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Ovarian Steroid Hormones and Endometrial Response

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As a bioassay of the steroidogenic function of the corpus luteum, endometrial biopsy has been proposed as the most efficient way of diagnosing corpus luteum insufficiency. However, analysis of our data on luteal phase evaluation in infertility shows that most cases (86 %) of endometrial luteal inadequacy are associated with normal hormone (progesterone, estradiol) stimulation. This apparent lack of endometrial progestational response may be explained by an end organ defect localized to the endometrial steroid receptors.

Key words: Endometrium, Estradiol, Progesterone, Luteal defect, Steroid receptors.

Cyclic menstruation is the culmination of a series of hormonal interactions on the endometrium. In the course of a normal ovulatory cycle, FSH stimulates an ovarian follicle to maturation. The stimulated ovarian follicle begins to secrete increasing quantities of E_2. In response to increasing ovarian E_2 secretion, the endometrium undergoes proliferation; the stroma thickens and becomes compact; the endometrial glands increase in number and length. When the rising plasma concentration of E_2 reaches the peak necessary to induce ovulation, an LH surge occurs, and ovulation follows. Ovulation is followed by the formation of a corpus luteum at the site of the ovarian follicle, and the corpus luteum begins secreting progesterone (P) within 24 hours of ovulation. P acts on the endometrium to suppress the mitogenic action of E_2 and converts the proliferative endometrium into secretory endometrium. The straight, narrow endometrial glands become tortuous and dilated; the thick, compact endometrial stroma becomes edematous and the endometrium is prepared for implantation of a fertilized ovum.

Thus, some authors have emphasized the importance of the endometrial histological pattern as a bioassay of the steroidogenic function of the corpus luteum (11, 15). However, on the basis of our data, the endometrial luteal phase insufficiency (LPI) is associated with normal hormonal levels in the great majority of cases, thus showing the lack of predictive value of midluteal plasma progesterone

determinations regarding the progestational transformation of the endometrium.

Luteal phase evaluation

Endometrial biopsy is the method most commonly used to evaluate the luteal phase. By using such a diagnostic procedure, the reported incidences for LPI in infertility were between 3.5 and 20 % (5). The incidence is higher (23-60 %) when only patients with repeated abortions are considered (5). However, with the advent of radioimmunoassay for plasma P, the concept that endometrial histology is sufficient to diagnose luteal insufficiency has been challenged, and it has been postulated that mid-luteal plasma P determination might offer a better assessment of luteal function (14).

As previously reported, we routinely use basal body temperature, plasma P, E_2 and prolactine (PRL) determinations, and endometrial biopsy in the same cycle to evaluate luteal function in infertility (3, 4). When a luteal defect is diagnosed by endometrial histology, a second biopsy is taken in a later cycle, consecutive whenever possible. Hormones are measured by radioimmunoassay. For assessment of midluteal plasma P levels, three blood samples are obtained between the fifth and tenth postovulatory days, according to basal body temperature. Midluteal plasma P levels higher than 10 ng/ml are considered as normal. Plasma E_2 and PRL are quantitated simultaneously with the second P sampling. The upper limit of normal (mean+2 standard deviations) for PRL in our laboratory is 20 ng/ml.

Hormonal correlates of endometrial luteal phase insufficiency

The endometrial LPI was associated to normal midluteal plasma P in the great majority of cases (table I): 86 % of our infertile patients or women with early repeated abortion. P, E_2 and PRL levels in infertile and aborting patients with defective endometria, were similar to those of patients with normal endometria, and not different from those found in 10 control fertile women (table II).

Thus, midluteal plasma P determination cannot predict the progestational transformation of the endometrium. This is still true when the average of the midluteal P concentrations for each patient are considered according to Abraham's criteria (2), who claims that ovulation and normal luteal function are confirmed when P totals 15 ng/ml or more in three serum samples obtained during an interval from 11 to 4 days prior to the next menstruation. They think this approach is more reliable than taking single blood samples in the midluteal phase. In a previous study, we found that 21.5 % of 200 women (infertile patients and patients with repeated abortion) had an endometrial LPI in two separate cycles in the face of normal P output using Abraham's criteria (7).

This situation characterized by delayed endometrial maturation despite normal plasma P values has been termed «dysharmonic luteal phase» (9). We concur with Gravanis *et al.* (9) that the incidence of this variant of luteal phase abnormality is far more frequent than generally recognized.

The apparent lack of endometrial progestational response may be explained by an end organ defect localized to the endometrial steroid receptors, which has been called «pseudocorpus luteum insufficiency» by Keller *et al.* (12). However, there is no consensus regarding alterations in endometrial P receptor concentrations in patients with LPI. P receptor levels in defective secretory endometrium have been found to be increased, unchanged, or decreased (13). We have recently performed the very first study on sequential endometrial sampling for receptor analysis at multiple points in the same cycle (10).

Table I. *LPI in aborters and infertile patients (5).*

Group	Endometrial biopsy	Plasma P	No.	%
Aborters (n=50)	Normal	Normal	34	68
	Normal	Low	1	2
	Defective	Normal	13	26[a]
	Defective	Low	2	4
Total			50	100
Infertile (n=300)	Normal	Normal	249	83
	Normal	Low	9	3
	Defective	Normal	36	12[b]
	Defective	Low	6	2
Total			300	100

[a] 86.6 % of aborters with defective endometria
[b] 85.7 % of infertile patients with defective endometria

The serial sampling of endometrium in individual patients provided the opportunity to observe progressive changes in receptor levels in a group of patients with and without LPI. Twenty-one ovulatory cycles were studied in fifteen patients. Ten cycles demonstrated LPI diagnosed by a histologic lag in endometrial maturation, normal luteal phase length, and normal plasma P levels. Both normal and LPI cycles demonstrated a maximum amount of endometrial cytosolic P receptor on days 13-15 (periovulatory period) with a significant decrease thereafter. LPI cycles had normal cytosolic and nuclear P receptor levels during the luteal phase of the menstrual cycle, but we found a significant decrease in proliferative phase (days 8-12) endometrial nuclear P receptor in LPI cycles. These findings support the results of ABASSI *et al.* (1) who demonstrated a decrease in total P receptor concentration in the follicular phase in patients with luteal phase defect. This lower concentration of receptor in LPI may reflect inadequate estrogenic induction of the P receptor, and may explain discrepancy between endometrial histology and plasma P determination. Furthermore, this fact stresses the importance of follicular phase determinants in the cause of LPI.

Finally, it should be emphasized that

Table II. *Hormonal levels and luteal phase length (LPL) of the groups studied in table I and controls[a] (5).* Group 1: aborters, defective endometria-normal P; group 2: infertile, defective endometria-normal P; group 3: aborters, normal endometria-normal P; group 4: infertile, normal endometria-normal P; controls: fertile women, normal endometria-normal P

Group	Progesterone (ng/ml)	Estradiol (pg/ml)	Prolactin (ng/ml)	LPL (days)
Controls (n=10)	16.5 ± 3.7	181.7 ± 66.7	7.7 ± 3.4	13.8 ± 1.3
1 (n=13)	15.7 ± 4.2[b]	198.2 ± 80.0[b]	7.5 ± 2.2[b]	12.9 ± 0.9[c]
2 (n=36)	14.9 ± 4.0[c]	210.0 ± 88.6[c]	10.1 ± 4.6[c]	13.4 ± 1.2[c]
3 (n=34)	16.0 ± 4.5[b]	179.2 ± 59.5[b]	9.3 ± 4.8[b]	13.1 ± 1.2[b]
4 (n=249)	17.5 ± 5.1[c]	182.0 ± 64.6[c]	10.5 ± 5.8[c]	13.9 ± 1.3[c]

[a] Mean ± S. D. [b, c] Not significant.

the lack of correlation between plasma P and endometrial histology, is even higher after ovulation induction. Thus, we found a defective endometrial secretory pattern in 42.3 % of patients on clomiphene citrate despite plasma P above normal levels (6). This fact may be explained by the antiestrogenic effect of clomiphene citrate on the endometrium (8).

Resumen

En base a que el endometrio es el elemento diana de la función esteroidogénica del cuerpo lúteo, la biopsia de endometrio ha sido propuesta como el método más exacto de diagnosticar la insuficiencia luteínica. Sin embargo, el análisis de nuestros datos, sobre el estudio de la función luteínica en esterilidad, demuestra que la mayoría de casos (86 %) de defectos progestacionales de endometrio se asocian a niveles normales de hormona (progesterona, estradiol) en plasma. Esta aparente falta de respuesta endometrial a un estímulo hormonal normal, puede explicarse por un trastorno a nivel de los receptores esteroideos endometriales.

Palabras clave: Endometrio, Estradiol, Progesterona, Defecto luteínico, Receptores esteroideos.

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