 28.2g/l.

Conclusion: no differences between the three treatment regimens could be detected in this study.

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Security, participation and integrity is a common need regardless of early postpartum discharge or family suite

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Objective: In recent decades, postpartum care has a stronger emphasis on the significance of self-care, the family has come into greater focus and the length of time spent in maternity ward has successively decreased. The aim of this study was to describe new parents? choice of maternity care, family suite or early discharge, and to gain a better understanding of parents? experiences in different care alternatives.
Setting and participants: Eleven couples and one mother participated in the study, including both first-time and experienced parents. Six families received care at a family suite while the others had chosen to return home within 24 hours after delivery.

Measurements: The parents were interviewed using a semi-structured questionnaire and the interviews were analysed by content analysis.
Findings: The postpartum period was an unpredictable time for the new parents, when the need of security, participation in decision-making and integrity was central and decisive for the choice of care. The type of care in which the parents felt their needs to be met in the best way varied according to the child´s and mother´s health status, the parents´ requirements and experience and the way in which they as parents handled the opportunities and demands of different environments. However, the opportunities for the parents to choose the form of care they considered best for their family were limited. Implications for practice: To best fulfil the parents wishes and needs in postnatal care it is necessary that there is alternative care forms, a way to treat the family as a whole on an individual family basis and the ability of parents to choose the form of care they consider to best.

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No increased health care utilization regardless of early postpartum discharge or family suite

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AIM: The study describes the utilization of health care services by mothers and newborns following discharge after childbirth by different type of maternity care Maternity Ward, Family Suite, and Early Discharge on the number of rechecks (outpatient visits) or readmissions, support and outcome of breast-feeding.

METHOD: The design was a cohort with all term childbirths (37^{0}+) in which 773 women and 782 newborns were followed using questionnaires, register data, and chart notes. Information from electronic patient charts was linked to register data and served as a basis for analyzing utilization of health care services by mother and child during the first 28 days post-delivery. Descriptive statistics was used with Chi-square test and presentations of prevalence by 95 % confidence limits. The study was approved by the local research Ethics Committee.

RESULTS: Of the 773 mothers 39 % had been in Maternity Ward, 38 % in Family Suite and 23 % in Early Discharge. During the first 28 days post-delivery, 1.7 % (0.8-2.6) of the women were readmitted and 15 % (12.4-17.4) sought medical care, mostly because of signs of infection, breast-feeding problems, and bleeding. Of the children, 2.9 % (1.7-4.1) were readmitted, and 17 % (14.2-19.4) received medical care, where 1/30 was readmitted because of jaundice and 1/50 because of signs of infection. Half, 54 % (50.5-57.5), were completely breast-fed for over five months, and 43 % of the women sought help from the health care system for breast-feeding questions. There was no difference in utilization of health care services based on whether mother and child came from the Maternity Ward, Family Suite, or Early Discharge services whether for outpatients visits, complications, or breast-feeding outcome.

CONCLUSION: Mothers and infants sought care relatively frequently, but rarely needed to be readmitted after discharge from the maternity department. The risk of readmission during the first month after childbirth was not greater for mothers and children who received care through the Family Suite or Early Discharge programs.