33. Discontinuous therapy with bromocriptine in hyperprolactinaemic patients with amenorrhea, D. FONZO, G. GALLONE, G.P. PAPINI, R. SIVIERI and F. CERESA, Clinica Medica II, Istituto di Medicina Interna, Università di Torino

Hyperprolactinaemia is present in 15-25% of cases of amenorrhea and bromocriptine restores normal ovulatory cycles in virtually all hyperprolactinaemic patients. However, the mechanisms by which prolactin inhibits the cyclic pituitary-ovarian activity remain to be elucidated. We have observed that most of the patients treated with bromocriptine, despite long-lasting amenorrhea, often ovulate within 30 days: prolactin suppression in these patients is followed by hormonal changes that mimic a spontaneous ovulatory cycle, which is apparently initiated concomitantly with therapy. With the aim of elucidating the temporal relations between hyperprolactinaemia and the neuroendocrine events which eventually lead to ovulation and menstruation, we monitored the hormonal profile of 7 hyperprolactinaemic patients with amenorrhea and galactorrhea not related to a pituitary tumour. After an initial period of continuous bromocriptine therapy (2.5 mg t.i.d.) during which all patients presented regular hormonal profiles and had regular menses within 35 days, bromocriptine therapy was limited to the first 10 days of the cycle. All patients menstruated after 28 to 35 days and hormonal profiles were undistinguishable from the previous cycles with the exception of prolactin. Subsequently in three of the patients bromocriptine therapy was limited to the first five days of the cycle: these patients had two consecutive cycles with a shortened luteal phase. The data obtained indicate that hyperprolactinaemia inhibits ovulation and menstruation only when present in the first few days of the cycle. Normal prolactin levels appear to be crucial only in this initial phase when normal oestrogen levels (which are low in hyperprolactinaemic patients) are needed to allow a sufficient hypothalamic oestrogenic impregnation, in order to initiate the sequence of neuroendocrine events which will lead automatically to ovulation, even if interruption of bromocriptine allows a new rise of prolactin.

34. Failure of progesterone to enhance prolactin response to TRH in estrogen-primed ovariectomized women, P.M. KICOVIC, F. FRANCHI and M. LUISI, Postgraduate School of Endocrinology and Endocrine Unit of the CNR, University of Pisa, Pisa, Italy

It is not yet known whether progesterone (P) plays some role in the estrogen-modulated regulation of TRH-stimulated prolactin (PRL) release in women. The present study was undertaken to assess the effect of P on PRL response to TRH in 6 ovariectomized women aged 32-45 and primed with 25 µg/day of ethynylestradiol (EE) for 8 days. Circulating PRL was measured daily at 10:00 h prior to, and during, EE priming. P was administered by continuous i.v. infusion at a rate of 20 mg/24 h during the last 48 h of EE priming. TRH (200 µg i.v.) was administered 3 times — before EE, and on days 6 (EE alone) and 8 (EE + P): circulating PRL was determined frequently during the 2 h following TRH. PRL and P were assayed in plasma by radioimmunoassays. Data were statistically evaluated by means of Student's t-test. EE priming led to a significant increase in mean circulating PRL levels ($P < 0.001$) from 4.4 to 9.0 (on day 6) and 9.4 ng/ml (on day 8). Mean ΔPRL following TRH rose from 34.8 ng/ml before EE to 39.5 ng/ml on day 6 (NS). Intravenous infusion of P resulted in a sharp rise in plasma P, which was maintained at levels between 16.3 and 20.6 ng/ml. Following TRH on day 8, mean ΔPRL was 38.8 ng/ml, which was not different from mean ΔPRL on day 6. In the light of the present data it seems unlikely that P plays a role in the estrogen-modulated regulation of TRH-stimulated PRL release in women.

Supported by the CNR (Rome) - Grant no. 78.02319.04/115.1130.

35. Androgen secretion and skin metabolism in hirsutism, P. MAUVAIS-JARVIS, Department of Reproductive Endocrinology, Faculté de Médecine Necker, 75730 Paris Cedex 15

Hirsutism in women may result from either one of the following factors:

1. Hypersecretion of virilizing androgens by the ovaries or the adrenals, or
2. Hypersensitivity of androgen target cells to circulating androgens.

Therefore an in vivo and in vitro study has been carried out in 40 hirsute women with the aim of clarifying the respective roles of these 2 factors in the genesis of hirsutism. The concentration of testosterone (T), androstenedione (A) and dihydrotestosterone (DHT) in the plasma and 5α-androstene-3α,17β-diol (Adiol) in the urine were measured in 24 women presenting with idiopathic hirsutism, in 12 patients with polycystic ovaries (PCO) and in 4 women with adrenal virilism due to acquired congenital adrenal hyperplasia (CAH). Simultaneously, in vitro, the conversion of radioactive T into DHT and Adiol was calculated in the homogenates of pubic skin from each patient. Values for the levels of T, DHT in the plasma and Adiol in the urine of hirsute patients were all above control levels for normal women ($P < 0.001$). This finding was particularly marked in patients with CAH and PCO. Conversion of ^{3}H-T to 5α-reduced metabolites by homogenates of skin obtained from hirsute patients was significantly greater than by homogenates of skin from normal women ($P < 0.001$) but was the same as the value for normal men. The highest values for conversion were obtained from the patients with idiopathic hirsutism. These results indicate that androstenedione is the principal androgen secreted in hirsutism whatever its origin (idiopathic, adrenal or ovarian). In sexual skin this steroid may be converted to DHT and 3α- and 3β-androstanediols and the increased activity of T 5α-reductase may result in an exaggerated "utili-

zation" of A in this tissue. The high rate of excretion of Adiol in the urine of patients with hirsutism of adrenal origin primarily reflects the elevated secretion of A by the adrenals. In patients with virilism of ovarian origin (PCO) both the elevated secretion of A and the increased transformation of A into T-DHT and Adiol may be responsible for the elevated excretion of urinary Adiol. In women with idiopathic hirsutism the high excretion rate of Adiol in the urine may be essentially explained by an abnormal ability of sexual skin to transform in situ inactive androgen precursors supplied by the blood, into active androgens. The genetic or acquired origin of the enzymatic abnormality of the androgen responsiveness of sexual skin observed in idiopathic hirsutism remains unclear.

36. Correlations between hirsutism, cycle disturbances and normal menstrual cycle stages with plasma androgen levels, G. MAGRINI, F. MÉAN, P. BURCKHARDT, B. RUEDI and J.P. FELBER, Division de Biochimie Clinique, Département de Médecine, C.H.U.V., 1011 Lausanne, Switzerland

The aim of this study was to investigate some biochemical parameters that might better reflect clinical hyperandrogenism and the relative frequency and correlates of elevated plasma androgen levels in hirsutism, compared to the levels found at different stages of the normal menstruating cycle.

Eighty hirsute women, 70 of whom had abnormally high levels of at least one androgen were divided into 3 groups: 40 had normal cycles, 30 irregular cycles and 10 amenorrhoea. A control group of 20 normally menstruating women was also studied in the early and mid-late follicular, peri-ovulatory and luteal phases.

Plasma testosterone (T), androstenedione (A), 17αOH-progesterone (17αOHP), DHEA-S and cortisol (F) were measured by specific radioimmunoassays.

The correlative study shows that: 1) whereas more than two thirds of the cases of hirsutism had elevated 17αOHP and A levels, plasma T was increased in only half of them, and DHEA-S and F in a third; 2) in the group of hirsute women with irregular cycles, mean 17αOHP, T and A levels were even more significantly increased compared to the group with normal cycles; 3) whereas the percentage of increased A and 17αOHP levels in hirsutism with irregular cycles (90-95%) was not substantially greater than in the group with normal cycles (70-80%), the percentage of increased T levels was doubled (72% vs. 38%, $P < 0.005$). Moreover, the data show that in the group of hirsute women studied, only 17α-OHP and A had a very high frequency of clearly abnormally raised levels. On the other hand, under basal conditions, simultaneous determination of A + T + 17αOHP seems to be a good biochemical parameter for reflecting clinical hyperandrogenism.

The results also show significant modifications in the ratios between the different androgenic steroids, depending on the stage of the menstrual cycle.

37. Modern diagnostic methods for the detection and management of ovarian disease, G. LEYENDECKER, Universitäts-Frauenklinik 53 Bonn-Venusberg

The review will be confined to hypothalamic ovarian failure, its pathophysiology, diagnosis and management.

As an introduction, a concept of the normal endocrine regulation of the HPO axis in the human female is presented. An adequate hypothalamic secretion of Gn-RH is regarded as the primum movens. This secretion is considered to be permissive in that the cyclicity of events in the human menstrual cycle is regulated only of the levels of the pituitary and ovary.

Hypothalamic ovarian failure is considered to be the consequence of deficient hypothalamic Gn-RH release with corpus luteum insufficiency, anovulatory cycle, oligomenorrhoea and amenorrhoea forming a pathophysiological entity on the basis of a gradually reduced hypothalamic Gn-RH secretion.

On the basis of this understanding of the pathophysiology of hypothalamic ovarian failure the various clinical tests (Gn-RH-, oestradiol-provocation-, clomiphene-, progesterone-test) propagated and used for classification of this disorder are analysed and evaluated.

Finally, various therapeutic regimens are reviewed and special emphasis is put on the aspects and prospects of Gn-RH-substitution. It will be demonstrated that, with chronic intermittent administration of Gn-RH, normal pituitary and ovarian function can be instituted in hypothalamic ovarian failure.

38. Infertility with normal menstrual rhythm: hormone profiles in response to HMG (pergonal) treatment, W.P. BLACK[1], R. FLEMING[1], M.C. MACNAUGHTON[1], A. CRAIG[2], P. ENGLAND[3] and J.R.T. COUTTS[1], [1]Department of Obstetrics and Gynaecology, University of Glasgow, Glasgow Royal Maternity Hospital, Rottenrow, Glasgow, G4 0NA, [2]Clinpath Services Ltd., Lane End Rd., High Wycombe, Bucks, and [3]Department of Path. Biochemistry, Royal Maternity Hospital, Rottenrow, Glasgow G4 0NA, U.K.

Unexplained infertility may be a result of ovulation after poor follicular development (1). Twenty-seven infertile women, with a normal menstrual rhythm, were therefore treated with HMG in an attempt to improve follicular growth. Patients provided serial daily blood samples — throughout two menstrual cycles — the first was a control cycle and in the second patients received three ampoules of HMG intra-muscularly on each of days 1, 3 and 5. Using sensitive, specific, precise radioimmunoassays the levels of prolactin, LH, FSH, progesterone and oestradiol were determined in all plasma samples. The responses of patients to HMG were variable. Comparison of follicular phase oestradiol