oxytocin may be mediated through the release of uterine PGF2α.

27. Disturbances of menstrual cycle , B. LUNENFELD, Institute of Endocrinology, The Chaim Sheba Medical Center Tel-Hashomer, and the Department of Life Sciences, Bar-Ilan University, Ramat-Gan, Israel

The regulation of the menstrual cycle and ovulation is the result of the balanced and coordinated effects of the hypothalamic gonadotrophin releasing hormone (GnRH), the pituitary gonadotrophins, and ovarian response.

The GnRH, secreted by the hypothalamus in a specific quantity must impinge upon a responsive pituitary. The information carried by the releasing hormone must be received and interpreted by the target cell of the pituitary, and these cells, in turn, must be capable of synthesizing and releasing gonadotrophins in adequate quantities and with a specific rhythm. The gonadotrophic hormones then act on the ovary and stimulate three balanced and appropriately coordinated processes, namely, growth of the follicle, differentiation of the follicular cells, and steroid production. The steroidogenic function of the ovary resulting in the release of appropriate steroids at the proper time and in the correct amount constitutes a multipurpose system. It acts as a messenger system in the feedback mechanism which regulates the secretion of the gonadotrophins and it modulates follicular responsiveness to gonadotrophins, exerts specific action upon the various functional compartments of the ovary, including the vascular apparatus; it stimulates changes in the genital organs in preparation for the transport of the ovum and the sperm cells, and prepares the endometrium for implantation of fertilized eggs.

Any interruption of the complex feedback system regulating the function of the hypothalamic-pituitary-ovarian axis may lead to anovulation.

Roughly one-third of the infertile population seeking advice at sterility clinics present with cycle disturbances and/or ovulation failure.

Anovulation may be accompanied by a variety of menstrual disorders, the nature of which is directly related to the level and type of fluctuation of the ovarian steroids, or interfering hormones, metabolites or other substances.

We will not consider in depth in this paper studies oriented to assessing the diagnosis and treatment of systemic diseases (e.g., cirrhoses, hematochromatosis, sickle cell anemia, renal failure) or endocrinopathies associated with cycle disturbances, but not directly related to the hypothalamic-pituitary-gonadal-axis (adrenal, thyroid, diabetes).

Rather, we will focus on the endocrine pathology resulting in anovulation, cycle disturbances and the so called "luteal insufficiency" which may benefit from treatment with gonad-regulating agents.

Such patients may be classified into distinct groups depending on the aetiological origin of the disturbance.

a. Hypothalamic-pituitary failure.
Amenorrheic women with little or no evidence of ovarian oestrogen production, non-elevated prolactin levels, low or non-measurable gonadotrophin levels, and no detectable space-occupying lesion in the hypothalamic-pituitary region.

b. Hypothalamic-pituitary dysfunction.
Women with a variety menstrual cycle disturbance (luteal phase insufficiency, anovulatory cycle or amenorrhea) with distinct evidence of ovarian oestrogen production and with non-elevated prolactin or gonadotrophin levels.

c. Hyperprolactinaemic patients with a space-occupying lesion in the hypothalamic-pituitary region.
Women with a variety menstrual cycle disturbances (luteal phase insufficiency, anovulatory cycles or amenorrhea) with elevated prolactin levels and evidence of a space-occupying lesion in the hypothalamic-pituitary region.

d. Hyperprolactinaemic patients with no detectable space-occupying lesion in the hypothalamic-pituitary region.
Women with a variety of menstrual cycle disturbances (luteal phase insufficiency, anovulatory cycles or amenorrhea) with distinct evidence of ovarian steroid production and with elevated prolactin levels.

A number of effective drugs and hormones are available for regulating ovarian function in such patients. These can be classified into three groups: 1. Human gonadotrophins; 2. Clorotrianisene analogues; and 3. Ergoline derivatives. Each group of these agents acts through a different mechanism. Gonadotrophins stimulate the ovary directly, chlorotrianisene analogues stimulate the hypothalamic-pituitary system, and ergoline derivatives inhibit excessive prolactin secretion which interferes with the normal reproductive function.

Each of these agents may be used at various dosage levels and in different treatment schemes sometimes in combination, or in conjunction with oestrogens or anti-gonadotrophins, and all of them carry risks of various, sometimes severe, complications.

28. Effect of epimestrol treatment on endocrine and clinical features of short and inadequate luteal phase, A.R. GENAZZANI[1], G. D'AMBROGIO[1], C. MASSAFRA[1] and P. KICOVIC[2], [1]Department of Obstetrics and Gynaecology, University of Siena, Via P. Mascagni 46, 53100 Siena, Italy, and [2]Reproductive Medicine Programme, Medical Unit, Organon, Oss, Holland

A short luteal phase is characterised by an adequate rise of plasma progesterone levels after the mid-cycle LH ovulatory peak which rapidly decline after a few days to follicular phase levels. In an inadequate luteal phase, progesterone plasma levels after ovulation show only a small rise, reaching levels which are normally less than half those expected. The aetiopathogenesis of these conditions has until now been poorly under-

stood with the exception of cases in which the syndrome is associated with elevated or slightly elevated plasma levels of prolactin.

11 subjects, 7 with the chronic inadequate luteal phase and 4 with a short luteal phase (2 not desiring pregnancy and the others sterile) were studied in detail during a control cycle to define their respective endocrine features. The presence of an LH ovulatory peak was found in 9 cases. All cases demonstrated estradiol (E2) values which, though indicating follicular growth, were slightly lower than expected. The subjects were treated with Epimestrol (3-methoxy-ether-17-epiestriol) at a dose of 5 mg x 2/day for 10 days from the 5th day of cycle. In 7 subjects the treatment induced adequate luteal phase from the first cycle of treatment. One case of inadequate luteal phase gave a short luteal phase. In 2 other subjects an increased daily dose of Epimestrol and/or length of treatment (5 mg x 3/day for 10 days and 5 mg x 4/day for 15 days) induced an adequate luteal phase. Only one case failed to respond. Two subjects became pregnant in the first cycle of treatment. The hormonal assays performed during treatment indicated that E2 levels in the follicular phase were significantly higher than before treatment while no apparent modification was found in basal gonadotropins in 4 cases except for a more marked rise of plasma LH during the ovulatory peak.

Independently of the clear clinical usefulness of Epimestrol treatment for short and inadequate luteal phase, it seems that besides the known effect it has on pituitary gonadotropin secretion in hypogonadic subjects, Epimestrol improves follicular maturation and E2 production probably through a peripheral effect on the response of granulosa cells to endogenous gonadotropins.

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29. Plasma steroid response of pubertal girls to human menopausal gonadotropin (HMG), M. ZACHMANN, B. MANELLA, L. SANTAMARIA, W. ANDLER and A. PRADER, Department of Pediatrics, University of Zurich, Kinderspital, 8032 Zurich, Switzerland, and Department of Pediatrics, University of Essen, Universitätsklinikum, 4300 Essen, Federal Republic of Germany

To study their response to ovarian stimulation, plasma steroids were measured radioimmunologically in 31 girls before and after 5 daily i.m. injections (75 IU of LH and FSH each) of HMG. In normal girls (n = 7; 6 familial tall stature, 1 mild idiopathic hirsutism, age 13 to 18, mean 13.9 years), estradiol (E2) increased from 91 ± 11 (SEM) to 292 ± 26 pg/ml ($P < 0.001$). Estrone (E1, n = 5), testosterone (T), androstenedione, and 17OH-progesterone (17OHP, n = 3) did not change. In XO Turner syndrome (n = 11, age 8-16 years), E2 (47 ± 5 to 55 ± 8 pg/ml), E1 (n = 9) and the other steroids (n = 2) remained unchanged. In XO/XX Turner mosaicism (n = 4, age 12-14 years), there was an insignificant E2- (55 ± 12 to 77 ± 23 pg/ml), and no E1-response. One girl with acanthosis nigricans, virilization, and diabetes mellitus showed no E2-, but a marked T-response (214 to 678 ng/dl). In one girl with congenital adrenal hyperplasia (CAH, 21-hydroxylase deficiency) off treatment, there was no E2-response, and T and 17OHP were high without further increment. In another girl with CAH (3β-hydroxysteroid dehydrogenase deficiency) on adrenal suppression, there was no E2-response, but DHA increased (312 to 450 ng/dl). In 3 patients with isolated gonadotropin deficiency and anosmia, hypergonadotropic hypogonadism, and testicular feminization (gonadectomized) respectively, and in 2 patients with malignancies on cytostatic treatment, E2 and E1 did not respond. It is concluded that this test allows an evaluation of ovarian E2-secretion already in early puberty.

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30. Hyperprolactinemia syndrome, C. ROBYN, Human Reproduction Research Unit, Université Libre de Bruxelles, Hôpital Saint-Pierre, 322 rue Haute, 1000-Brussels, Belgium

Prolactin secretion is normally under permanent inhibitory influence from the hypothalamus. Most of such inhibition, if not all, is due to dopamine. However, hyperprolactinemia is rather frequent. In women, it is associated with menstrual cycle disorders such as amenorrhea, anovulatory bleeding and a short luteal phase. Galactorrhea is a bad marker of the syndrome.

High circulating levels of prolactin are seen in pathological cases (prolactinoma, hyperplasia of the lactotrophs, suppressed inhibition of prolactin release) but also in a physiological condition, i.e. long-lasting lactation. Psychotropic drugs induce hyperprolactinemia by antagonizing the inhibitory effect of dopamine on prolactin release.

Whatever the cause of the syndrome is, it is characterized by anovulation or corpus luteum defect. Prolactin interferes with the control of ovulation both at the hypothalamic and at the ovarian level. Blood flow conveys pituitary hormones to the hypothalamus where the neurones are sensitive to prolactin. The hormone is even found inside some hypothalamic neurones on immunohistochemical staining. There are close relationships between gonadotropin releasing hormone (LH-RH) nerve terminals and dopaminergic nerve terminals in the median eminence. Prolactin inhibits its own secretion, likely by increasing dopamine turn-over in the median eminence. Furthermore, dopamine inhibits LH release.

In hyperprolactinemia, the pulsatile release of LH is suppressed or altered; the positive feedback of estrogens on LH release is abolished; the LH and FSH responses to gonadotropin releasing hormone are enhanced; the basal levels of serum oestradiol are low; and ovarian responsiveness to gonadotropins is not impaired. But in some hyperprolactinemic women, ovulation is not suppressed. In these cases, oestradiol secretion during the follicular phase is normal, with a normal