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Clinical Observations on Luteal Phase Inadequacy

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The inadequate luteal phase still has to be considered a poorly understood clinical entity. Its diagnostic criteria have not been well defined. Consequently, therapy has remained to a large degree empirical.

The defective luteal phase has been defined as a condition in which, presumably due to an inadequate progesterone secretion by the corpus luteum, the secretory transformation of the endometrium is not optimal for the nidation of the blastocyst. Estimations on the frequency of this entity as a cause of infertility vary considerably. Israel (1959) found that curettings of 406 infertile patients showed inadequate secretory transformation of the endometrium in 19%. Since only 3.5% of the cases showed persistent luteal phase deficiency when more than one curetting was examined, it appears that this condition is not a frequent cause of infertility. A somewhat higher figure was reported by Gillam (1965), who estimated that approximately 10% of the infertility patients belong into this category. It is generally agreed upon that the diagnosis cannot be made without the aid of an endometrial biopsy or a curettage. The diagnosis may be corroborated by an analysis of the basal temperature recording or of pregnandiol excretion in the urine. It was stated by Noyes and Hertig (1950) that this diagnosis should be made only if there was a difference of 2 days or more between the dating of the endometrium and the actual date according to the presumptive time of ovulation and the onset of menses.

Material

The present report deals with observations obtained from 53 infertility patients who were seen between January 1967 and March 1, 1969. The presumptive diagnosis of luteal phase inadequacy was based on the following observations: 1. an abnormal basal temperature recording, i.e. hyperthermic phase of 10 days or less, or a curve with a step-wise uncharacteristic rise; 2. histologic examination of the endometrium.

Methods

It was attempted to obtain endometrial biopsies on day 21–22 of the menstrual cycle, presupposing that the rise in the basal temperature curve occurred on day 14. It was felt that a specimen showing a luteal phase defect at the time of implantation would provide a better means for diagnosis than if obtained in the premenstrual phase. For

various reasons it proved to be impossible to adhere strictly to this schedule. In some cases no biopsies could be taken at all. Repeat biopsies were obtained from 3 patients. Endometrial biopsies were performed on patients up to 30 years of age, and older patients underwent full curettage.

Endometrial specimen were fixed in alcohol-formalin, blocked, and cut into sections of 5 μ. The slides were stained with hematoxylin-eosin. Dating of the endometrium was done according to the standards established in 1950 by HERTIG and NOYES. Consequently, the following criteria had to be met for the diagnosis of luteal phase inadequacy. The glandular epithelium varied from cuboidal to cylindrical. Even in the presence of an elevated basal temperature recording subnuclear vacuoles were absent or could be found only in isolated glandular epithelial cells. The lumina of the endometrial glands were rounded; their diameter were wider than usually seen, and there was a remarkable lack of tortuosity in the glands. The glandular lumina were commonly devoid of any secretions. The glands were found to be spaced widely apart, but were also found to lie "dos-à-dos". In some instances abnormal stromal edema was found, and the stroma appeared to be usually rather dense. At times one or several glands with weak secretory activity could be identified. The biopsies were dated according to the onset of menstruation and the presumptive date of ovulation as outlined by MOSZKOWSKI et al. (1962).

Progestin therapy was initiated as a rule on the 4th day after the estimated day of ovulation, i.e. from day 17 through 26 of a normal cycle with ovulation on day 14.

Results

The diagnosis of luteal phase defect (LPD) was assigned according to the results of the endometrial biopsy and the basal temperature record in the following manner:

1. Absolute luteal phase defect: unequivocal histologic findings.
2. Relative luteal phase defect: discrepancy between histologic findings, the day of the cycle, and the onset of bleeding, respectively.
3. Suspected luteal phase defect: a) no biopsy available, abnormal basal temperature recording; b) normal histology, abnormal or normal basal temperature curve.

Age and diagnosis. 53 patients were studied whose age ranged from 24 to 44 years. The mean age was with 31.7 ± 4.8 years significantly higher than the mean age of 60 unselected infertility patients (29.4 ± 4.6 years, $p < 0.01$), and of 60 patients with anovulation (26.4 ± 4.7years, $p < 0.01$). This seems to indicate that the incidence of luteal phase inadequacy increases with age. The correlation between age, diagnosis and results of treatment are summarized in Table I. Primary infertility occurred more often in women under 30 years of age. In the age group beyond 30 years the ratio between primary and secondary infertility was at par. The histologic diagnosis of absolute LPD was made in approximately 50% of all age groups.

Distribution of various types of luteal phase defect:

a) Absolute luteal phase defect: 27 cases out of 53 were considered to meet the criteria of absolute LPD.

b) Relative luteal phase defect: In 15 patients the diagnosis of relative LPD was established. Most of these patients showed a hyperthermic phase of the cycle lasting less than 10 days.

Table I

Distribution of inadequate luteal phase according to age groups and type of infertility

Age group	Number of cases	Infertility		Inadequate luteal phase			
		primary	secondary	absolute	relative	suspected	pregnant on treatment
20–24	2	1	1	1	–	1	1
25–29	19	16	3	10	6	3	4
30–34	18	8	10	9	5	4	9
35–39	11	6	5	5	3	3	6
40–44	3	–	3	2	1	–	–
Total	53	31	22	27	15	11	20

c) Suspected luteal phase defect: 11 times the diagnosis of suspected LPD was made without compatible histologic findings. 3 of these patients were found to have a normal appearing endometrium and a normal biphasical basal temperature curve. They conceived on progestin therapy after sustained infertility. Two other patients of this group conceived on progestin therapy without a biopsy having been obtained prior to therapy. The remaining 7 patients had fairly normal histologic findings, but abnormal basal temperature curves. As will be discussed below, the highest pregnancy rate subsequent to progestin therapy was found in the group with suspected LPD.

Effect of therapy

52 out of 53 patients studied received progestin therapy in the second half of the menstrual cycle. The remaining patient was treated with HCG only. The correlation between the type of progestin and the classification of LPD was incidental.

A. Progestins

1. Dydrogesterone (6-dehydro-retroprogesterone)[1]*:* The majority (46 out of 53) of patients was treated with dydrogesterone in a cyclic fashion. This compound was considered to be an effective progestin with no androgenic or anabolic effects (Schöler, 1960; Schöler, 1962). Unlike most other orally effective progestins, dydrogesterone does not suppress ovulation (Ullery et al., 1962) and does not affect the basal body temperature. This effect is shared by other retroprogesterones.

Dydrogesterone was used in doses of 5–10 mg per day from day 17 through 26 of the cycle for a total of 146 treatment cycles. Because break-through bleeding occurred on dydrogesterone treatment alone, 5 of the 46 patients

[1] Duphaston, Philips-Duphar, Amsterdam (Holland).

received a combination of 10 mg dydrogesterone and 0.02 mg ethinyl-estradiol per day.

13 out of 46 patients conceived on dydrogesterone therapy, and 2 pregnancies were observed when the combination of dydrogesterone and ethinyl-estradiol was used.

In 3 cases repeated endometrial biopsies could be obtained under dydrogesterone therapy. One patient showed improvement, one did not show any change, and in the third patient the result was worse than prior to initiation of treatment. None of these patients became pregnant.

2. *Ro 4-8347*[2] (6-chloro-9β,10α-pregna-1,4,6-triene-3,20-dione): Ro 4-8347 is a retroprogesterone which has been shown to induce ovulation in approximately 45% of carefully selected patients with anovulation (Stamm et al., 1968). 5 patients were treated with 4 mg/day from day 17 through 26 during 7 cycles. This therapy did not result in any pregnancies.

3. *Chlormadinone acetate (6-chloro-6-dehydro-17α-acetoxy-progesterone-acetate)*[3]: Chlormadinone acetate was used in one patient in doses of 4 mg per day beginning one day after the rise of the basal temperature curve. In this case, therapy was not given to facilitate conception but to alleviate profuse vaginal bleeding coincidental with a markedly shortened hyperthermic phase. An endometrial biopsy had not been taken. A pregnancy occurred during the first treatment cycle.

4. *Chlormadinone acetate + ethinyl-estradiol*[4]: This combination therapy was administered to two patients in three treatment cycles (chlormadinone acetate 4 mg, ethinyl-estradiol 0.02 mg/day). One patient conceived during the first treatment cycle.

B. Non-progestational agents

1. *Human chorionic gonadotropin:* Since it was assumed that inadequate stimulation of the corpus luteum by endogenous LH might play a role in the pathogenesis of LPD, HCG was administered to 8 patients for a total of 12 treatment cycles. 5 of these patients had previously failed to respond to dydrogesterone treatment. The remaining 3 were treated with HCG without previous progestin therapy. HCG was applied in the following manner: 10.000 IU HCG were injected on day 12, and 5000 on day 14 of the cycle. In some cases this regimen was continued by daily application of 1500 IU HCG every other day until bleeding or pregnancy ensued.

3 out of 8 patients responded once or more than once with a definitely prolonged hyperthermic phase. One patient with absolute LPD conceived during the first treatment cycle after the injection of 10.000 and 5000 IU HCG respectively. The remaining 4 patients failed to show a discernible response.

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[2] Hoffmann-La Roche & Co. Ltd., Basel (Switzerland).

[3] Gestafortin, Merck AG, Darmstadt (Germany).

[4] Menova, Merck AG, Darmstadt (Germany).

Table II

Pregnancies in successfully treated luteal phase defect

	Luteal phase defect before treatment			
	absolute	relative	suspected	Total
Number of pregnancies	6/27	6/15	8/11	20/53
Dydrogesterone	3	4	6	13
Dydrogesterone + Estrogen	–	2	–	2
Oral Progesterone	–	–	1	1
Oral Progesterone + Estrogen	–	–	1	1
HCG	1	–	–	1
Clomiphene	2	–	–	2
Additional treatment of husband	3	2	2	7
Abortion	1	1	3	5
Still pregnant	1	2	–	3
Healthy infant	4	3	4	11

2. *Clomiphene:* Clomiphene was used for the treatment of luteal phase defect in 2 patients in the dosage of 50 mg/day from day 5 through 9 of the cycle. In both cases biopsies had proven the diagnosis of absolute LPD. Both patients conceived during the first treatment cycle.

C. Outcome of pregnancies

The outcome of pregnancies occurring subsequent to therapy and their relationship to the type of LPD is summarized in Table II. The total pregnancy rate was 20 out of 53 (38%). The highest rate was observed in the poorly defined group of suspected LPD. It is not without interest that the highest relative number of abortions was also found in this group. The lowest pregnancy rate was obtained in the best documented group with absolute LPD (6 out of 27 = 23%).

The partners of 7 out of 20 patients who conceived had been found to have impaired fertility of varying degrees and had undergone treatment. In addition, 12 of the patients who failed to become pregnant had been shown to have either severe pathologic changes of the Fallopian tubes or infertile husbands. This indicates that the observed pregnancy rate has to be interpreted with caution, because it has not been corrected in either direction.

11 patients were delivered of healthy infants at term, including those 2 patients who conceived subsequent to clomiphene administration. 4 patients required a cerclage for cervical insufficiency. 5 pregnancies terminated in abortions.

Comment

Inadequacy of the luteal phase has been considered to be a physiologic condition in the premenopausal female, which possibly could account in

part for the decreased fertility in this age group. It appears, therefore, not to be purely coincidental that the mean age of patients who were believed to suffer from LPD was significantly higher than that of women with anovulation.

The diagnosis of LPD on the basis of histologic examination of the endometrium according to morphologic criteria alone must be considered to be rather problematic. Even biopsy specimens obtained during normal and fertile cycles hardly ever exhibit an overall picture entirely compatible with the day of the cycle. Consequently, the diagnosis of LPD depends largely on the findings of obvious deviations in secretory transformation from the accepted pattern, absent or very weak secretory activity of the endometrial glands being the second most important criterion. This implies that several features of endometrial morphology will have to be assembled into a composite picture before the degree of abnormality can be judged. It is obvious that this leaves a wide margin for subjective interpretations. The histologic examination of endometrial specimens also requires cognizance of the fact that biopsies taken from the lower uterine segment, scanty specimens, or biopsies taken without regard to the rise of the basal temperature curve may be the cause of an erroneous diagnosis of luteal phase inadequacy.

Moszkowski et al. attempted to obtain endometrial curettings as close to the 12th postovulatory day as possible, because they felt that a longer exposure of the endometrium to progesterone would permit a more accurate evaluation of corpus luteum function. In the present study biopsies were taken at an earlier time, i.e. 7–8 days after the presumptive date of ovulation. It was assumed that the appearance of the endometrium at the theoretic time of implantation would be a more meaningful indicator of disturbed function of the corpus luteum than those obtained in the premenstrual phase.

Though progesterone secreted by the corpus luteum after ovulation is responsible for the hyperthermia during the second phase of the cycle, no strict correlation between an abnormal basal temperature recording and deficient progesterone secretion has yet been established. The significance of findings, such as delayed or step-wise rise of the basal temperature curve, as criteria for luteal phase inadequacy is open for question. Similar recordings were also seen in many healthy women with proven fertility who had volunteered for participation in various projects of clinical investigation. On the basis of our data it appears that the most constant findings in the basal temperature recordings justifying the presumptive diagnosis of LPD is a constantly shortened period of hyperthermia of less than 10 days observed during 2–4 cycles.

There is at present no indication that LPD represents an etiologic entity. Inadequate stimulation of the corpus luteum by LH, insufficient response of this organ to normal LH-levels, or abnormal ovarian enzymatic patterns might contribute to impaired steroidogenesis, which will be reflected by an abnormal endometrial morphology. It is also of considerable consequence

that the synthesis of estrogens might be affected as well as that of progesterone.

As the histologic morphology of the endometrium allows only very limited insight into its functional state, considerable effort has been expended on investigations of enzymatic activities during normal and disturbed cycles (Schmidt-Mathiessen, 1963; Luh and Brandau, 1967). It could be shown by several investigators that the endometria of infertile women contain significantly less glycogen than endometria of fertile women (Zondek, 1940; Vacek, 1960; Hughes, 1963). The highest activity of various enzymes was found at the beginning of the luteal phase at the inner surface of the endometrial glands, and glycogen synthesis could be closely correlated to changes of enzymatic activities under the influence of ovarian steroid hormones (Luh and Brandau, 1967).

It can be assumed that impairments of enzymatic activities and of glycogen synthesis will precede the appearance of morphologic alterations in the endometrium which are at present thought to be indicative of LPD. This might explain to a certain extent the relatively large number of pregnancies obtained in the group of patients with suspected LPD, some of whom actually had morphologically normal endometria. Contrary to this, the lowest pregnancy rate was found in patients with endometrial pathology interpreted as absolute LPD.

It is not without interest to note that two patients who conceived following clomiphene treatment were considered to have had absolute LPD. Neither one had responded previously to 3 and 5 cycles of progestin therapy respectively. The possibility cannot be ruled out that these patients were actually anovulatory, and the incomplete secretory transformation of the endometrium had been caused by a luteinized follicle.

The results of this study showed clearly that the presently available diagnostic criteria for LPD are grossly inadequate. This was illustrated by the findings that only 50% of the cases showed unequivocal histologic findings. Since more than one half of the patients with relative or suspected LPD became pregnant on replacement therapy, it may be postulated that there was insufficient progesterone secretion from the corpus luteum to some degree.

Dydrogesterone had been chosen as the main therapeutic agent because it does not have a centrally inhibiting or hyperthermic effect. Because the basal temperature curve remained unaffected by its administration, it proved to be possible to diagnose pregnancy very early by means of a steep rise of the basal temperature curve to a higher plateau. Since it was felt that all patients conceiving after LPD should receive replacement therapy with progestins for several months, the possibility of diagnosing early pregnancy offered an obvious advantage.

Since only a few cases were treated with other progestins, ethinyl-estradiol, and HCG, no comparison could be drawn in respect to the efficacy of the different therapeutic regimens. We are concluding that the data obtained

from the study of 53 patients with presumptive LPD, who were treated with various forms of replacement therapy, strongly indicated that the existence of the LPD as a clinical entity appears acceptable as a working hypothesis.

Summary

53 infertility patients, aged 24 to 44, who were diagnosed as suffering from luteal phase defect (LPD) by means of endometrial biopsies and basal temperature records, were studied. The findings were classified as 1. absolute LPD (27 cases), 2. relative LPD (15 cases), and 3. suspected LPD (11 cases).

17 of the 53 patients conceived on progestin replacement therapy, 2 on clomiphene, 1 on HCG. The uncorrected overall pregnancy rate was 38% (20 women).

Most patients were treated with dydrogesterone in doses from 5 to 10 mg per day from day 17 through 26 of the cycle. The results of this study and factors possibly contributing to the etiology of the complex syndrome of LPD were discussed.

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