

# Abstracts of poster presentations

## 201 Postpartum pituitary insufficiency: Discover of a rare complication following a septic shock

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**Background:** We report a case of postpartum pituitary insufficiency after an emergency C-section performed for abnormal labor on a patient with pregnancy-induced hypertension. Her postoperative status was complicated by uterine necrosis and a phlegmon of the right broad ligament which urged us to remove the uterus and right adnexa.

**Methods and results:** The analysis of the clinical symptoms and paraclinic tests (usual lab, CT, pituitary and peripheral hormones testing) revealed an unusual pituitary failure on TRH line

**Conclusions:** We think this unusual uni-lined pituitary failure could be due to postpartum septic shock associated with a deficient vascularization secondary to pregnancy-induced hypertension. The long-term vital prognosis is good with substitution hormone therapy.

## 202 Pinopode number is reduced in women with unexplained infertility

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**Background:** Pinopodes are round protuberances developing on the surface of the human endometrium at the time of implantation. The exact function of pinopodes is unknown but it has been shown that adhesion molecules are present on their surface. There are women enrolled in vitro fertilization (IVF) treatment, whose cause of infertility is unknown. It is possible that women with unexplained infertility might suffer from a defect endometrial development. The aim of the study was to compare the endometrium from fertile women with endometrium from infertile women.

**Material and Methods:** Biopsies from fertile and infertile women were obtained during the luteal phase, and a comparison of the endometrial maturation from infertile women and fertile women was performed. Scanning electron microscopy was used to examine the surface of the endometrium, while transmission electron microscopy to characterize the morphology inside the luminal epithelial cells. Immu-

nohistochemistry was used to reveal the distribution and staining intensity of Glutaredoxin, a marker for pinopodes.

**Results:** Analysis with transmission electron microscopy showed that protrusions seen on the endometrial surface of endometrium obtained before day LH+6 and after LH+9, differed in morphology from pinopodes. The incidence of pinopodes in biopsies obtained on days LH+6 to LH+9 was 83% in normal fertile women, and 50% in women with unexplained infertility. In biopsies with pinopodes, only 43% of the surface of endometrium was covered in infertile women, compared to 69% of the surface of endometrium from normal women. The apical immunostaining of glutaredoxin in the pinopodes was not seen in infertile women.

**Conclusion:** The use of different microscopic techniques illustrate that not all protrusions seen on the endometrial surface can be regarded as pinopodes. Some women with unexplained infertility have a defect in endometrial development indicated by lower amount of pinopodes and absent apical staining for Glutaredoxin.

## 203 Adrenomedullin expression in the decidua in normal and pre-eclamptic pregnancy

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**Background:** Adrenomedullin (AM) is a multifunctional peptide involved in angiogenesis, vasodilation, cell growth and differentiation. We have previously demonstrated that in placenta AM mRNA is expressed in abundance by invasive extra-villous cytotrophoblast, suggesting that it may play a role in establishing the blood supply to the placenta, a process which is deficient in pre-eclampsia. The aim of this study was to measure levels of AM and its precursor, preproadrenomedullin (preproAM) in decidua from normal and pre-eclamptic pregnancies. Access to such tissues is normally restricted to small placental bed biopsies. Therefore, we have developed a suction technique for collecting decidua from the uterine cavity at caesarean section which gives much greater yields of tissue, sufficient for molecular analysis.

**Methods:** Decidual samples were obtained by suction of the uterine wall at the placental site after removal of the placenta during caesarean section from eight normal and eight pre-eclamptic pregnancies and snap frozen in liquid

nitrogen. RNA was isolated and analysed by RNase protection assay using specific probes to determine the levels of mRNA for AM and b-actin (as a loading control). In parallel, proteins were extracted from the same samples and the levels of preproAM and b-actin determined by Western blotting. Adrenomedullin mRNA and preproAM protein levels were expressed as a ratio to b-actin controls. Statistical analysis was performed using Mann-Witney test.

**Results and Conclusions:** Adrenomedullin mRNA and preproAM protein were found to be expressed in the decidua samples, demonstrating the feasibility of studying this material. Levels of both mRNA and protein were reduced in pre-eclampsia compared to normal pregnancy, however due to the small number of samples examined, the differences were not statistically significant. Our results suggest that adrenomedullin synthesis in the decidua may be compromised in pre-eclamptic pregnancies and further research using a larger number of clinical samples is underway.

## 204 Imprinting diseases and IVF

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**Objectives:** To assess the frequency of imprinting diseases in children born without and after in vitro fertilisation (IVF).

**Material & methods:** All singleton children born in Denmark from January 1, 1995 through December 31, 2001 were stratified into children born without and after IVF, and were followed from birth until the end of year 2002 in the National Register of Patients (NRP) and Central Register of Psychiatric Diseases (CRPD) which include all discharge diagnoses from somatic and psychiatric hospitals/clinics respectively.

**Results:** During the seven-year study period 442,349 singleton children without prior IVF and 6,052 after IVF were born within 2.0 and 0.025 mio follow-up years, respectively. Number of specific imprinting diseases in the non-IVF group was 54 (kidney cancers (DC 54): 44, neuro/retinoblastoma (DC692A): 5, Prader Willi syndrome (DQ871E): 3, Russel Silver syndrome (DQ871G): 2, and Beckwith Wiedeman syndrome (DQ873A): 0. Thus, many children are not diagnosed with the specific imprinting disease codes within their first years of life. Anticipating same occurrence in IVF children, the expected number was 0.74. The observed number in the IVF group was 0. It is not very likely that missing diagnosis or mis-classification occurred differentially in the IVF and non-IVF group. We found a significantly increased risk of cerebral palsy in the IVF group, with a rate ratio of 1.8 ( $n=20/819$  in +IVF/-IVF group) and of sleeping disturbances: RR 2.0 ( $16/572$ ). The latter finding could be influenced by the older parental age in the IVF group. The incidence rate of childhood cancers, mental diseases, congenital syndromes, and developmental disturbances was equal in the two groups.

**Conclusion:** We found no indication of an increased risk of imprinting diseases after IVF, especially not a several fold increased risk, but a 80% increased risk of cerebral palsy, and equal frequencies of childhood cancers, mental diseases, congenital syndromes and developmental disturbances in the two groups. Danish register data does not support casuistic reports of an increased risk of imprinting diseases after IVF.

## 205 Case of successful remodeling of endometrium with transdermal estradiol - Divigel (Orion Pharma)

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**Background:** The aim of this study was assessment of transdermal estradiol (Divigel) conformity for per oral one for hormonal replacement therapy (HRT) preparing of endometrium (HRTPE) that was assessed with scanning electron microscopy (SEM).

**Methods:** We investigated 27-years old women with two IVF failures. Under pituitary/ovarian suppression with buserelin (Suprefact) was done stimulation of proliferative changes of endometrium with transdermal estradiol Divigel (Orion) with 1 mg of estradiol valerate in one pouch following scheme: 5 days 1 mg (one pouch) per day; then 4 days 2 mg (one pouch twice) per day; then 4 days 3 mg (one pouch three times) per day; then after ultrasound exam of endometrium thickness 4 mg (7 mm) (one pouch four times) per day. Secretory changes carried out with oil injection of progesterone 50 mg till second biopsy of endometrium when dose of Divigel was changed to 1 mg per day. The double endometrial biopsy was done on 6-th and 8-th day of progesterone exposure. The pinopode formation as a marker of endometrial receptivity was investigated with the use of SEM.

**Results:** Speed of endometrium growing was sufficient: 7 mm on 14-th day of Divigel exposure and 12 mm after 4 days. SEM micrograph of endometrial epithelium on 6-th day of progesterone exposure showed the secretory changes: secretory cells which was covered with short and slender microvilli. The ciliated cells was seen but in decreased number. SEM micrograph of endometrial epithelium on day on 8-th day of progesterone exposure had demonstrated most fully developed pinopodes also with decreased number of the ciliated cells.

**Conclusion:** We may confirm that transdermal estradiol - Divigel quite effective remedy for endometrium remodeling and thus we can speculate that its will be quite effective in assisted reproductive technologies endometrium remodeling.

## 206 SHBG levels in women with prior gestational hypertension and preeclampsia in the northern Finland 1966 birth cohort (NFBC 1966)

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**Background:** Sex hormone binding globulin (SHBG) has been shown to be a good indicator for insulin secretion/insulin resistance. There is previous data that support the hypothesis that insulin resistance with low SHBG levels contributes to the pathogenesis of preeclampsia (PE). To our knowledge, there are no previous long-term studies on SHBG in women with a history of gestational hypertension (GH). In this prospective population-based study, we tested the a priori hypothesis that women with prior GH or PE during their first pregnancy have low SHBG levels at age 31.

**Methods:** All births in the two northernmost provinces of Finland in 1966 were eligible for the NFBC 1966 (coverage 96%). 4074 women were invited to a clinical follow-up at age 31 (Pouta 2004). Women with chronic hypertension at first pregnancy, hormonal contraception or diabetes at blood draw were excluded. Of the whole female cohort with blood samples and written consent ( $n=1274$ ), 30 women had previous hospital-treated GH and 30 had PE during their first pregnancy (average age 25 years), 681 had normotensive first pregnancy and 366 were nulliparous.

**Results:** The serum SHBG levels were lowest in the GH group (median 49.3 nmol/l), and the levels in the PE group were 52.3, in normotensive pregnancy 57.3 and in nulliparous women 62.9 nmol/l (Kruskal-Wallis test  $p=0.066$ ). After stratification by BMI, among normal weight women ( $BMI < 25 \text{ kg/m}^2$ ), but not among obese, the SHBG values were lower in the GH group compared with the whole female cohort ( $p=0.079$ ). No difference was seen between the PE group and the whole female cohort.

**Conclusion:** Women with prior hospital-treated GH had the lowest levels of SHBG suggesting an association between GH and insulin resistance. Pouta A et al. Manifestations of metabolic syndrome after hypertensive pregnancy. Hypertension, 3/2004; in press.

## 207 Top quality embryo transfer in low responders

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**Background:** A low ovarian response (LR) to gonadotropin stimulation is associated with diminished pregnancy rates (PRs). On the other hand, the transfer of a top quality embryo is associated with a better outcome after IVF/ICSI. The aim of this study was to investigate the significance of the transfer of a top quality embryo in subjects with LR.

**Methods:** Analysis was initiated in 141 cycles of women with an initial LR (age:  $34.6 \pm 3.8$  years) and in 117 cycles of subjects with an initial NR (age:  $34.5 \pm 5.6$  years) who had undergone gonadotropin stimulation for IVF/ICSI. These represented the first three treatment cycles of women who had at least one LR cycle ( $n=86$ ). LR was defined as yielding  $\leq 3$  oocytes and normal response (NR) as 4–14 oocytes at pickup. Recurrent low responders were excluded from analysis because of low numbers.

**Results:** After the first treatment cycle, a higher gonadotropin dose was needed for ovarian stimulation in women with an initial LR than in those with an initial NR ( $2992.8 \pm 969.9$  vs.  $2657.1 \pm 914.8$  IU,  $p=0.01$ ). The numbers of collected oocytes and transferred embryos were similar in the two groups ( $1.8 \pm 0.7$  vs.  $1.6 \pm 0.9$ ), as were PRs (12.8% vs. 16.7%). However, in cycles with top quality embryos transferred, women with an initial LR had a lower PR than those who had an initial NR (15.0% vs. 47.6%,  $p=0.01$ ).

**Conclusions:** The majority of IVF/ICSI patients are not recurrent low responders. More than one embryo could be transferred in patients with an initial LR to obtain a pregnancy, even if top quality embryos are transferred. In contrast, the higher PR in top quality embryo cycles of women with an initial NR makes them suitable candidates for a single embryo transfer.

## 208 Previous human papilloma virus infection effect the clinical pregnancy rate in in vitro fertilization

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**Background:** The history of previous chlamydia trachomatis (CT) infection is strongly associated with tubal factor infertility. Not much is known of the effect of human papilloma virus (HPV) infection on fertility, but it is thought to affect only the lower female genital organs. In in vitro fertilization we have a possibility to examine the gametes and the embryos morphologically.

**Methods:** Couples attending our in vitro fertilization programme were invited to this study between May 1, 1999 and April 30, 2000. Serum samples from 99 women were exam-

ined for the presence of CT-EB specific IgG and IgA as well as HPV-VLP specific antibodies. The women were divided in four groups according to the results of the antibody analysis (CT+/HPV+ 18 women, CT-/HPV+ 25 women, CT+/HPV- 23 women, CT-/HPV- 33 women). The quality of embryos was analysed by looking at the number of blastomeres at 42-44 hours after insemination or ICSI, the number of multinucleated embryos and the degree of fragmentation in embryos with mononucleated blastomeres. The number of positive pregnancy tests and clinical pregnancies were calculated.

**Results:** There was no difference in the proportion of embryos with four blastomeres, the proportion of embryos with fragmentation maximally 20% or the proportion of multinucleated embryos between the four groups. After transfer a positive pregnancy test was seen in 64.7% (11/17) of CT+/HPV+, in 44.8% (13/29) of CT-/HPV+, 52.4% (11/21) of CT+/HPV- and 50% (16/32) of CT-/HPV-. The clinical pregnancy rate was 35.3% (6/17), 31.0% (9/29), 47.6% (10/21) and 46.7% (15/32), respectively.

**Conclusions:** There was no difference in the quality the embryos in the different groups. A lower clinical pregnancy rate was seen in women, who had antibodies against HPV, compared to women who did not have HPV antibodies.

## 209 Andropausal symptoms and general health in aging men

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**Background:** The aging of men is associated with subjective and objective biological changes, which can appear as symptoms of decreased physical, mental and sexual performance. In the literature this condition is termed partial androgen deficiency of the aging male (PADAM) or simply andropause. The present study was aimed to evaluate the andropausal symptoms and issues of general health in Finnish male population in the city of Turku, Finland (population approx. 170.000).

**Methods:** Men aged 40-70-years (n=28.622) received in 2000 a questionnaire composed of three parts: the Turku 3-question (T3Q) - and the Heinemann's Aging Male Symptoms (AMS) -questionnaires concentrating to andropause and an epidemiological questionnaire concentrating to general health. The results were reported in 5-year age groups: 40-44, 45-49, 50-54, 55-59, 60-64 and 65-69 years of age.

**Results:** 15.931 men responded (56%). In both andropause questionnaires and in the general health questionnaire an increasing trend of symptoms and illnesses were observed with increasing age. In average, positive criteria for andropausal symptom (AMS score higher than 36 or > 1 points in T3Q) was observed in 21.3% by T3Q and in 30.0% by AMS.

The age-dependent development of andropausal symptoms was most clearly seen in decreased sexual functions. Additionally, subjectively estimated health status correlated significantly to the healthy life style like the amount of exercise, non-smoking and low alcohol consumption.

**Conclusions:** A significant proportion of men are suffering from andropausal symptoms and general illnesses and these seem to increase steadily with increasing age. The association of these symptoms to aging alone, common diseases or to possible androgen decrement needs to be clarified further.

## 210 Molecular profiling of polycystic ovaries for markers of cell invasion and extracellular matrix turnover

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**Background:** Our previous results on non-hormone-primed mouse ovaries and on normally functioning, postmenopausal and polycystic human ovaries support the hypothesis that ovarian connective tissue components exhibit not only structural, but also active roles in ovarian function and dysfunction.

**Methods:** In order to study more efficiently possible alterations of gene expression in PCOS connective tissue, we carried out cDNA array analyses using filters containing 588 clones, including several components of connective tissue, extracellular matrix degrading enzymes and their inhibitors. Eight individual anovulatory PCOS samples were compared to two pooled follicular phase controls. Significant changes were further analysed by two-way hierarchical cluster analysis and some of the findings were chosen to be validated by real-time RT-PCR.

**Results:** A majority of the 30 genes down-regulated in PCOS ovaries represent those related to cell adhesion and motility, and angiogenesis, followed by regulators of cell cycle and growth. The 14 up-regulated genes represent those regulating cell fate and development, growth factors, cytokines, chemokines and cell-cell interactions. Of the 44 transcripts exhibiting marked changes in the cDNA array analysis, only one (cyclin mRNA) was systematically down-regulated, and transcripts for CDC27HS protein and CD9 antigen were down-regulated in 7/8 PCOS samples. Despite this heterogeneity in gene expression in the PCOS samples, a hierarchical cluster analysis suggested that PCOS patients can be subdivided into distinct subgroups based on their gene expression patterns.

**Conclusions:** Based on the results of the present study, considerable heterogeneity can be expected between individual samples. Therefore, particular emphasis should be given to sample patient characterization and sample col-

lection. This study suggests that a genome-wide microarray analysis of PCOS samples would help to identify metabolic and gene-protein systems involved in the pathogenesis of PCOS.

## 211 No association between serum testosterone levels and andropause related symptoms in healthy aging males

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**Background:** Aging is associated with changes in several hormones. In men the decrease in testosterone levels occurs slowly over several years and the hormone related symptoms may be difficult to identify. Furthermore, andropause or partial androgen decline in aging males (PADAM; 1), i.e. decrease in serum levels of androgens and related symptoms only affects about 20% of men by the age of 60-80 years. As changes occur in several hormonal glands during this period, it is unclear which symptoms are caused by the lack of specific hormones and which may be considered normal and part of the aging process. In this study, we wanted to estimate the frequency of andropause related symptoms and their correlation with serum levels of testosterone (T) and luteinizing hormone (LH).

**Methods & results:** A questionnaire of andropausal symptoms was sent to 28,622 men between 40-70 years of age living in Turku, Finland (popul. 170 000). Healthy men with high symptom score were invited for hormonal measurement (n=2513). Factor analysis on symptoms showed three significant independent factors. We named these factors: decreased mental, sexual, and physical fitness. Severity of several of the symptoms increased clearly with age. However, no correlations between the three identified factors and serum LH or T levels could be detected. Furthermore, only little change in serum levels of T was observed with aging. Serum LH levels increased significantly with age ( $p < 0.001$ , test for trend).

**Conclusions:** Our study shows that a large proportion of aging men with andropause related symptoms have normal serum T and LH levels. Whether our method of estimating androgen action is inadequate or the symptoms are caused by changes in other hormones remains open. Consequently, with regard to appropriate androgen replacement therapy for PADAM more research is needed before proper selection of men can be achieved.

## 212 WITHDRAWN

## 213 A randomised controlled trial of hysterectomy or levonorgestrel releasing intrauterine system in the treatment of menorrhagia - effect on FSH levels and menopausal symptoms

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**Background:** Hysterectomy is one of the most common surgical procedures performed on women. However, studies reporting the effect of hysterectomy on ovarian function are rare and provide contradictory results. To compare the effects of hysterectomy and levonorgestrel-releasing intrauterine system (LNG-IUS) on serum FSH levels and menopausal symptoms we conducted a randomised controlled trial.

**Methods:** The study population consisted of 236 women referred for menorrhagia to five university hospitals who were randomly assigned to treatment with hysterectomy (n=117) or LNG-IUS (n=119). Menopausal symptoms were characterised by the Kupperman menopausal distress test. Serum FSH and oestradiol levels were measured at baseline and six and twelve months after hysterectomy, or application of LNG-IUS. Analyses were by intention to treat.

**Results:** After six months there was no difference between the groups, but after twelve months follow-up hysterectomised women had higher FSH levels than women with LNG-IUS ( $p=0.005$ ). There was a significant association between FSH levels and treatment modality ( $p=0.020$ ). Hot flushes increased significantly in the hysterectomy group ( $p=0.02$ ). There was a significant association between hot flushes and both treatment modality and age ( $p=0.02$  and  $p=0.01$ , respectively).

**Conclusion:** Hysterectomy may impair ovarian function as shown by rising serum FSH levels and hot flushes. However, these results should be interpreted with caution, and longer follow-up is needed.

## 214 Sensitivity to a neurosteroid is increased during postmenopausal hormone replacement therapy.

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**Background:** To further deepen the studies on symptom cyclicity during postmenopausal hormone replacement therapy (HRT) the aim of this study was to compare the phar-

macodynamic response to a neuroactive steroid, pregnanolone, before and during different hormonal settings of HRT, using natural progesterone. A second aim was to investigate whether the response to pregnanolone was associated with cyclicity in negative mood symptoms during treatment.

**Method:** 26 postmenopausal women with climacteric symptoms were administered HRT in a randomized, double blinded, placebo-controlled, crossover study. The women received 2 mg oral estradiol (E2) continuously during two 28-day cycles and 800 mg of vaginal progesterone or placebo sequentially for the last 14 days of each treatment cycle. Pharmacodynamic response to pregnanolone was assessed before treatment, and during the last week of each treatment cycle, by comparing the effects of intravenous pregnanolone (3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one) on saccadic eye velocity (SEV), saccade acceleration, saccade latency and self-rated sedation. Throughout the study daily symptom rating scales were kept. According to the daily symptom rating scales, patients were divided into two groups; one group who displayed a significant variance in negative mood symptoms during HRT (cyclicity) and one group with no cyclical changes in negative mood symptoms during treatment.

**Results:** During treatment with either E2 alone or E2+progesterone the response in saccadic eye movement parameters and in self-rated sedation to pregnanolone was enhanced compared to pre-treatment values. The SEV, saccade acceleration and sedation responses to pregnanolone was also increased in women expressing cyclicity in negative mood symptoms compared to women with no cyclical changes in negative mood during HRT.

**Conclusions:** During treatment with either E2 alone, or E2+progesterone pregnanolone sensitivity was increased. Women expressing cyclicity in negative mood symptoms were more sensitive to pregnanolone than women without symptom cyclicity during HRT.

## 215 Dose-dependent rises in serum C-reactive protein to increasing doses of oral but not transdermal estradiol in postmenopausal women: Evidence of no role of medroxyprogesterone acetate or of a history of intrahepatic cholestasis of pregnancy

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Background: Liver dysfunction may affect the production and release of C-reactive protein (CRP). This protein has been studied recently, because its somewhat higher serum levels, even though well below levels indicative of infection, seem

to predict the risk for cardiovascular risk. We compared the responses of CRP to increasing doses of oral and transdermal estradiol, followed by oral progestin, in women with or without a history of intrahepatic cholestasis of pregnancy (ICP).

**Methods:** A double-blind prospective cross-over study on 40 women with (n=20) or without a history of ICP. In a randomized order women used estradiol with increasing doses either orally (estradiol 2mg 14 days, 4mg 14 days with concomitant placebo patches) or transdermally (estradiol 50ug/day 14 days, 100ug/day 14 days with concomitant placebo tablets). After the completion of the last estradiol only-treatment, the women continued with the same estradiol dose in combination with oral medroxyprogesterone acetate (MPA) daily (10mg) for 14 days. After four weeks' wash-out period, the regimens were switched over and the procedures were repeated.

**Results:** Both regimens were accompanied by significant rises in estrone and estradiol although the former were 16 times higher during oral than transdermal regimen. Oral but not transdermal estradiol increased CRP dose-dependently by a median of 49% at two weeks, by 91% at four weeks and 98% at six weeks from baseline, and this response was unaffected by MPA or by a history of ICP. The activities of liver transaminases varied but stayed in the normal range.

**Conclusions:** The synthesis of CRP is readily and dose-dependently stimulated by oral but not by transdermal estradiol already in two weeks and progestin had no effect. ICP is not characterized by any effect on the baseline or on estrogen stimulated CRP.

## 216 Abstract Physical training and hormone replacement therapy reduce the decrease in bone mineral density in perimenopausal women - a pilot study.

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The effects of physical training and hormone replacement therapy (HRT), on bone mineral density in perimenopausal women were studied. Sixty perimenopausal women were randomised to either physical training (n=20), HRT (n=20) or to a control group (n=20). The study period was 18 months. Bone mineral density (BMD) in the femoral neck and in the lumbar spine was measured using Dual X-Ray absorptiometry (DXA). DXA was performed before treatment and after 6 and 18 months. Blood samples for analysis of the bone markers uridyridinolin and osteocalcin were collected at the same time points. After 18 months the BMD in the spine had not decreased in either the training group or in the HRT group. In the control group the spine BMD had significantly decreased (p=0.014). Uridyridinolin and osteocalcin was increased significantly in the control group (p=0.0198, p=0.0295). No significant changes in bone marker levels were found in the training group or the HRT group. We found

that both HRT and physical training can prevent loss of spine BMD in perimenopausal women over a period of 18 months. HRT remains a cornerstone in the treatment of vasomotor symptoms and preservation of BMD. However HRT can only be used for limited periods of time due to the potential serious side effects. This study indicates a beneficial effect of physical activity on spine BMD in the perimenopausal period, and highlights its potential as an alternative to HRT during this period.

## 217 Menstrual pattern 12 months after IUS-LNG application

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The purpose of this paper is evaluation of menstrual pattern 12 months after IUS LNG application in women with menorrhagia. We had studied 35 women in reproductive age; the following items were analysed - age, menarche, BMI, WHC and menstrual pattern basal and 12 months after. Results are represented in mean±sd, absolute and relative values: age 42.8±7.49 years, menarche 12.9±2.08 years, BMI 30.3±6.65 kg/m<sup>2</sup> and WHC 88.4±11.3 cm; regarding menstrual blood loss 12 months after - 12 cases of amenorrhea (34%), 11 hypomenorrhea (31%), 5 with normal blood loss, 5 cases of spotting (14%), 1 case of persisting menorrhagia (3%) and 1 case of IUS expulsion (3%). The LNG IUS was applied in women with average 43 years old; mean BMI value is classified as obesity and a high mean of WHC. The LNG IUS induce significant changes on menstrual blood loss in 23 (65%) women from total 35.

## 218 Erythrocytes parameters in women with menorrhagia 12 months after LNG IUS application

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The purpose of this paper was erythrocytes parameters evaluation 12 months after LNG IUS application. We had studied 20 women in reproductive age with menorrhagia and with conditions for LNG IUS application. The following items were analysed, basal and 12 months after - age, menarche, number of red blood cells (RBC), hemoglobin concentration (Hb) and hematocrits (Htc). Results are represented in mean±sd: age 44.7±6.44 years, menarche 13.7±1.94 years; basal values - RBC 4 113 500±577 900/mm<sup>3</sup>, Hb 11.1±1.8g/dL and Htc 34.3±5.75%; 12 months values: RBC 4 579 375±713 652/mm<sup>3</sup>, Hb 12.5±1.67g/dL and Htc 38.3±3.75%; those last results were compared by Student's t test and signifi-

cance was found for RBC (p=0.029), Hb (p=0.017) and Htc (p=0.013). IUS LNG application 12 months after, improves significantly erythrocytes parameters as RBC, Hb concentration and Htc so there is an important role of this IUS in anemia management.

## 219 The effect of long-term oestrogen therapy on cognition

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**Background:** The purpose of the study was to evaluate the effect of long-term oestrogen treatment (ET) on cognitive functioning.

**Materials and Methods:** Sixty-two healthy postmenopausal women participated in a study of cognition during years 1994-1996. After 5 years they were contacted and 60 women agreed to participate in the present study. The incessant use of ET for last 5 years served as a criterion for study groups. Twenty-one women had used ET during the past 5 years (ET-users) and 18 women had not have any use during last 5 years (non-users). Among 21 women the use of ET was irregular and they were excluded from the study. This single-blinded study consisted of measurement in verbal and visuomotor performance, episodic memory and attention.

**Results:** Compared to their baseline measurements 5 years earlier the ET-users had maintained reaction times in automatic information processing better than non-users (2-choice reaction time p=0.031, 10-choice reaction time p=0.069). In verbal test of objects' naming the reaction times had increased in ET-users (4.4 sec) but decreased in non-users (1.7 sec, p=0.037). ET-users had also less correct answers (-0.5) than non-users (1.1, p=0.041). The cognitive performance testing comprised several other attentional, visuomotor and memory tests (18 additional tests), but in those tests the groups did not differ in their performance.

**Conclusions:** Cognitive performance is well maintained after menopause. The findings in the comprehensive test battery were sparse and random. Thus the use of ET gives no advantage in preservation of cognitive capacity but neither impair cognitive performance.

## 220 Sleep Deprivation, Cognitive Performance and Hormone Therapy in Postmenopausal Women

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**Background:** To study the effect of stress on cognitive performance in postmenopausal women and to evaluate whether hormone therapy (HT) has a modifying effect on coping. The stress was induced by acute sleep deprivation.

**Methods:** Twenty-six postmenopausal women, aged 58-72 years (mean 64 years), volunteered for the study (oral-HT-users, n=10; transdermal-HT-users, n=6; non-users, n=10). They spent four consecutive nights in the sleep laboratory (adaptation, baseline, deprivation, recovery). The cognitive tests were carried out three times: after the baseline night, after one night of sleep deprivation and after the recovery night. The cognitive measures included visual episodic memory, visuomotor performance, verbal attention and shared attention.

**Results:** The performance was preserved after sleep deprivation and showed improvement at the recovery measurement in visual episodic memory (immediate recall  $p<0.01$ , delayed recall  $p<0.05$ ), visuomotor performance ( $p<0.001$ ), verbal attention ( $p<0.001$ ) and shared attention ( $p<0.05$ ). Oral-users performed better than non-users in the visual episodic memory test. Otherwise HT did not influence the results.

**Conclusions:** The stress induced with sleep deprivation had a moderate effect on cognition. Despite of prolonged wakefulness the performance was not impaired, but remained at the baseline level. In repeated measures of cognitive tests a practice effect is common. In our study the lack of practice effect after sleep deprivation could be considered as deterioration caused by stress. After one recovery night performance improved compared to the baseline. HT did not have a major effect.

## 221 Risk factors for abnormal blood glucose values in polycystic ovary syndrome

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**Background:** As PCOS is a major risk factor for type 2 DM, it is important to find clinical and/or biochemical parameters that can be used to identify the women at highest risk for glucose intolerance.

**Methods:** A cross sectional study of 91 women referred with infertility or menstrual problems with PCOS, defined as oligomenorrhoea and elevated plasma testosterone. Examina-

tions and tests: Blood pressure, waist-hip ratio, body mass index (BMI), vaginal ultrasound, fasting levels of venous plasma glucose (FPG), total cholesterol, triglycerides, total testosterone and sex hormone binding globulin (SHBG). Twenty-five women also had an oral glucose tolerance test (OGTT).

**Results:** FPG was normal in 80 of the women, ten women had impaired fasting glucose (IFG) and one woman was diagnosed with type 2 DM. Women with fasting glucose values above normal were significantly older and had higher BMI, plasma cholesterol and triglycerides and lower SHBG than women with normal fasting plasma glucose. An analysis of the measured parameters in age groups showed significantly higher fasting glucose values in women older than 34. The OGTT was normal in all women under 35 and abnormal in 33 % of women older than 34: Three had IFG, and two of these also had impaired glucose tolerance (IGT). One woman with normal fasting blood glucose had IGT.

**Conclusions:** PCOS women with abnormal blood glucose values have a higher BMI and are older than women with normal values. In our study, there was a prevalence of 38 % of abnormal blood glucose values in PCOS women older than 34. It is mandatory that all these women receive blood glucose testing.

## 222 Serum SHBG in postmenopausal women taking raloxifen: preliminary results and comparative study regarding first degree family history of breast cancer

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The purpose of this paper is to evaluate serum concentration of SHBG in postmenopausal women taking raloxifen and to relate it with positive first degree family history of breast cancer (PFDIBC). We had studied 64 postmenopausal women; the following items were analysed: age, menarche, menopause, reproductive age, BMI, PFDIBC and SHBG basal values. Results were distributed as relative and absolute values and compared by Student's t test. Results: data were represented as mean $\pm$ sd; SHBG were expressed in nmol/L; total results -  $56\pm2.66$  (n=64); PFDIBC -  $60\pm39.77$  (n=13); no PFDIBC -  $55.9\pm22.25$  (n=51). No statistical differences were found when those samples were compared. Conclusions: although no significance was found, PFDIBC had basal SHBG concentration higher than no PFDIBC. SHBG have more affinity for testosterone than estradiol and higher level can increase free serum estradiol; it is very well established the relation between estradiol and risk of breast cancer in postmenopausal women. Our further investigation is to evaluate the modulation on the sexual hormones induced by raloxifen intake.

## 223 Serum SHBG in postmenopausal women taking raloxifen: preliminary results and correlation with body mass index.

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The purpose of this paper is to correlated SHBG serum concentration with body mass index (BMI) and evaluated if there is any relation with positive first degree family hystory of breast cancer (PFDIBC). We had studied 64 postmenopausal women taking raloxifen. The following items were analysed: age, menarche, reproductive age, menopause, BMI, PFDIBC and basal SHBG values. Results were distributed as mean±sd, absolute values, total results (n=64), PFDIBC (n=13) and non-PFDIBC results (n=51). Pearson correlation were established between those 3 samples. Student's t test was used to compare BMI from those samples. No significant correlation was found - total (n=64 and  $r=-0.16$ ; PFDIBC n=13 and  $r=-0.38$ ; non PFDIBC n=51 and  $r=-0.08$ ); no statistical differences were found comparing BMI; regarding BMI, even when we distributed total results in more or less than 28kg/m<sup>2</sup>, correlation had no statistical significance. Conclusions - In those samples of postmenopausal women, SHBG serum concentration is not influenced by body composition as BMI.

## 224 Comparison between iodine urinary excretion and the breast mammographic state

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In the Czech Republic the iodine supply used to be often insufficient, in spite of the consumption of iodinated table salt. The adequate and optimal daily income varies between 100 - 300 mg iodine, but app. 15.5 % of adult women have still an insufficient supply of iodine and their iodinuria decreases with age. The frequent coincidence of thyropathies in patients with breast diseases were recorded by many authors. One of the connections between diseases of the thyroid and breast glands could be the disturbance in iodine supply. Six years ago we started to detect the iodinuria in women categorized according to the finding of calcification, breast density and mammographic types (types according to Tabár I- V). The women with iodinuria lower then 100 mg/l were substituted with 138 mg of kalium iodide per day (JODID 100, Merck) and in next years controlled according to their health status. The iodinuria and the mammographic state were evaluated and compared again after 5-6 years. In 50 (100 %) women (age  $49 \pm 7$  years) the situation after the first detection was as fol-

lows: 29 patients were characterized as group III or IV with iodinuria lower then 100 mg/l in 25 of them (50 % of all controlled women). Groups I or II consisted of 17 patients with iodinuria lower then 100 mg/l in 12 of them. Out of 4 patients of group V had two of them normal and two the lower iodinuria. The situation after 5-6 years was the same in 11 women, the same number of patients underwent the operation, 2 women had involution (Tabár's group o) and in 26 women the mammographic type was changed. These findings led us to follow up in studies of connection between thyreopaties and diseases of breast glands.

## 225 Androgen secretion from reproductive age to menopause in healthy women and in women with PCOS

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**Background:** Ovarian steroid secretion capacity starts to decline already around the age of 30 years. Whether a similar age related decrease of androgen secretion as in healthy women occurs also in PCOS women and whether the enhanced androgen production in PCOS remains throughout fertile life are not known. Similarly, the changes in androgen profile at menopause are poorly understood. The aim of this study was to determine the age related serum basal and gonadotropin stimulated androgen levels in women with PCOS and the hormonal changes after menopause in healthy women.

**Methods:** Human chorionic gonadotropin (hCG) stimulation test was performed in 45 women with PCOS (aged 19-44 years), 44 healthy women (aged 20-44 years) and in 19 healthy postmenopausal women (aged 50-62 years). 5000 IU of hCG was given (i.m.) 2-5 days after menstrual bleeding (in a random day in postmenopausal women) and blood samples for 17-hydroxyprogesterone (17-OHP), androstenedione (A), testosterone (T) and estradiol (E2) assays were collected at 0, 24, 48 and 96 hours.

**Results:** In women with PCOS basal serum T and A levels were about 50% higher than in healthy women. In postmenopausal women serum 17-OHP and A levels were decreased when compared to those of fertile women under and over 30 years, but T levels were comparable. The responses of A and T to hCG [area under the curve (AUC) 96 h] were significantly higher in women with PCOS than in young healthy women. The AUCs of all androgens were decreased in postmenopausal women compared to healthy controls. In PCOS subjects E2 levels were similar to those observed in normal women, but in postmenopausal women E2 levels were almost undetectable. In contrary to control women FSH levels remained unchanged until 44 years in PCOS women.

**Conclusions:** In PCOS the basal serum androgen levels and androgen secretion capacity are markedly increased and remain high throughout the reproductive years, although the decreasing ovarian capacity to release androgens in response to hCG seen in healthy women occurs also in PCOS. Even though 17-OHP and A levels are decreased in postmenopausal women, T synthesis remains stable until late postmenopausal years.

## 226 Effects of continuous combined HT and clodronate on bone mineral density in osteoporotic postmenopausal women

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The adding of bisphosphonates to hormonal therapy (HT) may improve the anti-resorptive effects of HT. In the Kuopio Osteoporosis Study bone density measurement (BMD) was measured by DXA (Lunar) from 3200 women. In case of osteoporosis (T-score <-2.5 SD), she was offered participation to a 5-year trial. In absence of contraindications for HT or bisphosphonates, she was randomized to estradiol hemihydrate (E2) 2 mg + noretisterone acetate (NETA) 1 mg (Kliogest®, Novo Nordisk, Denmark) + Boneplac. Boneplac consists of either 800 mg/day clodronate (Bonefos®, Leiras Ltd, Finland) or placebo. In case of contraindications or refusal of HT, she was offered clodronate 800 mg/day. In all 164 women participated the study; Kliogest® + Bonefos® (KB, n=54), Kliogest® (K, n=53), Bonefos® (B, n=57). Kruskal-Wallis one-way ANOVA and paired t-tests were used. The results are based on intention to treat analyses. The baseline there were no differences in BMD. After one year, the KB and K groups showed similar increases in LBMD of 4.8±5.2% and 5.0±4.1%, respectively, while the B group showed an increase of 1.8±4.9%. After 3 years, the KB and K groups showed increases of 2.7±6.7% and 3.4±5.2% from the baseline, while B had a decrease of -3.2±5.3% (p<0.001). After 5-years LBMD had increased by 7.2±11.9% and by 6.1±7.3% in KB and K-groups, respectively, but in B-group, the LBMD was stable (-0.5±8.8%) (p<0.01). In the FBMD, KB and K groups showed increases of 3.1±4.5% and 3.1±3.4% respectively, while the B group showed a decrease of -0.1±5.3% (p=NS) in one year. After 3 years, the KB and K groups showed increases of 2.3±6.5% and 2.7±5.9%, while group B showed a decrease of -2.7±5.9%. After five years, FBMD benefit was 2.8±6.9% and 3.0±6.8% in KB and K groups, but the net loss of FBMD in B-group was -3.2±6.5%. In conclusion, E2 2mg in combination with NETA 1 mg increases spinal and femoral BMD in postmenopausal women with severe primary or secondary osteoporosis. However, the addition of clodronate 800mg does not further increase the BMD values. In contrast, 800 mg/day clodronate could not preserve BMD in five years.

## 227 Effects of alendronate and hormone replacement therapy, alone or in combination, on bone mass and markers of bone turnover in elderly women with osteoporosis

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**Background:** In the menopause estrogen deficiency results in increased bone resorption and a reduction in bone mass; 30 percent of 65–70-year-old women have osteoporosis. Independently of bone mineral density (BMD), advancing age is an important risk factor as regards osteoporotic fractures. Independently of bone mineral density (BMD), advancing age is an important risk factor as regards osteoporotic fractures. Not surprisingly, according to an American cost-benefit analysis, examination and treatment of osteoporosis are most profitable when directed to 65–70-year-old people.

**Methods:** To compare alendronate, hormone replacement therapy (HRT), and their combination in treatment of elderly postmenopausal women with osteoporosis, 90 patients, aged 65–80 (mean 71) years, and with a T-score of bone mineral density (BMD) <-2.5 at either the lumbar spine or the femoral neck were randomised to receive 10 mg of alendronate (n=30), 2 mg of estradiol plus 1 mg norethisterone acetate (n=30), or their combination (n=30) for 2 years. BMD of the lumbar spine and the upper femur was measured at baseline and after 1 and 2 years of treatment. Urinary excretion of type I collagen aminoterminal telopeptide as related to creatinine (U-NTX) and serum type I procollagen aminoterminal propeptide (S-PINP) were assayed at baseline and with 6 months' intervals thereafter.

**Results:** Increases of 9.1–11.2% in lumbar spine BMD at 2 years were similar in the study groups. Only HRT increased femoral neck BMD statistically significantly (p<0.0001) at both 1 (+4.9%) and 2 years (+5.8%; p<0.05 for differences to the other groups). The alendronate group exhibited the biggest increases in trochanter BMD both at 1 (+5.8% p<0.01 for differences to the other groups) and 2 years (+8.5% p<0.01 for a difference to the combination treatment group). Total hip BMD increased similarly in all study groups. Percent reductions in U-NTX in the HRT group (60.2–62.7%) were significantly less (p<0.05) than in the combination group (78.1–80.4%) and in the alendronate only group (72.4–76.1%). Also S-PINP decreased less (p<0.05) in the HRT group (-53.6% to -59.8%) than in the other groups (-73.0% to -75.0% in the alendronate group; -67.0% to -71.5% in the combination group). Six patients discontinued the study due to gastrointestinal complaints (2 in each group), and 5 receiving HRT due to breast tenderness.

**Conclusions:** We conclude, that in elderly postmenopausal women with osteoporosis the combination of hormone replacement therapy and alendronate did not offer an extra gain of bone mass over either treatment alone. In terms of

BMD changes the single treatments were equally effective, but the reductions in bone markers were less on HRT than on alendronate.

## 228 Serum resistin levels in women taking combined oral contraceptives containing desogestrel or gestodene.

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**Background:** Resistin is a hormone secreted by adipose tissue that could be involved in the development of insulin resistance. Previous studies confirmed that endogenous sex steroids may influence serum resistin concentration in women. The aim of our study was to investigate the influence of combined oral contraceptives containing desogestrel or gestodene on circulating levels of resistin.

**Methods:** Fifty three women were enrolled into the study. Thirteen patients received 20 µg ethinylestradiol(EE)/150 µg desogestrel(DSG), 15 women were treated with 20 µg ethinylestradiol/75 µg gestodene(GST), 11 with 30 µg ethinylestradiol/150 µg desogestrel and 14 with 30 µg ethinylestradiol/75 µg gestodene. Blood samples for estimation of serum resistin and insulin levels were drawn before administration of OC and after 6 cycles of therapy.

**Results:** Treatment with the OC containing GST significantly lowered plasma resistin concentrations. The effect was seen in group receiving 20 µg EE (before treatment;  $29.9 \pm 9$ , after 6 cycles of OC;  $21.4 \pm 10.9$ ,  $p=0.03$ ) and in group on formulations containing 30 µg EE (before treatment;  $51.8 \pm 15.8$ , after 6 cycles of OC;  $38 \pm 16.9$ ,  $p<0.05$ ). This was not observed in patients receiving OC formulations containing 150 µg DSG. The six cycles of OC treatment regardless of the type of progestin did not have significant effect on body weight, BMI, fasting plasma glucose and insulin concentrations. We conclude that ethinylestradiol combined with desogestrel or gestodene is unlikely to induce insulin resistance through resistin pathway.

## 229 Serum insulin and waist hip circumference in postmenopausal women. Preliminary results in patients taking raloxifen

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The purpose of this paper is to evaluated insulinemia in postmenopausal women and establish the relation with waist hip circumference (WHC). We had studied 33 post-

menopausal women taking raloxifen. The following items were analysed: age, menarche, menopause, reproductive age, WHC and insulinemia. Data were compared by Student's t test and r Pearson correlation. Patients were distributed as WHC less than 88cm (A group -  $n=11$ ) and equal or more than 88 cm (B group -  $n=22$ ) (88cm - this value is a metabolic syndrome criteria). Results - A group data: Insulinemia  $6.2 \pm 1.5$  mU/L - WHC  $80.6 \pm 4.5$  cm. B group data: Insulinemia  $9.95 \pm 3.95$  mU/L - WHC  $94.7 \pm 5.53$  cm. Comparing data from those different groups, significance was found regarding insulinemia ( $p=0.000$ ) and WHC ( $p=0.000$ ); no significance was found in Pearson correlation.

**Conclusions:** Fasting insulinemia is higher in postmenopausal women with WHC equal or more than 88cm comparing with women with WHC less than 88cm. Insulin resistance and higher WHC can be related with increased risk for cardiovascular disease.

## 230 Addition of medroxyprogesterone acetate (MPA) to conjugated equine estrogen (CEE) treatment enhances cerebral vascular contraction induced by calcium and endothelin-1 (ET-1)

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**Background:** A possible preventive effect of Hormone Replacement Treatment (HRT) on ischemic vascular disease has been dismissed by the HERS and WHI trials. The lack of a preventive effect may be explained by the applied progestogen. This study elucidates the cerebral vascular effects of various hormone regimens.

**Methods:** Fifty-six non-atherosclerotic, ovariectomized New Zealand White rabbits were randomized into 7 groups ( $n=8$ ) receiving hormonal treatment in phytoestrogen free chow for 4 weeks: MPA+CEE(10mg/day+1.25mg/day); norethisterone acetate (NETA) + 17- $\beta$ -estradiol (E2)(3mg/day+4mg/day); CEE(1.25mg/day); E2 4mg/day; MPA(10mg/day); NETA(3mg/day) o placebo. Ring segments from the posterior cerebral artery (PCA) were microdissected and mounted for isometric tension recordings in a myograph. The maximum electromechanical response was measured by depolarisation of the artery segments with 124mmol/l K+-Krebs buffer. The dose-response relationship between calcium ( $10^{-6}$  to  $10^{-2}$ ) and ET-1 ( $10^{-11}$  to  $10^{-6}$  M) and vessel tone was established. The theoretical maximum effect ( $E_{max}$ ) and the concentration of agonist required to give half-maximal response ( $EC_{50}$ ) were calculated and compared by Student's t-test.

**Results:** Combined treatment of MPA and CEE caused a significant increase in  $E_{max}$  (mN/mm, mean $\pm$ SD, (n)) compared to treatment with CEE alone in response to calcium ( $3.47 \pm 0.14$  (6) vs.  $2.69 \pm 0.30$  (8),  $p<0.05$ ) and endothelin-1 ( $2.73 \pm 0.85$  (7) vs.  $1.64 \pm 0.88$  (8),  $p<0.05$ ). CEE caused a significant decrease in  $E_{max}$  compared to placebo in response to calcium ( $2.69 \pm 0.30$  (8) vs.  $3.70 \pm 0.20$  (8),  $p<0.05$ ) but not

endothelin-1. No differences were observed in EC<sub>50</sub>. No differences were found when comparing the combined treatment of NETA and E<sub>2</sub> with E<sub>2</sub> alone, nor when comparing E<sub>2</sub> with placebo.

**Conclusion:** Combined MPA and CEE treatment enhances vascular contraction induced by calcium and endothelin-1 in small non-atherosclerotic cerebral arteries when compared to CEE treatment alone. Similar effects are not observed with NETA and E<sub>2</sub>. This suggests that some progestogens applied in HRT may have adverse effects on vessel function.

### 231 Knowledge and attitudes about the climacteric period and HRT-use in two comparative random samples with six years interval

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**Background:** In 1992, a random sample of Swedish women were assessed about the climacteric period. Six years later, 1998, a comparative random sample of women were investigated. The aim was to study changes in: (i) the prevalence of hormone replacement therapy and (ii) women's attitudes and knowledge about the climacteric.

**Methods:** In 1992, a random sample of 5990 women, from five birth cohorts, 46, 50, 54, 58 and 62 years in the city of Göteborg, were assessed using a postal questionnaire technique. In 1998 the same technique was used and a similar questionnaire was sent to a new cohort of women (n=5411) of the same ages, resident in the city of Göteborg. The overall response rate was 76%. Information was obtained regarding: (1) socio-demographic variables, (2) general and reproductive health, (3) climacteric symptoms and use of hormone replacement therapy and (4) attitudes and knowledge about the climacteric period.

**Results:** The prevalence of hormone replacement therapy (HRT) use with medium potency estrogens had increased from 13% (1992) to 31% (1998) with the highest prevalence in the 54 year old group (46%). Low potency estrogens were currently being used by 6% (8%,1992). Nine percent preferred transdermal therapy (3%,1992). Forty-four percent of the women would consider HRT life-long if treatment was free from withdrawal bleedings (35%,1992). Eighty percent believed that the risk of osteoporosis decreased during HRT use (61%,1992) and 68% thought that the risk of breast cancer increased (58%,1992).

**Conclusions:** A marked increase in the use of HRT was reported between 1992 and 1998. Women's attitudes regarding HRT were more positive in 1998 compared to 1992. Knowledge about HRT among women had increased during the same six years period.

### 232 Effects of hormone replacement therapy on the immune system

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**Background:** The aim of this study was to analyze the effects of different postmenopausal hormone replacement regimens on the parameters of the immune system.

**Methods:** The study was carried out on a randomized group of 40 patients. The first group(n=20) was prescribed tibolone (Livial, Organon) 2.5 mg/day while the second group (n=20) recieved 17-beta estradiol 1 mg plus noretisterone acetate 0.5 mg/day (Activelle, Novo Nordisk). Twenty premenopausal patients were also included in the study as a control group. Immune phenotypology of the lymphocytes was carried out using flow cytometers of the blood samples taken. Serum immunoglobulin (Ig G, Ig A, Ig M) levels, lymphocytes, number of lymphocyte subgroups (total B and T lymphocytes, T helper, T cytotoxic/suppressor) and the number of natural killers prior to therapy and three months post-therapy were compared.

**Results:** When post-therapy values were compared, there was a significant increase in CD3, CD4, CD8 and CD56. While there was a significant increase of IgM and a significant decrease in total T lymphocyte and T helper lymphocyte numbers in Group I, there was a significant decrease in IgG, IgA and the number of total T lymphocytes and an increase in T cytotoxic/suppressors and natural killers in Group II.

**Conclusion:** Although a decrease in immunoglobulin levels and total T lymphocytes may be considered to be an adverse effects of hormone replacement therapy, the increase in immunoglobulins and natural killers and decrease in the T helper/T cytotoxic-suppressor ratio may be regarded as a positive outcome.

### 233 Changes in attitudes and use of hormone replacement therapy among Scandinavian Gynecologists

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**Introduction:** Climacteric medicine has been in focus during the last two decades and an intensive debate has been ongoing regarding possible pros and cons of hormone replacement therapy (HRT). Recently several randomised controlled studies could not find evidence for primary or secondary preventive effects of HRT on coronary heart disease and more studies have indicated an increased risk of breast cancer and venous thromboembolism among HRT users. In 2001 we reported on knowledge, attitudes, management strategies and use of HRT among Scandinavian gynecologists (Maturitas 39:83-90, 2001). The aim of the present study was to re-assess the same parameters concerning HRT among Scandinavian gynecologists in 2003 and compare the results with the data collected in 1995-1997.

**Material & Methods:** All practicing gynecologists in Denmark, Norway and Sweden were invited by letter to complete and return an enclosed questionnaire regarding their knowledge, attitudes and management strategies concerning HRT. Female gynaecologists who had climacteric symptoms or were postmenopausal were questioned if they were currently using HRT. Male gynaecologists were requested to indicate if their wives were currently taking HRT if they had climacteric symptoms or were postmenopausal.

**Results:** The questionnaire was completed and returned by 60-75% of all practicing gynecologists in Denmark, Norway and Sweden. The results are at present being analysed and will be presented in Helsinki.

### 234 Estrogen and phytoestrogens: effect on eNOS expression and in vitro vasodilation in cerebral arteries in ovariectomized Watanabe heritable hyperlipidemic rabbits

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**Background:** To evaluate the effect of estrogen replacement therapy or soy isoflavones supplement on endothelium-dependent relaxation in vitro and gene expression of endothelial nitric oxide synthase (eNOS) in cerebral arteries in a rabbit model of human hypercholesterolemia.

**Methods:** Thirty-six female ovariectomized Watanabe heritable hyperlipidemic (WHHL) rabbits were randomised to treatment with 17 $\alpha$ -estradiol, SoyLife 150® or control for 16 weeks. Ring segments of basilar and posterior cerebral artery were mounted in myographs for isometric tension recordings. Concentration response curves to carbamylcholine chloride, sodium nitroprusside (SNP) and L-NAME were evaluated after precontraction with potassium. Total RNA was extracted, reverse transcribed and eNOS quantitated by real-time PCR.

**Results:** Plasma cholesterol was significantly higher at termination in the SoyLife® group ( $p < 0.0001$ ), whereas LDL-cholesterol was comparable in all treatment groups. Neither treatment influenced the endothelium-dependent responses to carbamylcholine chloride or L-NAME or the endothelium-independent response to SNP in any of the arteries. Correspondingly, eNOS mRNA was similarly expressed in all treatment groups in both arteries.

**Conclusions:** Improvement of cerebral endothelial function by estrogen or soy isoflavones in ovariectomized WHHL rabbits is not supported by the present data. The findings may be unique to the WHHL rabbit in which the hypocholesterolemic effect of estrogens mediated by upregulation of liver LDL receptors is excluded.

### 235 The role of estrogen metabolizing 17 $\beta$ -hydroxysteroid dehydrogenases in human fetal ovaries

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**Background:** Estrogens are pivotal in regulation of female reproduction. However, much less is known about the role of estrogens during ovarian development. During pregnancy, the fetus is exposed to large quantities of maternal estrogens and estrogen receptor expression has been observed in the fetal ovaries. The 17 $\beta$ -hydroxysteroid dehydrogenases (HSD) modulate the estrogen activity. Type 1 and 7 enzymes are responsible in converting estrone into more potent estradiol while type 2 enzyme performs an opposing action. In order to gain further insight into the role of estrogens in the ovarian development, the expression of 17HSD's in the fetal ovaries was studied.

**Methods:** Human ovaries were obtained from recently deceased fetuses (fetal age 12 – 33 weeks) or neonates who had died in less than 24 hours after birth (fetal age 23 – 40 weeks at birth). 17HSD-1, 17HSD-2 and 17HSD-7 mRNA was detected by using in situ hybridization.

**Results:** Expression of estrogen producing 17HSD7 was detected already at the age of 13 weeks and it decreased towards mid-term. 17HSD7 mainly localized to the pregranulosa and stromal cells. The expression of type 1 enzyme was

strongest near term and was only expressed in the follicular granulosa cells. 17HSD2 enzyme, antagonist to type 1 and 7 enzymes, was negative in all studied samples.

**Conclusions:** The present work demonstrates for the first time that 17HSD have differential expression in human ovaries. During early development, type 7 enzyme is the predominant form. When primordial follicles start to develop around oocytes, the type expression of type 7 enzyme is down-regulated and it is replaced by type 1 enzyme, which is more efficient in converting estrone into estradiol. The mechanism to respond to estrogen action is created already during the early ovarian development indicating, that estrogens can have a developmental function in the female gonad.

### 236 Serum Cholesterol Efflux Potential in Postmenopausal Women Receiving Extracted Isoflavonoids

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**Background:** The first step in reverse cholesterol transport involves efflux of cholesterol to extracellular acceptor. Wide spectrum of lipoproteins found in serum can act as cholesterol acceptors. In the present study we evaluated the effect of extracted isoflavonoids on serum cholesterol efflux potential in postmenopausal women. Furthermore, since approximately 20-30% of women produce large amounts of isoflavonoid metabolite equol we studied both equol-producers and non-producers separately.

**Methods:** 62 postmenopausal women received daily tablets containing 114mg of isoflavonoids (58% glycitein, 36% daidzein, and 6% genistein) or identical placebo for 3 months in a cross-over manner. Serum samples were collected before and after each treatment period and isoflavonoid, lipid, and lipoprotein levels were measured. We chose 15 women that were considered equol producers (5xbaseline or more equol levels after isoflavonoid treatment) and 15 comparable non-equol producers. The cholesterol efflux potential of the serum from each individual before and after treatments was evaluated by using 3H-cholesterol labelled Fu5AH cells in vitro.

**Results:** Isoflavonoid treatment increased serum daidzein ( $1133 \pm 757 \text{ nmol/L}$ ) and genistein ( $436 \pm 282 \text{ nmol/L}$ ) levels by a mean of 110- and 20-fold, respectively. Equol levels were increased in the equol-producers by mean of 30-fold ( $98 \pm 118 \text{ nmol/L}$ ) while no significant rise was seen in the non-producers ( $7.7 \pm 3.5 \text{ nmol/L}$ ). There was no change on total cholesterol, LDL or HDL after treatments. The ability of serum to promote cholesterol efflux in the Fu5AH cells was positively correlated with HDL ( $r=0.68$ ,  $p<0.00001$ ) and negatively correlated with LDL ( $r=-0.61$ ,  $p<0.0003$ ) concentrations. Serum after placebo treatment promoted  $19.9 \pm 3.4\%$  cholesterol efflux which was not affected by

isoflavonoid treatment ( $20.2 \pm 3.0\%$ ). No change was seen either when the equol producers and non-producers were evaluated separately.

**Conclusion:** We found no effect with extracted isoflavonoid intake on serum cholesterol efflux potential.

### 237 Effects on coagulation and fibrinolysis of a combined contraceptive vaginal ring compared to an oral contraceptive pill.

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**Background:** As part of development of a new combined contraceptive vaginal ring (CCVR, NuvaRing), where hepatic first-pass metabolism is avoided resulting in lower hormone requirements, its effects on various key parameters of coagulation and fibrinolysis were compared to a conventional oral contraceptive pill (OC).

**Methods:** A CCVR releasing 120 microg etonogestrel (active metabolite of desogestrel) and 15 microg ethinylestradiol per day and designed for one months continuous use (47 women), was compared with an OC containing 150 microg levonorgestrel and 30 microg ethinylestradiol daily (43 women) in an open-label, group-comparative trial. All women were non-pregnant, non-breastfeeding, aged 18-39, with regular cyclicity, BMI  $18-29 \text{ kg/m}^2$ , no evidence of abnormal coagulation or cervical dysplasia. Visits were for initial screening, at cycles 3 and 6 and post treatment.

**Results:** In the initial groups 25 women discontinued for various, mostly non-medical reasons and 65 women completed the trial (30 on CCVR; 35 on OC). Baseline characteristics of these women were similar. All hemostatic values were within normal range. Factor VII activity was higher at cycle 6 for the CCVR ( $p<0.0001$ ) due to decrease from baseline in the OC group ( $-14.2\%$ ) and increase in the CCVR group ( $+8.8\%$ ). Post treatment values returned to baseline. Levels of fibrinogen, FDP, D-dimer, prothombin fragments 1 and 2, protein S and AT3 and PAP and TAT complexes were comparable. Protein C levels were higher in the CCVR group. Changes in plasminogen and its activator t-PA went in opposite directions. No serious adverse events occurred and changes in BMI were comparable.

**Conclusions:** Effects on coagulation in the CCVR group were comparable to the OC group, - only the procoagulation parameter factor VII went in opposite directions. Anticoagulation, fibrin turnover and profibrinolytic activity was similar in the groups, with an overall minimal effect on hemostatic mechanisms and body mass.

### 238 Auto transplantation of cryopreserved ovarian tissue to the right forearm 4 1/2 years after autologous stem cell transplantation

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**Case-history:** A 25 year-old nulliparous woman with Pure Red Cell Aplasia underwent in 1998 autologous stem cell transplantation after receiving a combination of 8400 mg of cyclophosphamide and 8 Grey of total body irradiation. Prior to the treatment, one ovary had been laparoscopically removed, cut into small pieces and cryopreserved. Following treatment, her ovaries failed and she needed hormone replacement therapy. Approximately 7 months after the stem cell transplantation, her red blood cell production stabilized.

**Method:** In April 2003, ten small pieces of cryopreserved ovarian tissue were thawed and taken through decreasing gradients of the cryoprotectant (1 M propanediol for 5 minutes, 0.5 M propanediol for 5 minutes, and 0 M propanediol for 10 minutes) and finally transferred to a transport medium which consisted of 10 g/mL cefuroxim, 10 IU of FSH (Serono S.A.) and 20% fresh autologous serum in phenol-free - MEM. The tissue was then transplanted in a subcutaneous pocket over the fascia of the brachioradialis muscle of the right forearm. The patient was followed bi-weekly and then weekly with ultrasound examinations and hormonal tests.

**Result:** Almost 19 weeks after auto transplantation, a small follicle was observed at the site of the transplant. The follicle grew slowly, reaching a maximum diameter of 12.6 mm 244 days after transplantation. Follicle growth was to begin with associated with a significant oestrogen peak lasting for 9 days. Even when a second small follicle developed, the oestrogen levels stayed low thereafter (between 116 and 172 pmol/litre). The function of the transplant appeared to completely having ceased approximately 7 months after transplantation.

**Conclusion:** Auto transplantation of cryopreserved ovarian tissue to the forearm is feasible, but questions remain whether this is the optimal site, how to increase the number of surviving follicles to prolong tissue survival, and how to mature oocytes which can be fertilized.

### 239 First low-dose combi-patch releasing 0.025 mg estradiol and 0.125 norethisterone acetate daily: Endometrial safety and vaginal bleeding patterns

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**Background:** There is consensus that HRT should be used in lowest effective dose. This requirement is perfectly fulfilled with Estragest TTS®, which is the first low-dose combi-patch (already marketed in Germany since 1999). This continuous-combined HRT patch provides a daily delivery rate of 0.025 mg estradiol plus 0.125 mg norethisterone acetate [NETA] through the skin. It is generally accepted that cc-HRT effectively minimizes the risk of endometrial cancer/hyperplasia and leads to amenorrhea. The purpose of this study was to investigate the effects of low-dose cc-HRT on endometrial safety and vaginal bleeding patterns after 48 weeks of treatment with transdermal Estragest TTS®.

**Methods:** 411 postmenopausal women with an intact uterus, were enrolled in this study. Endometrial biopsies were obtained by using aspiration technique, performed at baseline and at Week 48. Vaginal bleeding patterns were assessed using patients' diaries. A patient was considered bleed-free, when no bleedings occurred (spotting allowed), whereas a patient was considered amenorrhoeic, when neither bleedings nor spotting occurred.

**Results:** 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 and amenorrhoeic patients 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 88.2 %, respectively.

**Conclusions:** Estragest TTS® combines perfectly the low dose regimen with a safe endometrial profile together with a desired high amenorrhea rate.

### 240 Characteristics of menstrual cycle in Latvian adolescents

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**Objectives:** To evaluate menstrual cyclicity in healthy, 11-16 year old schoolgirls from Riga regional comprehensive schools for 1 school-year.

**Methods:** Voluntary, healthy schoolgirls were asked to answer a questionnaire and record prospectively the precise time of their periods in a standard menstrual calendar for

the whole school year. Data statistical analysis has been performed by StatSoft computer program 'Statistica 6.0'.

**Results:** 1168 schoolgirls were asked to participate and 319 (27.3 %) responded. Mean age of menarche was 12.5 years (min.9.02-max.15.05; SD 1.09) and mean BMI 19.5 (min.13.1-max.31.4; SD 2.54). At BMI  $\leq$  18.4 (mean 17.2; SD 0.81); 18.5-24.9 (mean 20.6; SD 1.62);  $\geq$  25 (mean 27.5; SD 2.5) menarche occurred at the age of 12.7 years (min.11-max.15; SD 1.01); 12.5 years (min.9-max.15; SD 1.13); 11.7 years (min.11-max.12.09; SD 0.50), respectively. Correlation of BMI with menarche  $r = 0.2950$ ,  $p = 0.0000003$ . Mean menstrual cycle length was 30 days (min.15-max.74; SD 8.04). In 24 (2.0 %) cycle length  $\leq$  21 days, but 53 (4.5%)  $\geq$  35 days. Mean bleeding length was 5 days (min.2-max.10; SD 1.16). 45 % of girls noted painful menses.

**Conclusions:** The mean age of menarche in Latvian adolescents is 12.5 years. That is about 8 months earlier than recorded by Widholm and Kantero in the large study of Finnish girls. Menarche in undernourished girls occurred 2 months later than in girls with normal BMI. In overnourished girls menarche occurs 10 months earlier than in the normals. Correlation of BMI with menarche was slightly positive. Mean cycle length corresponds to normal interval, however, tendency towards long cycle is observed. The possible reason - long follicular phase, that is characteristic for pubertal menstrual cycles.

#### 241 The Epidermal Growth Factor (EGF) system in human endometrium is expressed cyclically.

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**Background:** The EGF system is ubiquitous in human organs, and play fundamental roles in embryogenesis, development, proliferation and differentiation. As the endometrium of fertile woman is characterised by proliferation and differentiation, we expect the EGF system to play a pivotal role. The EGF system consists of four receptors, HER1, HER2, HER3 and HER4, and numerous ligands. We investigated the receptors, and six ligands: epidermal growth factor (EGF), amphiregulin (AR), betacellulin (BCL), transforming growth factor- $\alpha$  (TGF- $\alpha$ ), Heparin Binding-EGF (HB-EGF) and epiregulin (EPI).

**Methods:** Fifteen women (median age in years 34.2 (range 24.2-40.7) were included. Endometrial samples were taken at day 6 $\pm$ 1 (early proliferative phase), and day 6 $\pm$ 1 (early secretory phase) and day 12 $\pm$ 1 (late secretory phase) after ovulation during one menstrual cycle. Total RNA was extracted from endometrial samples and analysed by real-time PCR. Immunohistochemical analysis was performed in

order to try to localize some of the components of interest, namely HER1, EGF, AR, BCL, TGF- $\alpha$  and HB-EGF.

**Results:** The pattern of the receptor expression varied during the menstrual cycle. HER 1 showed its highest mRNA value during early proliferative phase, HER2 and HER4 during early secretory phase and HER3 during late secretory phase. HER1 was identified by immunohistochemistry and was located in the luminal surface epithelium and the glands close by. The reaction was strongest in the secretory phases. AR and TGF- $\alpha$  showed the highest mRNA expression in early proliferative phase. HB-EGF showed no variation. The other three ligands were not identified by real-time PCR. Of the ligands only TGF- $\alpha$  was visible by immunohistochemistry and was located to the glands.

**Conclusions:** The EGF system in the endometrium of fertile women shows cyclic variation for all receptors and some ligands.

#### 242 Vaginal misoprostol for cervical priming before hysteroscopy

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**Background:** Difficulties in cervical dilatation prior to hysteroscopy are not uncommon. These have lead to cervical injuries, uterine perforation, creation of false passage or bleeding. It is well known that use of a cervical priming agent is effective in reducing complications during cervical dilatation in pregnant women. However, its use in non - pregnant women is not well established. The objective of this study was to evaluate the effectiveness and side effects of vaginal misoprostol for cervical priming in non-pregnant women before hysteroscopy.

**Methods:** This clinical study was performed at Kaunas University Hospital from January to August 2003. One hundred forty - four women scheduled to have hysteroscopy were randomised, by week's day, into 2 groups. The study group (n = 63) received vaginal misoprostol (400 microgram) at least 12 hours before surgery and the control group (n = 81) did not receive any cervical priming agent. The primary outcome measure in this study was the ease of dilatation as measured by the largest - number Hegar dilator that could be inserted into the cervix without resistance. Side effects of vaginal misoprostol and complications of procedure were noted.

**Results:** The mean cervical width was significantly different between the misoprostol group and the control group: prior to dilatation 5,4  $\pm$  2,1mm vs 3,7  $\pm$  0,9mm ( $p < 0,05$ ) and when the largest - number Hegar dilator was inserted without resistance 7,4  $\pm$  1,6mm vs 5,2  $\pm$  1,3mm ( $p < 0,05$ ). In the treated group 34 (54%) patients needed cervical dilation compared with 79 (97,5%,  $p < 0,05$ ) in the control group.

Only two (3%) women noted mild lower abdominal pain in the misoprostol group. There were no operative complications in either group.

**Conclusion:** Vaginal misoprostol applied before hysteroscopy reduced cervical resistance and the need for cervical dilatation, with only mild side effects.

#### 243 Cervical nitric oxide release is reduced in women going post-term

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**Objective:** Nitric oxide may be a factor in cervical ripening. We compared the nitric oxide metabolite levels in cervical fluid in women going post-term and in women delivering spontaneously at term.

**Methods:** We studied a total of 208 women with singleton pregnancies: 108 women who went post-term ( $\geq 294$  days), and 100 women who went spontaneously into labor at term. Cervical fluid samples, collected well before the initiation of labor, were assessed for nitric oxide metabolites, the detection limit of the assay being 3.8 mmol/L.

**Results:** Women going post-term less often ( $p = 0.001$ ) had detectable levels of nitric oxide metabolites in their cervical fluid (60%) than women delivering at term (87%). The nitric oxide metabolite concentration in cervical fluid in women going post-term (median 23.5 mmol/L, 95% CI  $< 3.8$ –31.8) was 4.5 times lower ( $p < 0.001$ ) than that in women delivering at term (median 106.0 mmol/L, 95% CI 81.8–135.0). Such a difference (14.0 mmol/L versus 106.0 mmol/L) also existed when only the 66 women going into spontaneous post-term labor were included in the comparison. Both nulliparous (median  $< 3.8$  mmol/L) and parous (median 31.3 mmol/L) women going post-term had lower ( $p < 0.01$ ) cervical fluid nitric oxide metabolite levels than nulliparous and parous women delivering at term (medians 76.1 mmol/L and 101.3 mmol/L, respectively). In the post-term group women with cervical fluid nitric oxide metabolite concentrations  $\geq$  median failed more often ( $p < 0.001$ ) to progress in labor and had longer ( $p = 0.02$ ) duration of labor than those with cervical fluid nitric oxide metabolite concentrations  $>$  median.

**Conclusion:** Reduced cervical nitric oxide release may contribute to prolonged pregnancy.

#### 244 Analysis of Various Risk Factors of Placental Abruption: A case-controlled retrospective study

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**Background:** Placental abruption is still one of the most dangerous pregnancy complications. We analysed the impact

of various prepregnancy and in-pregnancy risk factors on placental abruption.

**Methods:** Placental abruption occurred in 198 (0.42%) of 46,742 pregnancies in 1997–2001. To the control group we selected 396 women delivering at term before and after the index case. The histories and the courses of pregnancy were carefully perused and compared between the study groups.

**Results:** Age  $>35$  years, being unmarried, three or more previous deliveries, low social class, active and passive smoking, a history of spontaneous abortion or giving birth to an infant with growth retardation, caesarean section or preterm labor proved to be significant ( $p < 0.05$ ) pre-pregnancy risk factors of placental abruption. Factors that predicted ( $p < 0.05$ ) the risk of placental abruption during the index pregnancy were smoking, alcohol consumption, uterine malformations, bleeding during second or third trimester, placenta praevia, preeclampsia, preterm labor, or delivery by caesarean section. Also male fetus or fetal growth retardation indicated an increased risk of placental abruption. Nine women (7.9%) had experienced placental abruption repeatedly.

**Conclusions:** The risk of placental abruption can be approximated, at least to some extent, from various risk factors occurring both before and during pregnancy. This may help to select high risk individuals for intense follow-up and perhaps for future prevention trials.

#### 245 Calprotectin, a marker of inflammation, is elevated in maternal but not fetal plasma in preeclampsia

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**Background:** Preeclampsia is associated with excessive inflammatory response compared to normal pregnancy. Calprotectin is an inflammation marker not previously explored in pregnancies. Calprotectin is released by activated neutrophils. Elevated levels of calprotectin in plasma have been found in inflammatory states, autoimmune diseases and infections. As well as being a marker of inflammation, calprotectin has antimicrobial, cytotoxic and cytokine-like effects, and is proposed to be an important mediator with regulatory functions in inflammatory reactions.

**Methods:** Calprotectin in maternal and fetal plasma and amniotic fluid collected at cesarean section in normal pregnancies ( $n=38$ ) and preeclampsia ( $n=31$ ) was investigated by ELISA. CRP and plasminogen activator inhibitor type 1 (PAI-1) were also analyzed.

**Results:** The median level of maternal plasma calprotectin was two-fold higher in the preeclamptic group compared to

the control group (1081  $\mu\text{g/L}$  compared to 552  $\mu\text{g/L}$ ,  $P<0.001$ ). Median maternal CRP was also elevated in the preeclampsia group compared to the control group (4.8 mg/L and 3.8 mg/L, respectively,  $P=0.03$ ). Median PAI-1 concentration was also higher in the maternal circulation in preeclampsia compared to controls (51.0 U/mL compared to 36.5 U/mL,  $P<0.001$ ). In the umbilical arterial blood, there were no differences between preeclampsia and controls regarding calprotectin and CRP levels. Maternal calprotectin concentrations correlated with CRP and PAI-1 values for the total study group, but statistical significant correlations were not found in the preeclampsia group.

**Conclusions:** Calprotectin is elevated in the maternal circulation in preeclamptic pregnancies. We found no evidence of inflammatory response in the fetal circulation in preeclampsia.

#### 246 Elevated levels of soluble fms-like tyrosine kinase 1 (sFlt1) in fetal and maternal serum as well as in amniotic fluid in preeclampsia

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**Background:** Pregnancies complicated with preeclampsia are associated with augmented maternal serum levels of sFlt1 (placental soluble Fms-Like tyrosine kinase 1), also named VEGFR1 (Vascular Endothelial Growth Factor Receptor 1). sFlt1 binds VEGF (Vascular Endothelial Growth Factor) and PlGF (Placental Growth Factor), which reduces the free circulating levels of VEGF and PlGF, thereby opposing physiological vasorelaxation and endothelial homeostasis. Elevated maternal serum sFlt1 level has recently been proposed as the placenta-derived factor resulting in maternal endothelial dysfunction and consequent clinical signs of preeclampsia, namely hypertension and proteinuria. We hypothesized that also fetal serum sFlt1 level was augmented in preeclampsia. We also explored whether pregnancies complicated with diabetes were associated with elevated sFlt1 levels.

**Methods:** At cesarean delivery, maternal and umbilical vein blood and amniotic fluid samples were obtained from preeclamptic ( $n=37$ ), control ( $n=38$ ) and diabetic pregnancies ( $n=16$ ). ELISA for human sFlt1, VEGF and PlGF were performed.

**Results:** Preeclampsia was associated with elevated median sFlt1 concentrations as compared to normal pregnancy; in maternal (9932 and 3417 pg/mL,  $P<0.001$ ) and fetal serum (246 and 163 pg/mL,  $P=0.04$ ) as well as in amniotic fluid (51040 and 33490 pg/mL,  $P=0.03$ ). The maternal serum sFlt1 concentration was elevated in the diabetes group with superimposed preeclampsia as compared to the control group (6436 and 3417 pg/mL,  $P=0.01$ ). For the preeclampsia group there was a positive correlation between maternal

sFlt1 and fetal sFlt1 concentrations (Pearson's correlation 0.7,  $P<0.001$ ,  $r^2=0.5$ ).

**Conclusions:** The sFlt1 concentration is elevated in the fetal circulation in preeclampsia. Maternal serum sFlt1 levels rapidly decrease after delivery. Our results support a central role of the placenta for the elevated maternal sFlt1 level in preeclampsia. Possibly, manipulation of VEGF levels by neutralizing elevated sFlt1 levels could be of use in the treatment or prevention of preeclampsia in the future.

#### 247 8-Isoprostane, a marker of oxidative stress, is augmented in maternal circulation in preeclampsia and pregnancies complicated with type 1 diabetes mellitus

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**Background:** Isoprostanes are stable markers of oxidative stress. Both preeclampsia and diabetes mellitus have been associated with augmented oxidative stress. We wanted to assess total 8-isoprostane levels in preeclampsia as well as in pregnancies complicated with diabetes, compared to control pregnancies.

**Methods:** Maternal venous blood samples were obtained from preeclamptic ( $n=21$ ), control ( $n=38$ ) and diabetic pregnancies ( $n=50$ ). We measured total 8-isoprostane concentrations with GC-MS. Indices of antioxidant capacity were also measured, including FRAP (ferric reducing ability of plasma), vitamin E and d-ROM (diacron reactive oxygen metabolites).

**Results:** Median total 8-isoprostane concentration was elevated in preeclampsia (354 pg/mL,  $p=0.02$ ) and type 1 diabetes in pregnancy (488 pg/mL,  $p=0.02$ ) as well in the diabetes group with superimposed preeclampsia (691 pg/mL,  $p=0.06$ ) compared to uncomplicated pregnancies (218 pg/mL). Median FRAP level was elevated in preeclampsia (1061 nmol/mg,  $p<0.001$ ) and in the superimposed preeclampsia group (930 nmol/mg,  $p=0.06$ ) compared to the control group (835 nmol/mg). We found no differences in the mean Vitamin E levels between the groups. Median maternal d-ROM level was elevated in the preeclampsia group (554 CarrU,  $p=0.06$ ) as well as in the type 1 diabetes group (560 CarrU,  $p=0.02$ ) compared to the control group (462 CarrU).

**Conclusions:** Preeclampsia and diabetes with superimposed preeclampsia as well as type 1 diabetes in pregnancy is associated with elevated oxidative stress, measured as elevated total 8-isoprostane concentrations in maternal plasma.

## 248 C-reactive protein in metformin treated pregnant PCOS women.

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**Background:** Recently, we demonstrated that metformin reduces pregnancy complications in PCOS women. Elevated CRP level, as a marker for "low-grade inflammatory response" is associated with obesity, gestational diabetes and cardiovascular disease. CRP is elevated in non-pregnant women with PCOS. Recently metformin is reported to reduce CRP levels in such women. Our hypothesis was, that metformin would reduce CRP levels in pregnant PCOS women.

**Design:** A prospective, randomised, double blind, placebo controlled clinical intervention study. Forty women, 18-40 years with PCOS, and with singleton pregnancies were included before gestational week 12. Patients were treated with metformin 850 mg bid or identical placebo capsules. All participants received verbal and written diet- and lifestyle advice, folic acid 1 mg daily, and one multivitamin tablet daily. One woman in each group dropped out. High sensitive c-reactive protein (CRP HS) was analysed in serum.

**Primary aims:** 1) To investigate whether metformin had any effect on CRP levels in pregnant PCOS women. 2) Whether pregnancy complications were associated with elevated CRP levels.

**Results:** No differences in CRP between metformin and placebo treated PCOS women through pregnancy

- CRP levels were significantly higher throughout pregnancy in placebo treated women with pregnancy complications vs. those with uncomplicated pregnancies

### Conclusions:

- Metformin does not reduce CRP levels in pregnant PCOS women
- High CRP levels were associated with pregnancy complications

## 249 C-reactive protein in metformin treated pregnant PCOS women. Results of a prospective, randomised, double-blind study.

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**Design:** A prospective, randomised, double blind, placebo controlled clinical intervention study. Forty women, 18-40 years with PCOS, and with singleton pregnancies were included before gestational week 12. Patients were treated

with metformin 850 mg bid or identical placebo capsules. All participants received verbal and written diet- and lifestyle advice, folic acid 1 mg daily, and one multivitamin tablet daily. One woman in each group dropped out. High sensitive c-reactive protein (CRP HS) was analysed in serum.

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**Results:** No differences in CRP between metformin and placebo treated PCOS women through pregnancy CRP levels were significantly higher throughout pregnancy in placebo treated women with pregnancy complications vs. those with uncomplicated pregnancies

**Conclusions:** Metformin does not reduce CRP levels in pregnant PCOS women High CRP levels were associated with pregnancy complications

## 250 Prenatal Lifestyle: Neuropsychological Effects at Age 5

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**Background:** Little is known about the potential long-term effects of alcohol intake on a weekly level and binge drinking during pregnancy on neuropsychological development in childhood. The DNBC cohort offers a unique possibility to perform the long-term follow-up.

**Objective:** To examine the relation between alcohol intake and other maternal lifestyle factors during pregnancy and the neuropsychological development of 1500 children at the age of five years.

**Methods:** The Danish National Birth Cohort (DNBC) is a study of 100,000 pregnant women, in which all pregnant women in Denmark have been invited to participate since 1997. Data collection in the DNBC involves 2 prenatal and 2 postnatal maternal interviews. The prenatal interviews provide detailed information on maternal drinking patterns before and during pregnancy and other lifestyle factors. Additional medical and socioeconomic information on DNBC participants can be obtained by linkage with other Danish computerized registries, using the unique Danish personal identification number. Based on the DNBC, 1500 women with different drinking patterns during and before pregnancy have been selected. At the age of five years the children of these women are asked to undergo a neuropsychological development exam intended to assess both global measures of cognition, such as IQ, as well as more specific domains of neuropsychological development. All exams will

be performed by two trained psychologists. The particular instruments to be used are instruments that have been adapted for and (where possible) standardized among Danish children. The parents are asked to fill in a questionnaire on the health, behavior and social functioning of the child during the first five years of life. Anthropometrical measurements as well as control of vision and hearing is carried out. Time Schedule: Two pilot projects were carried out in 2003. The main project is carried out in the period 2003-2008.

## 251 Maternal deaths in Norway 1976 – 1995

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**Background:** Globally there are yearly some 585.000 maternal deaths, 99% of them in developing countries. It is difficult to assess levels of maternal mortality at the national level. To find the level requires knowledge about deaths of women of reproductive age, the cause of death and also whether the woman was pregnant at the time of death or had recently been so. In this study we report the maternal death rate in Norway in the period 1976-95 and describe the causes of death.

**Methods:** This is an observational, retrospective study. The maternal deaths in Norway were identified through Research Department of Statistics Norway and the Medical Birth Registry of Norway. We received copies of the hospital case records and in most cases the maternal death autopsies. Through these we classified the deaths and identified the causes of deaths.

**Results:** In the period 1976 - 1995 we found 50 maternal deaths in Norway. Sufficient reports from 46 of these cases were available for data collection. The maternal mortality rate was 4.5 / 100.000. Forty-two cases (91%) were classified as direct deaths, 3 as indirect deaths (7%) and one coincidental. There were 11 deaths caused by pregnancy-induced hypertension (24%), of these 7 had an intracranial haemorrhage. There were nine deaths (20%) from thromboembolism, 5 from sepsis (11%), 4 died following anaesthetic complications (9%) and 5 of amniotic fluid embolism (11%). Early pregnancy death occurred in five women (11%), 4 of these had an extra uterine pregnancy and one died following an abortion. Seven died due to other reasons. Twenty-nine had a caesarean section (64%), and twenty-eight of the infants survived.

**Conclusion:** The maternal mortality rate was 4.5/100.000 births. The dominating causes are pregnancy induced hypertension and thromboembolism. An important underlying cause seems to be caesarean sections.

## 252 Umbilical cord blood lactate: A valuable tool in the assesment of fetal metabolic acidosis

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**Background:** Fetal hypoxia and acidosis at delivery have traditionally been based on indirect parameters as Apgar scores, pH and Standard Base Excess (SBE). None of these values have however been shown to be sufficient in predicting adverse neonatal outcome. During anabolic metabolism lactate production increases resulting in metabolic acidosis, witch is far more harmful to the fetus than respiratory acidosis. Therefore lactate concentrations in umbilical cord blood might be a more direct and thereby more precise tool in the assessment of fetal metabolic acidosis. The aim of the present study was to evaluate the correlation between arterial umbilical cord blood lactate and Standard and Actual Base Excess (SBE and ABE) as well as pH.

**Methods:** A prospective, descriptive study of routinely collected umbilical cord blood samples from 2554 consecutive deliveries in a department of Obstetrics and Gynaecology at a university hospital in Denmark. Lactate, pH, SBE and ABE were registered. Umbilical cord blood sampling was performed according to standard procedures. The relationship between concentration of lactate and pH, SBE and ABE respectively were evaluated by calculating the correlation coefficient ( $r$ ). In order to determine a lactate value of umbilical cord blood indicating fetal metabolic acidosis (cut off level) receiver operating characteristic (ROC) curves were established.

**Results:** We found significant correlations between lactate and pH ( $r = -0.73$ ), lactate and SBE ( $r = -0.76$ ), and lactate and ABE ( $r = -0.83$ ). ROC-curves indicated a cut off value of 8.0 mmol/L.

**Conclusions:** The present study demonstrates a significant correlation between lactate concentration in umbilical cord blood and pH, SBE and ABE. This suggests that umbilical cord lactate could be used as an indicator of fetal asphyxia at delivery with a cut off level of 8.0 mmol/L.

## 253 Pregnancy outcome of HIV-infected women in Helsinki metropolitan area

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**Background:** Antiretroviral medication and proper obstetrical practices have greatly reduced the rate of vertical transmission of HIV-infection. Prevalence of HIV-infection has

remained low in Finland, however routine antenatal screening has been offered to all pregnant women since 1998.

**Methods:** We analysed the pregnancy outcomes of 52 pregnancies among 45 HIV-infected mothers delivering at our institute during 1993-2003. A multidisciplinary team planned the management strategy individually and supported mother's adherence to the treatment.

**Results:** The annual prevalence of HIV-infection among women delivering in the hospital district of Helsinki and Uusimaa increased from 0.6/10000 (95% CI 0-1.6) to 4.8/10000 (95% CI 1.4-8.2) between 1993-2002. HIV-infection was first diagnosed during pregnancy in 40% (18/45) of the mothers. Twenty of the mothers received antiretroviral medication already prior to pregnancy, in 58% the medication was started during the pregnancy. A good virological response (i.e. HIV RNA-load <1000/ml during the last trimester) to antiretroviral medication was reached in 90% (36/40) of the patients in whom the HI-viral load measurements were performed; in 60% (24/40) patients HIV RNA-load was below the detection limit of the assays. Of the infants 92% were born at term, and their mean weight was 3350g (SD +/- 395g). Caesarean section rate was low, 25% (13/52). All newborns were in good condition, their mean umbilical pH being 7.23. All newborns received antiretroviral medication and none of the infants born to mothers with predelivery diagnosis of maternal HIV-infection were infected.

**Conclusions:** We conclude that combination of universal antenatal screening and multidisciplinary co-ordination of care allow individualized treatment, and are effective in the prevention of vertical transmission of HIV-infection during pregnancy.

## 254 History of physical activity, occupation, and treatment in women with low back pain and pelvic pain during pregnancy

Ingrid Mogren  
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**Background:** The aim of the study was to investigate the history of physical activity, occupation and treatment in women with low back pain and pelvic pain (LBPP) during pregnancy.

**Methods:** All women who gave birth at one of two hospitals of northern Sweden from 1 January 2002 until 30 April 2002 were invited to fill in a questionnaire on their obstetric history, recent pregnancy and delivery. The cohort was analysed with calculation of odds ratios (OR) and their 95% confidence intervals (CI). Cox regression analyses were performed. Women with LBPP reporting a pain maximum of 7 or more on a VAS-scale were considered as having "high pain score LBPP" (hps-LBPP).

**Results:** The response rate was 83.2% (n=891). Mean age at start of regular physical activity (before pregnancy) did not differ between women with and without LBPP. Increasing number of years of regular physical activity decreased

the risk of LBPP during pregnancy. The risk of hps-LBPP was increased for women characterizing their occupation as "mainly active" (OR=2.0, 95% CI: 1.1-3.5) and "physically heavy" (OR=1.9, 95% CI: 1.1-3.2). Visit to a physician due to LBPP was reported by 46.2% and the mean number of visits was 2.0. Women with LBPP had received treatment in one third, and half of women with hps-LBPP had had any treatment. Self-reported treatment was mainly pelvic belt, other were water gymnastics, physical therapy, TNS, acupuncture, and pharmacological treatment.

**Conclusions:** Previous physical activity decreases the risk of LBPP during pregnancy. Occupation described as "mainly active" and "physically heavy" is associated with increased risk of hps-LBPP during pregnancy. One third of women with LBPP receive treatment during pregnancy.

## 255 Low back pain and pelvic pain during pregnancy - prevalence and risk factors

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**Background:** The aim of this study was to investigate prevalence and risk factors for low back pain and pelvic pain (LBPP) during pregnancy. All women who gave birth at one of two hospitals of northern Sweden from 1 January 2002 until 30 April 2002 were invited to fill in a questionnaire on their obstetric history, recent pregnancy and delivery.

**Methods:** The cohort was analysed by calculating the prevalence of LBPP during pregnancy. Univariate and multivariate logistic regression was performed to calculate odds ratio (OR) and its 95% confidence intervals (CI) where applicable. Non-parametric two-independent-samples testing was used to establish differences between groups. The response rate was 83.2% (N=891).

**Results:** The prevalence of LBPP during pregnancy was 72%. Most cases reported both anterior and posterior pain. Increasing parity, history of hyper-mobility and reported periods of amenorrhoea were risk factors for LBPP. Women with LBPP had significantly higher pre-pregnancy weight, end-pregnancy weight, and pre-pregnancy and end-pregnancy BMI. Age at menarche and use of oral contraceptives were not associated with LBPP. Non-respondents were of the same age and parity as respondents.

**Conclusions:** A majority of pregnant women report LBPP. Parity, low back pain and pelvic pain during a previous pregnancy, BMI, a history of hyper-mobility, and amenorrhoea are factors influencing the risk of developing LBPP during pregnancy.

## 256 Perceived health, sick leave, psychosocial situation and sexual life in women with low back pain and pelvic pain during pregnancy

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Umeå University

**Background:** Low back pain and pelvic pain (LBPP) is a common problem during pregnancy. The aim of the study was to investigate perceived health, sick leave, psychosocial situation, and sexual life among women experiencing low back pain and pelvic pain during pregnancy.

**Methods:** All women who gave birth at one of two hospitals of northern Sweden from 1 January 2002 until 30 April 2002 were invited to fill in a questionnaire on their obstetric history, actual pregnancy and delivery. Univariate and multivariate logistic regression was performed to calculate odds ratio (OR) and its 95% confidence interval (CI) where applicable. Non-parametric two-independent samples testing was used to establish differences between groups. Women reporting highest estimated pain during pregnancy due to LBPP (VAS  $\geq 7$ , scale 1-10 cm) was considered as having high-pain-score LBPP (hps-LBPP).

**Results:** The response rate was 83.2% (n=891). Most women were married or cohabiting (98%), and reported a  $\pm$  very good  $\pm$  or  $\pm$  good  $\pm$  partner relationship (96%) and a satisfying sexual life before pregnancy (91%). Only few women reported perceived health as  $\pm$  quite poor  $\pm$  or  $\pm$  poor  $\pm$  before pregnancy (2%), however this proportion increased during pregnancy (13%). Generally, satisfying sexual life declined during pregnancy, which also was the case for assessment of perceived health during pregnancy. Women with LBPP during pregnancy had an increased risk of reporting poor health (OR=3.05, 95% CI: 1.70-5.46). In general 68% of women had been on sick leave and a proportion of 22% had had maternity allowance. Women with LBPP reported sick leave in 72% of the cases.

**Conclusions:** LBPP and hps-LBPP demonstrate a negative impact on perceived health and sexual life during pregnancy. A great majority of pregnant women were on sick leave some time during pregnancy and the rate of sick leave was further increased for women with hps-LBPP.

## 257 Relationship between bone mineral density changes and back pain symptoms in pregnancy

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**Objective:** To evaluate whether back pain symptoms in pregnancy are associated with bone mineral density (BMD) changes using non-invasive ultrasound measurements of the os calcis.

**Methods:** Consecutive patients were prospectively recruited from a low risk obstetric clinic over a period of 12 months. BMD measurements were performed at the os calcis bilaterally between 14-20 weeks, and at 36-38 weeks, using a Hologic Sahara Clinical Bone Sonometer system. A computer derived BMD value was obtained with each measurement. Patients with significant medical disorders in pregnancy or who delivered preterm were excluded. These patients were then surveyed for back pain symptoms during pregnancy by means of a standard questionnaire in the early postpartum period. Patients included in this study constituted part of a larger cohort recruited for the study of BMD changes in pregnancy.

**Results:** of a total of 463 patients, 231 (49.8 %) reported one or more episodes of significant back pain during pregnancy. A mean fall in BMD of 0.0395 gm/cm<sup>2</sup> (SD 0.055) was demonstrable across the two measurements from early to late gestation. There were no significant differences between the age, parity of those who had back pain symptoms or those without. Those with back pain symptoms have a lower weight gain between the two measurements (9.21 kg Vs 10.3 kg;  $p < 0.001$ ). The mean BMD loss at the os calcis across the two serial measurements was significantly greater in the back pain group compared to those without back pain (0.0479 g/cm<sup>2</sup> Vs 0.031 g/cm<sup>2</sup>;  $p = 0.001$ ).

**Conclusion:** A significant fall in BMD was demonstrable using ultrasound measurement of the os calcis from early to late pregnancy. The incidence of back pain symptoms was high in this cohort of pregnant women. Those with back pain symptoms apparently had a greater fall in BMD values at the os calcis as measured by quantitative ultrasound compared to those without.

## 258 Implications of antenatal depression and anxiety on pregnancy and delivery outcome – a population-based study.

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**Objective:** To investigate the obstetric outcome and health care consumption during pregnancy, delivery and the early post partum period in an unselected population-based sample of pregnant women, diagnosed with antenatal depressive and/or anxiety disorders, compared to healthy subjects.

**Study design:** Participants were 1495 women attending two obstetric clinics in Northern Sweden. The Primary Care Evaluation of Mental Disorders (PRIME-MD) was used to evaluate depressive and anxiety disorders in the second trimester of pregnancy. To assess demographic characteristics, obstetric

outcome and complications, the medical records of the included women were reviewed.

**Results:** Significant associations were found between a PRIME-MD diagnosis of depression and/or anxiety and hyperemesis, prolonged sick leave during pregnancy and increased number of visits to the obstetrician, specifically visits due to fear of childbirth and due to contractions. Planned caesarean section and epidural analgesia during labor were also significantly more common in women with antenatal depression and/or anxiety.

**Conclusions:** There is an association between antenatal depressive and/or anxiety disorders and increased health care consumption (including caesarean sections) during pregnancy and delivery. The suffering of the individual and increased costs for society are both good reasons for diagnosing and treating.

## 259 Increased second-trimester concentrations of maternal serum soluble vascular endothelial growth factor receptor-1: an indicator of later pre-eclampsia?

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**Background:** Pre-eclampsia (PE), is associated with high concentrations of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) in third-trimester placentas, maternal serum and amniotic fluid.

**Methods:** Serum samples from 12–15 (mean  $\pm$  SD; 13.7  $\pm$  .5) and 16–20 (19.2  $\pm$  .6) gestational weeks from healthy women (n = 59), and those who later developed mild (n = 29) or severe PE (n = 20) or fetal growth restriction (FGR, n = 16) were analyzed for sVEGFR-1 by ELISA.

**Results:** At 16–20 weeks of pregnancy, an elevated concentration of sVEGFR-1 predicted development of PE (OR 3.85, 95% CI 1.03–14.45), and its concentration was related to the disease severity.

**Conclusion:** Increased maternal serum sVEGFR-1 concentrations precede the clinical manifestation of PE and identify women at risk for developing PE.

## 260 Previous adverse pregnancy outcome and the subsequent risk of stillbirth

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**Background:** There is a tendency to repeat adverse pregnancy outcomes such as stillbirth in successive pregnan-

cies. Some causes of stillbirth may also lead to fetuses that are small-for-gestational-age or are delivered preterm. We do not know whether a previous small-for-gestational-age birth or preterm delivery increases the risk of stillbirth in a subsequent pregnancy.

**Methods:** We studied the associations between adverse pregnancy outcomes such as preterm delivery and small-for-gestational-age birth and the risk of stillbirth in a Swedish nationwide study of 410,021 women's first and second consecutive singleton deliveries between 1983–1997.

**Results:** There were 1842 stillbirths during the first pregnancy (4.5 per 1000 births) and 1062 during the second pregnancy (2.6 per 1000 births). As compared with women whose first child was born at term and was not small-for-gestational-age, women whose first infant was small-for-gestational-age had an increased rate of stillbirth during their second pregnancy. The rate of stillbirth among women whose first infant was not small-for-gestational-age and born at term was 2.4 per 1000; 4.8 among women with a first infant who was born at term and was small-for-gestational-age, 9.5 among women with a first infant who was moderately (32–36 weeks of gestation) preterm and small-for-gestational-age, and 19.0 among women with a first infant who was very (before 32 weeks of gestation) preterm and small-for-gestational-age. The rate for repeating stillbirth was 7.6 per 1000. We estimated odds ratios (95% CI) adjusted for covariates known to be associated with increased risk of stillbirth. Compared with women whose first child was born at term and was not small-for-gestational-age, the risk of stillbirth during second pregnancy among women whose first infant was small-for-gestational-age and moderately or very preterm were 3.4 (2.1–5.6) and 5.0 (2.5–9.8), respectively.

**Conclusions:** A previous small-for-gestational-age delivery is an important predictor of the subsequent risk of stillbirth, especially if the infant was delivered preterm.

## 261 Performance of acupuncture as labour analgesia in the clinical setting.

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**Background:** We and others have shown earlier in randomised controlled trials that acupuncture can have an analgesic effect in labour. Since 1996, midwives have performed acupuncture in our department. The performance, however, of any intervention in everyday practice may be different from the performance in an RCT. We therefore wanted to investigate how acupuncture was used and what effect it might have in a clinical setting.

**Methods:** Since 2000, the labours at Ulleval University Hospital are recorded in a data base. From this database, characteristics of the patients receiving acupuncture during the years 2000 – 2002, were compared to those not receiving

acupuncture, and the influence of acupuncture on the use of other analgesics was analysed by means of the statistical program SPSS.

**Results:** Elective CS was left out of the analysis, which then comprised 12420 labours. 385 (3.1 %) patients had acupuncture. There was a significant difference between acupuncture patients and others in the following variables: Para o (68 % / 53%), being of Western origin (93 % / 75%), age (mean 31.2 / 30.5 years), duration of pregnancy (mean 280 / 274 days), and having induced labour (11 % / 17 %). In a logistic regression, the odds ratio for having epidural analgesia was 0.6 (95% CI 0.4-0.7) for the patients who had acupuncture compared to those who did not have. The patients who had acupuncture, had, however, a higher use of N<sub>2</sub>O (OR 1.6, 95% CI 1.3-2.0).

**Conclusions:** Despite large enthusiasm on many parts, acupuncture was little used in the department, but might have an analgesic effect.

## 262 Outcome of pregnancy with hepatitis C virus infection

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**Background:** Today, hepatitis C virus infection is not routinely screened in maternity care in Finland. This study explored the frequency of hepatitis C virus antibody (HCVAb) positivity among pregnant women in the Helsinki area, and examined the outcome of their pregnancies. HCVAb was tested from individuals who had an increased risk of contracting the disease.

**Methods:** Obstetric and perinatal data of parturients with HCVAb in 1991-1999 were collected and the results were compared to the results of all parturients of the hospital by using data obtained from the hospital and the national birth register of STAKES.

**Results:** 145 mothers out of 44,680 showed HCVAb. The frequency of HCVAb increased from 0.13% (1991) to 0.53-0.43% (1997-1999). Two mothers had acute hepatitis C during pregnancy (one of them fulminant). Young mothers (<25 years) had HCVAb more often than expected. The main risk factor for HCVAb positivity was drug abuse (71%). Chronic hepatitis C (CHC) did not worsen during pregnancy, but the risk of cholestasis was high (10%) compared to all pregnancies (0.7%) (OR 16.4, 95% CI 9.5 to 28.2). Alanine aminotransferase values of mothers with CHC decreased and normalised towards the end of pregnancy, but increased if the pregnancy was complicated by cholestasis. Newborns were often small for gestational age (OR 2.8, 95% CI 1.5 to 5.3) and delivered before 37 wks.

**Conclusions:** The frequency of HCVAb positivity increased during the study period. Obviously pregnancy will not worsen CHC, but CHC increases the risk of cholestasis during pregnancy. HCVAb positivity of pregnant woman was associated with teen pregnancies, growth retardation of fetus and prematurity. These risks need to be recognised in antenatal care.

## 263 The incidence of severe obstetric morbidity in Lithuania

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**Background:** Maternal mortality is a major indicator for monitoring of women health. Maternal mortality rate is low in more developed countries and maternal death is rare event. The alternative method for the assessment of the quality of obstetric care is to measure the rate of severe obstetric morbidity.

**Methods:** The study was designed to measure the incidence of severe obstetric morbidity in 7 secondary or tertiary maternity units in different regions over one year period. The data were collected prospectively. Women with clinical diagnosis of severe preeclampsia, eclampsia, HELLP, severe hemorrhage (>1.5 l), rupture of uterus or severe puerperal sepsis during pregnancy or delivery or until 42nd day post partum were included after verification of diagnosis.

**Results:** One hundred and one cases of severe obstetric morbidity and one maternal death were identified during study time among 13399 deliveries (75.4/10 000 deliveries). There were 49 cases of severe preeclampsia (36.6/10 000 deliveries), 4 cases of eclampsia (3/10 000 deliveries), 40 cases of severe hemorrhage (29.9/10 000 deliveries), 2 cases of uterine rupture (1.5/10 000 deliveries) and 6 cases of puerperal sepsis (4.5/10 000 deliveries). The one maternal death occurred due to HELLP syndrome so the case fatality ratio for severe morbidity was 0.99%.

**Conclusion:** The severe obstetric morbidity could be an indicator for measurement the quality of perinatal care and be helpful for comparing maternal health in different regions or time periods. The low case fatality rate of severe obstetric morbidity reflects an adequate quality of obstetric care in Lithuania.

## 264 Intrahepatic cholestasis of pregnancy: a prospective observational study of relationships between bile acid levels and fetal complication rates

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**Background:** Intrahepatic cholestasis of pregnancy (ICP), characterised by pruritus in the second half of pregnancy, entails an increased risk to the fetus regarding preterm delivery, fetal distress and intrauterine fetal death. Family clustering and variation of incidence in different geographic regions suggests an underlying genetic explanation. This study was designed to determine the incidence and fetal complication rates in ICP, and to define groups at increased risk.

**Methods:** In an prospective cohort study conducted between February 1, 1999 and January 31, 2002 all 45 485 pregnancies in a defined region of Sweden (Västra Götaland) were screened for ICP, defined as otherwise unexplained pruritus of pregnancy in combination with fasting serum bile acid levels  $>10\mu\text{mol/L}$ . 690 women were included in the observational part of the study, thereby monitored throughout pregnancy with weekly assessments of serum bile acids. Data regarding patient history and complications during pregnancy and at delivery were recorded.

**Results:** Pruritus was reported by 937 (2.1%) and ICP was diagnosed in 693 (1.5%) women. Fetal complication rates (preterm delivery, asphyxial events and meconium staining of amniotic fluid, placenta and membranes) were positively correlated to the severity of the disease measured as bile acid levels, but did not raise significantly until bile acid levels were  $>40\mu\text{mol/L}$ .

**Conclusion:** The incidence of ICP was 1.5%. From complication rates recorded prospectively, we could define a mild (81%) and a severe (19%) form of ICP, the latter with bile acid levels  $>40\mu\text{mol/L}$ . No increase in fetal risk was detected in ICP patients with bile acid levels below  $40\mu\text{mol/L}$ , and we propose that these women could be managed expectantly.

## 265 Spouse's unemployment during pregnancy enhances SGA risk among unemployed women

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**Background:** The objective of this study was to assess the effects of unemployment of one or both parents on obstetric outcome in women having free maternity attended by the entire pregnant population.

**Methods:** A retrospective cohort study was conducted, involving 24 939 singleton pregnancies associated with

known employment status in the family (1989 to 1999). The families were stratified according to parental employment status. In 13.6% of pregnancies the mother was unemployed, in 6.2% the father and in 4.2% both parents were unemployed. Employed families were used as a reference, and multiple logistic regression analysis was used to compare pregnancy outcomes.

**Results:** Unemployment of either parent was strongly associated with more frequent smoking, alcohol consumption during pregnancy, maternal obesity and diabetes, which in turn had an impact on obstetric outcome. Specifically, there were a significantly more small for gestational age (SGA) infants among unemployed mothers ( $p < 0.01$ ), with an absolute difference of 22.7% and an odds ratio of 1.26 (95% CI: 1.12 – 1.42) in multiple regression. In families where both future parents were unemployed, the risk of both SGA ( $p < 0.01$ ) and low birth weight infants ( $p < 0.05$ ) were increased, but after controlling for confounding factors, only SGA remained significant, with an absolute difference of 59.1% and an odds ratio of 1.43 (95% CI: 1.18 – 1.73). We found no statistically significant difference between study groups in incidence of preterm deliveries.

**Conclusion:** We conclude that unemployment remains an important public health issue regardless of free antenatal care provided by the state and that paternal unemployment during pregnancy further enhances SGA risk among unemployed women. Therefore effective measures should be considered to increase health consciousness in these high risk families.

## 266 Epidermal growth factor concentrations in amniotic fluid of diabetic women with pre-eclampsia

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**Background:** Diabetic pregnant women are at an increased risk of developing pre-eclampsia. The reason for this is unknown. The fetuses of the affected mothers are at an increased risk of hypoxia. In order to find a biochemical marker to predict forthcoming disease, we first examined amniotic fluid (AF) from term pregnancies to see whether the concentrations of epidermal growth factor (EGF) would differ between diabetic women with and without pre-eclampsia. EGF is a mitogen for various tissues. It might also be important for placental growth in mice.

**Methods:** AF samples, collected for assessment of fetal lung maturity, were analysed for EGF concentrations by an immunofluorometric assay (IFMA) from insulin treated diabetic women with ( $n=10$ ,  $29\pm4$  yrs) and without pre-eclampsia ( $n=7$ ,  $28\pm7$  yrs) at  $36\pm1$  gestational weeks.

**Results:** EGF concentrations (median, range) in AF of diabetic women, as analysed by the Mann-Whitney U-test, did not differ between those with (38 ng/l, 24-75 ng/l) or without (42 ng/l, 12-64 ng/l) pre-eclampsia.

**Conclusions:** In diabetic women amniotic fluid EGF concentrations during the third trimester are not affected by pre-eclampsia. Thus, EGF does not provide a tool for assessing the risk of pre-eclampsia in diabetic women, and other biochemical markers need to be sought.

## 267 Epidermal growth factor concentrations in amniotic fluid of women with pre-eclampsia or fetal growth restriction

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**Background:** Pre-eclampsia affects about 5% of all pregnancies. The etiology of this multiorgan failure is not known. Neither are there any preventive nor therapeutic treatments available. Fetal well-being is often compromised by intra-uterine hypoxia and growth restriction. Pathophysiological features include both maternal and placental vascular dysfunction. Similar placental changes are found in the presence of fetal growth restriction (FGR). Epidermal growth factor (EGF) is mitogenic for various tissues, is also expressed in the placenta and needed for placental growth in mice. The objective of this study was to determine whether the amniotic fluid concentrations of EGF would differ between healthy women and those with pre-eclampsia or FGR.

**Methods:** AF samples, collected for assessment of fetal lung maturity, were analysed for EGF concentrations by an immunofluorometric assay (IFMA) from women with pre-eclampsia (n=20), FGR (n=9) and healthy women (n=8) at gestational age 28-34 weeks.

**Results:** EGF concentrations (median, IQR) in AF of women with pre-eclampsia were higher (22.3 ng/l, 13.4-35.4 ng/l) than those of healthy mothers (12.1 ng/l, 4.2-22.1 ng/l,  $P = 0.033$ ). EGF concentrations in AF of women with FGR (14.3 ng/l, 8.1-32.4 ng/l) did not differ from those of compared with healthy or pre-eclamptic women.

**Conclusions:** Pre-eclampsia, but not FGR, is associated with increased amniotic fluid EGF concentrations. EGF may be associated with the pathophysiology of pre-eclampsia. It remains to be seen whether EGF provides a marker for assessing the risk of pre-eclampsia, or possibly a tool in predicting the prognosis of manifest disease.

## 268 A randomised controlled trial of open versus closed vaginal vault at vaginal hysterectomy

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**Aims:** Vaginal hysterectomy is associated with a potential risk of vault haematoma and consequent febrile morbidity. The aim of this study was to determine febrile morbidity rates and longer-term morbidity of non-closure of the vaginal vault compared with closure at vaginal hysterectomy.

**Methods:** A randomised-controlled trial was conducted. Women were randomised at the time of vaginal hysterectomy to closure or non-closure of the vaginal vault. The primary outcome measures were febrile morbidity, pelvic haematomas and pelvic abscesses.

**Results:** From May 1999 - Mar 2001, 50 patients were enrolled in the study (n=23 open, n=27 closed). At this stage it was decided to stop recruitment for the trial following two cases of organ prolapse in the open vaginal vault group.

**Conclusions:** Premature closure of this trial, because of serious complications in the open vault group, prevents conclusions to be drawn about differences in febrile morbidity rates between closure and non-closure of the vaginal vault at vaginal hysterectomy. However, reporting of bad outcomes from properly conducted randomised controlled trials is important in order to avoid publication bias.

## 269 One- and two-day mifepristone - misoprostol intervals are both effective in medical termination of second trimester pregnancy

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**Background:** The grief following termination of pregnancy because of fetal anomaly is similar to that experienced following spontaneous perinatal loss. Thus termination of pregnancy because of fetal anomaly requires the utmost clinical sensitivity and individualized patient care. The combination of mifepristone and prostaglandin is safe and effective; however, the previously published protocols of second trimester medical abortion involve use of a two-day interval between mifepristone and prostaglandin administration. Yet couples who have chosen to terminate their pregnancy because of fetal anomaly often wish to proceed rapidly with the abortion process.

**Methods:** We compared the efficacy of a one-day mifepristone and misoprostol -interval in medical termination of second trimester pregnancy performed because of fetal anomaly with that of the standard two-day interval among the first 100 women in each group. A 200 mg dose of mifepristone was used; 0.4 mg of misoprostol was administered vaginally at three-hour intervals until abortion occurred.

**Results:** When calculated from ingestion of mifepristone, the time to abortion was 28:25 h (23:10 – 50:40 h) (median (range)) and 52:43 h (45:55 – 83:15 h) ( $p < 0.0001$ ) in the one- and two-day mifepristone-misoprostol groups, respectively. However, following initiation of misoprostol administration the time to abortion (7:25 h (1:00 – 23:15 h)) was longer ( $p < 0.05$ ) in the one-day interval group than in the two-day interval group (6:20 h (0:45 – 36:30 h)); by 12 h 82 and 87% (n.s.), respectively, of the subjects had aborted. The proportions of cases undergoing surgical evacuation of the uterus were 64 and 45% ( $p < 0.001$ ), in the one- and two-day interval groups, respectively.

**Conclusions:** Both one- and two-day mifepristone-misoprostol intervals are both valuable in termination of second trimester pregnancy.

## 270 Natural history of oral papillomavirus infections in female and male partners; a prospective follow-up study

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**Background:** The concepts of oral HPV infections as STD have been challenged by the recent data in children. Origins of oral HPV are incompletely understood and nothing is known about their natural history. In the Finnish HPV Family Study, oral HPV status of infants, mothers and fathers were prospectively followed-up.

**Methods:** This cohort includes 331 women enrolled at pregnancy (mean age 25.5+3.4 years) and their 131 male partners (mean age 28.8+5.0 years), meticulously sampled for oral, cervical and urethral HPV infections during the 2-year follow-up. HPV DNA was detected by nested PCR and confirmed by Southern blot hybridization using 12 high risk (HR) oligoprobes.

**Results:** In women, HR HPV DNA detection varied from 16% to 27%, and in males from 18% to 25%. Oral HPV in both partners at baseline was closely related (OR 4.338, 95%CI 1.581-11.907,  $p = 0.006$ ). During the follow-up, oral HPV status in both partners was very similar; some 50% of both remained HPV negative, one third acquired an incident HPV, and persistent HPV infections were detected in 7%. Altogether, 7% of males and 9% of women cleared their oral HR HPV DNA. The cumulative incidence of new infections in the partners was marginally different (Kaplan-Meier,  $p = 0.0592$ ), but the cumulative clearance was faster in males ( $p = 0.02$ ). In univariate survival analysis (Kaplan-Meier), partner's oral status did not significantly predict the clearance and acquisition rates of the other partner.

**Conclusions:** This study sheds new light on the natural history of oral HR HPV infections among married couples, and helps understanding the dynamics of HPV infections within family.

## 271 Pathological aspects of teens' pregnancies

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**Background:** We analyzed the teenaged pregnancies hospitalised in our III Obstetrics Department of the Emergency County Hospital of Constanta (Romania) between 1st of January 2002 and 2004. This study is only the beginning of a large prospective study concerning teens' problems of pregnancy and childbirth which we intend to perform in the next years.

**Methods:** The analysis of clinical and paraclinical data.

**Results and conclusions:** We found a multitude of diagnoses and most of them had a far more aggressive evolution than those of non-teens pregnant women. Also we tried to find solutions regarding social impact of the early pregnancies. Therefore we believe that a major interest showed by local authorities, church and general doctors could solve a part of this important problem.

## 272 The prevalence and bother of nocturia in women and men aged 60-80 years in Denmark.

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**Objective:** To study the prevalence and bother of nocturia in an unselected population of women and men aged 60-80 years.

**Methods:** A postal questionnaire was sent to 2000 women and 2000 men aged 60, 65, 70, 75, and 80 years. The population was selected at random from The Danish Civil Registration System (CPR), in which every person living in Denmark is identified by a unique ten digit number. Since no validated questionnaire addressing nocturia was available, a new questionnaire was generated and tested addressing nocturia and associated factors. Nocturia was defined as waking up at night to void (ICS 2002). This study focuses on the association between prevalence of nocturia and age, sex, and bother.

**Results:** Ninety two percent (3.664) returned the questionnaire; 70% completed the questionnaire and was included in the study. The prevalence of nocturia increased with age. Overall prevalence of nocturia was 77% and no difference between men (M) and women (F) was observed ( $p = 0.11$ ). However, with nocturia two or more times more men (40%) than women (35%) were affected ( $p = 0.0009$ ). Among all possible reasons, nocturia was the most frequent reason to wake up at night. The bother of nocturia in women and men increases with the severity of nocturia.

**Conclusions:** To the best of our knowledge this is one of the largest studies addressing prevalence of nocturia in an elderly population of men and women. Our data confirmed that the prevalence of nocturia increased with age. Nocturia was the major reason for waking up at night followed by thirst. No difference between sex was observed in the overall prevalence of nocturia, but when nocturia >2 more men than women were affected. The degree of bother increased with the severity of nocturia.

### 273 Impact of Nocturia on Quality of Life measured by SF-12

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**Objective:** To assess the Quality of Life (QoL) in relation to nocturia in an unselected population of women and men aged 60-80 years.

**Methods:** A postal questionnaire was sent to 2000 women and 2000 men aged 60, 65, 70, 75 and 80 years. The population was selected at random from The Danish Civil Registration System (CPR), in which every person living in Denmark is identified by a unique ten digit number. Nocturia was defined as waking up at night to void (ICS 2002). As a generic measure of health status we used the validated short-form (SF) questionnaire SF-12. The questionnaire is a 12-item generic QoL measure that assesses physical and mental functioning over the previous four weeks. A low score indicates more impairment of QoL.

**Results:** Ninety-two percent (3664) returned the questionnaire ; 55% (2206) fully completed the SF-12. Mean scores and SD for mental component summary (MCS-12) and physical components summary (PCS-12) are shown in table 1. Physical and mental functioning was significantly impaired in women and men with increasing degree of nocturia ( $p < 0.0001$ ). Women were most impaired ( $p < 0.0001$ ). Controlled for age a significant impairment in PCS-12 and MCS-12 in men and women with nocturia were demonstrated ( $p < 0.0001$ ). Linear regression was used in the statistical calculations.

**Conclusion:** A significant age-independent effect between increasing degree of nocturia and decreasing SF-12 QoL in an unselected population of women and men 60-80 years was demonstrated.

### 274 Increased release of cervical nitric oxide in spontaneous abortion before clinical symptoms: A possible mechanism for preabortal cervical ripening

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**Objective:** Nitric oxide (NO), expressed in human cervical cells, may affect the cervical ripening. We studied the release of cervical NO in women with spontaneous or tubal abortion before commencement of bleeding or other signs of abortion.

**Study design:** Women with a random diagnosis of missed abortion ( $n = 56$ ), blighted ovum ( $n = 36$ ), or tubal pregnancy ( $n = 7$ ) were selected with vaginal ultrasonographic examination from a population ( $n = 2200$  women) seeking a termination of early pregnancy; 140 women with amenorrhea-matched normal gestation were studied as controls. Cervical fluid samples were assessed for NO metabolites (Nox) by Griess reaction. Sera were assessed for human chorionic gonadotrophin (hCG) and progesterone in 110 women.

**Results:** Cervical fluid Nox was more often detectable in women with missed abortion (90%) and with blighted ovum (87%) than in the control women (55%) ( $p = 0.01$ ), and Nox level in the group of missed abortion (median, 59.4  $\mu\text{mol/l}$  CI 30.3 – 81.8) and in that of blighted ovum (median, 25.6  $\mu\text{mol/l}$  95% CI 14.1 – 53.0) were 14 and 6 times higher ( $p < 0.001$ ,  $p = 0.002$ , respectively) than that in the control group (median, 4.3  $\mu\text{mol/l}$  CI < 3.8 – 6.4). The Nox levels in women with tubal pregnancy were normal. Cervical fluid Nox was negatively related to progesterone in the whole study group ( $r = -0.31$ ,  $p = 0.003$ ), but not in any subgroup. In women with abortion, the lower was the level of progesterone, as expressed in percentages of the progesterone levels in the control women, the higher ( $r = 0.49$ ,  $p < 0.001$ ) was the cervical fluid Nox. In the combined abortion group, women with "low" pretreatment cervical fluid Nox failed to abort completely more often ( $p = 0.04$ ) than women with "high" pretreatment Nox (28 % vs 4%); no such relation was seen in the control group.

**Conclusion:** Increased preabortal cervical nitric oxide release may contribute to the cervical opening and to the onset of clinical abortion.

### 275 Body Mass Index - effect of treatment and quality of life of patients with urinary incontinence

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**Background:** The purpose of the study was to investigate the influence of Body Mass Index (BMI) on the effect of treatment and quality of life of patients with urinary incontinence.

**Methods:** The participants were women seeking treatment for lower urinary tract symptoms (n=761). They received a questionnaire at study entrance in which they were asked to report weight and height, and their Body Mass Index (BMI) was calculated. The women were classified as being under normal (BMI < 18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9), or obese (BMI >29.9). After relevant treatment (treatment depending on aetiology) the effect of treatment was evaluated by the patient. Furthermore 319 patients in the group were asked to plot the degree of discomfort to a Visual Analogue Scale before and after treatment. Thus all the patients acted as their own control group.

**Results:** The study shows that in average 87 % of the patients were cured/considerably better. Patients in the groups with a BMI under 29.9 had the best effect of treatment: 87 to 95 % indicated they were cured/considerably better, whereas only 81 % of the obese patients (BMI >29.9) were cured/considerably better. The results of the Visual Analogue Scale plotting show that the degree of discomfort after treatment is reduced by between 47 and 60 %. The biggest change is seen in the group of patients with normal weight and overweight. The obese patients and underweight patients have less improvement in quality of life.

**Conclusion:** Our study shows that obese patients do not seem to have as good an effect of treatment as patients with a BMI under 29.9. Treatment of incontinence improves quality of life in all groups. The degree of improvement is influenced by BMI in the way that underweight and obesity reduce the improvement.

## 276 One image, variety of diagnoses: a research of interobserver variability among colposcopists

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**Background:** To check the interobserver variability among colposcopists and the importance of clinical experience.

**Methods:** The study material was collected in the annual meeting of Finnish Colposcopy Association. 33 attendees of this meeting were asked to participate our study workshop, in which 15 colposcopic images were shown. Information of patient age was given. The participants were asked to evaluate on each image whether 1) the junction area is visible, 2) the colposcopic image as whole is within normal limits, 3) the image is suspect to HPV-infection only, 4) the image represents pre-cancerous or dysplastic lesion or 5) invasive cervical cancer. The images were shown two minutes time continuously, during which the participants were allowed to answer the questions (yes or no). At the end of the workshop the same images were re-presented, this time with cytological and histologically verified diagnosis. To evaluate the importance of clinical experience, the participants were divided into three groups on the basis of their personal experience they all had asked to announce.

**Results:** The interobserver variability turned out to be poor, despite the clinical experience. Best kappa-estimate values were observed among the most experienced colposcopists in visualising the junction area ( $f\hat{U}$  0.42), finding a normal image ( $f\hat{U}$  0.40) and finding an image with pre-cancerous or cancerous lesion ( $f\hat{U}$  0.47). In all other study groups kappa estimates were under the limit of 0.4 (poor reproducibility). Identifying abnormal images succeeded quite well in all study groups (sensitivity 85-91%), the most experienced performed the best. Pre-cancerous or cancerous lesions were identified with 69-75% sensitivity.

**Conclusion:** The result correspond well to the other studies performed in this area. The variability was high and kappa estimates poor. The clinical experience seems to have some sort of influence in finding cell abnormalities: the sensitivity grew together with increasing colposcopy experience.

## 277 Soluble Fas ligand concentration in peritoneal fluid of patients with endometriosis

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Peritoneal fluid (PF) is a biologically active environment. Mostly ectopic endometrial tissue is in contact with peritoneal fluid. Fas (CD95-APO) is a member of tumor necrosis factor/nerve growth factor receptor/ligand family. Fas ligand is responsible for rapid apoptosis after binding Fas membrane receptor present at Fas bearing cells. Fas ligand has also soluble form after exfoliation as a result of the action of metalloproteinases. Various cells in different tissues express Fas receptor and Fas ligand. We previously found different distribution of Fas receptor (overexpression) on peritoneal fluid macrophages in endometriotic patients. Concentration of soluble form of Fas ligand in peritoneal fluid of patient with endometriosis was measured using ELISA method. 56 patients who underwent laparoscopy were included to the study. Endometriosis was diagnosed in 35 patients. Stage I of endometriosis was found in 15 patients, stage II in 13 patients and 7 patients were diagnosed as III/IV stage of endometriosis. Reference group consists of 21 patients with benign, non inflammatory ovarian pathology. Endometriosis was confirmed by histological examination. Mean peritoneal fluid FasL concentration was significantly higher ( $p=0.01$ ) in reference group comparing to endometriotic patients (8.26ng/ml vs 4.07ng/ml). Mean PF FasL concentration was also significantly higher ( $p=0.03$ ) in reference group comparing to stage I of endometriosis (8.26ng/ml vs 3.93 ng/ml) whereas there were no differences ( $p>0.05$ ) amongst reference group and endometriosis stage II and III (8.26ng/ml vs 4.61ng/ml and 3.36ng/ml). There were no statistical differences in mean PF FasL concentration among patient with different stages of endometriosis. Distribution of Fas