

## CLINICAL SIGNIFICANCE OF THE LUTEINIZED UNRUPTURED FOLLICLE SYNDROME AS A CAUSE OF INFERTILITY \*

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The luteinized unruptured follicle syndrome (LUF) exists and is a cause of infertility. Although the data of the laparoscopic inspection of the ovaries and the corpora lutea and of steroid hormone concentrations in peritoneal fluid constitute strong evidence that the syndrome exists, its role as a cause of infertility is less clear. The only evidence available that the LUF syndrome is a cause of infertility, is the finding that the syndrome occurs statistically more frequently in women with unexplained infertility than in a control group of women. It still has to be proven whether the LUF syndrome occurs repetitively in each cycle and causes infertility, or whether the syndrome occurs intermittently and only reduces the probability of conception.

Diagnosis of the syndrome can be made by laparoscopic inspection of the ovaries and by the assay of  $17\beta$ -estradiol and progesterone, in peritoneal fluid between day 14 and 20 of the cycle.

The relationship between the LUF syndrome and pelvic endometriosis and luteal phase insufficiency is discussed. We suggest that the LUF syndrome might be the cause of endometriosis thus explaining the statistical association between both syndromes, and the infertility of women with only mild endometriosis.

We favor the hypothesis that the LUF syndrome might be caused by stress thus constituting a 'psychological infertility' and we suggest that the syndrome could explain the spontaneous cure rate. Therefore, before any therapy can be accepted as the treatment of the LUF syndrome, it should be strictly assessed with adequate controls.

luteinizing unruptured follicle; luteal phase insufficiency; infertility; endometriosis; peritoneal fluid

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### INTRODUCTION

The exact cause of their infertility remains unclear in many couples even after extensive examination of man and woman. Not only women, in whom the infertility work-up was found to be normal can be considered as having 'unexplained infertility'; also women in whom mild or moderate pelvic endometriosis was found and who remain infertile despite a regular ovulatory cycle should be considered as having unexplained infertility, since the mechanism by which endometriosis causes infertility is still unknown.

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The clinical significance of the luteinized unruptured follicle (LUF) syndrome, as a frequent cause of infertility in women with regular cycles, with or without endometriosis has only recently been recognized and investigated. These data will be reviewed.

The idea of a LUF is not new. In the human, Stein and Leventhal already suggested in 1935 rupture of the follicle beneath the cortex with entrapment of the oocyte. Luteinization of the follicle, without release of the oocyte was proposed to explain the discrepancy (Kase et al., 1967) between ovulation rate and pregnancy rate during clomiphene treatment. In the rat (Tsafiriri et al., 1972) and subsequently in the rabbit (Armstrong et al., 1974), and the monkey (Wallach et al., 1976; Maia et al., 1978) a LUF syndrome could be induced by indomethacin treatment.

#### CLINICAL AND BIOCHEMICAL EVIDENCE THAT THE LUF SYNDROME EXISTS

##### *Laparoscopic evaluation of the ovulation ostium*

Recently, two groups described independently that in women with infertility and apparently normal 'ovulatory' cycles, the ovulation ostium could often not be seen at laparoscopy (Brosens et al., 1978; Koninckx et al., 1978; Marik and Hulka, 1978). This observation was not, however, proof of the existence of a LUF syndrome, since the ovulation ostium could have been reepithelialized following ovulation, and since the ovulation ostium could have been missed or misinterpreted at laparoscopy.

The repair of the ovulation ostium has been studied in rats (Rosenbauer et al., 1976), rabbits and guinea pigs (Motta and Van Blerkom, 1975). In these animals the entire site of disruption is covered by a layer of connective tissue cells within 2 days. Simultaneously epithelial cells from the intact lateral areas proliferate and migrate over the newly established connective tissue matrix, repairing the ovulation ostium after 5 to 7 days. In the human the repair of an ovulation ostium has not yet been studied in detail. The animal experiments suggest, however, that an ovulation ostium will not be reepithelialized before about a week following ovulation and that it could thus be recognized as such during that period.

In the human the repair process could even take a much longer time since the incidence of an ovulation ostium or scar in women with unexplained infertility, in women with pelvic endometriosis, and in a control group of women (Brosens et al., 1978; Koninckx et al., 1978) was not significantly different between the early (days 14–20) and the late (days 21–28) luteal phase. Moreover, we observed occasionally an ovulation scar during the early follicular phase of the following cycle.

The laparoscopic inspection and the interpretation of an ovulation ostium has been subjected to much criticism, since the ostium could have been missed or misinterpreted.

Unless ovarian mobility is limited, i.e. by adhesions, both sides of the ovary can always be inspected completely either by using a dual puncturing technique, or by moving the uterus down and sideways while the ovary is lifted out of the fossa ovarica. In our hands this technique – the ovary resting upon the uterus – is the method of choice for a careful inspection of the ovary. The evaluation of an ovulation ostium is often dubious (14%) (Koninckx et al., 1980a), but in most cases

the ostium can unequivocally be classified as absent (sometimes even a corpus luteum cannot be seen -- sometimes the corpus luteum is cystic) or present. Even pictures can easily be recognized as such by everyone (Koninckx et al., 1980a). Final proof that this visual interpretation corresponded to some real phenomenon was given by the study of peritoneal fluid (Koninckx et al., 1980a).

*Steroid hormone concentrations in peritoneal fluid of women with or without an ovulation ostium*

In women with, according to their BBT, plasma progesterone concentrations or endometrial biopsies, ovulatory cycles, the volume of peritoneal fluid increases progressively during the follicular phase, then abruptly at ovulation and declines progressively thereafter (Fig. 1) (Maathuis et al., 1978; Koninckx et al., 1980d). During the follicular phase concentrations of  $17\beta$ -estradiol and progesterone (Koninckx et al., 1980b) are slightly higher in peritoneal fluid than in plasma, but following ovulation, the concentrations in peritoneal fluid increase sharply, and are some 5 to 10 times higher than in plasma (Fig. 2). These concentration differences are even more impressive when the free steroid hormone concentrations are considered: indeed both transcortin and sex-hormone binding globulin concentrations are some 30% lower in peritoneal fluid than in plasma (Koninckx et al., 1980b).

Subsequently, when this group of women with so-called ovulatory cycles was subdivided in women with and without ovulation ostium, we found that only women with an ovulation ostium have these very high concentrations of  $17\beta$ -estradiol and

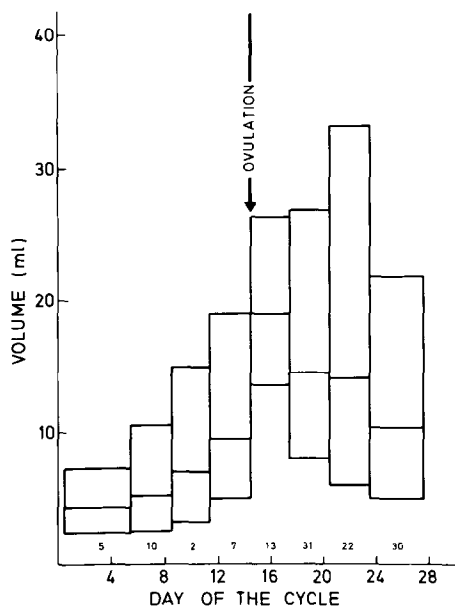


Fig. 1. Volume of peritoneal fluid in normal women during the menstrual cycle ( $\text{mean}_{\log} \pm \text{SD}$ ). The number of women in each group is indicated (Koninckx et al., 1980d).

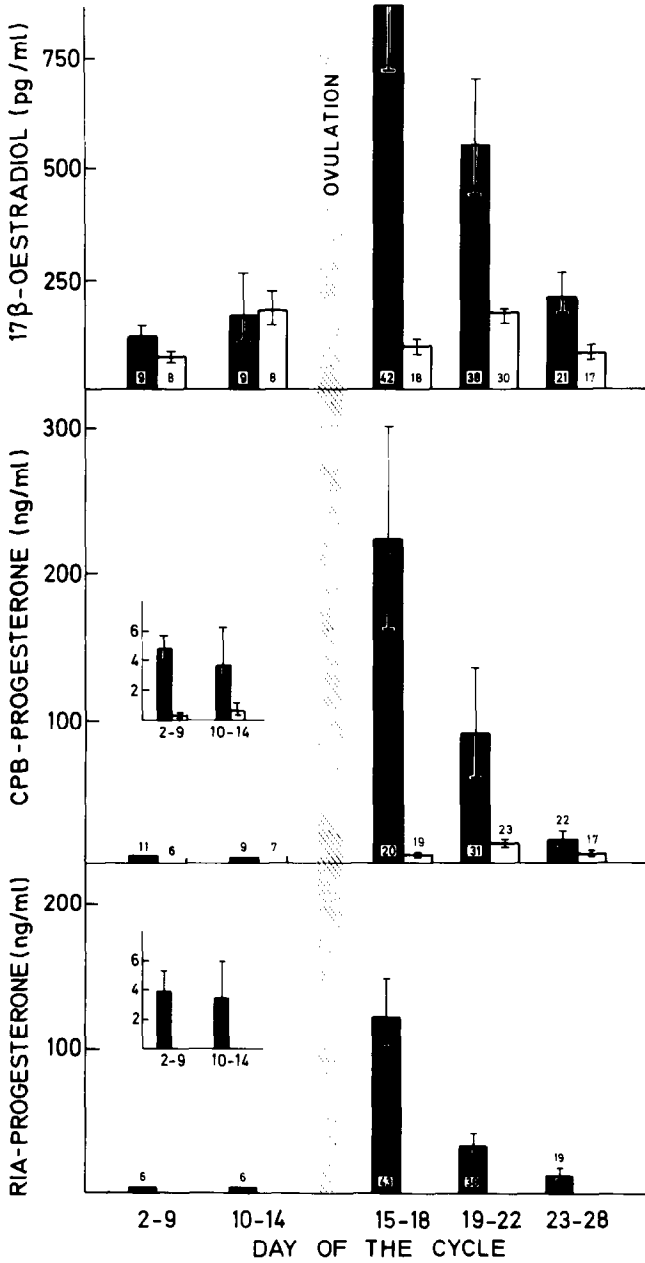


Fig. 2. Concentration of 17β-estradiol and of progesterone assayed by CPB and by RIA, in peritoneal fluid (closed bars) and paired plasma samples (open bars). The mean<sub>log</sub> ± SE and the number of determinations are indicated (Koninckx et al., 1980b).

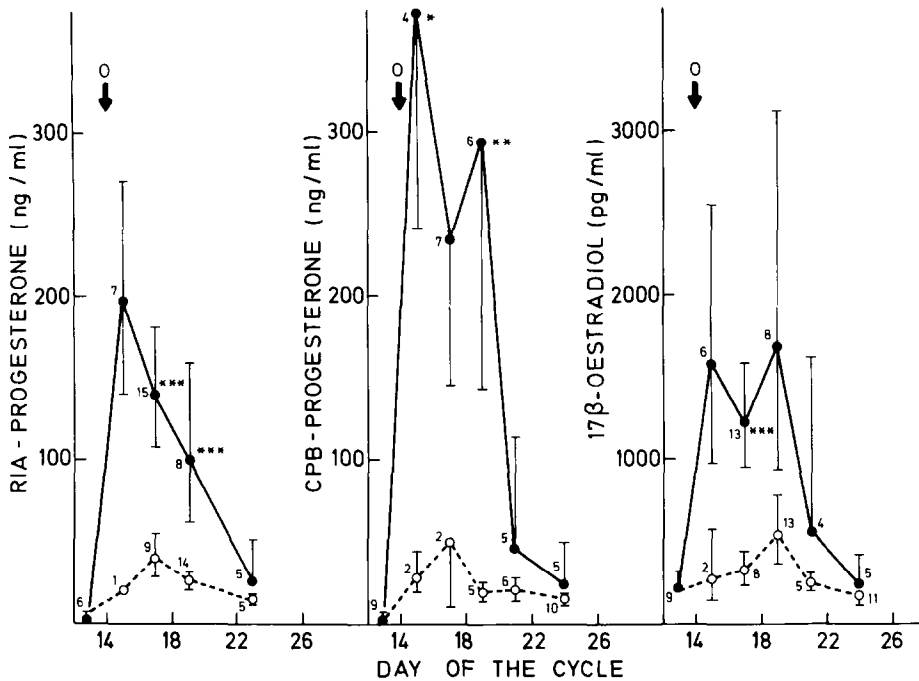


Fig. 3. Concentration of progesterone measured by radioimmunoassay, progesterone measured by competitive protein binding, and  $17\beta$ -oestradiol in peritoneal fluid of women with (●—●) and without (○—○) an ovulation stigma. The mean<sub>log</sub> ± SE, the number of determinations (\* < 0.05, \*\* < 0.001, \*\*\* < 0.005) and the ovulation (O) are indicated (Koninckx et al., 1980a).

progesterone in their peritoneal fluid for at least 6 days following ovulation. Women without an ovulation ostium have barely elevated steroid hormone concentrations during the early luteal phase (Fig. 3) except the women in whom the corpus luteum is cystic (Fig. 4). These differences in  $17\beta$ -oestradiol or progesterone concentrations cannot be explained by differences in the concentrations of the binding proteins (Koninckx et al., 1980a) nor by differences in the volume (Koninckx et al., 1980d) of peritoneal fluid.

Peritoneal fluid data thus strongly support the concept of a LUF. Firstly, peritoneal fluid seems to be formed mainly by ovarian exudation: the volume of peritoneal fluid is not affected by the absence of the fallopian tube; in cycling women the volume increases paripassu with ovarian activity and finally the volume is uniformly low in women with suppressed ovarian activity, i.e. postmenopausal women and women taking combined oral contraceptives or lynestrenol, 5 mg daily (Koninckx et al., 1980d). Secondly, in order to maintain such a high concentration gradient of  $17\beta$ -oestradiol and progesterone between peritoneal fluid and plasma, up to day 20 of the cycle, continuous secretion of these steroid hormones into the peritoneal cavity has to be postulated. Thirdly, since steroid hormone concentrations are significantly higher when an ovulation ostium is present, we suggest that leakage of fluid through the ovulation ostium takes place. This fluid comes from the corpus

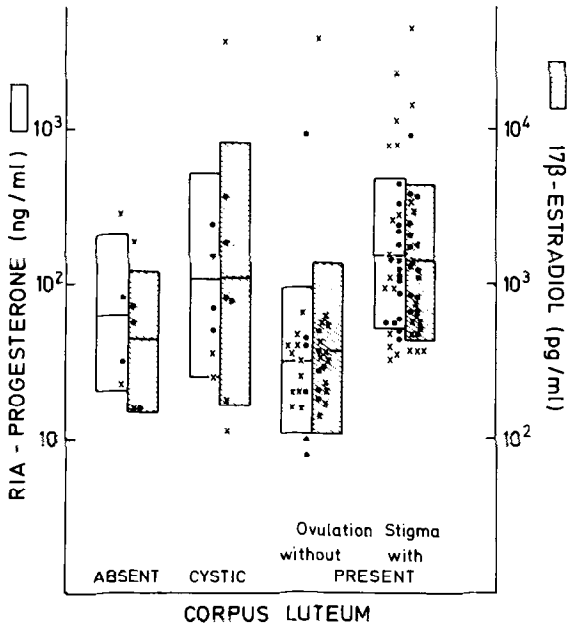


Fig. 4. Concentration of progesterone measured by radioimmunoassay and of  $17\beta$ -estradiol in peritoneal fluid of women according to the laparoscopic appearance of their corpus luteum. The mean<sub>log</sub>  $\pm$  SE and the absence (x) or presence (●) of pelvic endometriosis are indicated (Koninckx et al., 1980a).

luteum and is laden with estrogens and progesterone. When a luteinized unruptured follicle is formed, less exudation occurs with consequently lower steroid hormone concentrations in peritoneal fluid.

#### THE LUF SYNDROME IS A CAUSE OF INFERTILITY

There can be no doubt that during a cycle, in which a LUF is formed, conception is excluded. In order to demonstrate, however, that the LUF syndrome is the cause of the infertility in a woman, it should be proven that the syndrome occurs repetitively in each menstrual cycle. For obvious reasons laparoscopy, however, cannot be performed in successive cycles.

Indirect evidence for the LUF syndrome being a cause of infertility was obtained by the fact that the syndrome occurs in more than 50% of women with unexplained infertility (Koninckx et al., 1978) but in less than 10% of a control group of women ( $P < 0.001$ ). This very high incidence should not, however, be interpreted as proof that the LUF syndrome occurs repetitively in over half of the patients with otherwise unexplained infertility. The data only indicate that the LUF syndrome occurs statistically more frequently in these women.

Also in women with endometriosis, a LUF syndrome was significantly more frequent than in a control group of women. The original observation, based upon the laparoscopic inspection of the ovulation ostium (Brosens et al., 1978) was later confirmed by steroid hormone assays in peritoneal fluid (Koninckx et al., 1980c).

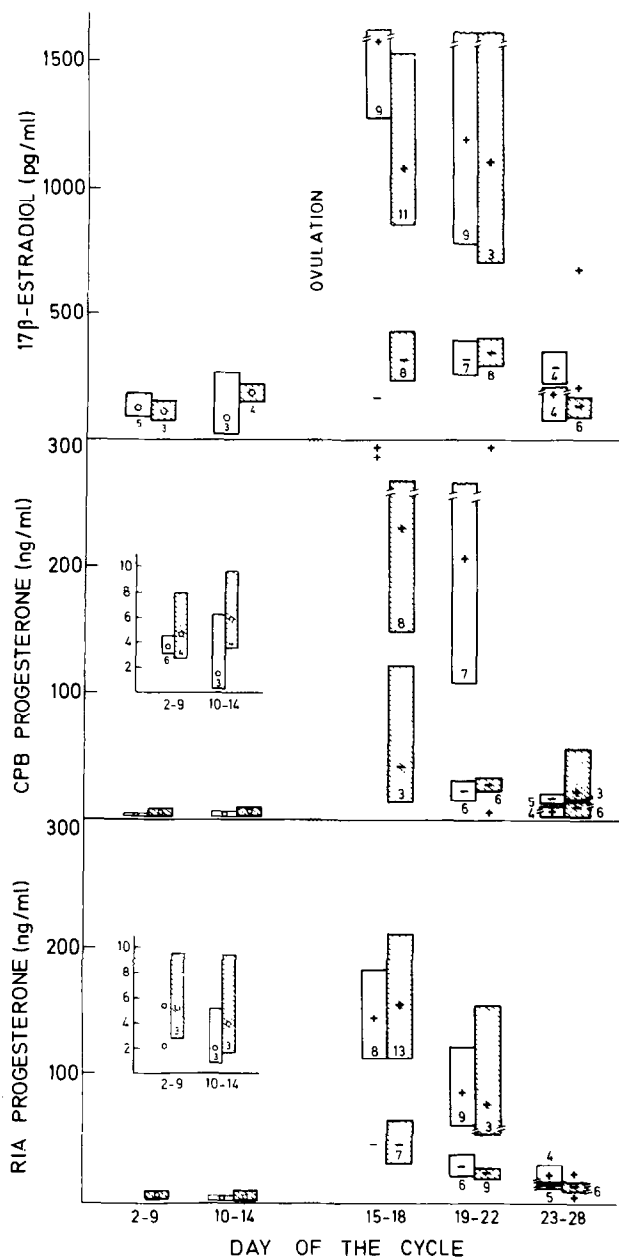


Fig. 5. Concentrations of progesterone and  $17\beta$ -estradiol in peritoneal fluid of women without endometriosis (open bars) and of women with mild or moderate endometriosis (striped bars). The bars represent 1 SE above and 1 SE below the mean calculated on a log scale. The presence (+) or absence (-) of an ovulation ostium are indicated in the bars at the mean point. The number of samples in each group is indicated. When a group included only one or two women individual results are indicated (Koninckx, 1981).

Moreover, when subsequently peritoneal fluid steroid hormone concentrations of women with and without endometriosis were compared, no differences were found between both groups when the presence or absence of an ovulation ostium was taken into account (Fig. 5), suggesting that endometriosis itself does not influence peritoneal fluid concentrations of  $17\beta$ -estradiol or progesterone.

#### THE LUF SYNDROME IS THE CAUSE OF INFERTILITY IN WOMEN WITH MILD OR MODERATE PELVIC ENDOMETRIOSIS: A NEW HYPOTHESIS

Endometriosis is known to be associated with infertility (Meighs, 1960; Ranney, 1970). The etiology of endometriosis and the physiopathology of the associated infertility, however, are still unknown, except when extensive adhesions constitute a mechanical infertility factor.

The first observation was the frequent association of endometriosis and the LUF syndrome. Ovulation ostia were seen at laparoscopy in 94% of a control group of women, but only in 21% of patients with endometriosis and regular biphasic cycles. This difference was highly significant for mild, moderate and severe endometriosis (Brosens et al., 1978). This frequent occurrence of the LUF syndrome in women with endometriosis was subsequently confirmed by peritoneal fluid steroid hormone assays (Koninckx et al., 1980c).

The second observation was the presence of viable endometrial cells in peritoneal fluid in almost 60% of women with or without endometriosis (Koninckx et al., 1980c). The question thus arises as to why these endometrial cells do not implant more frequently. We suggest that this can be explained by the steroid hormone concentrations in peritoneal fluid, and the following hypothesis for the etiology of endometriosis is proposed (Koninckx et al., 1980c): endometrial cells, regurgitated during menstruation into the peritoneal cavity, are normally prevented from implanting on the peritoneum by the sex steroid hormone concentrations in peritoneal fluid. Whenever this inhibiting mechanism fails, as occurs when a LUF is formed, endometriosis may develop. Endometriosis thus would be the consequence and not the cause of infertility in such cases. Once established, however, and more particularly when the ovaries themselves are involved, endometriosis might aggravate infertility since ovarian function has been shown to be disturbed in women with moderate and severe ovarian endometriosis (Brosens et al., 1978) and since ovum transport can be disturbed by tubo-ovarian adhesions.

#### RELATIONSHIP BETWEEN THE LUF SYNDROME AND THE 'SO-CALLED' LUTEAL PHASE INSUFFICIENCY

Luteal phase insufficiency is widely accepted as a cause of infertility and the diagnosis is made, by an endometrial biopsy dating which is out of phase for 2 days or more on 2 occasions (Jones, 1973), by subnormal plasma progesterone concentrations during the luteal phase (Abraham et al., 1974; Radwanska and Swyer, 1974) or by a shortened luteal phase of less than 12 days duration.

The relationship between the short luteal phase, and the LUF syndrome was not yet investigated. The short luteal phase seems to be a syndrome (Strott et al., 1970;



Sherman and Korenman, 1974; Wilks et al., 1976) characterized by diminished FSH concentration in the early follicular phase, by a slightly lower LH concentration during the follicular phase, by reduced  $17\beta$ -estradiol concentrations in the late follicular phase, and by a reduced progesterone concentration during the luteal phase which is of shortened duration. The corpus luteum pathology thus seems to be preceded by an impaired follicular development which is possibly triggered by a changed bioactivity of LH (Sakai and Channing, 1979) or by an insufficient FSH secretion in the early follicular phase, since the syndrome can be induced in the rhesus monkey by the injection of charcoaled follicular fluid (= inhibin?) and thus

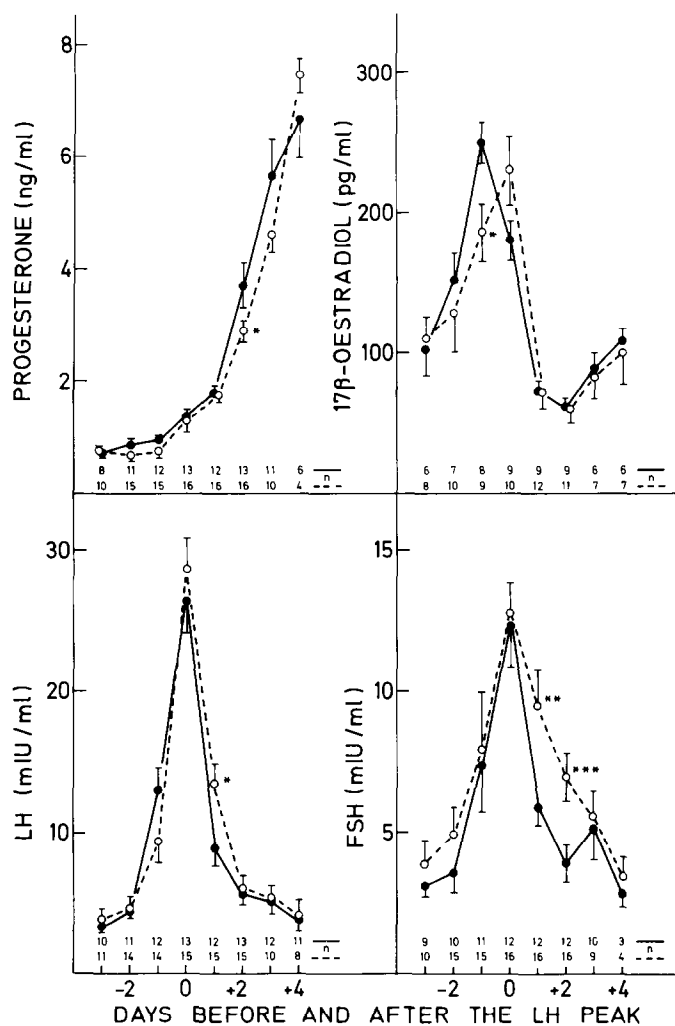


Fig. 6. Periovulatory plasma concentrations of LH, FSH, progesterone and  $17\beta$ -estradiol in women who ovulated (●-----●) and in women with an unruptured luteinized follicle (○-----○). Mean  $\pm$  SD, and the number of women in each group are indicated (\*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ ) (Koninckx et al., 1981).

by lowering the FSH concentration in the early follicular phase (Stouffer and Hodgen, 1980).

In order to investigate the relationship of the so-called luteal phase insufficiency and the LUF syndrome we compared periovulatory plasma hormone concentrations and endometrial biopsy datings in women with regular cycles and a luteal phase of 12 days or more in women with and without a LUF syndrome. Plasma FSH concentrations in women with the LUF syndrome were significantly higher during 2 days following the LH peak than in women who ovulated. Contrary to this, preovulatory and peak concentrations were comparable in both groups of women (Fig. 6). No clear-cut differences were found between the periovulatory concentrations of plasma LH, progesterone and  $17\beta$ -estradiol except that the  $17\beta$ -estradiol peak occurred on the day before the LH peak in the ovulatory group but on the day of the LH peak in the women with the LUF syndrome. Prolactin concentrations, although slightly higher in women with the LUF syndrome, were comparable in both groups of women (Koninckx et al., 1981).

The duration of the luteal phase defined as the interval between the LH peak and the onset of the next menstruation was comparable in both groups of women:  $13.4 \pm 1.5$  ( $n = 12$ ) and  $13.5 \pm 1.2$  ( $n = 14$ ) days, respectively. Also, the dating of the endometrial biopsy was not different between the two groups of women (Koninckx et al., 1981). The delay between the expected day of the cycle as determined by the LH peak localization and the endometrial biopsy dating was  $0.6 \pm 1.7$  days in the ovulatory group of women ( $n = 8$ ) and  $1.2 \pm 1.1$  days in the women with the LUF syndrome ( $n = 12$ ).

#### DIAGNOSIS OF THE LUF SYNDROME

Diagnosis of the LUF syndrome cannot be made by endometrial biopsy datings or plasma hormone assays. A LUF syndrome can, however, be suspected in those women in whom after ovulation, the plasma FSH concentrations remain elevated for a few days.

Diagnosis can only be made by direct inspection of the ovaries and by peritoneal fluid assays of progesterone and  $17\beta$ -estradiol. The correlation between the progesterone concentration measured by radioimmunoassay and the  $17\beta$ -estradiol concentration was highly significant (Fig. 7). Between days 15 and 20 of the cycle, progesterone concentrations of more than 80 ng/ml and  $17\beta$ -estradiol concentrations of more than 750 pg/ml were found respectively in 89 and 63% of peritoneal fluids in women with an ovulation ostium, whereas in women without an ovulation ostium these concentrations were found in only 25 and 20%. The use of both hormones together would lead to an accurate diagnosis of ovulation in 92 and 80% of women with and without an ovulation ostium, respectively (Koninckx et al., 1980a). The accuracy of the diagnosis by peritoneal fluid assays diminishes progressively as the luteal phase progresses, and disappears after days 19–20 of the cycle. The use of progesterone and  $17\beta$ -estradiol concentrations in peritoneal fluid for the diagnosis of the LUF syndrome is further hampered by the fact that women with a cystic corpus luteum have high concentrations of both steroid hormones in their peritoneal fluid in spite of the absence of an ovulation ostium. A cystic corpus

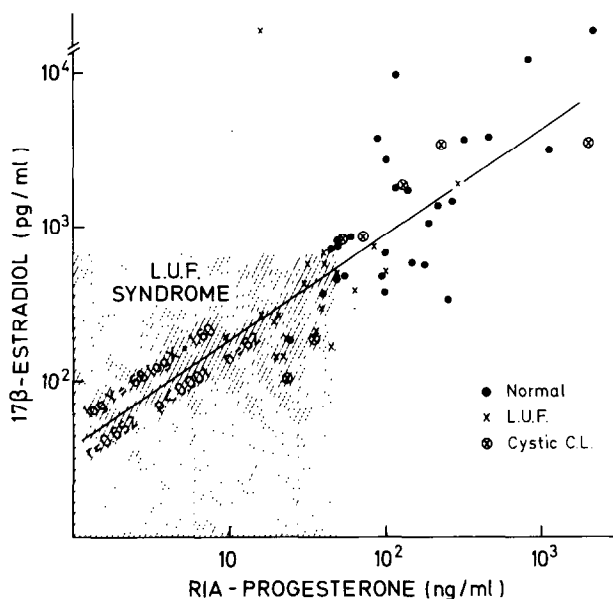


Fig. 7. Correlation between progesterone concentrations and  $17\beta$ -estradiol concentrations in peritoneal fluid (Koninckx et al., 1980a).

luteum probably constitutes such a large exudation area that steroid hormone concentrations are elevated in spite of a LUF syndrome.

Since the evaluation of an ovulation ostium at laparoscopy may sometimes be difficult and eventually erroneous the question should be asked if the diagnostic accuracy of peritoneal fluid assays is not higher than 92 and 80% in women with and without an ovulation ostium, respectively. The false positives and false negatives found could indeed be the consequence of ovulation ostia which were erroneously interpreted at laparoscopy.

#### ETIOLOGY OF THE LUF SYNDROME: A SPECULATIVE APPROACH

Although one has no difficulty in accepting the LUF syndrome as a mechanism of infertility, the frequency of occurrence is puzzling. We found a LUF syndrome in over half of our patients with otherwise unexplained infertility or with pelvic endometriosis, and in 40% of all infertile women with a luteal phase of more than 12 days and without transport infertility. This suggests that even in many married couples with so-called impaired fertility, i.e. by slight oligospermia, a LUF syndrome is (occasionally?, persistently?) present.

The mechanism which causes a LUF syndrome, is still unknown, but we speculate that the LUF syndrome might be psychological infertility. Moderate hyperprolactinemia was claimed to cause infertility (Seppala et al., 1976; Sarris et al., 1978). When we assayed plasma prolactin concentrations in our women with infertility we were unable, however, to diagnose reliably moderate hyperprolactinemia because of

the frequent occurrence of stress hyperprolactinemia (Koninckx, 1978). Although we concluded that an infertility clinic is particularly stressful, it cannot, however, be excluded that not the clinic is stressful but that the patients are stress-prone. Indeed, it is known that some subjects, i.e. neurotics, react to stress with a much more pronounced rise in prolactin and growth hormone concentration than a control group (Miyabo et al., 1976), while it is well known how 'stressed' women become when their infertility is not quickly solved. We therefore speculate that stress-prone subjects, by constitution, i.e. neurotics, or as a consequence of lasting infertility, could react daily to many insignificant incidents with a prolactin peak and that these recurrent prolactin peaks cause the LUF syndrome.

This hypothesis, although only speculative at this moment, can furthermore explain many well recognized but not yet understood facts in infertility, i.e. that 30% of all pregnancies of an infertility clinic occur during the investigations, the so-called spontaneous cure rate, even in women with long standing infertility. The same phenomenon – an unexpected pregnancy – is seen relatively often in women with unexplained infertility, when therapy is stopped after years of treatment. All these observations have stress in common, and we suggest that the LUF syndrome is the mechanism of the often mentioned, but never proven 'psychological infertility' (Denber, 1978; Mai, 1978).

#### TREATMENT OF THE LUF SYNDROME

Since the etiology of the LUF syndrome is totally unknown, we do not yet know how to treat these patients.

Marik and Hulka (1978) reported that 28 patients with unruptured luteinized follicles at the time of laparoscopy and with no other obvious infertility factor were treated with ovulation induction agents such as clomiphene and hMG. Fifteen of these patients conceived subsequently. Our results of the treatment of the LUF syndrome with ovulation stimulating agents are certainly much lower (in preparation).

Since it is not yet proven that the LUF syndrome is constantly present in successive cycles, and since the LUF syndrome might explain the spontaneous cure rate in women with infertility we want to stress that any form of treatment should be strictly assessed in comparison with a control group before conclusions are made.

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