

# Abstracts of oral presentations

## 1 Prevention and treatment of osteoporosis

Roger M. Francis  
*University of Newcastle Upon Tyne and Bone Clinic, Freeman Hospital, Newcastle Upon Tyne, UK*

Osteoporosis has been defined as a skeletal disorder characterised by compromised bone strength, predisposing a person to an increased risk of fracture after minor trauma. The major osteoporotic fractures are those of the vertebra and hip, which cause excess mortality, substantial morbidity and health and social service expenditure. The risk of fracture is determined not only by skeletal factors such as bone mineral density (BMD), bone turnover, trabecular architecture and skeletal geometry and bone quality, but also by non-skeletal factors which increase the risk of falls. Strategies to prevent osteoporotic fractures should therefore ideally include measures to improve bone strength and decrease the risk and impact of falls. Lifestyle measures such as regular physical activity, decreasing tobacco and alcohol consumption and increasing dietary calcium intake may improve bone density, but there is no convincing evidence that they decrease the incidence of fractures. Hormone replacement therapy (HRT), raloxifene and bisphosphonates have all been shown to prevent bone loss in normal postmenopausal women, but with the exception of HRT, have not been shown to decrease the incidence of fractures. The Womens' Health Initiative study demonstrated that HRT reduced the risk of vertebral and hip fractures, but overall the risks outweighed the benefits of treatment. The absolute risk of fractures in normal postmenopausal women is so low, that HRT, raloxifene and bisphosphonates cannot be advocated for the primary prevention of osteoporosis. HRT, raloxifene, bisphosphonates and teriparatide have all been shown in randomised controlled trials to improve BMD and decrease the risk of vertebral fractures in postmenopausal osteoporosis. Teriparatide also reduces the incidence of non-vertebral fractures, whereas alendronate and risedronate decrease the risk of hip fractures. Calcium and vitamin D supplementation reduces the risk of hip and other non-vertebral fractures risk in older people. In addition to any beneficial effect on BMD, calcium and vitamin D decreases body sway, improves muscle function and reduces the risk of falls. Multidisciplinary assessment and intervention also decreases the risk of falls, but it is unclear if this will prevent fractures. The role of hip protectors in the prevention of hip fractures is also unproven at the present time.

## 2 Reproduction-related glycoprotein secretion in fertilisation and implantation revisited: Clinical implications

Markku Seppälä  
*Biomedicum Helsinki, Finland*

Cyclical changes in endometrium result from functional changes in genes and the proteins they encode to uphold procreation. At the time of fertilization, the estrogen-dominated microenvironment in the uterus is strikingly different from the progesterone-regulated changes present during the peri-implantation period. About one percent of human genes encode enzymes that contribute to glycosylation, and as many as 80 percent of the proteins encoded by the human genome are glycoproteins. The specific role of glycosylation on glycoprotein function is becoming increasingly obvious in health and disease. Glycodelin provides an excellent model for such studies. Glycodelin is the major progesterone-regulated secretory glycoprotein of the reproductive axis, with diverse actions in cell recognition and differentiation. Depending on its unique glycosylation pattern, glycodelin appears in various isoforms, three of which have been characterized in the female and male reproductive tissues. In endometrium, glycodelin-A (GdA) is the major glycoform, whereas GdF predominates in ovarian follicular fluid, and GdS is characteristic of the male seminal plasma. GdA and GdF have contraceptive effects, as they potently and dose-dependently inhibit human sperm-egg interaction by binding on sperm. Differently glycosylated native GdS has no such effect. The anti-fertilization propensity of uterine GdA during the luteal phase of the cycle and of follicular fluid GdF is highly glycosylation-dependent, wherein GdA shares one of the two binding sites of GdF present on human spermatozoa, and deglycosylation of either glycoform results in a complete loss of contraceptive activity. Importantly, contraceptive GdA is absent from endometrium during the fertile window and it appears around day LH+5 and peaks at the onset of menstruation. In vivo, all the three glycodelin isoforms may meet and bind on human spermatozoa during sperm migration, and their diverse effects on acrosome reaction and sperm-zona binding are intricately modified by the cumulus/corona cells that surround an unfertilised oocyte. Progestagen-containing contraceptives induce endometrial glycodelin expression over the fertile window, suggesting another contraceptive mechanism. GdA can be chemically modified to yield a molecule with anti-HIV activity based on potent and dose-dependent inhibition of gp120-CD4 binding. This may be significant for the development of locally applied antiviral contraceptive strategies. To this end, a cell line for mass production by recombinant technology of contraceptive GdA has been described. The

role of GdA, abundant at the fetomaternal interface, will be discussed in respect of increased insulin and androgen secretion and early pregnancy loss in women with PCOS.

### 3 One embryo transfer is clinically appropriate

Aila Tiitinen  
*Dept of Obstetrics and Gynecology, Helsinki University Central Hospital*

**Background:** In many countries more than 2% of new-borns are born after ART. At the same time ART has been associated with a 20-fold rate of multiple pregnancies compared with spontaneous pregnancies. Neonatal outcome after IVF is worse than that in the general population of similar maternal age, parity and social standing, but this is mainly due to the large proportion of multiple births after IVF. Thus, one of the main challenges in assisted reproductive treatment (ART) programmes is to avoid twin pregnancies. **Methods and results:** The multiple pregnancy rate in our IVF programme in 2002 was only 6.7 %. At the same time the overall ongoing PR has fallen slightly, but is still above 30%, which is even more than the natural conception rate. Elective SET combined with embryo cryopreservation can result in a cumulative pregnancy rate near to 50% per cycle, at least in our hands. Laboratory expertise is highly important in an eSET programme, especially in terms of embryo culture, embryo selection, and freezing and thawing techniques. The quality and outcome of ovarian stimulation seems to be predictive: a good ovarian response to FSH stimulation leads to several mature oocytes, and could be a marker of good reproductive function as such. This leads to more numerous embryos and allows more choice for selection of one good embryo for transfer. Correct counselling is very important, as infertile couples are known sometimes to desire multiple pregnancies. **Conclusion:** The need to prevent twin pregnancies is widely accepted, although transfer of two embryos is standard policy in many IVF centres. Our eSET programme shows that multiple PR under 10% can be achieved with acceptable delivery rates. The additional impact of a well-functioning cryopreservation programme on the overall cumulative PR per ovum pick-up is very important to bear in mind. The effect of the increased use of this policy has already been observed as reduction in the proportion of twin deliveries following ART in Finland, as well as in a reduction of the proportion of multiple births in the Finnish Medical Birth Register.

### 4 Cross-talk between genetics and IVF

Hans Jakob Ingerslev  
*Fertility Clinic, Aarhus University Hospital, Skejby Sygehus*

During the last decades both genetics and reproductive medicine has experienced a number of major technical breakthroughs that have improved understanding of pathogenetic processes, but also radically changed both

diagnostic capability (genetics) and treatment options (reproductive medicine). The aim of this presentation will be to give an update to interrelations between genetics and infertility treatment. The focus will be on genetic aberrations in infertile couples with possible etiological relevance for the reduced fecundity and on the occurrence of aneuploidy in human embryos as a probable cause of a relatively low cycle fecundity in humans. A number of structural and numerical chromosomal aberrations are known to occur with significantly increased frequency in both infertile men and women. Balanced translocations may give rise to unbalanced aberrations in embryos, but breakpoints of reciprocal translocations may also damage genes of possible relevance to spermiogenesis or similar reproductive functions in women. Examples of specific genetic deletions or mutations associated with compromised reproductive function are Y microdeletions associated with loss of normal spermatogenesis, mutations in the CFTR gene associated with congenital absence of the vas deferens, and a number of mutations are known to disturb the development and function of the hypothalamic-pituitary-gonadal axis. Several lines of evidence suggest that there is an underlying genetic cause for PCOS. IVF technology has allowed genetic examination of the early embryo. Used in a clinical setting this is termed pre-implantation genetic diagnosis (PGD). Present knowledge indicate that at least 50% of morphologically normal human embryos are aneuploid. Most of these involve chromosomes not known to be aberrant in abortions suggesting that they cause early embryo death. The high rate of aneuploid embryos seem to explain the relatively low cycle fecundity in natural conception and a ceiling of implantation success in IVF of around 30%.

### 5 Longterm outcome of children born by ART

Ulla-Britt Wennerholm  
*Dep Ob Gyn, Sahlgrenska Univ Hospital East, Göteborg, Sweden*

Since the birth of the first test-tube baby in 1978 and the birth of the first intracytoplasmic sperm injection (ICSI) child in 1992 many couples with longstanding female-factor or male-factor infertility can be helped to overcome their infertility resulting in a delivery and birth of a child. More than one million children have been delivered worldwide after assisted reproductive technology (ART) and today they represent 2% of all newborns in some countries, such as Sweden. There is a continuous debate about safety aspects and paediatric health and development consequences. The major problem related to children outcome after ART is the substantial increase in multiple pregnancies, which is due to the replacement of multiple embryos. However, from several publications of the last decade it has become evident that there is an as yet unexplained higher risk of adverse outcome in IVF singleton pregnancies with a higher incidence of prematurity and low birth weight. Most studies of children conceived in vitro have shown a negligible or only a slight excess risk of congenital malformations. In a

large Swedish population based controlled study an overall increase in congenital malformations was found (odds ratio 1.47). Taking into consideration confounders (maternal age, parity, years of infertility) there was no increase in malformation rate (odds ratio 0.89). The introduction of the ICSI technique raised further concerns about the risks for the children. Some studies conclude that ICSI causes a small but statistically significant increase of congenital anomalies at birth, compared to the general population, but not compared to conventional IVF. A higher risk of prenatal chromosomal anomalies has been documented. In another Swedish population based controlled study a fourfold increased risk of cerebral palsy in children born after IVF was found. Pre-term birth, low birth weight but also IVF per se contributed independently to the increased risk. There is still an ongoing debate on the developmental long-term outcome, however most of the published studies on young children conceived after IVF and ICSI have been generally reassuring. Recently a series of case reports and small studies has suggested that births involving ART may have an increased risk of imprinting disorders such as Beckwith-Wiedeman syndrome and Angelman syndrome. Ultimately whether IVF/ICSI children have normal fertility will be a sensitive issue to investigate. Continuing surveillance of children conceived with ART is needed including monitoring birth defects, development and cancer.

## 6 Legal issues in ART in Nordic countries

Arne Sunde  
IVF-Unit, Dept of Ob. & Gyn. University Hospital of Trondheim,  
Trondheim, Norway

The Nordic countries are remarkably different when it comes to legal and moral attitudes towards medical use of biotechnology. Norway was in 1987 the first country in the world to pass a law regulating ART. Laws were later passed in Sweden in 1988, in Iceland in 1996/97 and in Denmark in 1997. Finland still does not have a specific law regulating ART.

The Norwegian law limits research as well as clinical practise. Research on human embryos is forbidden, oocyte and embryos donation is forbidden, no PGD and until recently no donor sperm in IVF or ICSI with non-ejaculated sperm.

Research on human embryos is allowed/practised in Denmark, Finland, Iceland and Sweden enabling ART-units in these countries to do research and clinical development which is in the absolute forefront internationally.

Oocyte donation is allowed/practised in Iceland, Denmark and Finland, but forbidden in Norway and Sweden. Sweden was the first country in the world who removed the anonymity for sperm donors by law and recently the new Norwegian law adopted the same position. In Denmark the sperm donors are anonymous while in Iceland the couple can decide themselves if they anonymous or non-anonymous donors.

The contribution to the development of ART the mid/end of the 1980'ties was equal from all of the Nordic countries. The situation now is very different and is correlated to the regulation of ART in the country. Finland with its liberal practise is now a leading country, in Sweden and Denmark important research and clinical development takes place, while Norway with its strict law is lagging behind and is totally dependent on import of knowledge from it's neighbouring countries.

Acknowledgements. I wish to thank Lars hamburger, Johan Hazekamp and Karl-Gösta Nygren for access to their manuscript on the legal issues in the Nordic countries prior to publication.

## 7 Association for preeclampsia on chromosome 2p25

Hannele Laivuori 1,2,3) Erja Kerkelä 3) Hanna Peterson 3)  
Hong Jiao 3) Ville-Veikko Mäkelä 3) Risto Kaaja 2) Olavi Ylikorkala 2) Juha Kere 3)  
1) Department of Clinical Genetics, Helsinki University Central Hospital 2) Department of Obstetrics and Gynecology, Helsinki University Central Hospital 3) Department of Biosciences at Novum, Karolinska Institutet, Stockholm, Sweden

**Background:** We have previously mapped three candidate susceptibility loci for preeclampsia on chromosomes 2p25, 4q32 and 9p13-p21 in 15 Finnish families, recruited predominantly from the Kainuu province (Laivuori et al. Am J Hum Genet 2003; 72: 168-177). Now we present our efforts to narrow down those candidate regions.

**Methods:** First, we increased the marker density in the three loci by adding 34 microsatellites at approximately 1 cM intervals. Linkage was assessed by the affecteds-only non-parametric multipoint linkage (NPL) analysis method. To study if the overall haplotype distribution in the loci differs among the chromosomes of the affected vs. non-affected individuals, haplotype association analysis using the haplotype pattern mining algorithm was done, including testing of significance by permutation tests (Toivonen et al. Am J Hum Genet 2000; 67: 133-145). In one locus we have narrowed the associated haplotype further using high-density single nucleotide polymorphism (SNP) genotyping.

**Results:** We were able to narrow down the candidate area on chromosome 2 with the highest peak showing significant linkage (NPL score 4.09,  $p = 0.00036$ ). Instead, NPL scores for two other loci showed only suggestive linkage with no apparent improvement to the previous scan. Significant haplotype association was observed on chromosome 2p25, supporting and refining considerably the linkage results. We have sequenced 80 kb area, between the three SNPs showing the best association, from one woman homozygous for the associated haplotype. We are currently performing the additional finemapping using 20 of 57 SNPs found in that region.

**Conclusion:** Chromosome 2p25 may harbor a susceptibility gene for preeclampsia.

## 8 Tumor suppressor and growth regulatory genes are over-expressed in severe early-onset preeclampsia. An array study on case-specific human preeclamptic placental tissue

Annaleena Heikkilä 1,2) Tiina Tuomisto 2) Sanna-Kaisa Häkkinen 2) Leea Keski-Nisula 1) Seppo Heinonen 1) Seppo Ylä-Herttuala 1, 3, 4)

1) Department of Gynecology and Obstetrics, Kuopio University Hospital 2) A.I. Virtanen Institute, University of Kuopio 3) Department of Medicine, University of Kuopio 4) Gene Therapy Unit, Kuopio University Hospital, Kuopio, Finland

**Background:** Preeclampsia is an important clinical condition with unknown etiology. The placenta is considered to be the pathogenic focus for all manifestations of preeclampsia. There seems to be a subgroup of patients who get the most severe form of preeclampsia early in gestation leading to the need of Caesarean section and the delivery of very preterm infants.

**Methods:** We used DNA array technique to compare placental gene expression profile in severe early onset preeclampsia from 25 and 27 gestational weeks with strictly non-affected placental samples from similar gestational weeks. DNA arrays were validated by showing the up-regulation of several genes typical for preeclampsia, such as hCG-beta, Tissue factor pathway inhibitor and ICAM-1.

**Results:** In DNA array 5 % of genes displayed  $\geq 2$ -fold increase in expression level and only 0.2 % of genes showed  $\leq 0.5$ -fold decrease in expression in preeclampsia versus control. Signs of immunological factors, hypoxia, apoptosis, oxidative stress and altered thrombosis and coagulation as well as endothelial injury were seen in the gene expression profile. As a new finding we identified a group of 13 genes with a function in tumor suppression and growth regulation which were significantly up-regulated in preeclampsia. Three out of the five most highly up-regulated genes belonged to this group which included genes, such as Protein phosphatase 2, Phospholipid scramblase 1, Transcription elongation factor, Melanoma adhesion molecule, Retinoic acid receptor rasponder 3 and RANTES.

**Conclusions:** It is concluded that up-regulation of tumor suppressor and growth regulatory genes may play an important role in the pathogenesis of early onset preeclampsia.

## 9 Does ISG12 play a role in preeclampsia?

Camilla Jensenius Skovhus Kronborg 1) Ulla Breth Knudsen 2) Pia Møller Martensen 3)

1) Department of Gynaecology and Obstetrics, Randers County Hospital 2) Department of Gynaecology and Obstetrics, Odense University Hospital 3) Department of Molecular Biology, University of Aarhus

**Background:** Preeclampsia is a pregnancy specific syndrome, which consists of hypertension and proteinuria. The pathogenesis is not clear in all aspects. A two-stage model has been suggested to take a central place in disease development. 1. Deficient invasion of trophoblasts into the maternal spiral arteries at 18th week of gestation, which renders the placenta hypoxic. 2. The maternal syndrome with immune activation and dysfunction of the endothelium. ISG12 is a gene stimulated primarily by type I interferon. The function of ISG12 is largely unknown, but research shows that ISG12 is expressed in the endometrium during the putative time of implantation. Therefore, differences in expression of ISG12 could influence the implantation and placentation.

**Methods:** The expression of ISG12 was evaluated in two different cell lines. The primary cell line HUVEC and the stable cell line HeLa. Cells were stimulated with serum from healthy pregnant women and serum from preeclamptics. ISG12 expression was analyzed by transient transfection of HeLa cells, further by RT-PCR in both HeLa and HUVEC cells.

**Results:** Sera from normal pregnant women stimulate ISG12 expression in both HeLa and HUVEC cells, whereas preeclamptic serum has diminished or no stimulatory effect on ISG12 expression. The stimulatory pattern of normal pregnancy serum differs from that of type 1 interferon.

**Conclusion:** Sera from normal pregnant women stimulate ISG12 expression, whereas sera from preeclamptic women have diminished or lack this effect. ISG12 and other ISGs are expressed in the endometrium during the putative time of implantation. Although the function of ISG12 is unknown it could be an actor in early implantation and placentation. The preeclamptic pathogenesis commences with incomplete invasion of trophoblasts into maternal spiral arteries. The lacking stimulatory effect of preeclamptic serum on ISG12 expression could take part in the pathogenesis leading to this deficient placentation.

## 10 Paternity change and the recurrence risk of familial hypertensive disorder in pregnancy

Sigrun Hjartardottir 1) Reynir Tomas Geirsson 1) Björn Geir Leifsson 2) Valgerdur Steinhorsdottir 3)

1) Department of Obstetrics and Gynecology, Landspítali University Hospital 2) Department of Surgery, Landspítali University Hospital 3) DeCode Genetics Inc., 101 Reykjavik, Iceland.

**Background:** Family history and previous hypertensive disorder carry an additive risk of recurrence of hypertensive

disorder in pregnancy. New paternity may contribute to this, but so may a longer interbirth interval.

**Methods:** Data on 614 multiparous women with a history of de novo hypertensive disorder in a first pregnancy and familial connectivity to other women with hypertension in pregnancy were used to assess the effect of paternity and interbirth interval on recurrence.

**Results:** There were 121 women (19.7%) with a new partner. Recurrent hypertensive disorder occurred in 64.5% with the same and 62% with a new partner. The OR for recurrence with the new partner was 0.897 (CI95% 0.595-1.353). The mean interbirth interval was longer for women with recurrent hypertensive disorder (4.9 vs. 4.0 years,  $p=0.0002$ ). The OR for developing hypertensive disorder anew was 1.154 (CI95% 1.049-1.269) for every interval year between pregnancies with the same and 1.145 (CI95% 0.958-1.368) with the new partner, after correction for maternal age.

**Conclusions:** In women with a positive family history as well as previous hypertension in pregnancy, and therefore considerably increased risk, a change of paternity did not appear to influence risk of recurrence. Increasing interbirth interval accounted for a 15% rise of risk for each year with the same or a new partner, independent of maternal age. Change of partner may not influence the recurrence risk as much as previously thought.

#### 11 Acute atherosclerosis: Not only associated with preeclampsia

Nina Kittelsen Harsem 1) Borghild Roald 2) Kristin Brække 3) Anne Cathrine Staff 1)

1) Dept. of Obstetrics and Gynecology, Ulleval University Hospital 2) Dept. of Pathology and Anatomy, Ulleval University Hospital 3) Dept. of Pediatrics, Ulleval University Hospital 4) Dept. of Obstetrics and Gynecology, Ulleval University Hospital

**Background:** The spiral arteries in decidua basalis play an important role in the development of preeclampsia. Preeclampsia is associated with lipid deposition in the walls of spiral arteries; a phenomenon named “acute atherosclerosis”. Maternal hyperlipidemia is seen in pregnancies complicated with preeclampsia and diabetes. Studies of extravillous trophoblasts and placental bed spiral arteries are essential for a better understanding of pathological pregnancies. A major challenge is to obtain representative and sufficient tissue for morphological and functional investigations. We use a vacuum suction method to obtain a large volume of decidual tissue from the placental bed, thereby more decidual spiral arteries.

**Methods:** Decidual tissue from the uterine wall underlying the placenta was collected by vacuum suction following the delivery of the baby and the placenta in 99 cesarean deliveries. The tissue was fixed in 4% formaldehyde and embedded in paraffin. Five  $\mu$ m tissue sections were routinely stained with hematoxylin and eosin, and immunoreacted with antibodies to CD68, actin and cytokeratine. We defined

acute atherosclerosis as the presence of foamy CD68 positive cells in spiral artery walls with fibrinoid necrosis.

**Results:** In 84% ( $n=36$ ) of the 43 preeclamptic pregnancies, at least one decidual spiral artery was identified in the decidual tissue section investigated per patient (mean 6.2 spiral arteries per section). Acute atherosclerosis was present in 44% ( $n=16$ ) of the 36 preeclamptic patients with spiral arteries visualized. Acute atherosclerosis was however also seen in the spiral arteries of three of the 25 normal pregnancies, and in two of the 13 patients with diabetes without superimposed preeclampsia.

**Conclusions:** Acute atherosclerosis is not a feature unique for preeclampsia. It seems to be more of a quantitative than qualitative variable for the disease. Clinical characteristics and maternal lipid profiles, correlated to the presence or not of acute atherosclerosis, will be presented at the meeting.

#### 12 Is there an association between the intake of vitamin C and preeclampsia? A prospective study among 42,295 women.

Åse Kathrine Klemmensen 1) Vibeke Knudsen 2) Ann Tabor 1) Ivanja Orozovz-Bekkevold 2) Tina Mikkelsen 2) Sjurður Olsen 2)

1) Department of Obstetrics and Gynecology, H:S Hvidovre Hospital, University of Copenhagen 2) Maternal Nutrition Group, Danish Epidemiology Science Centre, Statens Serum Institut

**Background:** Preeclampsia (PE) is responsible for maternal and perinatal morbidity and mortality worldwide. A recent epidemiological study suggests an inverse association between measures of vitamin C intake and PE risk among US women. We tested this hypothesis in a large database on maternal nutrition, the Danish National birth cohort (DNBC). Approval was obtained from the Scientific-Ethical Committees.

**Methods:** DNBC collected prospective information on life style and other factors through four telephone interviews of the mother in gestation weeks 12 & 30 and when the child was 6 & 18 months. Dietary patterns and use of food supplements were recorded in gestation week 25 through a 300-item food frequency questionnaire. The daily intake of vitamin C was obtained by aggregating the contributions from food and food supplements. Women were diagnosed with PE when they reported it in the third interview (when the child was six month old), and when PE was recorded in the Danish National Patient Registry. We divided the women into quintiles of vitamin C intake (mean intake per day in brackets): Q1(85 mg); Q2(139 mg); Q3(177 mg); Q4(228 mg); Q5(412 mg). We used multiple logistic regression to adjust for confounding.

**Results:** 42,295 women had both returned the FFQ and participated at interview 3. The lowest quintile was chosen as reference. The OR (the 95% confidence intervals in brackets) of PE were 1.14(0.87;1.48), 0.99(0.75;1.30), 0.88 (0.67;1.17), 1.14 (0.88;1.49) for quintiles Q2, Q3, Q4 and Q5 respectively.

As expected we found reductions in risk of PE among smokers, multipara and tall & lean women.

**Conclusions:** In our study PE and vitamin C intake seemed not to be associated.

### 13 Effect of ASA on the risk of gestational hypertension and prostanoid synthesis in pregnant women screened by Doppler ultrasound

Merja Vainio 1) Erkki Kujansuu 2) Asko Riutta 3) Johanna Mäenpää 4)

1) Hyvinkää Hospital 2) Tampere University Hospital 3) Department of Pharmacological Sciences, University of Tampere 4) Tampere University Hospital

**Background:** To evaluate the efficacy of ASA on gestational hypertension and prostanoid synthesis in high-risk women screened by Doppler ultrasound.

**Methods:** Seven pregnant hypertensive women and five non-pregnant healthy women received ASA in three periods, each lasting 10-12 days. The daily dose of ASA was 0.5mg/kg, 1.0mg/kg and 2.0 mg/kg. Serum thromboxane and urinary metabolites of thromboxane A<sub>2</sub> and prostacyclin were measured at baseline and after each treatment period. After that 120 high-risk women for pre-eclampsia were screened by Doppler ultrasound at 12-14 weeks of gestation. Ninety women with bilateral notches in uterine arteries were randomised to ASA (0.5mg/kg/day) or placebo groups. Main outcome measures were gestational hypertension or intrauterine growth restriction (IUGR). The predictive value of bilateral notching of uterine arteries at 12-14 weeks of gestation with regard to hypertensive disorders of pregnancy was evaluated. The urinary metabolites of prostacyclin and thromboxane A<sub>2</sub> were measured throughout pregnancy.

**Results:** Within a dose range of 0.5-2.0 mg/kg/day, ASA had a favourable effect on the prostanoids in hypertensive pregnant women. The use of ASA was associated with a statistically significant reduction in the incidence of gestational hypertension (11.6% vs 37.2%, RR = 0.31, 95% CI 0.13-0.78) and pre-eclampsia (4.7% vs 23.3%, RR = 0.20, 95% CI 0.05-0.86). Bilateral notching of uterine arteries evidenced sensitivity, specificity and positive and negative predictive values of 84%, 50%, 29.6% and 90.6% respectively in predicting gestational hypertension. The balance of prostacyclin and thromboxane A<sub>2</sub> sifted to an unfavorable direction in pregnancies complicated by gestational hypertension. ASA had a favorable effect on the prostanoids.

**Conclusions:** ASA treatment from 12-14 weeks of gestation significantly reduced the incidence of gestational hypertension in high-risk women. Bilateral notching at 12-14 weeks of gestation appears to afford a useful basis in screening for pregnancies involving a high risk of hypertensive disorders of pregnancy.

### 14 Why and in what way will NFOG and NFJ (Nordiske Jordmorförbund) promote international reproductive health?

Peter Hornnes

Department of Obstetrics and Gynecology, Hvidovre Hospital, Copenhagen, Denmark.

During the latest years there has been accumulating interest within the NFOG for working to improve fetal maternal health in the Third World. Several factors have been active in raising this interest:

- The Nordic countries have a tradition for aiding and working in the Third World.
- Obstetricians and Gynecologists from all Nordic countries have personally contributed to projects in the Third World. Some of these projects have been very successful, others have been less so.
- During the 1997 FIGO Congress in Copenhagen the subjects of maternal mortality and in general obstetrics in the Third World received much attention and left a profound feeling of responsibility in the national societies and NFOG.
- The Nordic countries are small. Cooperation helps achieve critical mass in terms of finances and manpower.
- Nordic obstetricians are used to working with midwives. This experience is crucial in Third World settings.

After the 2002 Umeå Nordic Congress with the symposium: NFOG Going South, the Board of NFOG has decided the following point to be essential for the efforts:

- NFOG wishes to explore the possibilities of establishing projects in the Third World with the aim of improving fetal-maternal health.
- The projects should be carried out in a well defined geographical region.
- Cooperation with the Nordic Association of Midwives (NFJ) should be established and also midwives should be active participants utilizing our tradition for cooperation.
- The projects should have practical and measurable endpoint and yield sustainable results.
- The NFOG is able to provide the projects with seed money, thereafter the projects must be financed externally.

## 15 NFOG-NJF going south II - whom will it benefit?

Birgitta Essén

## 16 Research in international reproductive health at Nordic universities during the last two decades

Staffan Bergström

*Division of International Health (IHCAR), Karolinska Institutet, Sweden*

Nordic research efforts in reproductive health with emphasis on low-income countries started only in the 1980s. The Swedish agency for research cooperation with developing countries (SAREC) had early as one of its priority issues 'population', implying huge investment in research on 'population' with emphasis on development of contraceptive technology. There was a very small real attention paid to 'reproductive health', a concept that came into common use only after 1985. Around 1980 Swedish researchers initiated studies on maternal morbidity and maternal mortality, also covering maternal health services research. After the important Safe Motherhood Initiative Conference in Nairobi 1987 more research was initiated in maternal mortality and the Nordic research groups, above all in Sweden and Norway saw an increasing trend in research in reproductive health, which was stimulated by two events. Firstly, the publication in 1993 of the World Bank Report, 'Investing in Health' and, secondly, the International Conference of Population and Development (ICPD) in Cairo in 1994. The upsurge of the HIV pandemic also stimulated further research and this has gradually incorporated Danish and Finnish research groups and there is now a well established network of researchers and research students in this field with formal, regular research training courses financed by Nordic sources. There is a trend to establish bilateral links with universities in low-income countries in order to establish a critical mass in departments of obstetrics and gynaecology in universities in such countries. More and more of this research has moved away from purely clinical and laboratory-oriented research towards epidemiological initiatives focusing upon maternal and perinatal morbidity and mortality and gradually more and more on HIV issues. One breakthrough has been the establishment of a joint PhD degree between Makerere University and Karolinska Institutet, which indicates not only scientific collaboration but also a university collaboration at a formal academic level. This new line of practice entails a joint responsibility, joint assessment committees and joint responsibility for faculty examination of PhD theses. The concept of 'partnership' has come to stay, in line with the new paradigm of mutuality between high income and low-income countries. Gradually, it has become clear that much of pathology burdening low-income countries can be given attention with the technical and professional competence in university departments in high income countries.

## 17 ALARM International - the experiences of an education program to reduce maternal mortality

Kit Hansen, Midwife (Denmark), Kenneth Björklund, ObGyn (Sweden)

In 2003 the Society of Obstetricians and Gynaecologists of Canada (SOGC), invited its Nordic counterparts, NFOG and NJF, into a partnership in the ALARM International Program, which is a 3 to 5 day training course for health professionals in essential obstetrical care in developing countries. The program builds on evidence based medicine and current international guidelines and standards, and is intended also as a tool to disseminate the information available in the WHO Impac Manual ("Managing Complications in Pregnancy and Childbirth, a Guide for Midwives and Doctors"), while advocating women's sexual and reproductive rights. So far, 28 ALARM courses have been given in partnership with the local professional societies in 12 countries, with an emphasis on Guatemala, Haiti and Uganda.

Through the NFOG-NJF Going South Initiative, a Nordic midwife and an obstetrician participated in two ALARM courses in India in February 2004 and provided an evaluation as a basis for further decisions. The NFOG-NJF Going South Work Group decided to go ahead and prepare a proposal for Nordic participation in the ALARM Program based on:

- Cooperation between midwives and doctors
- A geographically defined target area
- Targeting those who actually assist deliveries in the target areas.
- Using an existing infrastructure to deliver the program.

Tanzania, Mocambique, Angola and Zambia have been identified as potential target areas for ALARM partnerships. Initially, a one week training course for Nordic ALARM Instructors (midwives and obstetricians) is to be arranged in Uganda, utilising Ugandan, Canadian and Nordic instructors. The Division of International Health at Karolinska Institutet, Stockholm, has offered to provide a Nordic base for delivering the ALARM Program utilising existing channels, including seeking funds for the project. The work plan has been prepared in cooperation with SOGC, Canada.

## 18 SAMOUZA-project - toward safer motherhood in the area of AIDS

Kenneth Björklund

## 19 Use of MIRENA® after birth

Jean-Luc Brun

*Dept of Obstetrics and Gynecology, University Hospital of Bordeaux, France*

MIRENA®, an intrauterine system (IUS that releases 20 µg of levonorgestrel per day for 5 years, has been shown to be a reliable method of contraception in all reproductive age women. Insertion is rather easy, and the efficiency (Pearl index < 0.2) and the good tolerance of MIRENA® result in a

continuation rate of 80 to 89% after one year. Non hormonal IUDs have been proposed to be inserted either immediately after delivery, or after 4 to 6 weeks postpartum. However, because of a trend toward a higher expulsion rate in the former group, a delayed insertion is mostly used in developed countries. Copper-releasing IUD has no effect on lactation or on the infant's health, and is an effective method of contraception. However, there is a risk of expulsion due to uterine contraction resulting from oxytocin release stimulated by suckling, and menorrhagia may occur once menses resume. Low-dose progestins are available in various combinations and delivery systems: progestin-only pills (POP), long-acting injectables, subdermal implants, vaginal rings and IUS. They are usually started within 6 weeks postpartum and are considered as effective contraceptives. Low-dose progestins did not show any deleterious effects on the quality and the quantity of milk, except for prolonged use of depo-medroxyprogesterone acetate. Low-dose progestins are safe for the nursing mother-infant pair. They do not affect infant growth, as assessed by the rate of change in weight or arm circumference. The infant development from mothers under progestins, assessed by tests covering gross and fine motor, language, self help and social skills, was not significantly different from controls. MIRENA® may be considered as an alternative to progestins given usually by pills or injectables in postpartum. The initial levonorgestrel levels in maternal serum are lower in MIRENA® users than in POP levonorgestrel users and in Norplant® users. Indeed, the performance of this IUS and the slight systemic transfer of levonorgestrel result in an efficacy/safety ratio at least as favourable as the other contraceptives. In 1982, Heikkilä assessed the clinical and biological maternal tolerance, the levonorgestrel levels in plasma and milk, the duration of breastfeeding and the development of children, in lactating mothers after the insertion of levonorgestrel-releasing IUS prototypes or copper-IUDs. With the exception of the first month post-insertion, menses-like bleeding was significantly more common in the copper-IUD group, compared to LNG-IUS groups, during 12 months of follow-up. However, since then, no specific study dealt with the use of MIRENA® in postpartum. Therefore, an open, multicentric, non comparative study is conducted in France, in order to assess at one year the tolerance, the acceptability and the efficacy of MIRENA® inserted 6 to 12 weeks after delivery.

## 20 Non-contraceptive benefits and acceptability of YASMIN®

Diana Mansour  
Consultant in Community Gynaecology and Reproductive Health Care, Head of Contraception and Sexual Health Services, Newcastle Upon Tyne, UK

Health professionals are aware that women complain of hormonal side-effects with different oral contraceptives. Progestogens in oral contraceptives differ, with some improving cycle control and others having anti-androgenic effects on the skin, leading to improved well-being and higher continu-

ation rates. However, complaints related to salt and water retention continue, with women taking these oral contraceptives still complaining of bloatedness, weight gain, breast tenderness and swelling. In the natural cycle, water retention due to estrogen in the follicular phase is counteracted in the secretory phase by the antimineralocorticoid effects of progesterone. With conventional oral contraceptives, no such balancing effect occurs. A new oral contraceptive, YASMIN®, has been developed which contains drospirenone, a progestogen resembling progesterone. This progestogen is quite unique as it is derived from 17 $\alpha$ -spiro lactone and has antimineralocorticoid as well as antiandrogenic properties. The addition of this compound to an oral contraceptive results in additional non-contraceptive benefits, leading to a reduction in salt and fluid retention caused by the action of ethinylestradiol and an improvement in skin conditions such as acne. The natriuretic action of drospirenone is consistent with the effect of being on a mild sodium diet. The effect of YASMIN® on skin has been evaluated over 9 cycles in 82 subjects with mild to moderate facial acne. A positive effect on acne and seborrhoea was observed with the median acne lesion count decreasing by 62.5% from baseline to cycle 9, whilst seborrhoea decreased by 25.1%. Initial studies investigating the contraceptive effects of YASMIN® in normal women suggested a non-significant improvement of premenstrual symptoms in YASMIN® users when compared to the women taking ethinylestradiol/desogestrel. The effect of YASMIN® on premenstrual symptoms has also been evaluated in a non-comparative 13-cycle study, with significant decreases from baseline observed in all subjects for negative affect, water retention and increased appetite.

## 21 Long-term Contraception for Young Women

Päivi Pakarinen  
Dept of Obstetrics and Gynecology, Helsinki University Central Hospital, Finland

The intrauterine delivery of levonorgestrel (LNG) from MIRENA® combines the beneficial effects of intrauterine and oral contraceptives. First of all, MIRENA® is highly effective in prevention of pregnancy. Unlike many other fertility control methods, the efficacy of MIRENA® is unrelated to the age of the user. MIRENA® has also non-contraceptive health benefits. The risk of pelvic inflammatory disease is lower during the use of MIRENA® than during the use of a copper IUD. The intrauterine release of LNG suppresses the endometrial epithelium, leading to a decreased number of bleeding days and decreased menstrual blood loss. This offers special health benefits: a better iron balance and the prevention of anemia. Dysmenorrhea associated with endometriosis has been reported to improve as well.

Traditionally, intrauterine devices have not been considered as contraceptives of first choice for young women. The reason is that young age, combined with frequent change of sexual partners, increases the risk of sexually transmitted diseases (STDs). However, intrauterine devices can be con-

sidered for a selected, well-informed group of young women who are not at risk of STDs.

To compare the clinical performance of MIRENA® with the traditionally used method in young nulliparous women, oral contraceptives, a randomized study comparing MIRENA® (n=94) with Marvelon® (30µg ethinyl estradiol and 150 µg desogestrel) (n=99), was carried out in Finland and in Sweden. The continuation rate at 12 months was higher in the MIRENA® group (79.8%) compared with the Marvelon® group (72.7%). In most cases (85%), the insertion of MIRENA® was reported as easy by the doctor. No perforations occurred. Moderate or severe pain was reported in 58.5% of insertions. In one case, MIRENA® had to be removed because of a partial expulsion at six months. No pregnancies or infections were reported in either group. Dysmenorrhea was alleviated to a greater degree in the MIRENA® group, compared to the Marvelon® group.

Another recent study with a 5-year follow-up compared the postabortal insertion of MIRENA® (n=305) and a copper IUD (Nova T®, n=133). The insertions were performed immediately after the termination of a first trimester pregnancy, and 31.6% of patients in the Nova T® group and 25.6% in the MIRENA® group were nulliparous. The expulsion rates for MIRENA® and Nova T® were highest during the first 2 years and also higher than previously reported for interval insertion. The discontinuation rate at 5 years because of pregnancy in the MIRENA® group (0.8%) was significantly lower than in the Nova T® group (9.5%). The incidence of PID was low in both groups.

**Conclusions:** In a selected, motivated and well-informed group of young and/or nulliparous women, MIRENA® offers a safe and effective long-term contraceptive option with added health benefits. Special attention should be paid to pain relief at interval insertion of MIRENA® in nulliparous young women. Insertion of MIRENA® immediately after termination of a first trimester pregnancy is both safe and feasible.

## 22 The background to a worldwide success in treatment of female stress incontinence

Carl Gustaf Nilsson  
Dept Obstet Gynecol, Helsinki University Central Hospital,  
Finland

**Background:** Female urinary incontinence is a common problem for more than 200 million women, causing substantial negative impact on quality of life of the individual and significant expenses for the community. The existence of a great number of surgical procedures for treatment of stress incontinence indicate that there has been poor consensus on how to surgically cure incontinence.

Complications related to the degree of invasiveness or failures due to inadequate ability of a method to create dryness results in figures of only 50 % of treated subjects to be both cured and complication free.

A great need for the development of new minimally invasive, effective surgical procedures for treatment of stress incontinence has for a long time existed. It requires an ability to question matters of course and a capacity to utilise interdisciplinary knowledge to succeed in a field that has made only modest progress for a long period.

**Methods:** Basic research and experimental work that span two decades, including development of modern urodynamics, imaging studies, and survey of tissue composite and character, has resulted in presenting a new theory explaining the cause of stress incontinence. Putting in to practice this "Mid-urethra Theory" resulted in the development of the Tension-free Vaginal Tape (TVT) procedure.

**Results:** By now, with eight years of experience, the TVT operation has been proven to result in excellent cure rates with low rates of complications. It has also been shown that the TVT procedure is suitable for treatment of the majority of women who are thought to benefit from surgical intervention.

**Conclusion:** Long lasting, systematic, interdisciplinary developmental work have resulted in an effective, new, minimally invasive operation for treatment of stress incontinence.

## 23 The choice of prolapse surgery

Erkki Kujansuu  
Tampere University Hospital, Finland

Half of women may have signs of pelvic organ prolapse (POP) and 1/5 of them may have symptoms as urinary, defecation and pelvic discomfort. POP is thought to affect women's sexual well-being through physical and emotional effects. In WHI study the rate of uterine prolapse was 14.2%; the rate of cystocele was 34.3%; and the rate of rectocele was 18.6%. Surgery for POP is frequent, in USA the lifetime risk of undergoing a single operation for POP or incontinence by age 80 is 11.1%. Reoperations occur in even 1/3 of cases, and the time intervals between repeat procedures decrease with each successive repair. The symptoms do not necessarily correlate to the degree of the POP. The presence of the anatomical defect does not imply dysfunction. Incomplete bladder or bowel emptying, frequency and urgency may be associated with POP. The prevalence of symptoms suggests the need for close questioning and the selective use of investigations for some women before surgery. Women with prolapse do not differ from continent women without prolapse in measures of sexual satisfaction. Deterioration of quality of life (QoL) associated with POP has not systematically been evaluated by valid methods. Routes of access for the repair of anterior, superior and posterior defects can be divided in abdominal, vaginal and laparoscopic. The choice often depends on the surgeon's experience. The laparoscopic approach is seldomly utilised due to its technical challenge. Sacrocolpopexy with mesh is the 'gold standard' of abdominal operations. of the vaginal procedures, uterosacral ligament vault suspension and iliococcygeous and

sacrospinous fixations have their proponents. The use of biological prostheses (allografts/xenografts) and synthetic absorbable meshes has been vividly promoted. Presently the evidence on operative treatment of POP relies heavily on case series and feasibility studies. Randomised studies comparing different operative methods for POP surgeries are emerging usually describing anatomic endpoints but also symptom relief as endpoints. Several case series of operative intervention for POP describe long-term satisfactory relief of the symptoms and even quality of life and social aspects of daily living. Valid responsive instruments for disease-specific QoL in POP exist and are utilised in newer studies. However, objective cure is not related to satisfaction. Operative treatment does not necessarily correct and may contribute to bowel and sexual dysfunction, particularly in those requiring multiple procedures and may be associated with emergence of varying degrees of urinary symptoms including incontinence. Dissatisfaction has been associated with feeling 'unprepared for surgery'. Currently the volume of controlled studies is still insufficient to give support for the choice of operation for an individual patient. The primary challenge of selection in POP surgery is not the choice of operation but the choice of patients who will have improvement of their QoL brought by the operation. For that decision it is essential to analyse patient's goals and expectations of the operation. To have scientific grounds to choose between different POP techniques we have to wait for decent randomised studies employing at least one disease specific and one generic QoL instrument with at least 2 years follow-up.

## 24 Sphincter lesion after delivery

Karl Møller Bek  
Aarhus University Hospital, Skejby Sygehus, Denmark

Anal sphincter rupture occurs in 2 % - 4 % of vaginal deliveries. Known risk factors are: primiparity, instrumental deliveries, shoulder dystoci, long second stage of labor, birth weight more than 4000g and episiotomy. Most interest has been addressed to episiotomy. The median episiotomy increases the risk of sphincter rupture more than the medio-lateral episiotomy. Lowering the rate of episiotomy does not always decrease the incidence of sphincter rupture. In recent years more interest has been given to control the baby's head when crowning. This may decrease the rate of sphincter rupture.

Anal incontinence following sphincter rupture is reported to be as high as 48 %. As a result of this coloproctologist has claimed that they should do the primary repair although it is the obstetricians who treat most patients. More education is needed. In most literature there is a lack of systematization of anal incontinence. A use of simple standard evaluation would make it easier to compare different studies.

There is no standard way of suturing the sphincter some use an end to end suture other use an overlap suture. No difference has yet been shown between the two ways of suturing.

Handling the patients after primary suturing of the anal sphincter advocate stool softener others do not. There are no reports of treating anal incontinence in the first weeks after a primary suture. Transanal ultrasound investigation can detect a torn sphincter. Early secondary suture can in our hands be done with good functional results within the first 2 week after delivery. This is important since the results of late secondary repair is good in only 80 % and the result deteriorates by time.

It is important to evaluate the sphincter function after primary repair some month after delivery.

## 25 How to deal with concomitant incontinence and prolapse

Ellen Borstad  
Ullevål University Hospital

The incontinence mechanism is in various ways affected by a genital prolapse. The prolapse may cause incontinence or mask incontinence. Prolapse surgery does not cure incontinence and may even cause or worsen incontinence. All types of prolapse can affect continence mechanism. About 20-25 % of women with prolapse have urinary stress incontinence (USI), even more have overactive bladder (OAB). USI could be masked by prolapse. Both prolapse and incontinence can be treated conservatively. This talk will be restricted to the surgical management. USI is caused by hyper mobility or weakness of the urethral sphincter. OAB in the case of prolapse is probably caused by stimulation of stretch receptors in the bladder wall. Scientific evaluation in this field is difficult because pathophysiology behind incontinence is multifactorial, and the prolapse and surgical procedures for correction of prolapse differ a lot even if the methods are described in the same way. Many studies agree that prolapse surgery alone is not enough to cure concomitant incontinence. The questions to be addressed: Which incontinence-procedure gives the best results? Burch colposuspension and sling procedures. Which procedures are most convenient to perform at the time of prolapse surgery? All vaginal procedures. Could risk of USI after prolapse surgery be predicted by preoperative testing? No reliable test available. Should incontinence surgery be performed at the time of prolapse surgery or at a later date? We don't know yet. Multicenter randomised studies are going on to clarify this. These questions will be discussed in detail Conclusion: The voiding function should always be investigated before prolapse surgery. The treatment of incontinence should be planned at the time of prolapse surgery or the patient properly counselled about the risk of not being cured of incontinence or the risk of even developing incontinence after prolapse surgery.

## 26 Molecular genetics in gynecology

T. Simoncini, L. Fornari, P. Mannella, A. Caruso, S. Garibaldi,  
A. R. Genazzani  
*Molecular and Cellular Gynecological Endocrinology  
Laboratory (MCGEL), Dept. of Reproductive Medicine and  
Child Development, University of Pisa, Italy*

The accomplishment of the Human Genome Project has opened in the recent past the unique opportunity to expand our knowledge on the basis of human physiology and disease as it was never imagined before. However, while the informations in our hands become available, we continue to discover how complex and difficult is to decrypt the basis of the living organisms, and we step everyday into new and unexpected findings. The comprehension of how the specific gene environment of an individual will turn into peculiar molecular processes that will influence her physiology or disease is of primary interest in gynecology, where we still face several important conditions that are still poorly understood. The old and wise attitude of collecting the familiar anamnesis in our patients is nowadays integrated by the growing possibility of obtaining a precise genetic portrait related to specific conditions. We now have the chance of identifying mutations in genes associated with cancer or with increased likelihood of developing adverse effects during steroid hormone administration. Through the understanding of the molecular genetics we now hope to increase our therapeutic weapons to treat cancer, endometriosis, uterine fibroids, infertility and other common gynecological conditions. In parallel, we have the burden of learning how to manage and treat and communicate to patients sensitive genetic informations, such as the knowledge of the presence of a deadly mutation that will develop its effects only years afterwards or the risk that a certain genetic condition will seriously affect the life of a newborn. Together with knowledge, we now have to build the medical ethics of the post-genome era.

## 27 Hormone therapy today - where now?

Margaret Rees

## 28 9-year results from a trial in Finnish women - safety and efficacy

Peter van de Weijer

## 29 9-year results from a trial in Finnish women - effects on bone

Jorma Heikkinen

## 30 Possible benefits of hormone therapy

Andrea R. Genazzani  
*Department of Reproductive Medicine and Child  
Development. Division of Obstetrics and Gynecology,  
University of Pisa, Italy.*

The use of HRT for prevention is based on biology, epidemiology, animal and preclinical data, observational studies and randomized clinical trials. The reduction of clinical consequences of estrogen deficiency is statistically significant, clinically relevant and, last but not the least, biologically plausible. The Women's Health Initiative (WHI) study clearly confirms overwhelming evidence accumulated in epidemiological, experimental and observational studies, showing that HRT reduces vertebral, hip and other nonvertebral fractures even in postmenopausal women not at risk of fracture. In this trial combined HRT reduces the relative risk of hip, spine and total fractures by 33%, 35% and 24% respectively. Being the most effective treatment in the management of climacteric symptoms, HRT has an important role in reducing bone turnover, preserving bone density and quality, leading to the prevention of osteoporosis and related fractures. When perimenopausal women use HRT to treat climacteric disturbances, they are effectively preventing the onset of osteopenia-osteoporosis. The osteoporosis prevention can be actually considered as a major additional effect of HRT. The WHI trial was unable to confirm the protective effect of HRT on cardiovascular risk. Methodological issues should be considered mainly concerning the age and the health status of the population included in that trial. Patient selection is the key factor to balance the benefits and the relative risks mainly related to the woman characteristics. In addition, the long-term safety of HRT may be related by the HRT regimen used. Now we know that lower doses of those used in the WHI trial elicit similar clinical effects on symptoms and superimposing bone sparing actions. New products and new combinations may help the clinicians to personalize the HRT for any given woman.

### 31 Fear of childbirth - does it matter for obstetricians?

Runa Heimstad, Raija Dahlø, Ingebjørg Laache, Eirik Skogvoll, Berit Schei  
Trondheim University Hospital

**Background:** Medical studies considering fear of childbirth has not previously been done in Norway. The aim of the study was to assess the prevalence of fear of childbirth, and relate this to selected sociodemographic factors and life events. A secondary aim was to explore the relationship between fear of childbirth and mode of delivery.

**Methods:** Questionnaire booklets were sent to 2680 women attending a routine ultrasound scan at 18 weeks of gestation, of whom 1368 women responded (51%). The questionnaire included different background factors, W-DEQ (measurement of fear of childbirth) and STAI (measurement for subjective anxiety).

**Results:** The prevalence of serious fear of childbirth (W-DEQ > 100) was 5.5 %. The W-DEQ and STAI scores were positively correlated ( $r = 0.44$ ,  $p = 0.000$ ). Among the anxious women, a trend towards more frequent operative vaginal delivery was noted (12.1 % vs. 6.9 %,  $p = 0.09$ ), but not regarding emergency caesarean section (10.6 % vs. 7.6 %,  $p = 0.34$ ). Women exposed to physical abuse in childhood had significantly higher W-DEQ score (71 vs 61,  $p = 0.01$ ), while physical abuse in adult life did not influence the score. Taking sexual abuse in childhood into account via regression analysis did not increase this score further ( $p = 0.34$ ). Considered separately, however, women sexually abused in childhood had higher scores (69 vs. 61,  $p = 0.05$ ). This factor was also strongly associated with mode of delivery, as only half of women sexually abused in childhood had uncomplicated vaginal delivery at term (54 % vs. 75 %,  $p = 0.001$ ).

**Conclusion:** The prevalence of serious fear of childbirth was 5.5 %. Physical abuse in childhood was associated with fear of childbirth, whereas sexual abuse in childhood strongly and negatively influenced mode of delivery.

### 32 Cesarean sections and neonatal outcome

Toril Kolås 1) Ola Didrik Saugstad 2) Anne Kjersti Daltveit 3) Dag Hofoss 4) Stein Tore Nilsen 4) Pål Øian 5)  
1) Department of Obstetric and Gynecology 2) Department of Pediatrics, Oslo University Hospital 3) The Norwegian Birth Registry of Norway 4) The Norwegian Medical Association 5) Department of Obstetric and Gynecology, Tromsø University Hospital

**Background:** To investigate the neonatal outcome after cesarean sections in Norway.

**Methods:** Prospective survey using information provided by clinicians at 24 maternity units. A specially designed form for each delivery was used and the neonatal data were derived from birth logs and infants journals. Data from vaginal births were derived from the Medical Birth Registry of Norway. 2380 singleton cesarean sections were included

in the survey from January 1. 1999 to July 1. 1999 representing 70.1% of all cesarean sections and 71.2% of all births in Norway in the same period.

**Results:** The cesarean section rate in singleton pregnancies was 12.5 %. About 63% of the cesarean sections were emergency operations. Bagging, intubation and chest compression were carried out in 8.5%, 4.3% and 1.9% of the cesarean sections, respectively. A comparison between elective cesarean sections and vaginal deliveries disclosed: 1) significant more children admitted to the NICU ( $p = 0.000$ ) in the section group, 2) increased risk for pulmonary disorders (TTN and RDS) ( $p = 0.000$ ) and respiratory treatment ( $p = 0.002$ ) after cesarean section, 3) no difference in the risk for cerebral irritation and cerebral depression ( $p = 0.582$ ) and for neonatal convulsions ( $p = 0.581$ ). Low Apgar score at 5 min (<6) was a risk factor for pulmonary disorders ( $p = 0.000$ ) and need for respiratory treatment ( $p = 0.000$ ).

**Conclusions:** This prospective study represents more than two thirds of all deliveries in Norway in the study period. The most important findings were that a vaginal delivery resulted in reduced risk for transferring to the NICU and for pulmonary disorders compared to an elective section. We stress the importance of trying to limit the use of elective operations to cases that benefit the mother or child.

### 33 Psychotherapy and relaxation in a group - an effective intervention against fear of childbirth

Terhi Saisto 1) Riikka Toivanen 2) Katariina Salmela-Aro 2) Erja Halmesmäki 1)  
1) Dept Obst Gyn Helsinki University Central Hospital 2) Dept Psychology Helsinki University

**Background:** The increase in numbers of women fearing childbirth and subsequent requests for cesarean sections (CS) call for new forms of antenatal classes.

**Methods:** In Finland, nulliparous women, at their 31st gestational week experiencing severe fear of childbirth (subjects,  $n = 102$ ) attended once a week 5 group classes (6 women per group) with psychologist and one with midwife. One postnatal class took place 3 months after the delivery. Each class consisted of psychotherapeutic analysis and discussion of fear and feelings towards becoming birth and parenthood, and after that relaxation exercises focused on an imaginary childbirth. The results were compared with 85 women treated for fear of childbirth conventionally by 2 appointments with an obstetrician (controls).

**Results:** Before the sessions, the subjects scored their fear of childbirth on a scale of one to ten to be  $6.9 \pm 2.0$  (mean  $\pm$  SD), and this fear interfered with their lives by a score of  $7.4 \pm 2.0$  (mean  $\pm$  SD). After the sessions, 84 subjects (82.4%) and 57 controls (67.1%) chose to have vaginal delivery ( $p = .02$ ). The subjects scored the help of the sessions by  $8.5 \pm 1.6$  (mean  $\pm$  SD) on a scale where 10 equaled maximum help and 1 equaled no help at all. The subjects mentioned 'sharing their feelings' as the most helpful factor in relieving

the fear, mentioned twice as often as 'receiving information'. The usefulness of the relaxation exercises was scored at 6.9+1.8 (mean+SD)(range 3-10) on a scale from one to ten.

**Conclusions:** Group psychotherapy and relaxation exercises were well accepted and estimated highly helpful. More CS requests were withdrawn in the subjects's group than in the controls and in previous studies. The strength of this therapy lies on small intense group of women sharing a common and limited problem.

### 34 Intimate Partner Abuse and Reproductive health - A Nordic, cross-sectional, multicenter study

B. Schei 1) B. Wijma 2) K. Swahnberg 2) M. Hilden 3) K. Offerdal 1) U. Pikarinen 4) K. Sidenius 3) T. Steingrimsdottir 5) H. Stoum 1) E. Halmesmäki 4)  
1) The Dept of Gynaecology, St Olavs University Hospital, Trondheim, Norway 2) Division of Women's Health, Dept of Molecular and Clinical Medicine, Faculty of Health Sciences, Linköping University, Sweden 3) Center for Victims of Sexual Assault, Rigshospitalet, Copenhagen University Hospital, Denmark 4) The Dept of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland 5) The Dept of Gynaecology, Landspítalinn, Reykjavik, Iceland

**Background:** The harmful effect of abuse on both physical, psychological and social health is a major concern. The impact on reproductive health has recently been acknowledged. The differential effect of abuse dependent on type of abuse and the nature of victim-perpetrator relationship remains to be explored. In this study we wanted to assess the impact of intimate partner abuse (IPA) on reproductive health factors.

**Methods:** We did a cross-sectional, multicenter study of 3641 women (77% of eligible) attending five departments of gynaecology in Denmark, Finland, Iceland, Norway and Sweden. Participants confidentially completed a postal questionnaire: NorVold Abuse Questionnaire (NorAQ). Women reporting physical abuse and identified current or former partner as offender were classified as victims of IPA. Questions were asked about experience with the gynecological examination, prior gynecological interventions and childbirths.

**Results:** IPA was reported by 20 % of the responders (ranging from 18 % to 26 % between countries). Experience of IPA was associated to uneasiness with gynecological examination, negative or mixed feeling of contact with gynecologist and negative or mixed experience with last childbirth.

**Conclusion:** To be abused by an intimate partner might effect trust in other people as e.g. health care workers and might therefore influence encounters with reproductive health service providers and thus act as risk for non-optimal care.

### 35 Associations between ill health and sexual abuse history among 3,593 gynaecological patients

Malene Hilden 1) Berit Schei 2) Katarina Swahnberg 3) Erja Halmesmäki 4) Jens Langhoff-Roos 5) Kristin Offerdal 6) Ulla Pikarinen 4) Katrine Sidenius 1) Tora Steingrimsdottir 7) Hildegun Stoum-Hinsverk 6) Barbro Wijma 3)  
1) Center For Victims of Sexual Assault, National University Hospital Rigshospitalet/ Dept. of Obstet. and Gynaecol., Copenhagen University Hospital Glostrup. 2) Department of Community Medicine, Norwegian University of Science and Technology. 3) Division of Women's Health, Faculty of Health Science, Linköping University. 4) Dept. of Obstet. and Gynaecol, Helsinki University Central Hospital 5) Dept. of Obstet and Gynaecol, National University Hospital Rigshospitalet 6) Dept. of Gynaecol., St Olav Hospital, Trondheim 7) Dept. of Gynaecol., Landspítalinn, Reykjavik

**Background:** There is reason to assume that a history of sexual abuse can be associated to a broad range of both mental and physical health problems. Sexually abused patients frequently complain of symptoms generated from the lower abdomen and the pelvic area. However, it is most likely that not all patients with a history of sexual abuse develop long-term sequelae. Characteristics of the abuse such as timing, course, and circumstances as well as the relationship with the abuser might influence the negative impact of abuse on health. Our aim was to determine if a history of sexual abuse was associated with objective and subjective indicators of health, and if certain abusive incidents were more strongly associated to ill health than others.

**Methods:** A cross-sectional, multicenter study at five gynaecological departments in the five Nordic countries. A total of 3,593 patients completed The NorVold Abuse Questionnaire on abuse-history and current health.

**Results:** Approximately 20 % of respondents reported a history of sexual abuse. A history of sexual abuse was significantly associated with chronic pelvic pain as reason for index visit ( $p<0.01$ ), laparoscopic surgery ( $p<0.01$ ), psychosomatic symptoms ( $p<0.01$ ), self-estimated poor health ( $p<0.01$ ), many health care visits ( $p<0.01$ ), and high incidence of sick leave ( $p<0.01$ ). Several subgroups within the group of sexually abused women were more likely to report poor health: women abused as both children and adults, women who experienced additional emotional and/or physical abuse, and women abused by a person they knew.

**Conclusions:** Sexual abuse history was strongly associated with ill health. Taking a history of sexual abuse seems particularly warranted when the patient presents with chronic pelvic pain or returns repeatedly with symptoms of a general and non-specific character.

### 36 Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on infant outcome

Tuija Heikkinen 1) Kari Laine 2) Ulla Ekblad 3) Pentti Kero 4)  
1) Dept. of Obstetrics and Gynaecology, University of Turku 2)  
Dept. of Pharmacology and Clinical Pharmacology, University  
of Turku 3) Dept. of Obstetrics and Gynaecology, University of  
Turku 4) Dept. of Pediatrics, University of Turku

**Background:** Ten to 20 percent of women suffer from mood and anxiety disorders during their pregnancy. Selective serotonin reuptake inhibitors have gained wide acceptance in the treatment of these mental disorders, but there seems to be an increased risk for neonatal adaptation problems after exposure to SSRIs in late pregnancy.

**Methods:** We conducted a prospective, controlled follow-up study with mothers taking 20 to 40 mg/d of either citalopram or fluoxetine for depression (n=10) or panic disorder (n=10) and their infants as well as 20 matched controls for confounding obstetric characteristics not receiving psychotropic medication. Maternal, cord blood and infant citalopram and fluoxetine and norfluoxetine concentrations as well as cord monoamine and metabolite and prolactin concentrations were measured. The newborns underwent standard clinical examination and specific assessment of serotonergic symptoms during the first 4 days of life and at the ages of 2 weeks and 2 months.

**Results:** There was a statistically significant ( $p=0.0078$ ), 4-fold difference in the serotonergic symptom score during the first 4 days of life between the SSRI group and the control group. The most prominent symptoms in the newborns included tremor, restlessness, rigidity and hyperreflexia. However, these adverse effects were essentially resolved by the age of two weeks. Citalopram and fluoxetine were detected in all mother-infant pairs. The SSRI-exposed infants had significantly lower cord blood 5-HIAA concentrations ( $p=0.015$ ) compared with the control group. A significant inverse correlation ( $r=-0.66$ ,  $p=0.0073$ ) was seen between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in the SSRI exposed but not the control infants. Exposure to SSRIs lead to lowered infant prolactin concentrations and this effect was stronger by fluoxetine compared with citalopram.

**Conclusions:** Infants exposed to SSRIs during late pregnancy are in increased risk for serotonergic central nervous system adverse effects and the severity of these symptoms was significantly related with cord blood 5-HIAA levels. Exposure to SSRIs during pregnancy seems to lower infant prolactin concentrations, which has been related to slow maturation of lungs and breathing difficulties after delivery.

### 37 Post partum pelvic pain - the 'Pelvic Joint Syndrome' - a diagnostic dilemma

Charlotte Wilken-Jensen 1) Annette Hansen 2) Dorte V Jensen 2) Elisabeth Larsen 1) Berit E Kaae 2) Frølich Søren 3) Henrik Larsen 4) Troels M Hansen 2)  
1) Department of Obstetrics and Gynecology 2) Department of Rheumatology 3) The Multidisciplinary Pain Center 4) Department of Diagnostic Radiology

**Background:** Chronic pelvic pain post partum – the pelvic joint syndrome – is a poorly understood condition and consequently there is a lack of methods to confirm the diagnosis. Objective of this study: To examine women with pelvic joint syndrome. The hypothesis is that there are characteristics in this group of women that separate them from women suffering from pelvic pain during pregnancy but who recover after delivery, and from healthy women.

**Material:** Fifty-eight women participated in the study, 21 with pelvic joint syndrome, 17 who suffered from pelvic pain during pregnancy but recovered within 2 months of delivery, and 20 controls with no history of pregnancy induced pelvic pain. Clinical examination, gynecological examination, psychological tests (MBHI – Million Behavioral Health Inventory), x-ray of the pelvis and the lumbar spine, magnetic resonance imaging of the pelvis, blood samples for inflammatory activity and signs of infection, and urine dipsticks for urinary tract infection were performed.

**Results:** No diagnostic method could explicitly differentiate between women with pelvic joint syndrome and the two control groups. No differences were found in x-ray, magnetic resonance imaging, or blood and urine analysis. Clinical – and gynecological examination, however, revealed significant differences with regard to provocative tests (letting one leg fall passively to the side provokes pain in the opposite iliac spine, standing on one leg provokes pain at the pubic symphysis) and tenderness in the muscles and ligaments in the low back and the pelvis. Furthermore, the psychological testing showed that women with pelvic joint syndrome had inefficient coping strategies compared to the control groups.

**Conclusion:** Women with pelvic joint syndrome have positive provocative tests. Bad coping strategies might be some of the explanation why these women develop pelvic joint syndrome. Whether this condition is amenable to therapy remains to be established.

### 38 Introduction: HRT at present

Sven Skouby  
Fredriksberg Hospital, University of Copenhagen, Denmark

For decades, hormone replacement therapy (HRT), which includes both estrogen and progestin, has been administered to postmenopausal women to mainly treat the symptoms of menopause and prevent osteoporosis, with the added benefit of preventing coronary heart disease (CHD). During the last few years, the Heart and Estrogen/progestin Replacement Study (HERS) and its extension trial, HERS II,

in postmenopausal women with CHD, the Women's Health Initiative (WHI) study (combined and estrogen-only arms) and the Million Women Study (MWS) have left clinicians wondering if HRT should be used at all, and if so, to whom and under what circumstances. The European Agency for the Evaluation of Medicinal Products (EMA) has pointed out through statements on the appropriate use of HRT the favourable benefit/risk balance in the treatment of climacteric symptoms that adversely affect the quality of life, but also emphasized that the minimum, effective dose and the shortest duration should be used. Most recently, however, the results from the estrogen-only arm of the WHI study have shown a reduced risk of breast cancer and a possible preventive effect on CHD in young postmenopausal women. In the light of these findings and based upon biological evidence, there are good reasons to believe that in the years to come hormonal treatment with lower doses, local progestin delivery and a wider range of progestins, used in a therapeutic window, will enable the establishment of individual beneficial effects on both climacteric symptoms and degenerative diseases after menopause. We truly believe that this particular symposium combined with NFOG lectures in general will substantiate and sustain the role of gynecologists as pivotal partners in taking care of the health and well-being of women at menopause and beyond.

### 39 MIRENA® in the perimenopause

Régine Sitruk-Ware  
Rockefeller University and Population Council, New York, USA

The levonorgestrel intrauterine system (LNG IUS) is an intrauterine device that directly targets the endometrium by releasing the potent progestin levonorgestrel (LNG) in low daily doses into the uterine cavity. The result is high local LNG concentrations that achieve uniform suppression of endometrial proliferation, inactive histology, thin epithelium and decidualization of the stroma. In addition the progestin has a potent effect on the cervical mucus that becomes totally hostile to sperm penetration. This is another key mechanism of action for contraception and prevention of fertilization. This major effect on the endometrium has many health benefits as well: By inactivating the endometrium and suppressing proliferation, LNG IUS decreases menstrual blood loss and pain. The LNG IUS also effectively provides local endometrial protection in perimenopausal women who often suffer of insufficient progesterone secretion and are at risk of endometrial hyperplasia. Several other conditions can be improved by the properties of the LNG IUS. These include treatment of idiopathic menorrhagia and associated anemia or menorrhagia due to leiomyomas. These are frequent conditions occurring during women's perimenopausal years. The LNG IUS also provides protection against endometrial proliferation in women receiving estrogen therapy. Therefore the system is well suited to the perimenopause condition and when menopause occurs, the system can remain in place and protect the endometrium when estrogen therapy is initiated. The LNG IUS is able to maintain these

contraceptive and therapeutic effects over 5 years by steady continuous release of low doses of LNG; this method thus avoids several of the side effects associated with systemic methods requiring high serum steroid levels.

### 40 Cost-effectiveness of MIRENA® in menorrhagia, new 5-year results

Ritva Hurskainen  
Helsinki University Central Hospital, Finland

Menorrhagia is an important cause of ill health in women worldwide. About one third report heavy menstrual bleeding at some time of their lives. Menorrhagia is the presenting symptom among the majority of women who undergo hysterectomy. Thus, it is important to consider the outcomes and costs of various treatment options to provide the most appropriate care. Studies on medical treatments, endometrial ablation and hysterectomy have raised important questions about health outcomes and allocation of resources for treatment of menorrhagia. Both the levonorgestrel-releasing intrauterine system (LNG-IUS) and hysterectomy have proven effective but no long-term comparative studies measuring cost and health-related quality of life have been carried out. We conducted a randomized trial between 1994-2002 to study these topics. Overall, 236 women aged 35 to 49 years who were menstruating, had completed their family size, and were eligible for both treatments were randomized to either receive a LNG-IUS (n=119) or undergo hysterectomy (n=117). The follow-up visits took place six months and 12 months after the treatment, and again five years after the randomization. After five years of follow-up, 233 women (99%) were analysed for the primary outcomes. The two groups did not differ in terms of health-related quality of life (measured by EQ-5D and Rand-36), or psychosocial well-being. Although 42% of the women assigned to the LNG-IUS group eventually underwent hysterectomy, the direct and indirect costs in the LNG-IUS group (\$2,817) remained significantly lower than in the hysterectomy group (\$4,660). There was equal satisfaction with the treatment in both groups. Of the 119 women randomized to the LNG-IUS group, 57 (48%) women (a replaced LNG-IUS in eight) had the LNG-IUS in situ and ten women (8%) were without the LNG-IUS. Fifty women (42%) had undergone hysterectomy. Of the 57 women with the LNG-IUS in situ, 43 (75%) reported amenorrhea or oligomenorrhea, 11 women (19%) had irregular bleeding and 3 women had only minimal spotting. Among the 60 women who did not continue treatment with the LNG-IUS, 42 (71%) reported intermenstrual bleeding, 19 (32%) heavy bleeding, and 18 (31%) hormonal symptoms (some had more than one complaints) as the reason for the removal of the LNG-IUS. Of the 117 women randomized to the hysterectomy group 109 underwent hysterectomy. Operative complications occurred in 33 (29%) women. In the treatment of menorrhagia, the LNG-IUS is a cost-effective alternative to hysterectomy. By providing significant improvement in HRQoL at a relatively low cost, the LNG-IUS offers a genuine improvement in

patient choice and reduces the burden of expensive surgical treatments.

#### 41 New progestins - different routes of administration and their use in hormone therapy

Regine Sitruk-Ware  
MD Rockefeller University and Population Council, New York,  
USA

The development of new generations of progestins to improve their selectivity profiles has been a great challenge. Steroidal and non steroidal progesterone receptor agonists have been synthesized as well, although the later are still in a very early stage of research. Several new progestins have been synthesized in the last decade and may be considered as a fourth-generation of progestins. This includes, dienogest, drospirenone, nestorone, nomegestrol acetate and trimegestone. They have been designed to have no androgenic or estrogenic actions and to be closer to the physiological hormone progesterone. Drospirenone differs from classic progestins as it derives from spiro lactone. It is essentially anti-mineralocorticoid with no androgenic effect but a partial antiandrogenic effect. The anti-ovulatory potency of the different molecules varies. All the molecules achieve the expected effect, but the less active compounds require higher doses to exert an antigonadotropic effect. Trimegestone and Nestorone are the most potent progestational compounds to date, followed by the gonanes, ketodesogestrel and levonorgestrel. Higher doses are required for the new molecules drospirenone and dienogest to achieve suppression of ovulation. The most potent progestins require low dosing and can be used in long-acting delivery systems such as transdermal systems, implants, vaginal rings or intra-uterine systems both for contraception and hormone therapy. Following the publications of the Women's Health Initiative study and the Million Women's study the controversy was raised regarding the role of progestins in hormonal replacement therapy (HRT) and some of the most prescribed molecules, with partial androgenic activity, have been shown to oppose partially the beneficial effect of estrogens on surrogate markers of cardiovascular risk. Unfortunately, this concern has been directed towards progestins as a class effect, although striking differences exist among the types of molecules used. Natural progesterone and some of its derivatives such as the 19 norprogesterone molecules or the new molecules drospirenone and dienogest do not exert any androgenic effect and have no negative effect on the lipids. The role of progestins on the breast tissue remains also controversial. However according to the molecule and the duration of application, cell differentiation and apoptosis may predominate over proliferation. Whether the progestins available to date are able to bind specifically to the progesterone receptors PR-A or PR-B and whether this is of clinical relevance to breast cell proliferation is still unknown. Although it is likely that the new progestins may be neutral on the coronary disease risk or on the breast, when administered to the younger postmenopausal women,

this has not as yet been documented by large randomized controlled trials and further research is warranted.

#### 42 Preeclampsia: New insights

James Roberts  
Magee-Womens Research Institute and University of  
Pittsburgh; Dept. Obstetrics Gynecology and Reproductive  
Sciences U of Pittsburgh; Dept. of Epidemiology U of  
Pittsburgh

Preeclampsia has been called 'The Disease of Theories'. New insights into clinical management and pathophysiology may change that title. Use of up to date clinical research tools has revealed that an empiric and not particularly rational approach to therapy is the appropriate management of eclampsia. Magnesium sulphate is more effective than conventional anticonvulsants to prevent recurrent eclamptic seizures and does prevent seizures safely in selected preeclamptic women. Attempts to prevent preeclampsia have been minimally successful but emphasize that eventual successful therapy must be initiated prior to evident disease. Pathophysiologically, preeclampsia is now approached as a two-stage disease. Stage 1 is abnormal implantation and failed vascular remodeling of maternal vessels supplying the intervillous space with consequent reduced placental perfusion. Stage 2 is the maternal syndrome. It is necessary to understand Stage 1 but Stage 1 is not sufficient to cause preeclampsia since IUGR pregnancies and pregnancies delivering preterm also have similar implantation abnormalities. This emphasizes the importance of a maternal contribution to the disorder, with genetic, environmental and behavioral factors influencing the maternal response to reduced perfusion. It also seems likely that the reduced placental perfusion may activate fetal signals to improve nutrient delivery that may not be tolerated by the mother, leading to preeclampsia. The most important question to direct therapy is what links the two stages of preeclampsia? There are many suggestions (microvillus fragments, placental cytokines, activated neutrophils and monocytes, sflt etc.) but many of these converge to support the concept that oxidative stress, generated in the intervillous space is transferred to the maternal systemic circulation causing Stage 2. There is abundant evidence to support this concept. Oxidative stress can be treated or prevented with antioxidant therapy. One small study suggests this therapy is effective and several large trials are now testing this definitively. There is reason for optimism!

#### 43 Preconceptional and antenatal care of Type 1 -diabetic pregnancies

Ulf Hanson, Department of Obstetrics and Gynecology,  
Uppsala University Hospital

Both from human and animal studies it is evident that increased blood glucose levels during conception and early pregnancy (first 10 weeks) is associated with increased

rate of major malformations. Recent data reveals that the increased risk starts already with close to normal HbA<sub>1c</sub> values and then increase with increasing deviation in blood glucose control. The mediating factor for malformation is probably increased level of free oxygen radicals. From animal research treatment with antioxidants as Vit C + Vit E has been shown to reduce malformations. Human studies are still not performed. Increased HbA<sub>1c</sub> in early pregnancy also independently increases the risk of preeclampsia. From other high-risk groups of preeclampsia treatment with Vit E + C has markedly reduced the rate of preeclampsia. Treatment with antioxidants may be a new exciting model to reduce both the malformation and preeclampsia rate in type 1-diabetic pregnancies.

Two remaining problems is increased intra-uterine fetal deaths (IUFD) and increasing rate of LGA-infants. CTG is commonly used to detect hypoxia but is of limited value to prevent IUFD since we don't know what we are looking for. A rapid intrauterine growth may be a risk factor for IUFD and probably indicate induction of delivery at 38 weeks. An increased placental transport of glucose and amino acids in spite of close to normal blood glucose may contribute to LGA-infants. We still lack good methods to predict the birth weight and risk of birth trauma before delivery. The possibilities to prevent IUFD and birth trauma in LGA-infants will be discussed from an epidemiological point of view.

#### 44 Drug and alcohol abuse

Erja Halmesmäki  
Dept of Obstetrics and Gynecology, Helsinki University Hospital

The most common teratogenic agent abused by a pregnant woman is alcohol. Alcohol abuse during pregnancy can cause fetal alcohol syndrome (FAS) or "fetal alcohol effects" (FAE). FAS is the full-blown teratogenic syndrome caused by alcohol; the newborn having

- 1) Birth weight, -length and head circumference < -2 sd for gestational age, poor growth in infancy and childhood
- 2) typical facial characteristics: broad short nose with prominent tip of the nose, thin upper lip, absent philtrum, narrow eyes and possible epicanthus folds, small chin, low and/or asymmetrical ears, etc
- 3) neurological symptoms and developmental delay

FAE means, that the infant has symptoms from 2 of the 3 categories and is known to have been exposed to alcohol during the intrauterine life. Most moderate drinkers stop or decrease their alcohol consumption markedly immediately they recognize the pregnancy. Of the heavy drinkers and alcoholics usually 2/3 succeed to decrease their drinking during pregnancy, but 1/3 continue to abuse alcohol through out the pregnancy. Heavy drinkers and alcoholics have a high incidence of cesarean sections, most often done due to suspected fetal asphyxia. The reason for this may be

the fact that the alcohol exposed fetus does not tolerate the normal stress associated with vaginal labor.

The most common drugs used by pregnant women in Helsinki are cannabis, amphetamine and opiates (heroin or buprenorphine), often associated with cigarette smoking, and use of high doses of benzodiazepines. Cannabis users are seldom motivated to quit smoking during pregnancy; amphetamine and opiate users, in stead, often say they will quit for the pregnancy. However, this seems to be very difficult, and even after a few weeks abstinence relapse to use drugs is commonly seen. Therefore, once the patient is recognized as a drug abuser during pregnancy, the personnel must always keep in mind the possible use of drugs, in spite of denial of use. The effects of cannabis on pregnancy and fetus are very much the same as nicotine: no fetal anomalies are associated with cannabis use, but heavy smoking may lead to intrauterine growth retardation.

Amphetamine users take their drug either intravenously, inhale it or mix it with tea or other drinks. These women are over energetic, thin, their weight gain during pregnancy is minimal, and fetal growth is often retarded. They are at risk of infections due to nonsterile and dirty infusions, and have a high risk of preterm delivery and chorioamnionitis. When exposed to amphetamine they usually give birth quickly, although the fetal CTG may have some decelerations. The withdrawal symptoms of amphetamine are exhaustion, sleepiness (2-3 days), and thereafter hunger and anger.

Most of our pregnant opiate users have been drug addicts for several years. Opiates are known to cause maternal bleeding and high risk of placental abruption, and fetal growth retardation. These women are at high risk of malnutrition and infections, and they do not seek adequate prenatal care in early pregnancy. Severe pain, hot and cold flushes, and cramps are typical withdrawal symptoms. Induction of labor for fetal indications is common among these patients, and for failed induction or suspected fetal asphyxia they may end up in cesarean section.

Hepatitis C is common among pregnant drug abusers: 70 % of our amphetamine and opiate users are Hepatitis C positive. Only two have been HIV positive. Because of Hep C, heavy smoking and continued drug abuse, breast feeding is not recommended.

#### 45 Pregnancy, nutrition and exercise

Torun Clausen  
Dept of Obstetrics, Ulleval University Hospital, Oslo, Norway

Nutrition in pregnancy has implications for maternal health and pregnancy complications and there are now substantial evidence that nutrition in pregnancy has implications for both short and long-term health of the newborn (Developmental Origins of Adult Disease).

Of great concern is the increasing prevalence of overweight and obesity worldwide and also in Nordic countries. The

main determinant of the obesity epidemic is an imbalance between declining energy expenditure due to physical inactivity and high energy in the diet (excess calories whether from sugar, starches or fat). Maternal overweight and obesity is associated with a broad spectrum of pregnancy complications like preeclampsia, pregnancy induced hypertension, gestational diabetes, operative deliveries, malformations, intrauterine fetal death, transfer of the newborn to neonatal intensive care unit, urinary tract infections, thrombo-embolic disorders and postoperative infections. Pre-pregnancy maternal overweight and gestational weightgain are strong predictors for macrosomia. The proportions of newborns with birthweight above 4000 and 4500 gram are increasing in Norway as well in other Nordic countries. "Macrosomic" pregnancies and deliveries are associated with increased risk of a number of serious pregnancy complications for both the baby and mother. Being born (too) large may have long-terms adverse health effects by increasing the risks of neurological sequels, overweight, diabetes and cancer.

Exercise has beneficial impact on obesity and on obesity-related disorders. In pregnancy exercise may limit weight gain and fat retention. In general exercise improves hypertriglyceridemia, improves insulin resistance and enhances resistance to oxidative stress which may be of importance to prevent pregnancy complications like preeclampsia.

Appropriate nutritional intervention before and during pregnancy may become an important area of preventive medicine in the future.

## 46 Carriers of hereditary disorders

Seppo Heinonen  
*Kuopio University*

Carriers of hereditary disorders, towards antenatal screening in maternal care Genetic tests are extending the potential of predictive medicine and it has become possible to examine future parents seeking advice before or during pregnancy. In a population level, screening for carriers of a number of recessively inherited diseases is currently feasible and could be incorporated to antenatal care. Screening tests, by definition, define who needs further testing and diagnostic tests are designed to provide definitive answers whether the fetus is affected or not. In 1968 the World Health Organization published criteria for screening (Wilson and Jungner 1968): condition sought should be an important public health problem, the natural history of the condition should be understood, disease screened should have recognizable latent or early symptomatic stage, screening test should be highly sensitive and specific, test should be ethically acceptable, there should be an accepted treatment for patients with recognized disease and this treatment at an early, latent or presymptomatic stage should favourably influence prognosis, facilities for diagnosis and treatment should be available, benefit of screening should justify the costs and case finding should be a continuous process. Commonly used molecular techniques used for antenatal

screening and prenatal diagnosis include PCR amplification and Southern blot analysis in large rearrangements. The visualization of amplified DNA products by gel electrophoresis, PCR and restriction enzyme analysis provides a simple, basic approach to the direct detection of mutations. Dot blot analysis is also popular for detecting small number of mutations and fluorescence-based automatic DNA sequencing is becoming the method of choice for characterization of unknown mutations. The development of genetic chips is underway and can revolutionize the gene technology in the near future. Chorionic villus sampling provides a good yield of DNA (35 ìg) for diagnostic tests and can be carried out in the first trimester of pregnancy. Less fetal DNA (1.5-5 ìg) is obtained in from an amniotic fluid sample than from chorionic villi and therefore it is advisable to set aside a small portion of the amniotic fluid sample for culturing in case of failure. The coamplification of maternal sequences if a potential diagnostic pitfall with all PCR-based techniques used for fetal DNA-diagnosis. Another potential source of error is the failure to amplify one of the target DNA alleles. A diagnostic error may also occur if the fetus inherits an unsuspected mutation as a result of non-paternity. Prospective parents should be adequately informed about antenatal screening, its purpose, its procedures and consequences. Genetic counselling should be neutral and nondirectional. Obstetricians are faced with the problems to provide guidance for judicious decisions and to maintain the public health perspective. We have explored the possibilities to integrate genetic testing into antenatal care. The spectrum of diseases consists Fragile X (FraX) and three monogenic disorders belonging to the "Finnish disease heritage" such as infantile neuronal ceroid lipofuscinosis (INCL), aspartylglucosaminuria (AGU) and congenital nephrosis (CNF), all four causing postnatal major morbidity. AGU and INCL are autosomal recessive diseases causing mental retardation and premature death, whereas CNF is a severe autosomal recessive kidney disease. Fragile X syndrome is a common X-linked cause of mental retardation. There is no cure for the diseases investigated. Employing carrier screening for these diseases has clearly shown that it is possible and reasonable to screen such difficult genetic diseases in an antenatal setting. As possibilities for genetic testing will become broader in the future, open public discussion will be needed to decide which diseases are worth screening. Accordingly, counseling and legislation concerning genetic testing should be further developed. Individual, social and financial issues should invariably be considered in any antenatal screening program.

#### 47 Lack of effect of isolated isoflavonoids on the climacteric symptoms, the vagina and endometrium

Eini Nikander 1, 2) Eeva-Marja Rutanen 2) Pekka Nieminen 2)  
Torsten Wahlström 2) Olavi Ylikorkala 2) Aila Tiitinen 2)  
1) Jorvi Hospital 2) Helsinki University Central Hospital

**Background:** Phytoestrogens are popular in treatment of climacteric symptoms although scientific evidence is insufficient as both to their efficacy and safety. We studied the effects of soy-derived isoflavonoids on climacteric symptoms, vaginal epithelium and endometrium.

**Methods:** Sixty-two postmenopausal women with a history of breast cancer used in a randomized order 114 mg of isolated isoflavonoids or placebo in tablets daily for three months; the treatment regimens were crossed over after a 2-month washout period. The women were studied before and on the last day of each treatment period. Menopausal symptoms were recorded on Kupperman index and visual analogue scale. Vaginal dryness, maturation index (MI) of vaginal epithelium, endometrial thickness, histology, and expression of estrogen and progesterone receptors and proliferation marker Ki-67 in the endometrium were assessed and the levels of isoflavonoids measured.

**Results:** The isoflavonoid regimen raised the circulating levels of phytoestrogens (daidzein, genistein, equol) 19- to 106-fold. The Kupperman index was reduced by  $4.2 \pm 9.6$  (mean  $\pm$  SD) (15.5%) during phytoestrogen use and similarly by  $4.0 \pm 8.1$  (14.7%) during placebo use ( $p=NS$ ). Isolated isoflavonoids did not relieve vaginal dryness. MI remained unchanged during the isoflavone regimen, but decreased during the placebo regimen ( $-5.6 \pm 17.2$ ,  $p=0.031$ ). No changes were found in any of the variables measured in the endometrium.

**Conclusions:** The daily administration of 114 mg of isolated isoflavones for three months did not alleviate menopausal symptoms. Neither had it effect on subjective perception of vaginal dryness nor on objective findings in the vaginal and endometrial epithelium.

#### 48 Apoptosis and expression of p53 in breast tissue during long-term hormone therapy in primates.

Peter Conner 1) Lambert Skoog 2) Bo von Schoultz 1) Mark Cline 3)  
1) Department of Obstetrics and Gynecology, Karolinska Hospital, Stockholm, Sweden 2) Department of Pathology and Cytology 3) Comparative Medicine Clinical Research Center, Winston-Salem, NC, USA

Conner P MD1, Skoog L MD PhD2, von Schoultz B MD PhD1, Cline J.M DVM PhD3. 1Departments of Obstetrics and Gynecology and 2Pathology and Cytology, Karolinska Hospital, Stockholm Sweden 3Comparative Medicine Clinical Research Center, Winston-Salem, USA

**Background:** Epidemiological studies have shown an elevated risk of breast cancer during combined estrogen/

progesterone hormone therapy (HT). Short term studies in women have shown higher breast epithelial proliferation during HT. The risk associated with HT may be due to increased proliferation which may cause transformation to the neoplastic phenotype. Inhibition of apoptosis is also regarded as a significant factor in carcinogenesis. The tumor suppressor gene p53 is known to regulate cell turn-over. For obvious reasons in-vivo studies on the cellular response to hormonal treatment are difficult to perform in women. The cynomolgus macaque has well documented similarities to women in terms of reproductive physiology. In the present study we analysed the expression of p53 and caspase-3 in breast tissue from surgically postmenopausal macaques after treatment with either estrogen alone (CEE), estrogen in combination with medroxyprogesterone acetate (MPA) or tibolone.

**Methods:** 60 oophorectomised macaques were randomised to receive either tibolone, CEE, CEE+MPA or placebo. Breast tissue was collected after 2 years and stained for p53, and caspase-3.

**Results and Conclusions:** The expression of p53 and caspase-3 was significantly lower in tibolone treated animals ( $p<0.01$ ). Levels of p53 and caspase-3 were also lower in the combined treatment group (CEE+MPA) when compared to both CEE and controls. Alternative regimens for HT seem to have different effects on p53 expression and apoptotic activity within the breast. The combination of increased proliferation and decreased apoptosis could be one possible mechanism to explain an increased risk for breast cancer seen with combined HT.

#### 49 Allopregnanolone serum concentrations decrease in response to a low dose of alcohol in the late luteal phase of the menstrual cycle.

Inger Sundström Poromaa  
Department of Women's and Children's Health

**Background:** Neurosteroids have been proposed to play an important role for the interaction between alcohol and GABAA receptors and for the symptomatology of premenstrual dysphoric disorder (PMDD). The aim of this study was to investigate possible alcohol-induced changes in allopregnanolone serum concentration in women with PMDD and controls across different menstrual cycle phases.

**Methods:** The allopregnanolone response to a low-dose of alcohol was evaluated in fourteen women with and twelve women without premenstrual dysphoric disorder in the mid-follicular phase and late luteal phase, by comparing the effects of an intravenous alcohol infusion (0.2g/kg) on allopregnanolone serum concentrations. Blood samples for measuring allopregnanolone were taken at baseline, after 25, 55 and 75 minutes of alcohol infusion.

**Results:** During the alcohol infusion in the late luteal phase, allopregnanolone levels decreased compared to placebo and compared to baseline levels. The difference between

alcohol and placebo was evident 25 minutes ( $p < 0.01$ ), 55 minutes ( $p < 0.01$ ) and 75 minutes ( $p < 0.05$ ) after start of the infusion. There was no change in allopregnanolone levels during the alcohol infusion in the follicular phase. Also, no difference in alcohol-induced allopregnanolone response between women with PMDD and control subjects was detected.

**Conclusion:** During the late luteal phase, independent of PMDD diagnosis, a low-dose alcohol infusion resulted in decreasing peripheral allopregnanolone levels.

## 50 Increased risk of Breast Cancer with HRT: Highest risk following the use of the continuous combined regimens.

Claudia Stahlberg 1) Anette Tønnes Pedersen 1) Elsebeth Lynge 2) Zorana Andersen 3) Niels Keiding 3) Yrsa Andersen 4) Erik Obel 4) Bent Ottesen 1)

1) Juliane Marie Centret, 4074, Rigshospitalet 2) Institute of public health, Panum Institute, University of Copenhagen 3) Institute of Biostatistics, Panum Institute, University of Copenhagen 4) The Danish Nurse Cohort, National Institute of Public Health, Copenhagen

**Background:** Observational studies and randomised trials have shown an increased risk of breast cancer in users of hormone replacement therapy (HRT). Scandinavian studies have suggested higher risk estimates than studies from USA. The aim was, to investigate how different treatment regimens of HRT frequently used in Scandinavia influence the risk of developing breast cancer.

**Methods:** The Danish Nurse Cohort was established in 1993 when all Danish nurses aged above 44 years, received a mailed questionnaire, which was returned by 19,898 women (86%). The questionnaire provided detailed information on the use of HRT, reproductive and lifestyle related factors. Women with previous cancer, previous hysterectomy, missing information on HRT, surgical- and premenopausal women were excluded, leaving 10,874 women for analysis. Breast cancer cases were ascertained using the Danish national registries. Follow-up ended 31. Dec 1999

**Results:** A total of 244 women developed breast cancer during follow-up. The risk of breast cancer was increased for current users of HRT compared to never users; RR 2.42 (1.81-3.26). The risk of breast cancer was increased two-fold with estrogen-only; RR 1.96 (1.16-3.34). With the combined use of estrogen and any progestin, the risk was increased with RR 2.65 (1.92-3.65). The highest risk was seen for users of the continuous combined HRT regimens and users of Tibolone; RR 4.16 (2.56-6.75) and RR 4.27 (1.74-10.51) respectively. The risk of breast cancer was statistically significant higher for the continuous combined regimen with testosterone-like progestins compared to cyclical regimens ( $p=0.01$ ), and was increased further with longer durations of use ( $p$  for trend 0.048).

**Conclusion:** The risk of breast cancer with different regimens of HRT was increased two to four-fold in current users

compared to never users. The highest risk was seen for the continuous combined regimens with testosterone-like progestins, which was further increased risk with longer durations of use.

## 51 Nationwide cohort study on cancer incidence among Finnish HRT users 1994-2001

Heli Kaarina Lyytinen 1) Olavi Ylikorkala 2) Eero Pukkala 3) 1) Department of Obstetrics and Gynecology, Helsinki University Central Hospital 2) Department of Obstetrics and Gynecology, Helsinki University Central Hospital 3) Finnish Cancer Registry, Helsinki, Finland

**Background:** National differences exist in cancer occurrence and in hormone replacement therapy (HRT). We studied cancer incidence in Finnish women using HRT (transdermal, oral and vaginal estrogens with or without progestins) in 1994-2001.

**Methods:** Women over 50 years using HRT ( $n=223\,464$ ) for at least 180 days between 1994-2001 were identified from the national medical reimbursement register. These data were linked to Finnish Cancer Registry data base covering almost 100% of cancer cases.

**Results:** A follow up to the end of 2002 revealed 13 040 incident cancer cases in HRT users versus 11 373 expected on the basis of national incidence rates: the standardized incidence ratio (SIR) was 1.15 and its 95% confidence interval 1.13-1.16. The SIR for breast cancer among HRT users was 1.38 (1.35-1.41) and highest in ages of 70-79 years (SIR 1.78; 1.63-1.94). The overall SIR for endometrial cancer was 1.40 (1.32-1.47) but in ages of 70-84 as high as 2.32 (2.03-2.62). The SIRs for cancer of the ovaries (SIR 1.05; 0.97-1.14), bladder (1.02; 0.88-1.16) or liver (0.81; 0.62-1.04) were not significantly different from the national average. The incidence of cervical cancer (SIR 0.68; 0.54-0.84) and biliary tract cancer (SIR 0.69; 0.57-0.82) was below the national average. The incidence of colorectal cancer was only reduced in age range 65-74 years (SIR 0.84; 0.75-0.94).

**Conclusions:** The elevated incidence rates of breast cancer and endometrial cancer induce an increased overall cancer incidence in Finnish HRT users. Further analyses in the present cohort will elucidate the impact of confounding factors and type and duration of HRT.

## 52 The risk of ischaemic heart disease with hormone therapy among women with early menopause

Ellen Løkkegaard 1,4,5) Zorana Jovanovic 2) Berit Lillienthal Heitmann 3) Niels Keiding 2) Bent Ottesen 1) Anette Tønnes Pedersen 1)

1) The Juliane Marie Centre, Copenhagen University Hospital

2) Department of Biostatistics, University of Copenhagen

3) Research Unit for Dietary Studies and the Danish Epidemiology Science Center at Institute of Preventive Medicine 4) Ob/Gyn Dept. Hvidovre Hospital, Denmark 5) The Danish Nurse Study, National Institute of Public Health

**Background:** Studies find that early menopause is a risk factor for ischemic heart disease. Randomised clinical trials find that use of hormone therapy after the age of 50 does not protect against development of ischaemic heart disease. Yet, a very relevant clinical question is whether substitution with female sex steroids reduces this risk associated with early menopause.

**Objective:** To analyse whether early menopause is a risk factor for ischaemic heart disease and to analyse whether the risk is modified by use of hormone therapy.

**Methods:** In 1993 a prospective Danish Nurse Cohort was established by mailing questionnaires to all female members of the Danish nurse association above 44 years of age. Information on menopause, use of hormone therapy and lifestyle was obtained. Cases of incident ischaemic heart diseases were identified through individual linkage to in national register until end of 1998. Multivariate Cox survival analyses were used.

**Results:** In total 380 women (3.6%) experienced menopause prematurely before 40 years and 1,967 women (18.7%) early between the age of 40 and 45. Early menopause was associated with an increased risk of ischaemic heart disease. In general we found no protection of hormone therapy on ischaemic heart disease among early menopausal women. However among women where early menopause was caused by ovariectomy, a 3-fold increased rate of ischaemic heart disease (hazard ratio 2.9 95% confidence interval (0.9-9.5)) was observed among never users compared to ever users of hormone therapy.

**Conclusion:** Our finding of a reduced risk of ischaemic heart disease among early-ovariectomised women using hormone therapy is of potential great clinical relevance, but need to be confirmed in other studies. Also potential risks associated with hormone therapy among early ovariectomised should be elucidated.

## 53 Hormone therapy and cardiovascular disease. A 1.8 million women Danish National cohort study

Ellen Løkkegaard 1) Øjvind Lidegaard 1,2) Agger Carsten 3) Andreassen Anne Helm 3) Møller Lisbeth 3)

1) Danish Centre For Human Reproductive Epidemiology

2) Dept Ob/Gyn, Herlev Hospital 3) Research Centre For Prevention and Health, Copenhagen County, Denmark

**Background:** The randomised controlled trial (Women Health Initiative Study) on continuous combined conjugated oestrogen and progestagen found no evidence of a protecting influence of hormone therapy (HT) on the risk of cardiovascular disease (CVD). Several new unanswered questions have emerged from the new evidence. Our aim has been to analyse the associations between various HT regimens/routes of administration and CVD in a National cohort of Danish women.

**Methods:** In 1977, the National Register of Patients (NRP) was established. NRP receives discharge diagnoses on all in- and outpatients from all Danish hospitals. A central prescription register (LSR) was established in Denmark in 1994. LSR collects information about all cashed prescribed medicine. There is now legal permission for scientists not only to get data from LSR and NRP, but also to merge information from the two registers through personal identification numbers. From Statistics Denmark information on potential confounders as education and job-status is achieved for all women.

**Results:** During the period 1995 through 2002, more than 500,000 Danish women 50-69 years old were followed with a daily update on all prescriptions of HT and of medical indicators for hypertension, hypercholesterolemia, cardiovascular disease and diabetes. During the eight-year follow-up period, we expect 11,000 incident myocardial infarctions and 10,000 incident strokes. By cox-regression analyses hazard ratios will be estimated among women exposed for specific types of hormone therapy, i.e. specific regimens, specific progestagen types, and specific routes of administration (oral, transdermal, IUD or local).

**Conclusion:** We hope to present the first results from the ongoing analysis. The merging of data in NRP and LSR provides together with other Danish registers one of the most powerful tools in pharmacoepidemiology available in our present post-HT randomisation era.

## 54 Genetics of endometriosis

Reynir Tomas Geirsson

Department of Obstetrics and Gynecology, Landspítali University Hospital

**Background:** Familial endometriosis is well recognised from several studies that have described smaller clusters and sister-pairs with a 5-9 times raised risk in first-degree relatives. Evidence from twin studies, from magnetic resonance studies in close relatives and from animal studies has sup-

ported an inherited susceptibility in what may be a genetically controlled and culture-related disease.

**Methods:** Existing data will be reviewed and new evidence presented of the way the disease presents in families, both in milder and particularly in the more severe forms, showing what is currently known about the genetic background of the disease. Use of kinship coefficients and minimum founder testing has cast a new light on heritability in endometriosis.

**Results:** A polygenic/multifactorial susceptibility is likely. Searches for a single gene defect among several candidate genes relating to detoxification and metabolic processes have been inconclusive or negative, but there is knowledge about aneuploidy and loss of heterozygosity in several chromosomes in endometriotic lesions and in endometrioid cancer. The relative risk is not only raised among sisters but also cousins. Family clustering in larger family trees based on multigenerational analysis has been verified, along with fewer family founders when reaching 5-6 generations back among patients compared with controls, giving higher kinship coefficients in endometriosis. The disease can be inherited through the paternal as well as maternal side. Studies in families have suggested two possible phenotypes with some concordance in close family members, one with early onset of disease characterised by severe dysmenorrhea and more infertility and the other with later onset and a shorter prodroma before diagnosis and a lesser effect on fertility. Genome-wide scans are as yet inconclusive.

**Conclusion:** Endometriosis is probably inherited through a multifactorial genetic pathway and may have more than one phenotypic form in families, while women with endometriosis may share more of a common inheritance than obvious on simple questioning of patients.

## 55 Endometriosis and medical treatment

Mutsuo Ishikawa  
*Asahikawa Medical College, Japan*

**Background:** Endometriosis is one of the common cause of pelvic pain and involuntary infertility in women. Unfortunately, treatment of this disease in women desiring future childbearing continues to be disappointing; surgical treatment is associated with high recurrence rates.

**Methods:** Setting University hospital in Japan Objective To determine the effect of medical treatment for endometriosis after surgery on pain and infertility 385 patients with surgical-confirmed endometriosis and significant endometriosis-associated pain and 420 patients with surgical-confirmed endometriosis and infertility were analyzed for efficiency of medical treatment.

**Results:** Recurrence rate on dysmenorrhea reached to 40% within one year after surgery. After 5 years, recurrence rate of dysmenorrhea was lower in the danazol group than in the Gn-RHa group (43% versus 70%). The respective pregnancy rates within 3 years after surgery were 60% and 55% in

women under 25 years old and 30 years old (difference not significant) and 37% and 20% in women under 35 years old and over 36 years old (difference statically significant). A significantly lower pregnancy rate was observed in the ovarian suppression group with danazol and Gn-RHa (35%) as compared with the nontreated group (50%).

**Conclusion:** This study does not support the medical treatment for endometriosis after conservative surgery in women with infertility.

## 56 Indications for surgical treatment of endometriosis

Axel Forman  
*Department of Obstetrics and Gynaecology, Aarhus University Hospital, Aarhus, Denmark*

Indications for surgical treatment of endometriosis depend on severity of symptoms relative to the clinical effects, complication rates and possibilities for other therapy. Infertility does not by itself represent an indication for major surgery since excellent results can be achieved by in vitro fertilisation. Pain, as well as impaired organ function may motivate even extended operative procedures, while absence of these problems indicates a more cautious attitude even in advanced endometriosis. The technical principles should include intended macroradical removal with use of minimal invasive surgery and preservation of genital organ function in fertile women. Ovarian endometriomas should almost invariably be removed with maximum preservation of functional tissue. Oophorectomy is not justified in women with continued wish of pregnancy. Comparative data on the various methods and the use of two-step procedure with intermittent GnRH treatment are however sparse. Rectovaginal endometriosis should be radically removed since medical treatment seems insufficient. The techniques applied range from local excision without penetration of the rectal wall over discoid full wall excision to more or less routine use of resection of the affected bowel segment. There is so far no general agreement on the optimal approach in this area. There is some evidence that a significant part of these patients would profit from laparoscopically assisted low anterior resection. Complications rates for these techniques need however to be evaluated in large series before the exact indications can be evaluated. The role for the levonorgestrel IUD as an alternative needs further evaluation. Ureteral stenosis should be released and neoimplantation may be motivated in a few cases. Bladder endometriosis often induces marked symptoms and should be excised laparoscopically. The use of minimally invasive techniques, the effectiveness of surgery and complication rate depend on the experience and skill of the operator. Surgery should therefore be performed in specialized centres.

## 57 Does endometriosis predispose to malignancy

Agneta Bergqvist 1) Anna-Sofia Melin 2) Pär Sparen 3)  
1) Department of Obstetrics and Gynecology, Karolinska Institutet, Danderyds Hospital, Stockholm, Sweden 2) Department of Obstetrics and Gynecology, Huddinge University Hospital, Stockholm, Sweden 3) Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Large register studies have shown an increased risk in endometriosis patients for malignancies, above all cancer in the ovaries, other endocrine organs, breast and brain, but also melanoma and non-Hodgkin's lymphoma. The highest risk has been found in women with ovarian endometriosis to develop ovarian cancer. Morphologic studies have shown a continuous growth of benign endometriosis to atypical endometriosis and further to cancer, mainly in the ovaries, but also in other structures as the rectovaginal wall. The majority of ovarian cancers are clear cell cancer and endometrioid ovarian cancer, two types that are not generally the most common types of ovarian cancer. There is a time factor involved as the risk is higher in women with endometriosis started in early ages and in long standing disease. The tumor markers bcl-2 and p53 are differently expressed in endometriotic tissue if bordered to ovarian cancer, indicating that bcl-2 and p53 are involved in malignant transformation of endometriotic tissue. Chromosome activation, Loss of Heterozygosity (LOH) in several genes, allele versions and somatic mutations in some genes as TP53 and PTEN indicate that early somatic genetic changes represent early phases of malignant transformation of benign endometriosis. Different pathogenic mechanisms will be discussed.

## 58 Cardiovascular effects of hormone therapy - timing is crucial

Tomi Mikkola  
Helsinki University Central Hospital, Department of Obstetrics and Gynecology, Finland

Postmenopausal hormone therapy (HT) is typically initiated around the age of 50 for the control of menopausal symptoms. Many women continue HT past the menopausal transition and from these women epidemiological data have been gathered on health effects of the long-term hormonal treatment. Numerous observational studies show that HT provides protection against coronary heart disease (CHD) and these favorable findings are supported with a large body of experimental data documenting that HT inhibits early stage atherosclerosis progression. Since no observational study can fully eliminate confounding factors, randomized, placebo-controlled trials (RCT) have been in demand. The Women's Health Initiative (WHI) was expected to solve this dilemma. Due to the difficulty to carry out RCT in women entering menopause WHI was designed to explore older postmenopausal women based on the assumption that HT would be beneficial regardless of when it was started. The women recruited to WHI were in average 12 years past menopause and had various CHD risk factors. Furthermore,

the treatment was with high 0.625mg dose of conjugated equine estrogen (CEE) alone or combined with medroxyprogesterone acetate (MPA). With huge publicity the CEE+MPA arm of the WHI study was prematurely halted in July 2002, and the CEE-only arm in February 2004, mainly because HT did not show protection against CHD. It has been shown that estrogen may have deleterious effect on existing atherosclerosis plaque while healthy vascular wall is protected. Therefore, the 'window of therapeutic opportunity' to reduce CHD risk by HT may be only in women entering menopause and not in older women well beyond menopausal transition, such as the WHI population. Thus, WHI results are not fully applicable to typical menopausal women starting modern HT in clinical practice.

## 59 Bleeding control and endometrium safety with special emphasis on low dose hormone therapy

Lars-Åke Mattsson  
Sahlgrenska University Hospital, Sweden

Epidemiological studies have shown that a majority of women taking HRT prefer to use formulations that will not induce bleeding disturbances. Accordingly many women prefer continuous combined HRT to obtain amenorrhoea. Lower doses of estrogens compared to those previously prescribed such as estradiol 1 mg, conjugated equine estrogens 0.3 mg orally per day or transdermally applied estradiol 25 g per 24 hours have been found to be effective in the treatment of vasomotor symptoms. Low dose HRT administered as continuous combined regimens induce amenorrhoea in most women after a few months of treatment. Adherence to treatment has also been shown to be higher in women on continuous combined treatment compared to in those given sequential regimens. Low doses of progestogens especially when given on a continuous basis have been shown to protect the endometrium from hyperplasia. Norethisterone acetate in a dose of 0.1 mg per day given together with 1 mg estradiol has been reported to effectively protect the endometrium from development of hyperplasia. In addition fewer side effects such as mastalgia have been found during treatment with low dose regimens compared to high doses. Individualisation of treatment with regard to dose and duration seems to be important. In women requesting HRT it might be a rational alternative to start with low dose formulations since these doses are sufficient for the majority of women.

## 60 Breast issues with hormone therapy

Ole-Erik Iversen  
Haukeland University Hospital, Bergen, Norway

Several questions are relevant to the issue: To what extent is the risk increased? Do progestins modify risk estimates? Is morbidity in HRT-users different? Is mortality of breast cancer affected? Can it be given to breast cancer patients? The available evidence consists mainly of more than 70

observational studies. Recently, some information from randomized controlled trials has become available and the results are mainly in line with those from the observational studies, although the target populations were of considerably higher age (mean 63-67 years) than the typical woman starting HRT. It is important to emphasize that for short term treatment (<3-5 years), cancer risk is of limited importance in the risk-benefit equation. In sum, the relative risk of breast cancer associated with more than five years of use is estimated to be approximately 1.35. The risk for every year of use is comparable to that of postponing the menopause for one year. The increased risk is not measurable five years or more after cessation of treatment. Several studies have been reported after the extensive collaborative review, published in 1997. More focus has recently been on risk modulation of the added progestagen. Many of the studies published after 1997 report a higher risk estimate for HRT compared to ERT, but the picture is not quite consistent. Neither is it consistent whether there is a difference if progestagens are given continuously combined or sequentially. Further, another unresolved issue is whether the drugs used in Europe (mainly E2/NETA) confers a different risk than the preparation mostly used in the USA (CEE/MPA). Most studies on the distribution of prognostic factors in breast cancer in HRT-users have so far shown favourable results regarding tumor size, stage and grade, while that was not the finding in the WHI-study. Similarly, it seems to be a fairly consistent observation that mortality and survival of breast cancer is better among previous HRT-users. The MWS-study on the other hand, tended in the opposite direction. Previous breast cancer has been considered to be an absolute contra-indication for HRT, although this has never been scientifically proven in clinical trials. A recent Norwegian Health Technology Assessment (HTA) concludes that there is not scientific evidence either to recommend or warn against use of HRT in women previously treated for breast cancer. In the overall equation regarding HRT and cancer, the consistent reduction of colorectal cancer incidence and mortality from it should also be brought into consideration.

## 61 Anti fracture efficacy of HRT in postmenopausal osteoporosis

Leif Mosekilde  
*Department of endocrinology and Metabolism C, Aarhus University Hospital, Denmark*

Osteoblasts, lining cells, osteocytes and chondrocytes express oestrogen receptors, whereas osteoclasts are influenced indirectly by members of the osteoblastic cell line through the RANK, RANK-L, OPG system. In the adult skeleton oestrogen reduces bone turnover, inhibit excessive osteoclastic resorption, promote osteoblastic bone formation, reduces the remodelling space, and increases bone mineral density (BMD). Thereby it increased trabecular thickness and reduces trabecular separation. Epidemiological studies have revealed a 25 % reduction in fracture risk by HRT. However, recall bias and healthy user effects may have

influenced these studies. Whereas the randomised HERS study showed no effect on hip fracture rate, the women's health initiative (WHI) demonstrated a 34% reduction (RR = 0.66, 95% CI 0.45-0.98). This antifracture effect has been supported by metaanalyses also including spinal fractures. However, none of the studies investigated the effect of HRT initiated within the first 2 years after the menopause.

In the Danish Osteoporosis Prevention Study (DOPS) we studied the 10-year fracture reducing potential of estradiol used alone or combined as primary prevention initiated early after menopause.

We used the comprehensive cohort study design with one study arm randomised to hormonal replacement therapy (HRT, n=502) or no HRT (n=504) and one study arm where the participants were allowed to choose HRT (n=221) or not (n=789) by own choice. A total of 2,016 randomly selected early postmenopausal (from 3 to 24 month past last menstrual bleeding) women with a median age of 50 years (range 45-58) were included and followed for 10 years. The first line HRT contained estradiol with or without norethisterone.

The women were followed for 18,653 person years. BMD increased significantly among HRT users in the spine, the hip and the forearm. Analysed by the intention-to-treat method the risk of any fracture was borderline reduced with HRT (OR=0.78, 95% CI: 0.60-1.03) mainly due to a decline in the early forearm fractures (OR=0.60, 95% CI: 0.39-0.93) (Fig). The number of spine fractures was not reduced (OR=0.95, 95% CI: 0.66-1.39). It is concluded that HRT containing estradiol has a fracture reducing potential even in a low risk group of early postmenopausal women treated for 10 years.

## 62 IUGR and macrosomia

Karel Marsal  
*Department of Obstetrics and Gynecology, Lund University Hospital, Lund, Sweden*

Fetal growth abnormalities, both the growth restriction (IUGR) and growth acceleration resulting in fetal macrosomia, are associated with adverse outcome of pregnancy, increase in perinatal mortality and morbidity. The rate of intrauterine death is significantly associated with IUGR throughout the second half of gestation. The most common cause of IUGR is uteroplacental insufficiency with risk of developing severe hypoxia/asphyxia antenatally or during labor. In addition to the risk of permanent hypoxic/ischemic brain damage, there is a risk of suboptimal postnatal development and programming for cardiovascular and metabolic disease in adult age. The risk to the macrosomic babies are mainly the complications during labor and intrapartum trauma. Identification of small-for-gestational age (SGA) and large-for-gestational age (LGA) fetuses is crucial for estimation of the individual intrauterine risks. A prerequisite is a reliable estimation of gestational age, optimally by a routine ultrasound examination in the first half of pregnancy. The

diagnosis of SGA fetus is done by finding an ultrasonically estimated fetal weight deviating from the expected weight. This allows for targeted monitoring of fetal wellbeing using biophysical examinations of fetal functions - doppler velocimetry, fetal heart rate monitoring, ultrasound examination of amniotic fluid volume and fetal activities. Based on these examinations, appropriate timing of delivery can be chosen in order to prevent intrauterine death and hypoxic damage. The methodological error in ultrasonic estimation of fetal weight in macrosomic fetuses is higher than in normally grown or small fetuses. Identification of risk factors, e.g., diabetes, post-term pregnancy, maternal obesity and weight gain, remains therefore an important way of detecting macrosomic fetuses. However, the clinical and ultrasound findings are usually not enough predictive with regard to intrapartum complications, e.g. shoulder dystocia. Possibly, the precision might be improved using 3-dimensional ultrasound and examining fetal soft tissue.

### 63 Chromosomal aberrations

Hulda Hjartardottir  
*Reykjavík University Hospital, Iceland*

The detection of chromosomal defects before birth has changed dramatically in Iceland in the last few years. In 1998 497 women in Iceland underwent amniocentesis due to advanced maternal age and two cases of trisomy 21 were detected. Two fetal losses occurred for every chromosomal defect detected. In Iceland nuchal translucency scans have been offered since 1999, at first only to a high risk group, adding biochemical screening to this service in 2002 and since 2003 opening the service to everyone. The results in the year 2002 were that out of 1194 women (30% of the pregnant population) screened 50 were screen positive (i.e. risk >1:300) or 4.2%. Out of those 49 had a chromosomal analysis performed by CVS or amniocentesis and this led to the diagnosis of 9 chromosomal defects. In the screen negative population 3 chromosomal defects were detected, two at birth and one after second trimester amniocenteses due to maternal concern. The sensitivity of the screening test was therefore 75%. These numbers suggest that using this screening method there should be one fetal loss for every 18 chromosomal defects detected. A further three chromosomal defects were detected in the group of women at risk due to maternal age or previous history, choosing a diagnostic test and declining the screening test. The total number of invasive tests was 204. In the year 2003 2194 women accepted the screening test or close to 60 % of the pregnant population. Screen positive tests were 72 and 11 chromosomal defects were detected. At 174 the total number of invasive tests is still dropping. An added advantage of first trimester screening is the early detection of serious fetal anomalies. Six such cases were detected in 2003. Further details of the effectiveness of the program will be discussed.

### 64 Parvo-virus infection

Morten Lebech

### 65 Fetal hemodynamics in risk prediction

Torvid Kiserud  
*University of Bergen, Haukeland University Hospital, Dept. Obstet. Gynecol., Bergen, Norway*

**Background:** Today ultrasound examination including Doppler measurements is one of the main methods of identifying and managing pregnancies at risk. Data from animal experiments and observations in human studies point at fetal hemodynamics as an interesting indicator of changes in risk pregnancies. The aim of this presentation is to give an overview of some hemodynamic mechanisms relevant in the clinical assessment.

**Methods:** By reviewing some of the literature on animal experiments and human clinical studies, a number of hemodynamic mechanisms and circulatory sections are presented as clinically applicable measurements or promising for future clinical assessment.

**Results:** Gestational age, regulation of cardiac output, regulation of local circulation and autoregulation, distributional priorities and redistribution capacity are important factors reflected in the hemodynamic assessment. The importance and relative inertia of the umbilical circuit makes the umbilical artery and vein important markers for placental compromise. The auto-regulation of the fetal brain makes the middle cerebral artery an important indicator for fetal responses to hypovolemia and hypoxemia, and has evolved to be a good predictor of fetal anemia and placental compromise. Similarly, the circulation of the fetal lungs, kidneys, adrenals and liver are of increasing interest in the global assessment. The isthmus aortae and the left portal branch are hemodynamically important watershed-areas. The pulsatile pattern of precordial veins including the ductus venosus and umbilical vein is increasingly useful in predicting cardiac decompensation and hypoxemia.

**Conclusions:** Umbilical artery pulsatility, umbilical vein flow and pulsation, precordial vein pulsatility, middle cerebral artery pulsatility and peak velocity have established themselves as predictors of anemia, hypoxia, circulatory compromise or demise. The isthmus aortae, left portal vein are promising indicators of shift in regional blood distribution. The pulsatility changes in the adrenals, kidneys, spleen, liver and lungs may form new contribution to a more complete hemodynamic assessment of the fetus at risk.

## 66 The diverse priorities of gynecological care in the enlarged EU

Gunta Lazdane

## 67 Hormonal contraceptives and venous thromboembolism

Øjvind Lidegaard  
Herlev University Hospital, Denmark

**Background:** The incidence rate of venous thromboembolism (VTE) in non-pregnant women of fertile age increases from one to three per 10,000 per year with increasing age. Current users of hormonal contraception (HC) have a 3-4 fold increased risk of VTE.

**Survey:** The majority of women experiencing a VTE have a genetic predisposition for VTE. These disorders (and their background prevalence) include factor V Leiden mutations (5%), deficiency in protein C, S or antithrombin (0.3%), Prothrombin 20210A mutation (2%), and hyperhomocysteinemia (3%), so that about 10% have a genetically increased risk of VTE. Prevention of VTE in young women, therefore, primarily should be focused on identifying women at risk, and thereafter attempting not further increasing the risk of VTE in these susceptible individuals. A relevant personal and family history is the primary screening tool in clinical practice, a coagulation screening the next. Only women with a suspect personal or family history should be offered a coagulation screening. Conditions increasing the risk of VTE more than 10 times should be considered as absolute contraindications against HC. Factors increasing the risk 3-10 times constitute relative contraindications whereas women with less than a three fold increased risk of VTE may use HC.

**Conclusion:** If women at an increased risk of VTE are prescribed HC, progestagen only contraception and oral contraceptives with 2nd generation progestagens should be the first and second choice.

## 68 HRT and SERMS

Sven O. Skouby 1) Johannes J Sidelmann 2) Lars Franch Andersen 3) Jørgen Jespersen 2)  
1) Department of OB/GYN, Frederiksberg Hospital, University of Copenhagen 2) Department for Thrombosis Research, University of Southern Denmark 3) Department of OB/GYN, Hillerød County Hospital

Convincing data from observational studies on post menopausal hormonal therapy (HT) combined with information from the recent randomized trials, the Heart and Estrogen/progestin Replacement Study (HERS), its extension trial (HERS II) and the Women's Health Initiative (WHI) study (combined and estrogen only arms) have demonstrated a two- to threefold increased risk of venous thromboembolism (VTE) during HT. The risk is increased for oral estrogen alone or estrogen combined with a progestin. The risk, however, is dose dependent and probably dependent of the route of

administration. Also an increased risk is found with the selective estrogen receptor modulators (SERMS) raloxifene and tamoxifen. The mechanisms responsible for this increased risk are not known in detail, but studies focusing on few HT-regimens indicate that there is an effect of HT on the inhibitory potential of coagulation, with possible consequence for the turnover of fibrin. This can contribute to the proneness of thrombosis. Inherited risk factors, such as Factor V Leiden- and the prothrombin G20210A-mutation, as well as acquired risk factors, such as obesity and smoking, are commonly present among women in the Western World, exposing a number of women at increased risk. We have undertaken a detailed study on healthy women treated with different types of oestrogen/progestin combinations. The study focussed on biochemical key risk markers for VTE using standardized and internationally recommended assay procedures. Our study demonstrates that HT reduces the inhibitory potential of coagulation significantly irrespective of the regimen, but also that the formulation and duration of the treatment is of importance. Combined with the epidemiological studies this indicates that HT can trigger precipitating of thrombosis in women already at risk. Furthermore, women developing VTE when treated with HT have a higher frequency of inherited risk factors for thrombosis, e.g. the Factor V Leiden mutation. Altogether these findings support that some women are in a thrombosis prone condition prior to HT treatment and that HT may cause the thrombosis to precipitate.

## 69 Pregnancy and puerperium

Risto Erkkola  
Dept Obstetrics and Gynecology, Turku University Central Hospital

Normal pregnancy is characterized by dramatic changes in hemostatic mechanisms. There is an overall increase in coagulation factors, particularly fibrinogen, and suppression of fibrinolysis. Together with increase of blood volume, these changes help to counteract the postpartum bleeding, but carry with them an increased risk of venous thromboembolism (VTE). VTE is a cause of serious morbidity during pregnancy and post partum. Pulmonary embolism (PE), although rare, is a substantial cause of maternal mortality. In Finland, in years 1970-94, one hundred maternal deaths occurred. PE was the leading cause of mortality in 22% of all deaths (together with bleeding catastrophes during pregnancy, labor and post partum, which also accounted for 22% of deaths). Yet the risk of death for PE was only 1/70 000 births. As the accuracy of the diagnosis is insufficient, the incidence of VTE during pregnancy and post partum is not known. However, the symptomatic, pregnancy related VTE has been reported to occur in 1-2/1000 pregnancies. In post partum period the risk may be as high as 3-5/1000, and after cesarean sections 3-16 fold to that after vaginal deliveries. There are also studies which maintain that the risk is substantial already in the first two trimesters, and doubling in the third trimester. These studies claim that the risk is equal during pregnancy and post partum. As the accuracy

of the diagnosis is insufficient, the incidence of VTE during pregnancy and post partum is not known. However, the symptomatic, pregnancy related VTE has been reported to occur in 1-2/1000 pregnancies. In post partum period the risk/week may be as high as 3-5/1000, and after cesarean sections 3-16 fold to that after vaginal deliveries. The main risk factors of a VTE in pregnancy are a previous VTE, congenital thrombophilia, multiparity, and cesarean section. In 90% of cases the VTE is in the left leg, and it is 8 times more often an iliofemoral VTE than in the calf veins. Septic pelvic thrombophlebitis occurs most often post partum with fever which is resistant to antibiotics. The clinical diagnosis of VTE is very inaccurate, and, instead, the objective diagnosis is crucial. Real-time or duplex ultrasonography is the first line diagnostic tool. If PE is suspected, ventilation-perfusion lung scan can be performed. Lung scans should be combined with ultrasound venography.

## 70 Travel and surgical procedures

Margareta Hellgren  
*Institute For Health of Women and Children*

Travel and surgical procedures M Hellgren, Antenatal Care Department, Southern Bohuslän County Primary Health Care and Institute for the Health of Women and Children, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden The occurrence of thromboembolism after travel has been known since 1954, although this particular category represents a minor proportion of all thromboembolic complications. The risks associated with air travel have recently attracted interest. Blood coagulation and fibrinolysis are activated during conditions simulating high altitude. The incidence of verified thromboembolic complication (TE) following flights of minimum 8 hours duration varies between 0 and 10 per cent. The absolute risk of pulmonary embolism has been reported at approximately 1 per 200 000 air travellers. Other risk factors for TE, such as increasing age, immobilisation, thrombophilia and hormone treatment are often present in these cases. The risk of TE is approximately doubled following air travel. Thrombophilia and oral contraceptive use are associated with a 16-fold and 14-fold risk, respectively. Most TE is diagnosed within 2-4 weeks after travel. Thromboprophylaxis can be achieved with compression stockings, exercise, and anticoagulants and by avoiding dehydration. TE has been well known complications of surgery for many decades. The prevalence of TE related to gynaecological surgery varies between 15 and 20 per cent. The incidence is probably lower today since more procedures are performed laparoscopically. Pelvic surgery is, however, performed closer to large veins, presumably increasing the risk of TE. Thromboprophylaxis with heparin/low molecular weight heparins and dextran has been reported to decrease the TE risk, without serious adverse events, and is recommended for certain risk groups. Some questions concerning dose and duration of thromboprophylaxis remain unanswered. Postoperative start and prolonged duration are new aspects. Low molecular weight heparins

have been reported to improve long-term survival in connection with malignancy.

## 71 Bone is a target of several different hormones

Kalervo H. Väänänen  
*Institute of Biomedicine, University of Turku, Finland*

Life cycle of bone includes a growing and maturation period and a remodelling period. Cellular processes during these are different and thus, for instance, their hormonal regulation could be different. In this presentation I will mainly discuss the hormonal regulation of bone remodelling and turnover. Bone remodelling is the most important physiological process maintaining bone quality through the life. Rate of bone turnover also directly regulates bone mass and most 'bone active' physiological and pharmacological agents somehow affect the remodelling cycle. During recent years it has become evident that most hormones acting on bone have more than one target cell and that the effects could be on differentiation, function or survival of specific cell types. Final action may involve cell-mediated interactions between different bone cell lineages. The effects of calcitonin and PTH are probably best characterized. They both have a dramatic influence on bone turnover, which in case of PTH is strictly dependent on duration and dose of exposure and in which both main cell lineages, osteoblastic and osteoclastic are clearly involved. In case of calcitonin bone actions could be satisfactorily explained by its effects on osteoclasts. The role of steroid hormones, especially sex steroids, is of paramount importance in the regulation of bone remodelling. However, their define actions are still somewhat obscure at the cellular level although they are well established at the tissue level. The main effect of oestrogen at the tissue level is balancing of bone turnover and inhibition of bone resorption. Recent results suggest that this may be mainly indirect effect on osteoclast differentiation being mediated via osteoblastic cells. In addition to its effects on osteoblastic lineage testosterone, in contrast to estradiol, seem to have a direct inhibitory effect on osteoclast differentiation. Bone is also a target for several other steroid hormones. Their effects are known mainly only at the tissue level. In addition of above mentioned hormones several other peptide hormones have been described to have effects on bone either in in vitro or in vivo experiments. In addition, various knock-out models have re-shaped our understanding on hormonal regulation of bone.

## 72 Biophysical detection of increased bone loss and risk of fractures

Marco Gambacciani  
*Department of Obstetrics and Gynecology, University Hospital Pisa, Italy*

Patients with low bone mineral density (BMD) are at higher risk for fracture. Not all people at risk have access to BMD

measurements. Inexpensive methods identifying high-risk patients could improve healthcare delivery. Quantitative bone ultrasound (QUS) is accepted as an effective, low-cost method to identify women for fractures. We determined the specific T-score cutpoint on the Lunar Achilles InSight that detects 90% of individuals with osteoporosis (T-score < -2.5). We compared the performance of ultrasound screening to a calculated risk assessment tool based on subject weight and age. A total of 272 women aged 40 to 83 years (mean age  $58 \pm 7$  years) had QUS using a Lunar Achilles InSight (GE Healthcare). Female reference values for Europe were used to compute T-scores based on Stiffness Index (SI), a linear combination of speed of sound (SOS) and broadband ultrasound attenuation (BUA). The same subjects had DXA measurements at the spine and hip using a Lunar DPX. T-scores for spine (L1-L4) or total hip were calculated using Italian female reference values. The osteoporosis risk assessment (ORA) tool was completed for each subject:  $((\text{Weight in kg} - \text{age}) \times 0.2)$ . ROC analysis based on Achilles InSight T-score and the ORA tool was performed to obtain the area under the curve and its 95% confidence interval. Logistic regression was performed to assess the predictive value of the combination of QUS and the ORA tool compared to the predictive value of QUS alone. The area under the curve (AUC) was 0.79 for the heel T-score and 0.69 for the ORA tool ( $p < 0.05$ ). For the combination of the Heel T-score and ORA Tool the AUC is 0.81 that was not significantly better than QUS T-Score alone. At a measured heel T-score of -1.0, sensitivity was 91% and specificity was 46% while at a ORA tool value of 2.4 the sensitivity was also 91% but the specificity was only 29%. Thus, QUS can be used as a valid screening tool for osteoporosis. Moreover, QUS performs significantly better than does the calculated osteoporosis risk assessment tool.

### 73 Prevention of bone loss and fractures by HRT and SERMs

Lars-Åke Mattsson  
Department Ob/Gyn, Sahlgrens University Hospital/East,  
Göteborg, Sweden

Bone fragility may lead to an increased susceptibility to fractures. Long-term disability and mortality are health consequences of osteoporosis-related fractures. The decrease in ovarian function among peri- and postmenopausal women is the single greatest contributor to bone loss. A number of pharmacological agents have been proposed for prevention and treatment of osteoporosis, e.g. hormone replacement therapy (HRT) and selective estrogen receptive modulators (SERMs). Both these compounds have a similar anti-resorptive mechanism and are effective in preserving cortical and trabecular bone at all stages of postmenopausal life. Clinical trials have found HRT to be effective in increasing bone mineral density (BMD) and it affects biochemical markers reflecting bone turn-over positively. Lower doses than those previously used have been reported to be equally effective. Evidence that estrogens prevent fractures is sparse,

compared to that regarding BMD. Epidemiological studies confirm a lower fracture risk among women taking HRT and suggest a protection magnitude of about 50%. Recently the Women's Health Initiative (WHI) study showed that five years of HRT reduced fragility fracture risk by at least 30%. One SERM compound (raloxifen) is approved for prevention and treatment of postmenopausal osteoporosis. This agent is an estrogen agonist in bone but an antagonist in the breast and uterus. One big four year study showed a significant decrease in the cumulative risk of new vertebral radiographically diagnosed fractures by 55% in women with low BMD. However, the cumulative risk of non-vertebral fractures after four years did not differ from placebo. Conclusion Both HRT and SERMs have been reported to have positive effects on BMD and fragility fractures. Recently, safety authorities recommended that HRT should not be considered as first-line therapy for prevention of osteoporosis in women aged over 50 due to an unfavourable risk/benefit ratio. Tibolone and SERMs were not included in these recommendations.

### 74 Prevention of bone loss and fractures by nonhormonal agents

Richard Derman

### 75 Comparison of two risk of malignancy indexes as a rationale for operative treatment of ovarian tumors

Annika Auranen 1) Juha Mäkinen 1) Pertti Palo 1) Seija Grénman 1) Seth Granberg 2)  
1) Department of Obstetrics and Gynecology, Turku University Hospital, Turku, Finland  
2) Department of Obstetrics and Gynecology, Karolinska Hospital, Stockholm, Sweden

**Background:** After clinical finding or suspicion of an adnexal tumour both ultrasound and tumour marker Ca 12-5 have been used to differentiate between benign and malignant disease. In order to help the evaluation of the tumour the so-called risk of malignancy index (RMI) has been developed. In this study two different RMIs presented by Jacobs (1990) and Tingulstad (1996) were compared.

**Methods:** 115 consecutive patients with suspected benign or malignant ovarian disease were enrolled into the study. Especially, the sensitivity and specificity of the models were compared.

**Results:** Final diagnosis of the 115 ovarian tumours showed 13 malignant, 6 borderline and 96 benign histology. The sensitivity of the Jacobs' model was 92.3% and that of Tingulstad even 100%. The corresponding figures for specificity were 94.8% and 89.6%, respectively.

**Conclusion:** From this study we can conclude that Tingulstad's RMI is better to exclude malignancy but Jacobs' RMI results in a smaller number of wrong positive cases.

## 76 Autopsy study of the prevalence of adnexal cysts in postmenopausal women.

Anne Dörum 1) Gustav Blom 2) Erling Ekerhovd 3) Seth Granberg 4)

1) Department of Gynecological Oncology, The Norwegian Radium Hospital, Norway, 2) Department of Pathology, Akershus University Hospital, Norway, 3) Department of Obstetrics and Gynecology, Sahlgrenska University Hospital, Göteborg, Sweden 4) Department of Obstetrics and Gynecology, Ultrasound Unit, Karolinska Hospital, Stockholm, Sweden

**Background:** Increasing numbers of cystic structures are detected due to the increased use of ultrasound. Thus the question is: How many malignancies will be found among these and is expectative management an option? The purpose of this autopsy study was to examine the prevalence and histology of adnexal cysts in postmenopausal women.

**Methods:** A total number of 468 adnexa from 234 women were included in the study. The adnexa were removed from the body, fixed in 4% formaldehyde solution, and examined by the team pathologist. Macroscopic appearance of the adnexa was assessed according to standard routine procedures, and presence and number of both ovarian and extraovarian cysts as well as solid tumors was registered.. The mean age of the women was 73 years, with a median of 75 years and a range of 45-96 years.

**Results:** Ovarian cysts were found in 36 (15.4%) women. Eight (3.4%) women had ovarian cysts with a mean diameter between 20 mm and 50 mm, while four (1.7%) cysts were more than 50 mm in diameter. Four women had bilateral ovarian cysts. Paraovarian cysts were found in 11 (4.7%) women. All cysts were benign, except one woman who had bilateral serous cystadenoma of borderline type. These two cysts were macroscopically multilocular.

**Conclusion:** Due to the high prevalence of benign adnexal cysts the identification of small unilocular cysts in postmenopausal women should be regarded as a normal finding.

## 77 Medical vs. Surgical abortion - comparing efficacy and complications in a partly randomised study

Christina Rørbye, Lisbeth Nilas  
H:S Hvidovre Hospital, Copenhagen University, Dept. of Obs/Gyn

**Background:** Observational studies have proven medical abortion to be safe and efficacious. Few comparative studies of medical and surgical abortion exist including only complications within the first few days. We compared efficacy, complications, leave of absence and unscheduled contacts to the health care system within three months follow-up.

**Methods:** A partly randomised study of 1,135 consecutive women with GA≤63 days receiving either a medical (mife-

pristone 600 mg and gemeprost 1mg) or a surgical abortion (vacuum aspiration in general anesthesia). 111 accepted randomisation, 1/3 (n=355) of the remaining women chose the medical and 2/3 (n=669) the surgical termination. Success was defined as no following surgical intervention or shift of method within three months. Surgical interventions and complications leading to readmission were identified through a computer system. Information about antibiotic treatment, leave of absence and the number of contacts to the health care system were obtained from mailed questionnaires.

**Results:** Compared to medical abortion, surgical abortion was associated with a higher success rate (97.7% (708/725) vs. 94.1% (386/410),  $p<0.01$ ) but also with a higher risk of antibiotic treatment (7.8% (37/476) vs. 3.7% (13/356),  $p<0.05$ ). The success rate after medical abortion decreased with increasing gestational age, but was unaffected by gestational age after surgical abortion. Within two weeks the median leave of absence was shorter in women choosing a medical (1 day) than a surgical termination (2 days),  $p<0.05$ . On average one third of all the women requested at least one extra unscheduled consultation apart from the routine follow-up visit.

**Conclusions:** The chance of a primary successful termination is higher after a surgical compared to a medical termination, but is followed by an increased risk of antibiotic treatment. The women's need for follow-up might be higher than we expect.

## 78 Multiparity predicts failure in medical pregnancy termination

Maarit Niinimäki 1) Hannu Martikainen 2) Anne Talvensaari-Mattila 3)

1) Department of Obstetrics and Gynecology 2) Department of Obstetrics and Gynecology 3) Department of Obstetrics and Gynecology

**Background:** Medical pregnancy termination has shown to be an effective and safe alternative to traditional surgical vacuum aspiration. With the combination of mifepristone and misoprostol the success rate has been over 90 % in most studies, and serious complications seem to be extremely rare. The aim of this study was to find out predictive factors for failure in first trimester medical abortion.

**Methods:** We analyzed results in the first two years with medical abortion using 200 mg mifepristone given orally and misoprostol 800 ug by vaginal administration. This study consisted of 316 consecutive women with a pregnancy of 63 days' gestation or less choosing medical pregnancy termination between September 2000 and August 2002. The patients were analyzed by demographic data, complications and results (failed abortion when curettage was needed for any reason).

**Results:** Curettage was needed in 29 (9.2 %) cases. Previous pregnancy terminations or miscarriages did not have

any correlation to success, while there was an association with curettage and age ( $p=0,0003$ ), previous pregnancies ( $p=0,008$ ) or live births ( $p=0,0001$ ). In logistic regression the risk for curettage was 4.4-fold when there were three live births or more.

**Conclusions:** Previous live births were the strongest predictor for failed medical abortion. Women with over 40 years of age or multiparity may have increased risk for failure in first trimester medical pregnancy termination.

## 79 Can ultrasound replace D & C? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer

Berit Gull, Bengt Karlsson, Ian Milsom, Seth Granberg  
Dept of Obst&Gyn, Sahlgrenska University Hospital,  
Göteborg, Sweden

**Background:** To evaluate postmenopausal bleeding (PMB) and transvaginal sonographic (TVS) measurement of endometrial thickness (ET) as predictors of endometrial cancer (EC) and atypical hyperplasia (AH) in women during a >10-year period following a PMB.

**Methods:** Women who presented with a PMB from November 1987 to October 1990 were included in this study ( $n = 394$ ). The women underwent TVS with measurement of ET and a dilation and curettage (D & C). It was possible to assess the medical records of 339 of the 394 women (86%) >10 years after referral for PMB. During the follow-up period the recurrence of a PMB, the development of EC and mortality were assessed.

**Results:** After the primary investigation, 39 of the 339 women were diagnosed as having EC (11.5%) and 5 women had AH (1.5%). The relative risk (RR) of EC in women referred for PMB was 63.9 (CI 46.0 – 88.8) and the corresponding RR for EC and AH together was 72.1 (CI 52.8 – 98.5). None of the women with an ET of  $\leq 4$  mm were diagnosed as having EC. The RR of developing EC in women with an ET of  $>4$  mm was 44.5 (CI 6.5 – 320.1) compared to women with an ET  $\leq 4$  mm. The reliability of ET (cut-off  $\leq 4$  mm) as a diagnostic test for EC was assessed: sensitivity 100%; specificity 60%; PPV 25%; and NPV 100%. After the primary assessment 82 women underwent hysterectomy or hysterectomy and salpingo-oophorectomy. The incidence of EC or AH in women with an intact uterus followed  $\geq 10$  year was 5.8% (15/257). The corresponding figure for women who had  $\geq 1$  recurrent bleeding during follow-up was 22.7% (15/66). No EC was diagnosed in women with a recurrent PMB who had an ET of  $\leq 4$  mm at the initial scan. No EC was diagnosed in the absence of a recurrent bleeding. Conclusion: PMB incurs a 64-fold increase risk for EC. No EC was missed when ET measurement (cut-off  $\leq 4$  mm) was used even if the women were followed  $\geq 10$  years. There was no increased risk of EC or atypia in women who did not have recurrent bleedings whereas women with a recurrent bleeding were a high

risk group. Finally, we would like to emphasize that a thick endometrium, with histopathological diagnosis of atrophy or insufficient for diagnosis, should be taken seriously and a guided biopsy should be taken or saline instillation sonography performed with ultrasound guided biopsy.

## 80 Hysterectomy after endometrial ablation - A National follow up 1996-2003

Øjvind Lidegaard  
Herlev University Hospital

**Background:** Unselected long-term follow up of endometrial ablations (EA) are rare. Our aim was to assess the frequency of secondary hysterectomy in all women undergoing endometrial ablation in Denmark.

**Material and methods:** During the period 1996-2002, a total of 8,543 EA were conducted at Danish Gynecological departments. These were identified in the National Register of Patients (NRP). All the women were followed in the NRP for later re-ablation or hysterectomy.

**Results:** Among those who underwent EA without fibroid resection, the proportion of hysterectomised increased almost linearly from 6% after one-year follow until 29% after seven years follow-up. The frequency of re-ablation increased correspondingly from 1% to 9%. Thus, within seven years follow-up, 38% are re-operated. The follow-up adjusted hysterectomy rate ranged from 4.4% until 12.8% per year follow-up at different departments. For each year the woman's age increased at the EA, the re-operation rate after three years follow-up decreased with 1%.

**Conclusion:** A substantial part of women undergoing EA are later hysterectomised. The age at the time of the EA is a major predictor for later hysterectomy, and the frequency of hysterectomy varies three fold between different departments.

## 81 Pelvic abscess aspiration under guidance of transvaginal ultrasound

Knut Gjelland 1) Seth Granberg 2)  
1) Haukeland University Hospital, Department of Obstetrics and Gynecology, Ultrasound Unit, Bergen, Norway. 2) Karolinska University Hospital, Department of Obstetrics and Gynecology, Ultrasound Unit, Stockholm, Sweden

**Background:** For treatment of suspected pelvic abscesses, the use of transvaginal ultrasound guided aspiration technique avoids many of the technical challenges of other minimal invasive methods. The purpose of this study was to evaluate the effectiveness and safety of sonographically guided transvaginal aspiration of suspected pelvic abscesses.

**Methods:** We retrospectively reviewed 350 patients with suspected pelvic abscesses who underwent single-step transvaginal pelvic aspiration between 1988 and 2002.

**Results:** Transvaginal aspiration or one step drainage was successful in 93.4% and failed in 6.6%. No complications, including bleeding, bowel perforation, and death, were reported in any of the procedures. At the follow-up no ovarian cancer has been reported in the material after the aspiration.

**Conclusion:** Transvaginal ultrasound guided aspiration technique is a safe and effective treatment for suspected pelvic abscesses.

## 82 Neuropharmacology of Stress Urinary Incontinence and duloxetine – Efficacy and safety of duloxetine

Søren Brostrøm

## 83 Gene expression and physiological changes of human pregnancy

William Dunlop  
United Kingdom

The physiological changes of human pregnancy are dramatic. They are also variable in quantity and in timing. Some early changes appear to revert towards non-pregnant values at later stages in pregnancy. During the second half of the 20th Century much effort was expended in describing these changes and in explaining the physiological interactions and endocrinological factors which might be responsible for them. It is now apparent, however, that the mechanisms responsible for physiological change are predominantly mediated at cellular level, usually involving complex intracellular biochemical changes. These changes are in turn the result of alterations in the interactions of genes, both in the frequency of their expression and in the regulation of the products for which they are responsible. There is therefore a pressing need to undertake research in order to explain the changes observed in human pregnancy. One area of overwhelming importance in relation to human pregnancy is the control of myometrial activity. Inappropriate myometrial contraction may result in premature delivery, the single largest cause of perinatal mortality worldwide. During most of pregnancy it is therefore essential that the myometrium remains relatively quiescent. It seems likely that enhanced activity of the enzyme adenyl cyclase is an important factor in this process. Production of this enzyme is in turn dependent upon the activity of a number of proteins in the cell membrane, all of which are under direct genomic control. However, the interactions of these substances are important in cells throughout the body, notably in other muscle cells, such as myocardium, in which quiescence would be hazardous. One mechanism by which tissue-specific physiological changes can be controlled is by the production of different isoforms of the relevant proteins. This can be achieved by alternative splicing of transcripts from the relevant gene. Evidence will be presented that this process occurs during normal pregnancy in human myometrium.

## 84 The role of nitric oxide in pregnancy disorders

Gautam Chaudhuri 1) Julian Herrera 2) Lauren Nathan 1) Ersheng Gao 3) Patricio Lopez Jaramillo 4)  
1) David Geffen School of Medicine at UCLA 2) Universidad Del Valle, Cali, Colombia 3) Shanghai Institute of Planned Parenthood Research, China 4) Fundacion Cardiovascular de Colombia, Bucaramanga

The role of nitric oxide (NO) in pregnancy is conflicting. In normal pregnancy, NO is involved in the maintenance of the vasodilatory state, in the maintenance of uterine blood flow and in the slowing of the motility of the gastro-intestinal tract. It is also responsible for the maintenance of the umbilical and placental blood flow. However, the role of NO in the maintenance of uterine quiescence is controversial. Some investigators have reported that NO is responsible for the uterine quiescence during pregnancy, whereas, others, including our group, have failed to identify such a role for NO. Similarly, there is controversy regarding the role of NO in pre-eclampsia. Some investigators have reported a decrease in nitric oxide and nitrate levels in pre-eclampsia, whereas, others have reported no change in these levels. The role of the polymorphism of the endothelial nitric oxide synthase in pre-eclampsia is also controversial. The potential reasons for the controversies will be discussed. Conclusion NO most likely plays an important role in some of the physiological changes observed during pregnancy but its precise role in some pathophysiological conditions like pre-eclampsia is controversial.

## 85 Glucose and insulin axis and its dysfunction in pregnancy disorders

F. Andre Van Assche  
Faculty of Medicine

Pregnancy is characterised by major metabolic and vascular changes in order to supply sufficient nutrition to the developing conceptus and the fetus. Glucose and insulin play a crucial role in the metabolic changes, furthermore a defect in this adaptation can explain disorders in pregnancy. Insulin resistance is a physiologic condition in pregnancy, in peripheral tissue but also in the liver, glucose is more released from the liver by glucogenolysis in order to have a constant glucose level in the blood, passing through the placenta to the fetus. Ten insulin resistance may be more pronounced than the physiological status, and this may induce gestational diabetes. Many factors, such as hormonal changes and insulin resistance, are responsible for an increased insulin secretion by the maternal B cells of the endocrine pancreas. It has been calculated that the amount of B cells is increased three times during pregnancy. When the B cells of the endocrine pancreas are not able to meet the increased demand during pregnancy, gestational diabetes may occur. Gestational diabetes can therefore be explained by a dysfunction of the glucose and insulin axis. In contrast in type I diabetes the B cells are not more functioning before pregnancy and the administration of insulin needs to mimic the

physiological adaptation during pregnancy. It is important to mention that insulin resistance as well as defective B cell adaptation may be induced in utero.

## 86 New estrogen/progesterone receptors modulators for future hormonal therapy

Philippe Bouchard  
France

## 87 Genital human papillomavirus infection in the student health clinical population

Eeva Auvinen 2) Marja Niemi 3) Christian Malm 3) Robert Zilliacus 3) Anu Trontti 3) Matti Lehtinen 4) Jorma Paavonen 1)  
1) Department of Obstetrics and Gynecology, University of Helsinki 2) Haarmann Institute, University of Helsinki 3) Student Health Clinic, Helsinki 4) Department of Public Health, University of Tampere, Finland

**Background:** Human papillomavirus (HPV) is the most common cause of viral sexually transmitted infections. HPV infections are highly prevalent in young populations and the prevalence decreases with increasing age. Most HPV infections resolve spontaneously. Persistent infection with high-risk HPV types is strongly associated with cervical neoplasia.

**Methods:** We studied the prevalence of HPV infection among 1307 asymptomatic first year female students attending general health examination at the Student Health Clinic Helsinki. Vaginal self-sampling or cervical sampling was used. HPV DNA was determined by Hybrid Capture II -test (Digene, Gaithersburg, US).

**Results:** The mean age of the students was 23 years (19-47). The overall HPV DNA positivity rate was 33% (434/1307). Of all HPV DNA positive women, 85% were positive for the high-risk HPV types.

**Conclusions:** The prevalence of HPV DNA in the student population was surprisingly high. Most HPV infections were caused by high-risk HPV types. More studies are needed of the natural history of HPV infection.

## 88 A multi-arm trial in cervical cancer control: HPV screening

Pekka Nieminen 1) Laura Kotaniemi 2) Ahti Anttila 2) Matti Hakama 2,3)  
1) Dept. Obst Et Gyn, Helsinki University Central Hospital, Finland 2) Finnish Cancer Registry / Mass Screening Registry, Helsinki, Finland 3) Tampere University School of Public Health, Tampere, Finland

**Background:** To evaluate the aspects of primary HPV-DNA testing in routine cervical cancer screening as a population-based prospective randomised trial incorporated in the Finnish cervical cancer screening programme.

**Methods:** January 2003 we introduced a new primary screening method, HPV-DNA testing, to the Finnish national cervical cancer screening programme. Three randomised screening arms (HPV-DNA based, automation-assisted and screening with conventional pap-smear) of equal size have been going on parallel, forming an unique study settlement we call The Multi-Arm Trial. Women invited to attend routine screening are randomly allocated to the three study arms. In HPV arm, one special cervical brush sample (HC II, Digene Ltd.) per woman is taken at every screening visit in addition to the two normal samples from ectocervix and vagina to get a normal VCE smear. The brush sample is used both for the conventional pap-smear and for the HPV-sample. The HPV-test is performed as the primary screening test, diverging from most of the other screening studies applying HPV-DNA technique. Only if the HPV test is positive, the simultaneously taken pap smear is screened. If the pap smear shows abnormal cells the same protocol used in the control arm is followed. Around 5,000 HPV samples have been taken in the year 2003. We intend to study the possibility of primary screening with HPV in next 5 years, as a yearly capacity of 40,000 HPV tests within The Multi-Arm Trial will be reached.

**Results:** Our preliminary experience of HPV screening arm show very similar figures than our pilot study, in which HPV-test was shown to be more sensitive than conventional pap-smear in finding severe and moderate dysplasias. On the full capacity there will be sufficient statistical power for detecting 50% marginal effects in cervical cancer incidence among the screened.

## 89 Comparison of HPV test vs. conventional and automation assisted PAP-screening as potential screening tools for preventing cervical cancer

Pekka Nieminen 1) Matti Hakama 2,3) Ahti Anttila 2)  
1) Dept. Obst et Gyn, Helsinki University Central Hospital 2) Finnish Cancer Registry, Helsinki, Finland 3) Tampere University School of Public Health, Tampere, Finland

**Background:** To evaluate new techniques in primary cervical cancer screening programmes.

**Methods:** We compared validity of the high-risk HPV DNA detection test to automation assisted and conventional pap-smear screening in a cross-sectional pilot study. Consecutive 2032 HPV DNA and Pap-smear samples were taken at the Department of Obstetrics and Gynaecology, Helsinki University Hospital. Histological diagnoses were obtained from 460 patients. Main outcome measures were specificity and sensitivity of screening methods.

**Results:** 23.3% of all women were HPV positive. 45/46 of all high-grade lesions and cancers were HPV DNA positive, whereas 72/93 of low grade+ lesions were HPV DNA positive. Sensitivity of HC 2 test was 98% compared to conventional pap-smear and Papnet tests, which performed 54 % and 58%, 83 % and 86%, and 93 % and 98 % sensitivity respectively, when high grade lesions were observed, using HSIL, LSIL or ASCUS as the cut-off. Specificity of HC II (76-

79%) was comparable with the ASCUS+ cytology, but lower when compared to LSIL+ or especially HSIL+ Pap-smear results.

**Conclusion:** Pap smear as a screening test, is different from HPV DNA detecting. If cut-off LSIL or more severe lesions is used, primary Pap smear is clearly more specific than HC II, but less sensitive. Due to high sensitivity of the HPV, very few histologically confirmed high grade+ lesions would be detected among HPV negatives using simultaneous cytology. However, using HPV DNA test alone would lead to multifold amounts of referrals for colposcopy. A posterior Pap-smear assessment among HPV positives might be helpful in increasing sensitivity and specificity of screening and defining those who need an immediate referral or treatment. We plan to incorporate primary HPV DNA test with posterior Pap-smear reading of HPV positives into our ongoing randomised prospective multi-arm trial evaluating new techniques in organised screening for cervical cancer in Finland.

#### 90 Intratumoral effects of medroxy-progesterone on proliferation, apoptosis, and sex steroid receptors in endometrioid endometrial adenocarcinoma

Marju Dahmoun 1) Karin Boman 2) Stefan Cajander 3) Torbjörn Bäckström 4)  
1) University of Umeå 2) Dep. of Oncology, Umeå University Hospital 3) Dep. of Pathology and Cytology, Centre of Laboratory Medicine, University hospital, Uppsala 4) Dep. of Obstetrics and Gynecology, University of Umeå

**Background:** Progesterone therapy has been used in the treatment of metastatic endometrial carcinoma empirically since clinical studies have shown a response to progesterone. Different response rates of 10%-30% have been reported, with a tendency towards lower rates in later studies, but the mechanisms of progesterone action has not been fully elucidated.

**Methods:** Ki-67 proliferation marker, estrogen and progesterone receptors (ER and PR), and bcl-2 and p53 immunohistochemistry in the epithelial part of endometrial carcinoma before, during, and after progesterone therapy. In biopsy 1, before the therapy, ER and PR in stroma as well as the amount of stroma were also studied. Apoptotic cells were morphologically identified in hematoxylin- and eosin-stained sections of the tumors and the apoptotic index (apoptotic cells/1000 cells) was calculated. Chances in feature factors were mainly evaluated by repeated measures ANOVA.

**Results:** Proliferation (Ki-67) was decreased in grade 1 (G1) and grade 2 (G2) tumors during progesterone therapy both in overall evaluation (Ki) and particularly in the areas of maximal proliferation (Ki-max). No change was seen in G3 tumors. A decrease in PR expression in the areas of maximal expression for PR (PR-max) was also observed in G1 and G2 tumors. Apoptosis as well as bcl-2 and ER expression were unchanged during therapy and withdrawal.

**Conclusions:** The effect of progesterone is seen only on proliferation in low grade (G1 and G2) tumors. The coexistence of high PR expression in the foci of high proliferation may contribute to the effect in G1 and G2 tumors. No effect of progesterone is seen on apoptosis in tumors of any grade.

#### 91 Hormone therapy and female cancers - A 1.8 million women Danish National cohort study

Øjvind Lidegaard 1,2) Ellen Løkkegaard 2) Carsten Agger 3) Anne Helms Andreasen 3) Lisbeth Møller 3)  
1) Herlev University Hospital, Dept Obstet Gynecology 2) Danish Centre for Human Reproductive Epidemiology 3) Research Centre for Prevention and Health, Copenhagen County

**Background:** Renewed focus on the association between female cancers and hormone therapy (HT) is a reality after publication of American randomised controlled trials and the British million women study. Our aim has been to analyse the associations between various HT regimens and potential hormone related female cancers in a National cohort of women.

**Methods:** In 1977, the National Register of Patients (NRP) was established. NRP receives discharge diagnoses on all in- and outpatients from all Danish hospitals. A central prescription register (LSR) was established in Denmark in 1994. LSR collects information about all cashed prescribed medicine. There is now legal permission for scientists not only to get data from LSR and NRP, but also to merge information from the two registers through personal identification numbers. From Danish Statistics information on potential confounders such as education and job-status can be achieved for all women.

**Results:** During the period 1995 through 2002, more than 500,000 Danish women 50-69 years old were followed with a daily update on all prescriptions of HT. During the eight-year follow-up period, we expect 25,000 female cancers, including breast, colon, cervical, endometrial, and ovarian cancers. Malignant lymphomas are also included. By cox-regression analyses hazard ratios will be estimated among women exposed for specific types of hormone therapy, i.e. specific regimens, specific progestagen types, and specific routes of administration (oral, transdermal, IUD or local).

**Conclusion:** We hope to present the first results from the ongoing analysis. The merging of data in NRP and LSR provides together with other Danish registers one of the most powerful tools in pharmacoepidemiology available in our present post-HT randomisation era.

## 92 Effects of testosterone treatment on insulin sensitivity, body composition and serum lipid profile in postmenopausal women

Hong Zang, Angelica Lindén Hirschberg  
Dept. of Obstetrics and Gynecology, Karolinska University  
Hospital, Stockholm, Sweden

**Background:** Beneficial effects of testosterone treatment in postmenopausal women have been demonstrated on initiative, energy and well-being, as well as sexual function and bone mass. However there is little knowledge about metabolic effects of androgen treatment in women. This study was to investigate the effects of testosterone treatment compared with estrogen treatment alone or the combined treatment with estrogen on insulin sensitivity, body composition and serum lipid profile in postmenopausal women.

**Methods:** Sixty-three naturally postmenopausal women were enrolled and randomly assigned to three different treatments: testosterone undecanoate 40 mg every second day; estradiol 2 mg daily; or the combined treatment. Insulin sensitivity assessed by the euglycemic hyperinsulinemic clamp, body composition determined by dual energy X-ray absorptiometry and serum lipid profile were measured at baseline and after three months of treatment.

**Results:** Testosterone treatment increased serum levels of testosterone to the upper limit of premenopausal range. Mean glucose uptake were significantly reduced after treatment with testosterone alone ( $P < 0.01$ ) and after combined treatment with estrogen ( $P < 0.05$ ) but not by estrogen alone. Body weight, but not body fat, increased significantly in all groups. Lean body mass was significantly increased in the group of combined treatment ( $p < 0.01$ ). HDL-cholesterol decreased and triglycerides increased significantly by testosterone treatment ( $P < 0.05$ , respectively). In contrast, HDL-cholesterol increased, whereas LDL-cholesterol and lipoprotein-(a) decreased by estradiol treatment ( $P < 0.001$ , respectively).

**Conclusion:** The short-term treatment with testosterone in postmenopausal women negatively influences insulin sensitivity and the serum lipid profile but may have positive effects on body composition.

## 93 Neurological sequelae in assisted reproductive twins: controlled national cohort study

Anja Pinborg 1) Anne Loft 1) Lone Schmidt 2) Gorm Greisen 3) Steen Rasmussen 4) Anders Nyboe Andersen 1)  
1) The Fertility Clinic, Copenhagen University, Rigshospitalet  
2) Institute of Public Health, Copenhagen University 3) Department of neonatology, Copenhagen University, Rigshospitalet 4) Health Statistics, National Board of Health, Copenhagen

**Background:** In most European countries approximately 40% of children born after assisted reproduction are twins. The existing literature about neurological sequelae in these twins is limited. The first aim was to compare neurological

sequelae in assisted reproductive twins with assisted reproductive singletons and naturally conceived twins. The second aim was to evaluate the role of intracytoplasmic sperm injection (ICSI) in the development of these sequelae.

**Methods:** Controlled national register based cohort study on neurological and psychiatric diagnoses. All assisted reproductive twins ( $n=3393$ ) and singletons ( $n=5130$ ) plus all naturally conceived twins ( $n=10239$ ) born in Denmark between 1995 and 2000 were included. Children were identified by cross-linkage of the National Medical Birth Registry and the National IVF Registry. Neurological and psychiatric diagnoses were retrieved from the National Patient Registry and the Danish Psychiatric Central Registry.

**Results:** The crude prevalence of neurological sequelae (defined as: cerebral palsy, mental retardation, infantile autism, Aspergers syndrome and retarded psychomotor development) was 8.8, 8.2 and 9.6 per 1000 in twins and singletons after assisted conception, and naturally conceived twins, respectively and of the specific diagnosis: cerebral palsy 3.2, 2.5 and 4.0 per 1000. Odds ratio of neurological sequelae and cerebral palsy adjusted for child sex and year of birth in assisted reproductive twins vs. control twins was OR 0.9 (95%CI 0.6-1.4) and OR 0.8 (95%CI 0.4-1.6), respectively. The corresponding risks for assisted reproductive twins versus singletons were for neurological sequelae OR 1.1 (95%CI 0.7-1.7) and for cerebral palsy OR 1.3 (95%CI 0.6-2.9). The risk of neurological sequelae was similar in ICSI vs. IVF children OR 0.9 (95%CI 0.5-1.7).

**Conclusions:** Surprisingly, twins from assisted reproduction have similar risk of neurological sequelae as their naturally conceived peers and assisted reproductive singletons. Children born after intracytoplasmic sperm injection have the same risk of neurological sequelae as children born after in-vitro fertilisation.

## 94 Single embryo transfer in frozen embryo transfer cycles - six years' experience

Leila Unkila-Kallio, Aila Tiitinen, Mervi Halttunen, Christel Hydén-Granskog  
Helsinki University Hospital, Dept. Obst and Gyn

**Background:** Our elective single embryo transfer programme in fresh IVF/ICSI-cycles has, in the last six years, reduced multiple pregnancy/delivery rates from 25/25% to 7/6%. As frozen embryo transfers (FETs) result in multiples we started to prefer one embryo transfer also in FETs.

**Methods:** A retrospective analysis of 1647 FETs from 1998 to 2003 was done. Embryos were transferred if at least 50% of the blastomeres survived without multinuclearity and fragmentation was  $< 50\%$ . Two embryos were transferred (2ET) in 872 cycles (53%), one embryo in 775 cycles (47%). FETs were performed either during a spontaneous ( $n=1004$ ) or a hormonally substituted cycle ( $n=643$ ).

**Results:** The overall clinical pregnancy rate (PR) was 30.7% (506/1647; range 20.3-36.9%) and was not dependent on

cycle type: spontaneous cycles 30.6% (307/1004), substituted cycles 30.9% (199/643). In 1998, 28% of FETs were SETs (78/276), most because only one embryo survived. of SETs 19% were planned either due to patients own wish or medical reasons to avoid twins. In 2003 the SET rate increased to 66% (185/279). of these, 66% were planned to be SETs, mostly due to patients own wish. The PR in SETs was 33.0% (61/185) with monozygotic twins in 3 cases, whereas the PR in 2ET-cycles was 44.7% (42/94) resulting in 9 twins and 1 triplet. Elective SET, because more than one embryo survived, was performed in 140 cases/6years with a PR of 40.7% (57/140). The multiple pregnancy rate in FET cycles has decreased from 18% to 10%. of SETs 2.4% were monozygotic twins compared to 19.7% of multiples after 2ETs.

**Conclusions:** Good pregnancy rates with low multiple delivery rates can be maintained with single embryo transfer in FETs. Both spontaneous and substitution cycles, depending on patient characteristics show equal results. SET policy can be adopted to cryopreservation programmes to increase the cumulative PR/treatment cycle.

## 95 Women with features of the metabolic syndrome. Is transdermal HT to be preferred?

G Samsioe, Y Shakir, C Nerbrand, J Lidfeldt  
Depts of Ob&Gyn, Medicine and Community Medicine, Lund University, Sweden

Features of the metabolic syndrome are considered pivotal risk factors for subsequent development of type II diabetes. Once developed diabetes cannot be cured whereas the most imminent pre-stage, the pathological glucose metabolism can be reverted. It is therefore of clinical significance to identify a subpopulation at risk of developing diabetes and to identify factors that could improve their glucose metabolism.

**Objective:** The Women's Health in the Lund Area (WHILA) study screened 10766 women aged 50-60 for features of the metabolic syndrome. Of those positively screened (n=3593) 2923 underwent an OGTT of which 600 had impaired glucose tolerance (IGT) according to the 1998 WHO criteria.

**Methods:** The effects by current HT preparations containing combinations of estradiol (E2) and norethisterone acetate (NETA) were particularly studied. Two oral preparations with 2 mg E2 + either 10 or 28 days of NETA per 28 day cycle were compared with a transdermal preparation releasing 50 µg E2 for 14 days and 50 µg E2 + 250 µg NETA for 14 days.

**Results:** There were no differences by preparation regarding systolic and diastolic blood pressure, waist-hip ratio or body mass index. Pulse rate was significantly lower with transdermal therapy compared to either oral regimen. There were only minor differences in serum lipids some of which reached border line significance. The percentage of pathological OGTT was lowest in the transdermal group followed by the cyclical oral group and among the continuous

combined women 31 % had IGT which was similar untreated control. The difference between tablets and patches was statistically significant.

**Conclusion:** IGT is common in women with features of the metabolic syndrome however only half as common in women using patches compared to using a continuous combined oral formulation.

## 96 Low-dose transdermal HRT: Special options to minimize risks

Alfred O. Mueck  
University Hospital For Women, Section of Endocrinology and Menopause, Tuebingen, Germany

There are approximately 20 established preparations which are currently available internationally for the transdermal application of estradiol in patch or gel form. Patches are always being improved; their development began in 1986 with Estraderm TTS®, a reservoir patch, followed by matrix patches, with Estracombi® and Estalis® being the first available combi-patches, and finally the optimum in transdermal technology was reached with Estradot®. As a result of the disappointing results from the studies HERS and WHI, which we all know were carried out with equine estrogens combined with medroxyprogesterone acetate, great hopes have been placed on the ability to use transdermal application forms with the same efficacy, but with less risks attached. This hope rests on physiological and pharmacological basic principles, which ought to remain the basis of our medical treatment, in spite of the age of 'Evidence based medicine'. Physiological estradiol, instead of animal estrogen is delivered via transdermal application, and the parenteral dose also equals the physiological supply from the ovaries. The primary dose amounts to only a fraction of that of the oral preparations, whereby doubtless hepatic bolus effects are avoided. This is a disadvantage for only a few patients, e.g., those with isolated hypercholesterolaemia and hyperandrogenaemia, where one should treat with an oral estrogen in preference. The reduced hepatic effect is mostly an advantage, e.g., for avoidance of drug interactions, avoidance of amplified angiotensinogen production in dependant forms of hypertension, reduction of the risk of gallstones, and the avoidance of toxic metabolites in smokers which is possibly of significance for risk of breast cancer. Transdermal application is an advantage when treating climacteric symptoms in patients with concurrent hypothyroidism, advanced liver diseases such as cholestasis, hypertriglyceridaemia, the latter being particularly relevant in metabolic syndrome, pancreatic disease and particular forms of diabetes. The reduction in venous thromboembolism risk has been particularly frequently quoted. Further specific options result from the low, steady estradiol level, such as, for example, use in certain forms of migraine. Still under discussion are the possible advantages for the arterial system, i.e., due to the avoidance of an increase in CRP or an increase in the size of LDL particles. Despite

methodological shortcomings (high withdrawal rate, high rate of unblinding), the PHASE study (80µg estradiol, 120µg norethisterone acetate) pointed out that in arteriosclerotic women (advanced age!) or in those with pre-existing cardiovascular diseases, transdermal patches in the lowest dose possible should be applied. With the newest developments, such as Estradot 25, or Estragest, the first low-dose continuous combined patch, one can expect comparably good efficacy, minimised risks and further options which are specific to transdermal systems.

## 97 DVT - an avoidable complication of HT?

Sven O. Skouby and Jørgen Jespersen  
*Department of Obstetrics and Gynecology, Frederiksberg Hospital, University of Copenhagen, and Department for Thrombosis Research, University of Southern Denmark*

The large bulk of data from observational studies on oral postmenopausal hormonal therapy (HT) combined with information from recent randomized trials have demonstrated a two- to threefold increased risk of venous thromboembolism (VTE) during HT. The risk is increased for oral estrogen alone or estrogen combined with a progestin and seems to be dose dependent. The mechanism responsible for this increased risk is not known in detail, but early evidence indicates that there is an effect of HT on the inhibitory potential of coagulation with possible consequence for the turnover of fibrin. This can contribute to the proneness of thrombosis. Avoiding the first-pass hepatic metabolism and the associated effects on coagulation may therefore be clinically important. However, studies investigating the effect of transdermal estrogen on the hemostatic system and the clinical occurrence of the thrombotic process are scarce. There are data to suggest that transdermal estrogen induces no APC resistance or activation of blood coagulation. The significance of these results are amplified by the fact that inherited risk factors, such as Factor V Leiden- and the prothrombin G20210A-mutation, as well as acquired risk factors, such as obesity and smoking, are commonly found among women in the Western World. At present the clinical effect of transdermal HT on the occurrence of DVT is based on only a few case control studies. Early data have given conflicting evidence, but the results of the most recent multicentre study point to the clinical significance of using transdermal versus oral HT in relation to the risk of DVT. The combined evidence from validated biomarkers in the hemostatic system and the published clinical data therefore suggest that transdermal estrogen containing HT is safer than oral HT with respect to thrombotic risk.

## 98 Different effects of oral and transdermal HT on C-reactive protein: Does it have an impact on cardiovascular risk?

Matti J. Tikkanen  
*Helsinki University Central Hospital, Finland*

Inflammation is currently regarded as having an important role in atherothrombosis. Because of this there is interest in the inflammatory biomarker high-sensitivity C-reactive protein (hs-CRP). hs-CRP is an acute-phase reactant which has a role in the immune response. hs-CRP has been demonstrated to increase up-regulation of adhesion molecules, induce complement and to be involved in the regulation of nitric oxide synthase expression. Several large epidemiologic studies have shown that hs-CRP is a strong predictor of myocardial infarctions, stroke and cardiovascular death. Trials of oral and transdermal HT have indicated that oral, but not transdermal HT causes elevation of hs-CRP levels in postmenopausal women. Some investigators have suggested that this could provide an explanation to the negative findings in recent large prevention trials using oral HT. This has provoked a debate concerning the role of hs-CRP as a disease marker, causative agent, or a consequence of atherosclerotic disease. Oral and transdermal HT differ in that the former exposes the liver to a much higher estrogen concentration resulting in a markedly increased production of estrone and other metabolites. While this results in more favorable changes in LDL and HDL levels during oral treatment, some other factors including the inflammatory marker hs-CRP is adversely influenced. Further analysis of large trial data may shed further light on the role of increased hs-CRP and other inflammatory markers on cardiovascular risk during oral HT. Cardiovascular endpoint trials are needed to clarify the possible superiority of transdermal HT in this respect.

## 99 Low-dose transdermal HRT: Endometrial safety of the first combi-patch

Alfred O. Mueck  
*University Hospital for Women, Section of Endocrinology and Menopause, Tuebingen, Germany*

Risks of HRT can be further minimised when not only the dose of estrogen, but also the dose of progestagen is reduced. Negative progestagen effects such as vasoconstriction have been demonstrated to be of clinical relevance, especially in women with pre-existing cardiovascular risks. In two randomised placebo controlled cross-over studies, we could prove that compared to healthy women, women who had suffered a heart attack could not adequately react to vasoconstrictor stress any more, as the endothelial reserve for an increased production of protective nitric oxide was greatly reduced. The requirement to use HRT in the lowest effective dose is perfectly fulfilled with @Estragest TTS, which is the first low-dose combi-patch, already marketed in some countries, such as Germany. This continuous-combined HRT patch provides a daily delivery rate of 0.025mg

estradiol plus 0.125mg norethisterone acetate through the skin. It is generally accepted that cc-HRT effectively minimizes the risk of endometrial cancer/hyperplasia and leads to amenorrhea. However, due to the very low dosage of the progestagenic component of this low-dose combi-patch, endometrial safety had to be demonstrated. For this reason we enrolled 411 postmenopausal patients with intact uterus in a prospective open-labelled study. Endometrial biopsies were obtained by using aspiration technique, performed at baseline and at week 48, and evaluated by two or three independent pathologists blinded to treatment. In order to avoid potential bias in this open study, the endometrial histology slides from the trial population were mixed with endometrial biopsy slides showing endometrial cancer/hyperplasia (pathological controls) and with biopsy slides from healthy postmenopausal women (normal controls). The incidence of endometrial hyperplasia in the intent-to-treat population (ITT) was 0.79% with a CI 2.03% (one-sided upper limit 95%-confidence interval), which is considered a safe endometrial profile. The incidence of bleed-free (i.e. spottings allowed) and amenorrhoeic patients (i.e. no spottings allowed) per cycle in the ITT population increased consistently from cycle 1 to cycle 12 from 91.5% to 97.2%, and from 80.3% to 88. %, respectively. These data confirm the endometrial safety of this first low-dose combi-patch, according to criteria specified by the Committee for Proprietary Medical Products. Thus ®Estragel TTS combines perfectly the low dose regimen with a safe endometrial profile together with a desired high amenorrhea rate.

## 100 The Role of HPV in Cervical Cancer: From Testing to Vaccination

Jorma Paavonen  
Dept of Obstetrics and Gynecology, University of Helsinki,  
Finland

Cervical cancer ranks second as a cause of cancer related deaths in women. More than 450,000 cases are diagnosed each year worldwide. Pap smear screening benefits only a small fraction of women globally. At least 80% of new cases of cervical cancer occur in developing countries. There is a strong link between persistent infection with high risk human papillomavirus (HPV) and cervical neoplasia. Approximately 20 years investigators in Germany established HPV 16 as the leading cause of cervical cancer. Most cervical HPV infections resolve spontaneously. Thus, cervical neoplasia develops in only a minority of all women exposed to HPV. HPV DNA testing was recently approved by FDA for use as an adjunct to cytology for cervical cancer screening in women aged > 30 years. It is expected that many women will request HPV DNA testing and clinicians also want to begin to incorporate the test into their practices. In order to balance test sensitivity against risk of overuse a reasonable conservative follow-up strategy must be developed for HPV DNA positive, cytology negative women. Because testing for HPV DNA has high sensitivity but relatively low specificity, screening for HPV DNA may not be a reasonable alterna-

tive to cytology based screening in settings with organized screening programs (Obstet Gynecol 2004;103:304-9). The scientific advance just 13 years ago was the discovery of papillomavirus-like particle (VLP) in the laboratory. VLPs are devoid of DNA and are therefore non-infectious but mimic the natural structure of HPV virion. VLPs generate a potent immune response. VLP vaccine can be tailored against most prevalent high risk HPV types. Early studies suggest that the VLP vaccine is highly immunogenic, safe, and effective. Cervical HPV infection, CIN, and most likely cervical cancer can be prevented by prophylactic vaccination. Since HPV is associated with many other human cancers, the vaccine may become an important cancer vaccine. Large phase 3 vaccination trials are currently ongoing. The future looks bright. It is important to emphasize that there is no evidence that HPV DNA testing reduces morbidity or mortality, but there is strong evidence that well organized cytologic screening programs do so. It is more than likely that cervical HPV infection and ultimately cervical cancer will be prevented by HPV vaccination.

## 101 Preoperative evaluation of endometrial pathology

Gunnar B. Kristensen  
Department of Gynecologic Oncology, The Norwegian Radium  
Hospital, Oslo, Norway

In the Nordic countries, endometrial cancer is often treated by simple hysterectomy and extirpation of the adnexa. A full staging procedure as recommended by FIGO is rarely performed. The risk of spread of the disease outside the uterus and thereby the risk of later recurrence varies with tumor size, depth of myometrial invasion, degree of differentiation and histological type. Also, some molecular factors are predictive of a later relapse. A number of these factors can be evaluated before surgery and thereby allowing the surgeon to decide on whether a full staging procedure should be undertaken or a simple hysterectomy will be sufficient treatment.

## 102 Ultrasound and risk-of-malignancy index in the evaluation of ovarian tumors

Seth Granberg  
Department of Obstetrics and Gynecology, Ultrasound Unit,  
Karolinska Hospital, Stockholm, Sweden

Several studies have been performed to evaluate the subjective assessment of ultrasonographic including Color Doppler images for discriminating between malignant and benign adnexal masses. Many of these studies have shown that by using some clinical information and their subjective assessment of ultrasonographic images can differentiate malignant from benign ovarian masses in most cases. However, the studies have mostly been performed by experts in gynecological ultrasound, which is a dilemma in places where there is no experts. During the past twenty years, several

more or less sophisticated scoring systems have been used for evaluating these tumors. Despite this, there still is need for better differentiation between benign and malignant ovarian tumors, to give the patients the best surgical treatment and prognoses. Thus the Risk of Malignancy Index (RMI) in primary evaluation of patients with adnexal masses has become an important tool in evaluating ovarian tumors and in the centralization of ovarian cancer surgery. The RMI is based on menopausal status, ultrasonographic findings, and serum CA 125 level. A cutoff level of 200 is often chosen as the threshold for referral for centralized primary surgery. The results from different studies and the future will be discussed in this presentation.

### 103 PET imaging of gynecological malignancies

Heikki Minn 1,2)

1) Department of Oncology and Radiotherapy, University of Turku 2) Turku PET Centre, University of Turku

Positron emission tomography (PET) with fluorine-18 labeled fluorodeoxyglucose (FDG) is a powerful imaging tool in clinical oncology. FDG PET completes structural information from computed tomography (CT) and magnetic resonance imaging (MRI) and assists in management of patients whose diagnostic work-up remains obscure in conventional staging. All three major gynecological cancers are FDG avid. In ovarian cancer, rising tumour markers and negative CT and MRI findings is a typical case for PET. PET is slightly more specific than CT and MRI in evaluation of primary and recurrent ovarian tumours although best diagnostic performance requires co-reading of structural and metabolic images. FDG uptake in ovarian cancer is often heterogenous depicting different metabolic activity of solid and cystic tumour components. Peritoneal seeding or small nodal metastases may be missed owing to the limited spatial resolution (5-6 mm) of the current PET devices. In cervical cancer FDG PET improves staging of pelvic and para-aortic nodal involvement as compared to CT and MRI and allows detection of unexpected distant metastases in, for instance, supraclavicular area. PET assists radiation treatment planning especially if irradiation of para-aortic area is considered. Early detection of recurrent cervical cancer a minimum of 2 to 3 months from treatment is also feasible. False positive cases of FDG uptake are linked to inflammatory response which may persist several weeks after irradiation. PET has likewise been suggested for post-therapy surveillance of endometrial carcinoma although larger trials are necessary to confirm this. In summary, a more rational diagnosis is possible with PET in ovarian and cervical cancers in selected cases. Combined PET/CT scanner is a new and attractive modality for planning of surgery and radiotherapy. Small-volume disease and inflammatory changes are sources for false negative and false positive findings on PET, indicating that a fool-proof and perfect imaging method is yet to be found.

### 104 Transplantation of genital organs

Mats Brännström

Dept of Obstetrics and Gynecology, Sahlgrenska Academy, Göteborg's University

**Background:** Methods for transplantation of the uterus and the ovary have been explored for many years in experimental animals as possible future treatments for various causes of infertility. Today ovarian autotransplantation is used in cases of fertility preservation in young female cancer patients. Uterine transplantation is presently developed in animal models as a possible future treatment for absolute uterine infertility, due to congenital absence of the uterus or previous hysterectomy (after cervical cancer, post partum bleeding, myoma etc). Our research on uterine transplantation will be reviewed in this presentation.

**Methods:** A mouse model was developed for syngeneic heterotopic uterine transplantation and evaluated regarding pregnancy and development of offspring. At allogeneic transplantation, the cellular infiltration at rejection was examined. Effects on mouse uteri of cold ischemia in UW were evaluated. Pieces of human uterine tissue were stored (4°C) in UW or Perfadex for 6 or 24 h before evaluation. A method for autotransplantation of the pig uterus was developed.

**Results:** The syngeneic heterotopically transplanted mouse uterus showed good viability. Transferred embryos resulted in normal pregnancies and offspring, which developed normally. Allogeneic transplanted mouse uteri showed typical signs of rejection. Syngeneic transplanted mouse uterus tolerated 24 h of cold ischemia in UW. Human uteri showed preserved contractility properties after 6 h cold ischemia. Autotransplanted pig uteri showed viability and good blood flow after reanastomosis.

**Conclusions:** The studies have demonstrated development of the first animal model for uterine transplantation with production of normal offspring. Moreover, the uterus is a tolerable organ in regards to cold ischemia. At present studies are undertaken to evaluate optimal immunosuppressants to control acute rejection and to develop larger animal models for further studies of surgical techniques and reperfusion injuries. We hope to be able to perform uterine transplantation in humans within five years.

### 105 Male and Female and all those in between

Kenneth Purvis

Andrology Centre, Oslo, Norway

It is becoming increasingly clear that male gender identity is determined to a major extent by the degree of pre- and/or peri-natal androgenisation of certain hypothalamic and limbic brain centres. The impact of the social environment and the presence of normal external genitals appear to be less important. Because of this, new guidelines have been proposed for the gender assignment of intersex newborns and

boys with genital abnormalities. Recent research suggests that subjects with gender dysphoria (transsexuals) share differences in the size/function of a specific brain nucleus which in the case of male to female dysphorics remains 'feminized' in spite of the normal masculinisation of other parts of the brain. It has been suggested that normal men, cross dressers, autogynophiles and transsexuals represent a continuum reflecting various degrees of feminisation of this gender identity nucleus. Men and women with gender dysphoria who choose gender re-assignment involving genital surgery and hormone treatment in the vast majority of cases do not regret their choice. Causes of abnormal differentiation of the gender identity nucleus and other brain nuclei involved in sexual behaviour include prenatal exposure to pollutants and estrogens in the environment, stress, alcohol and drugs. Gender preference also may be influenced by another hypothalamic nucleus suggesting that homosexuality may also have a predominantly biological basis. Within the normal heterosexual male and female population there appear to be grades of masculinity and femininity (so called androtypes and gynotypes) which may also reflect variations in the expression of the sex hormones. In these cases, accept of gender identity especially in the case of boys and men, appears to be greatly influenced by the social environment, in particular the close contact between the parents during the prepubertal/pubertal period.

## 106 Postponement of menopause by gene therapy?

Juha Tapanainen  
University of Oulu

From the seven million oocytes present in the human ovaries during early fetal life only 400 will be ovulated during a woman's reproductive life. The period of optimal fertility lasts until the age of about 30 years and decreases gradually thereafter. The follicle pool is decreased significantly by the age of 37–38 years, and at menopause; around the age of 50 years, the number of follicles is reduced to almost zero. Programmed cell death or apoptosis is the mechanism that regulates oocyte/follicle demise and makes the female biological clock tick. There is a relatively large individual variation in the timing of menopause, and it depends largely on the rate of apoptosis which in turn is regulated by several pro- and antiapoptotic genes. In attempts to preserve oocytes, ovarian function and to postpone menopause inhibition of apoptosis plays a central role. Today the manipulation of the germ cell line is prohibited, and this presentation does not take up an attitude to the question whether these actions are ethically acceptable or not. There are pathological conditions in which antiapoptotic treatment strategies for preserving ovarian function could be needed; these include premature ovarian failure and protecting ovarian function after cancer therapies. Apoptosis is a chain of events in which several genes are involved, and the crucial issue is to which point of this chain the actions should be targeted in order to stop the cascade before it gets irreversible. There are both in vitro and in vivo studies which

demonstrate that oocytes can be protected from apoptosis. The major question is whether these rescued oocytes/follicles only form a population of undead cells or whether they are capable of fulfilling their biological roles and preserve normal ovarian function and fertility. Another concern is that gene transfer vectors transfect cells in a nonspecific manner, and there is always a possibility that by suppressing apoptosis we may promote for instance the development of cancer. Therefore the therapy should be targeted strictly to the ovary or even to specific cells, perhaps to oocytes themselves or to granulosa cells, which are responsible for the well-being of the oocyte. In practice, using viral vectors or less efficient non-viral methods gene transfer could be made to ovarian arteries or directly into ovarian tissue. It has to be noticed, however, that so far no reliable gene transfer to germline in vivo has been demonstrated.

## 107 Never too early: fetal and neonatal education

Risto Näätänen  
Cognitive Brain Research Unit, Dept. of Psychology, University of Helsinki, Finland; Helsinki Brain Research Centre, Helsinki, Finland

The mismatch negativity (MMN) is an electric brain response which is automatically (task-independently) elicited by any discriminable change in a repetitive sound or sound pattern. When this change is made smaller in magnitude the MMN is attenuated in amplitude, eventually vanishing at around the discrimination threshold. Therefore the MMN provides a unique objective measure for a subject or patient's sound-discrimination accuracy. Furthermore, with the MMN, these discrimination thresholds can be separately determined for the different sensory attributes. Moreover, the individual's ability to discriminate complex sound stimuli and patterns such as different phonemes can also be measured by using the MMN. Recent MMN studies have also demonstrated that the MMN can be used in monitoring the development of central auditory processing in infants and in measuring training effects on this processing. These studies have, for example, shown that sleeping newborns can be trained to discriminate speech sounds such as /i/ and /y/ which differ from each other only in the second formant (F<sub>2</sub>). Very recently, Huotilainen and her colleagues succeeded in recording the magnetic equivalent of the MMN (MMNm) from a fetus in the womb. Furthermore, they have obtained some tentative MMN evidence in newborn infants for learning effects caused by fetal-stage auditory stimulation.

## 108 Poor pregnancy outcome in women with type 2 diabetes

Tine Dalsgaard Clausen 1) Elisabeth Mathiesen 2) Pia Ekbom 2) Thomas Mandrup-Poulsen 3) Peter Damm 1)  
1) Department of Obstetrics and Gynaecology, Rigshospitalet, Copenhagen, Denmark 2) Department of Medical Endocrinology, Rigshospitalet, Copenhagen, Denmark 3) Steno Diabetes Center, Denmark and Department of Molecular Medicine, Karolinska Institute Stockholm, Sweden

**Background:** Type 2 diabetes in pregnancy is a growing problem, which has been offered little attention.

**Methods:** Files of 70 singleton pregnancies in women with Type 2 diabetes from 1996 to 2001 were studied retrospectively. For women with more than one delivery in the study period, only the first pregnancy was included (n=61), except for calculations of perinatal mortality and major congenital malformations where all 70 pregnancies were included. Pregnancy outcome was compared to that of the background population, pregnant women with type 1 diabetes during 1996-2000 and pregnant women with type 2 diabetes during 1980-92 from the same department.

**Results:** Five of 70 pregnancies (7.1%) were complicated by major congenital malformations (CM), and the perinatal mortality (PM) was 7.2% (5/69). The PM found in pregnancies complicated by type 2 diabetes was increased 10 and 4 times compared to the background population and women with type 1 diabetes, respectively. The CM was more than doubled compared with these groups. The glycaemic control was similar or better in women with type 2 diabetes compared to women with type 1 diabetes. Multivariate logistic regression analyses in the pooled group of diabetic pregnancies from 1996-2001 showed that high HbA<sub>1c</sub> at admission and type 2 diabetes were independently associated with a serious adverse fetal outcome (PM and/or CM). The PM and the CM in type 2 diabetic pregnancies have increased during the last decade.

**Conclusions:** The perinatal outcome of pregnancies in women with type 2 diabetes is significantly poorer than in women with type 1 diabetes or the background population. The PM and the CM in pregnancies with type 2 diabetes have increased over time. Further studies are needed to elucidate whether these observations are related to the rising prevalence of the metabolic syndrome or other unknown factors associated with type 2 diabetes.

## 109 Prediction of diabetes in women with gestational diabetes: Risk for type 1 diabetes is similar to that of type 2 diabetes in fertile age

Ilkka Yrjö Järvelä 1) Jaana Juutinen 1) Pentti Koskela 1) Anna-Liisa Hartikainen 1) Mikael Knip 2) Juha S. Tapanainen 1)  
1) Dept Obstet Gynecol, Oulu University Hospital, Oulu 2) Hospital for Children and Adolescents, University of Helsinki

**Background:** The progression of gestational diabetes (GDM) to non-insulin-dependent (T2DM) and insulin-dependent

diabetes mellitus (T1DM), and the predictive value of diabetes associated autoantibodies to subsequent morbidity are not well known.

**Methods:** The presence of glutamate decarboxylase (GADA), tyrosine phosphatase (IA-2), islet cell (ICA) and insulin autoantibodies (IAA), and the subsequent morbidity to diabetes were studied in 435 women with GDM and their healthy controls.

**Results:** of GDM women 6.2 % were positive for GADA, 4.7 % for IA-2A, 12.2 % for ICA, and 1.1 % for IAA, compared to 2.1 % (GADA), 0.8% (IA-2A), 0.3 % (ICA), and 0.3 % (IAA) in healthy pregnant women. Among the subjects with GDM, 4.6% (20 of 435) developed T1DM and 5.3% (23 of 435) developed T2DM, while none of the controls developed diabetes during the follow-up of 6.7±2.7 years. 6.3% of those who developed T1DM were GADA positive, 62.5% ICA positive and 37.5% IA-2A positive. Only two subjects with T2DM (8.7%) were antibody positive. None with T1DM or T2DM was positive for IAA. 22.2% (20 out of 9) tested positive for two antibodies and 75.0 % (6 out of 8) of those tested positive for three antibodies developed T1DM. Insulin treatment was required in 35.6% of GDM patients. 18 of the 20 T1DM and 18 of the 23 T2DM women were treated with insulin during pregnancy.

**Conclusions:** It seems that impaired glucose tolerance will manifest during pregnancy as GDM. After the pregnancy 10 % of GDM patients developed either T1DM or T2DM, the risk for each being similar. T1DM patients were more often antibody positive than T2DM patients. The highest risk to develop T1DM after GDM is in patients under 30 years, who have required insulin for GDM and were tested positive for ICA and GADA.

## 110 High amniotic fluid erythropoietin levels are associated with increased frequency of fetal and neonatal morbidity in Type 1 diabetic pregnancies

Kari Teramo 1) M. Anneli Kari 2) Marianne Eronen 2) Helene Markkanen 3) Vilho Hiilesmaa 1)  
1) Department of Obstetrics and Gynecology, University Central Hospital, Helsinki 2) Hospital for Children and Adolescents, University Central Hospital, Helsinki 3) Department of Clinical Laboratory Diagnostics, University Central Hospital, Helsinki

**Background:** Elevated fetal erythropoietin (EPO) levels are indicative of chronic fetal hypoxia. Amniotic fluid (AF) EPO levels correlate highly significantly with fetal plasma levels before labor. Our aim was to study the occurrence of chronic fetal hypoxia and its association with perinatal morbidity using AF EPO as indicator in Type 1 diabetic (DM) pregnancies.

**Methods:** 331 women with DM had at least one childbirth between September 1995 and December 2000. Amniocentesis for fetal lung maturity was done at 37 pregnancy weeks in 82% of DM patients. AF EPO levels were measured 1 day

(median) (range 0-14 days) before onset of labor in 198 diabetics with singleton pregnancy delivered by cesarean section.

**Results:** Median (range) AF EPO levels in diabetic pregnancies was 13.0 mU/ml (2.0-1975) and 6.3 mU/ml (1.7-13.7) in healthy controls ( $p < 0.001$ ). Of 198 DM patients 21 (11%) had AF EPO levels  $> 63.0$  mU/ml (10x median of controls). AF EPO levels in diabetic pregnancies correlated negatively with umbilical artery (UA) pH ( $r = -0.43$ ,  $p < 0.001$ ), UA pO<sub>2</sub> ( $r = -0.48$ ,  $p < 0.001$ ) and lowest neonatal blood glucose level ( $r = -0.46$ ,  $p < 0.001$ ), and positively with UA pCO<sub>2</sub> ( $r = 0.46$ ,  $p < 0.001$ ), birth weight z-score ( $r = 0.33$ ,  $p < 0.001$ ) and last maternal HbA<sub>1c</sub> ( $r = 0.43$ ,  $p < 0.001$ ). Neonatal hypoglycemia ( $< 2.0$  mmol/l), cardiomyopathy and admission to the neonatal intensive care unit occurred significantly more often ( $p < 0.001$ ) in cases with high AF EPO levels than in cases with normal AF EPO levels. Multivariate logistic regression analysis showed that AF EPO was the only independent variable explaining low UA pH ( $< 7.21$ ) ( $p < 0.001$ ). Low UA pO<sub>2</sub> ( $< 2.0$  kPa) was explained by AF EPO ( $p < 0.001$ ) and birth weight z-score ( $p = 0.03$ ). Neonatal hypoglycemia was explained by AF EPO ( $p = 0.004$ ) and gestational age ( $p = 0.005$ ).

**Conclusions:** High AF EPO levels can identify antenatally fetuses and newborn infants with an increased risk of severe perinatal complications in Type 1 diabetic pregnancies.

#### 111 Complications to a high pre-pregnancy Body Mass Index in 8,092 Danish pregnancies - The influence of Parity

Line Rode, Lisbeth Nilas, Karen Wøjdemann, Ann Tabor  
*Department of Obstetrics and Gynecology, Hvidovre Hospital*

**Background:** The objective of this study was to investigate the relationship between pre-pregnancy BMI (Body Mass Index) and obstetric complications as well as foetal complications in a large unselected cohort of Danish women with low risk pregnancies.

**Methods:** A cohort of 8,092 women from the Copenhagen First Trimester Study with a registered pre-pregnancy BMI and a low risk pregnancy (single cephalic term delivery) was selected. The women were stratified into three BMI groups: normal weight (BMI  $< 25$ ), overweight (BMI 25-29.9) and obese (BMI  $\geq 30$ ). In these BMI groups the complications in nulliparous and multiparous women were compared using univariate and multivariate logistic regression analyses. We defined complications as maternal complications, complications during delivery and complications to the child.

**Results:** The maternal risk of diabetes, hypertension and preeclampsia increased with an increasing BMI. The caesarean section rate also increased, while there was no relationship between BMI and vacuum extraction or delivery complications, such as shoulder dystocia or perineal rupture. Overweight women had an increased risk of delivering a macrosomic as well as a low birth weight child.

We found no difference in infant morbidity as estimated by Apgar score, umbilical cord pH or admittance to a neonatal intensive care unit. Nulliparous women had an increased incidence of preeclampsia, hypertension, emergency caesarean sections, vacuum extraction and perineal rupture (correlated variables), whereas multiparous women had a higher incidence of elective caesarean section, mainly due to a previous caesarean section. Nulliparous normal weight and overweight women had a greater chance of giving birth to a normal weight child (2500 to 3999 g).

**Conclusion:** The rate of complications during pregnancy and delivery increases with an increasing pre-pregnancy BMI. Nulliparous women have more complications during pregnancy and delivery than multiparous, but have a better chance of giving birth to a normal weight child.

#### 112 Randomised controlled study of treatment of retained placenta with 100IE intraumbilical oxytocin injection via an infant mucus aspiration tube.

Priya Chauhan 1) Maria Rosendahl 1) Bente Sørensen 2) Jes G Westergaard 2)  
1) Kolding Hospital 2) Odense Hospital

**Background:** Intra umbilical vein injection of saline plus oxytocin appears to be effective in the medical management of retained placenta, as concluded by the Cochrane Review meta analysis (2001). However, among the included studies there is great diversity concerning the volume, concentration and the route of administration of oxytocin and saline. Pipingas (1993) demonstrated that injection via an infant mucus aspiration catheter introduced along the umbilical vein to 5 cm from the placenta insertion demonstrated a cotyledonary pattern in all patients when a volume of 30 ml of solution was used. Charlotte Wilken-Jensen (1989) reported an acceleration of delivery of placenta with the administration of 100 IU of oxytocin without any increase of maternal oxytocin level. Our aim was to combine the above two studies and compare them with plain saline injection and expectant management.

**Methods:** Sixty patients with retained placenta 30 minutes after vaginal delivery, enrolled from Odense University Hospital and Kolding Hospital. They were randomised into 3 groups: (A) Oxytocin group receiving 100IE oxytocin diluted with 20 ml. saline and injected via an infant feeding tube, (B) Saline group: receiving 30 ml saline injected as above, (C) Expectant group: where no active treatment was given for 30 minutes. Bleeding greater than 700 ml. preterm labour ( $< 34$  weeks) and multiple pregnancy was a contraindication. If the placenta did not deliver within 30 minutes after injection, manual removal was performed under universal anaesthesia.

**Results:** Sixty five percent of patients in the oxytocin group delivered within an average of 13 minutes after injection, with an estimated blood loss (EBL) of 237 ml. In the saline group, only 30 percent patients delivered the placenta after

the injection within an average time of 18.3 minutes and an EBL of 411 ml. In the expectant group 25 % patients delivered the placenta spontaneously within an average time of 84 minutes and an EBL of 433 ml. Ten percent of patients from both the oxytocin and the saline group delivered the placenta unrelated to the trial.

**Conclusion:** Intraumbilical vein injection of 100IE oxytocin via an infant mucus aspiration tube is effective in the treatment of retained placenta. The route of administration, volume of 30 ml and a concentration of 100 IE oxytocin is important for the effectivity. Expectant treatment until approximately 80 minutes after delivery can reduce the need for treatment in 25% patients without causing significant increase in postpartum haemorrhage.

### 113 Periodontitis and bacterial vaginosis before pregnancy increase the risk for adverse pregnancy outcome

Tapio Kurki 1) Juha Oittinen 2) Minnamaija Kekki 1) Minna Kuusisto 1) Pirkko Pussinen 2) Tiina Viikuna-Rautiainen 2) Anja Nieminen 2) Jorma Paavonen 1) Sirkka Asikainen 1)  
1) Department of Obstetrics and Gynecology, University of Helsinki 2) Institute of Dentistry, University of Helsinki

**Background:** Bacterial vaginosis (BV) is associated with both miscarriage and preterm delivery. Intervention trials of BV during pregnancy have failed to reduce the number of these complications perhaps due to the late onset of treatment. Maternal periodontitis may also increase the risk for prematurity. We studied the association between periodontitis, BV and pregnancy outcome among women planning to become pregnant.

**Methods:** An ongoing prospective study was launched on May 2001. Prepregnancy clinical oral and gynecological examinations were done and pregnancy follow-up visits were scheduled for 6-8, 28 and 32 gestational weeks. Periodontitis was diagnosed when at least one approximal periodontal pocket was >4 mm and attachment loss > 1 mm. BV was diagnosed by vaginal Gram-stain. Sociodemographic variables were collected.

**Results:** So far 239 healthy women have been enrolled and 105 of them became pregnant. Multivariate analysis showed a strong association between periodontitis and adverse pregnancy outcome (OR 11.7, 95% CI 2.2-63.6). of the four women with both periodontitis and BV, three had adverse pregnancy outcome (OR 37.3, 95% CI 1.8-776.8).

**Conclusions:** Periodontitis and BV have additive effects on adverse pregnancy outcome. Prepregnancy counseling should include both oral and vaginal examinations to exclude these infections.

### 114 Human chorionic gonadotropin (hCG) during third trimester pregnancy

Greta Edelstam 1) Christian Löwbeer 2)  
1) Fertility Unit, Dpt ObGyn, Karolinska university hospital, Stockholm 2) Div. of Clinical Chemistry, Dpt Lab. Med. Karolinska university hospital, Stockholm

**Background:** Separate reference values were recently established for routine blood parameters during pregnancy. Previously these were based on blood samples from healthy men or non-pregnant women. Normal variations in the levels of steroid hormones the last weeks of pregnancy before delivery, are also incompletely investigated. This study of the pre-term hormone levels was carried out in search for changes that might occur the weeks before delivery and potentially influencing the initiation of labour.

**Methods:** Blood samples during pregnancy weeks 33, 36 and 39 as well as 1-3 hours postpartum were collected from pregnant women (19-39 years, mean age 30) with at least one previous pregnancy without a history of hypertension or preeclampsia. All women (n=135) had a vaginal delivery and spontaneous start of labour. The blood samples were analysed for S-hCG, S-Estradiol and S-Progesterone and the values were postpartum rearranged to correspond the actual week before the day of delivery.

**Results:** During the last trimester of normal pregnancy a gradual increase was found in serum estradiol (median 52340 – 82410), progesterone (median 412-675) and serum hCG (median 14636-19494). A significant ( $p<0.03$ ) decrease in hCG was found from the third to the second week before delivery while estradiol and progesterone continued to increase.

**Conclusions:** Hormone levels during third-trimester pregnancy have not previously been systematically investigated. Recent data suggests that hCG may play a role as an endogenous tocolytic in normal pregnancy by directly promote relaxation of uterine contractions. In this study a significant decrease in HCG level has been found 2-3 weeks before spontaneous start of labour. This might contribute to increase the contractility in the uterine muscle and gradually initiate the onset labour.