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**Session 23. Reproductive endocrinology**  
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**130. Long term effects of time, pregnancy and medical treatment on plasma prolactin levels in 176 hyperprolactinemic women**

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In order to show evidence of prolactin changes specifically related to drug use, pregnancy or the simple effect of time, the evolution of plasma prolactin (PRL) levels were studied in 176 hyperprolactinemic women (87 carrying a prolactinoma) over a mean period of four years (range between 6-180 months).

Clinical presentation of the patients was amenorrhea for 110, oligomenorrhea for 37 while 29 had normal but anovulatory cycles.

107 patients underwent 191 cycles of medical treatment (mean length 11 months; range 2-43), 73 got pregnant spontaneously or during drug intake while in 38 subjects spontaneous evolution of plasma prolactin concentration was evaluated over a mean period of 19 months (range 6-72).

Evaluation of prolactin changes after medical treatment pregnancy or just waiting periods showed a significant lower mean PRL level only in the idiopathic group of patients after pregnancy.

PRL trend of the individual values in both groups of patients indicate that: pregnancy normalizes prolactin concentration in 49% of patients and medical therapy is linked with a normalization rate of 27%.

**131. Dose-dependent suppression of serum Prolactin by cabergoline in hyperprolactinemic patients: a placebo controlled, randomized, double blind multi-centre study**

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Cabergoline is a novel dopamine agonist with very long-lasting (7-14 days) Prolactin (PRL)-lowering activity after oral administration. We have investigated the efficacy and tolerability of a range of doses of cabergoline in suppressing Prolactin in hyperprolactinemic women.

Patients and methods. This was a multi-centre, prospective, randomized, double-blind study involving 188 women with hyperprolactinemia secondary to a microprolactinoma (n=113, 60.1%), idiopathic disease (n=67, 35.6%), empty sella syndrome (n=5, 2.7%), or following failed surgery for prolactinoma (n=3, 1.6%). The mean age was 31.8 years (range 16-46). Patients received either placebo (n=20) or cabergoline 0.125 mg (n=43), 0.5 mg (n=42), 0.75 mg (n=42) or 1 mg (n=41) twice weekly for four weeks, the first week's treatment being half dose; There were no significant differences in age, diagnosis or previous therapy

between the 5 treatment groups; mean ( $\pm$  SEM) pre-treatment prolactins were  $65.0 \pm 6.3$ ,  $90.8 \pm 14.8$ ,  $92.7 \pm 13.8$ ,  $129.0 \pm 20.1$  and  $70.0 \pm 6.6$  ng/ml respectively.

Results; After 4 weeks treatment PRL was suppressed to below half the pre-treatment level in 5%, 60%, 90%, 95% and 98%, and completely normalized in 0%, 30%, 74%, and 95% of patients taking placebo or cabergoline (0.125 mg, 0.5 mg, 0.75 mg and 1 mg twice weekly respectively, showing a dose-response relationship among cabergoline doses (Armitage test:  $p < 0.01$ ). In contrast, at these doses, adverse effects were reported in 45%, 44%, 50% and 58% of patients with no evident dose relationship. Over 95% of reported side effects were relatively trivial, most frequently transient nausea, headache and dizziness. Severe adverse events including dizziness, nausea, headache and fatigue occurred in 13 patients taking cabergoline (7.7%) but treatment had to be discontinued in only one patient who experienced severe dizziness.

Conclusions. Cabergoline is effective in normalizing PRL in hyperprolactinemia at doses of 0.5 - 1.0 mg twice weekly. Its tolerability and simple administration schedule represent a significant therapeutic advance in the management of hyperprolactinemia.

**132. Parlodel LAR in the chronic treatment of hyperprolactinaemic patients**

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Parlodel LAR, a new injectable long-acting form of bromocriptine, was administered to 78 patients (63 women and 15 men) affected by prolactinomas. At the CT-Scan/NMR macroadenoma was present in 31/78 patients (pts). The initial dose of Parlodel LAR was 25mg in 8 pts, 50mg in 62 and 100mg in the other 8 pts. All pts received repeated injections of Parlodel LAR at the dose of 25-200mg every 28-60 days for 3-48 months. In every patient clinical evaluation, PRL plasma levels, tumor size evaluation and visual field (VF) examination were monitored. A marked decrease in PRL plasma levels was achieved in all patients whereas PRL normalization in 45/78 pts after the first injection of Parlodel LAR. Eighteen of 78 pts also had bromocriptin plasma levels assessed after the first injection of Parlodel LAR 25mg, 50mg or 100mg (6 pts/dose) to assess the dose proportionality of this injectable bromocriptin preparation. Fifteen of 18 pts normalized PRL plasma levels independently of the dose. The duration of PRL suppression/normalization lasted 7 to 60 days with a positive correlation between the length of efficacy and the initial dose used. At the CT-Scan/NMR a marked tumor shrinkage (20-60%) was observed in 19/31 pts with macroprolactinoma within the first 28 days after the first dose of Parlodel LAR 50mg. After 6-12 month's therapy complete disappearance of the pituitary tumor was documented in 3/31 pts. Three of the 4 pts who had VF defects obtained a complete and quick normalization of their VF within 12-72 hours after the first injection of Parlodel LAR. The clinical symptoms/signs recorded in 72/78 pts regressed in 69/72 pts after 14-700 days treatment. No important side effects were reported except in 2 cases. Patients' compliance was very good due to the therapeutic

efficacy, good tolerability and long-lasting action of Parlodel LAR. Therefore, in conclusion, Parlodel LAR could be considered the first choice treatment in pts with prolactinoma.

### 133. Menses alteration in relationship to various percentage of weight loss

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We have evaluated the clinical and hormonal profile 203 of women, aged 18 to 26 years, who in the last year had suffered a loss of weight of 10-14% (group A), of 15-20% (group B) and more 20% (group C) in comparison with their initial weight. The frequency of amenorrhea and regular cycles was found to be greatly influenced by weight loss: in group A we saw amenorrhea in 75.3% of cases and regular cycles in 24.7%; in group B we saw amenorrhea in 87.2% of cases and regular cycles in 12.8%; in group C amenorrhea was present in 95.2% of cases and regular cycles in 4.8%.

Amongst those women with regular menses, all included in groups A and B, there was a major incidence of luteal phase defect (34.8% in A; 16.7% in B) showing variations in the secretion of gonadotropin-releasing hormone (GnRH) and in the luteinizing hormone (LH) peak, caused by the former.

The presence of a certain percentage of regular cycles including those in groups with a greater weight loss, demonstrate various responses to stress.

The endocrinal evaluation showed in amenorrheic women a gradual decrease in the blood levels of gonadotrophin and estradiol, in groups A and C. In groups A and B, even though we can note apparently normal plasmatic levels of luteinizing hormone, the hypoestrogenism and the high percentage of amenorrhea confirm that in cases of minor weight loss there exists a modification in the pulsatile secretion of GnRH and gonadotropin. In addition the mean plasma cortisol levels were significantly increased whereas the prolactin levels were lower than controls.

### 134. Effectiveness of urinary LH rapid assay in infertile women treated with clomiphene citrate

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Thirteen infertile patients (ages 25 - 40) previously submitted to Clomiphene Citrate (CC) therapy unsuccessfully, were treated again by CC at the same dose during 17 monitored cycles. Eight patients were affected by primary infertility while 3 had undergone a spontaneous abortion early in the pregnancy and 2 had a history of recurrent abortion. All patients had been evaluated by hysterosalpingography and/or laparoscopy without evidence of any abnormality. All CC cycles were controlled by intensive hormonal and ultrasound monitoring. When the dominant follicle diameter reached 14 mm. urinary LH rapid assay was effected every twelve hours (at 8 am and 8 pm) up to ovulatory surge evidence. Five patients underwent uneventful pregnancy while 2 did not conceive probably because husbands' semen analyses showed severe oligo-asthenospermia.

The use of an urinary LH rapid assay seems effective in raising the pregnancy rate of CC therapy in infertile patients.

### 135. Cumulative pregnancy rates after LHRH-treatment in hypothalamic amenorrhea

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In 49 patients with hypothalamic amenorrhea 272 LHRH induced cycles were studied retrospectively. Pulse dose varied from 2 - 100 µg/pulse; most patients received 10 or 20 µg. No difference in ovulation and conception rate was found between 10 and 20 µgram pulse dose cycles. Cumulative pregnancy rates (CPR) were calculated using the life table method. Forty-eight patients had 244 ovulatory cycles of which 55 resulted in pregnancy; the CPR was 78% after 6 and 93% after 12 ovulatory cycles. Eight pregnancies (= 14.5%) ended in abortion, 5 pregnancies were multiple (4 twins, 1 triplet).

Subdivisions of patients were made with respect to the presence of additional infertility factors, history of weight-loss, actual weight, estrogenic status and primary versus secondary amenorrhea. Evaluation of only first treatments per patients revealed a significant higher CPR in patients without other infertility factors compared to those with other factors (84% versus 60% after 6 cycles) ( $p < 0.05$ ). No differences were found in life table curves of the other subdivisions.

Using life-table statistics our data confirm the general opinion that LHRH therapy is highly successful in patients with hypothalamic amenorrhea, especially if no other infertility factors are present.

### 136. Clinical study of a new triphasic oral contraceptive (SH D 415 G, Milvane) in insulin dependent diabetic patients

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A new triphasic oral contraceptive (SH D 415 G, Milvane) was studied in 14 insulin-dependent diabetic (IDDM) women, aged 27 - 39. IDDM was diagnosed 1.5-19 years ago. All the patients were on monocomponent human insulin administered twice a day in the form of preformed mixture (Actraphane®) at a variable dose of 26-52 U/day. No patients presented with overweight higher than 10% of the ideal body weight (IBW). The metabolic parameters indicating glyco-metabolic balance (daily blood glucose curve, HbA1C, fructosamine, lipid profile, plasma uric acid), were within the normal range. Micro-albuminuria was recorded in 6/14 women, whereas glycosuria in 11/14 women and the latter was below 20 g/24 hours. All the patients were put on Milvane due to anticonceptional purposes and they were treated for at least 6 months without discontinuing the drug because of poor tolerance. Ovulation which was recorded in every patient was completely inhibited. The daily insulin requirement increased in all patients (from 4 to 8 U/day) without statistical significant change in blood glucose profile, HbA1C and body weight. In the past 7/14 women had to discontinue other oral contraceptives due to the worsening of the glycometabolic

balance. On the contrary, all the patients are still on Milvane. In conclusion, the anticonceptual treatment with Milvane is not hitherto resulted to be able to worsen the metabolic balance in diabetic patients. Further studies are required during more prolonged treatment to draw any definitive conclusions.

**137. Predictive value of the active renin assay for the early diagnosis of ectopic pregnancy**

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The increasing frequency of ectopic pregnancy and the need of its early diagnosis have focused our interest on the research of biochemical markers. We have previously studied the profile of hCG, progesterone, and renin in fertile cycles after IVF-ET or GIFT and shown that his last parameter did not increase in ectopic pregnancies contrary to evolutive or abortive intrauterine pregnancies. After having established the hormonal value in the plasma of 99 spontaneous ongoing pregnancies between the 4th and 10th week of amenorrhea we have compared them to the values observed in 21 ectopic and 20 abortive pregnancies. The hCG levels are significantly higher in ongoing pregnancies but there is no statistically significant difference between abortive and ectopic gestation. The progesterone levels are significantly lower in ectopic pregnancies than in intrauterine gestation but are not really discriminant. The best parameter appears to be low active renin immunoradiometric assay (Pasteur Diagnostic). The difference between ectopic pregnancy and evolutive or abortive intrauterine gestations is highly significant, the highest value corresponding to the 25th percentile of normal values. The association of low hCG (< 15000 UI/ml) and low active renin (≤ 30 ng/ml) seems to be highly predictive of the ectopic pregnancy. The renin angiotensin system has an important role in the process of implantation, but an early signal could also be transmitted by the implanted embryo to the corpus luteum.

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**Session 24. Reproductive endocrinology**  
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**138. The effect of polychlorinated Biphenyls (PCB) on estradiol synthesis of human cumulus cells**

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Chlorinated hydrocarbons, E.G. PCBs, DDT, HCB, can be found in various body tissues and fluids. In human follicular fluid (n=10) we could determine the following concentrations of various PCB congeners (Ballschmitter n° 15, 118, 138, 153, 169, 180) on estradiol synthesis of human cumulus cells was investigated. Cumulus cells were collected in an IVF programme and cultured in a modified Ham's F10 medium supplemented with 5% fetal calf serum and 50 ng/ml 17β testosterone (cell concentration: 25000/ml. The PCB congeners were added in

concentrations between 0.1 and 1000 ng/ml. The concentration of estradiol was determined in the cell free supernatants after a 24 hour culture period. All PCB congeners induced a dose dependent reduction of estradiol synthesis by human cumulus cells. The various PCB congeners showed different biological activities in regard to the inhibitory effect on estradiol secretion. A decrease of estradiol secretion could already be observed in PCB concentrations that correspond to the average load of human follicular fluid.

**139. Endocrine and immunological changes in women with chronic wood preservative exposition**

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The influence of environmental pollution on human reproductive performance is unknown. The toxicity of organochlorine compounds (OC) was recongized following accidental poisoning. In animal studies OC administration resulted in a reduced number of pregnancies, and increased number of stillbirths. In the subsequent generation reduced fertility and changes in the menstrual cycle were noted. Wood preservatives containing various toxic OC are frequently used in industrialized states. Therefore it was the aim of this study to measure the pesticides pentachlorophenol (PCP) and gammahexachlorocyclohexane (Lindane, L) in women with hormonal disorders. In 22 out of 90 women examined elevated OC concentrations were found by capillary chromatography and masspectroscopy. PCP serum levels above 25 µg/l were judged elevated, as were L blood levels above 100 ng/l. Elevated concentrations were found in 8 fertile women (6 of them with repeated abortions, aged 26-33 years), 8 women (aged 16 - 35 years) with menstrual disorders and androgenisation symptoms, and 6 women (aged 42 - 56 years) with climacteric symptoms. The source of emmission was identified in the residence of each patient, the duration of exposure ranged from 2 to 20 years. 16 women presented with adrenocortical malfunction (7 with hyperandrogenemia and 9 with partial adrenocorticoinsufficiency), 15 with immunological disorders, 6 with thyroid gland dysfunction (1 with hyper- and 5 with hypothyroidism) and 3 with luteal phase insufficiency. After elemination of the causative noxae and immunologic stimulation, blood OC concentrations decreased and the patients' physical conditions improved. menstruation normalized and, in case of conception, pregnancies resulted in healthy babies. On the basis of our data OC influence various hormonal systems including the adrenal and thyroid glands and reduce cellular immunity. Therefore an exact evaluation of environmental pollutions should be included in the endocrinological work-up of the patients with hormonal disorders and reproductive failure.

**140. Atrial natriuretic peptide (ANP) and progesterone in ovarian follicluar fluid**

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