LUTEAL PHASE DEFICIENCY—AN IMPORTANT CAUSE OF FEMALE INFERTILITY

By

SUBHASH C. SHARMA, R. C. RAY AND S. SEN

SUMMARY

Luteal phase deficiency (LPD) is an uncommon cause of infertility in females. Endometrial biopsy from 600 infertile women was studied. Serum prolactin, estradiol and progesterone values were estimated. Eighty (13.3 per cent) had LPD. They also had significantly low serum progesterone. The findings have been discussed.

Introduction

The concept of luteal phase deficiency (LPD) is not yet fully clear. It was first described in 1949 and is often associated with infertility, recurrent miscarriage and occult miscarriage (Jones, 1949, Seppala *et al*, 1978 and Harta *et al*, 1977). Terms such as 'Short', 'inadequate' or 'defective luteal phase' are often used to describe it. It is uncommon and the incidence varies from 3.4 to 5 per cent of infertile women (Jones *et al*, 1970). Despite controversy, the endometrial biopsy remains the main mode of diagnosis as it is reproducible and provides adequate histologic evidence of endometrial development and bioassay evidence of adequate progesterone output.

The main purpose of this study is to ascertain the incidence of the defect in a series of infertile patients, to determine whether more reasonable, guidelines might be established for taking the biopsy, and to test the criteria that two biopsies must be out of phase for the diagnosis.

From: Command Pathology Laboratory (CC) P.O. Dilkhusha, Lucknow-226002.

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Patients and Methods

Six hundred patients presenting with primary infertility underwent 760 endometrial biopsies as part of a routine infertility evaluation. All were below 31 years of age (mean 24.3 years). Both the partners had been thoroughly investigated.

Endometrial biopsy was performed on day 23, 24, or 25 of the cycle, as ascertained by history. A biopsy was obtained only to date the endometrium, and was not taken if menstruation was overdue or ovulation suspected. The biopsy was taken from the fundus and the tissue was examined for quantitative adequacy before being fixed in 10 per cent buffered formalin saline. Routine processing was performed. Histologic evaluation was carried out according to the criteria of Noyes *et al* (1950).

Patients were asked the expected date of onset of her next menses, arbitrarily

called day 28. Counting backward from the onset of menses, defined the expected endometrial date of biopsy; the histologic readings of the endometrium were compared with this expected date. If the histologic reading lagged the expected date by two or more days, the biopsy was diagnosed as out of phase (OOP). When a biopsy was OOP, the patient was requested to report for a biopsy in the next cycle. Diagnosis of LPD was made only if two biopsy readings were greater than 2 days out of phase in two different cycles.

Serum prolactin, estradiol and progesterone estimations were done in all cases, by the standard radio immunoassay technique, at the time of performing an endometrial biopsy.

Results

Endometrial evaluation was carried out in 600 patients complaining of infertility. Among 600 patients, the initial biopsy was in phase in 428 (71.3%), out of phase in 160 (26.6%) and could not be classified in 12 cases (Table I).

Of 160 patients with out-of-phase first biopsy, all underwent a second biopsy. 76 of these were in phase; review of the first biopsy showed a substantial lower segment tissue in 52 and in 24 the biopsy was taken too early. Four patients were biopsied in the cycle of conception. Eighty patients (13.3%) were thus identified as having luteal defect by the biopsy criteria. Three well defined histologic patterns were recognised.

(i) The first pattern was that of a very thin endometrium, with few and scattered glandular tubules, low glycogen concentration in the tubular epithelium and spiral arterioles with thin walls. This pattern, observed in four patients, appears to indicate a defect in both follicular and luteal activity. These had low estradiol

TABLE I
Endometrial Biopsy in Infertility

Biopsy result	Initial biopsy					Second biopsy			
	n	Per cent	Prolactin ng/ml	Progesterone ng/ml	Estradiol pg/ml	n	Prolactin ng/ml	Progesterone ng/ml	Estradiol pg/ml
In phase	428	71.3	8.1 ± 2.3	7.5 ± 2.1	45.3 ± 6.5	76	7.8 ± 1.9	7.0 ± 2.3	47.2 ± 7.5
Out of phase	160	26.6	9.2 ± 1.9	4.2 ± 2.7	42.8 ± 7.2	80	8.3 ± 2.1	2.5 ± 1.9	41.9 ± 6.9
Not classified	12	2.1	8.6 ± 2.1	8.1 ± 2.2	48.2 ± 7.9	4	7.9 ± 2.2	6.5 ± 2.9	45 8 ± 6.2
Total	600	100	—	—	—	160	—	—	—

values (31.2, 35.4, 41.9, 37.2 pg/ml respectively). The level, however, was not significantly low as compared to other groups (Table I).

(ii) A delay of endometrial maturation of atleast 2 days with abnormal distribution of intracellular glycogen, minimal intraluminal secretion, and persistent or predominent estrogen influenced endometrium was the most commonly encountered pattern. It was seen in 40 patients.

(iii) A third histologic pattern, observed exclusively in cycles with short luteal phase, consists of few but enlarged glands and stromal edema. The glands contained a small quantity of intraluminal glycogen. The individual cells were small, clongated or reticular. The spiral arterioles were sparse and poorly differentiated. This pattern was noted in 36 cases.

These 80 patients were diagnosed to have LPD on the basis of two biopsies out of phase greater than 2 days in two cycles. No predisposing aetiology suggesting a risk of LPD could be found. There were no 'failed' biopsies, in which biopsy was attempted and adequate tissue for evaluation not obtained.

Serum prolactin, estradiol and progesterone levels were also estimated in all these cases at the time of endometrial biopsy. Thus 760 serum samples were available for assay. Prolactin was within normal limits and no significant difference was recorded between the groups (Table I). Low serum estrogen was noted only in 4 patients showing type one histological pattern as above. Serum progesterone was low in those with out of phase endometrium. The difference was more striking in the group within the out of phase patients who were subjected to a second biopsy. The progesterone was significantly low ($P>0.05$) in the OOP group when compared with those having in phase second biopsy. (Table I).

Discussion

An overall 13.3% (80 out of 600 patients) incidence of LPD was detected by late luteal phase endometrial biopsy in an otherwise unselected series of infertile patients. In this series an endometrial biopsy was taken mainly to date the endometrium, and was not used to determine that ovulation had presumptively occurred or to diagnose endometrial hyperplasia. The main indication for endometrial biopsy was to make the diagnosis of luteal phase inadequacy as described by Jones (1976), using the histologic criteria of Noyes *et al* (1950). All the patients of LPD also had low serum progesterone levels indicating a state of luteal deficiency (Table I).

The 13.3% incidence slightly exceeds the usually described incidence of 3 to 5%, and possibly reflects the inherent bias of a patient population selected to include a high percentage of patients with menstrual and ovulatory dysfunctions, and some with miscarriage.

An increased incidence of the defect has been reported in patients with hyperprolactinemia (Del Pozo E., 1979), with recurrent abortions (Harta *et al*, 1977); at the extremes of reproductive life and taking clomiphene citrate (Garcia J. *et al*, 1977). All these cases were excluded from the protocol. Serum prolactin levels were measured in all patients and were found within normal range. This probably suggests hypoprolactinemia as an uncommon cause if at all, of luteal phase deficiency.

Although the LPD may occur sporadically, there was remarkable consistency between the first and subsequent biopsies. If the first out of phase biopsy con-

tained adequate tissue taken from the fundus (not from the poorly vascularised lower segment), then the subsequent biopsy was also likely to be abnormal. Similarly, patients with an in phase first biopsy, more likely had an in phase subsequent biopsy, unless some identifiable change had occurred such as ovulation induction.

The data demonstrates that the endometrial biopsy is a safe, well tolerated and reproducible procedure. The importance of adequate evaluation of the endometrial tissue is important. Biopsies containing substantial endometrial tissue from the lower segment are usually out of phase, whereas tissue from fundus in the same patient may well be in phase. Same strip of tissue frequently contains both fundal and lower segment tissue and allows this distinction to be made; This emphasizes the necessity for dating the latest and most developed tissue. Also the biopsy should be taken in the late secretory phase to allow full endometrial development; the tissue then reflects the entire progesterone output in the cycle, and is a bioassay of progesterone output. Biopsies taken more than six days before onset of menses were more frequently out of phase; in subsequent cycles, biopsies taken closer to expected menses were in phase. Alternatively, the possibility of local defects in endometrial response could be postulated irrespective of progesterone output (Keller *et al*, 1979) as only biopsy can document the presence of an appropriate endometrial development for implantation.

The etiology of LPD is not yet fully understood. Disturbances in hypothalamo-hypophyseal axis and ovarian function alone or in combination may play an important role. The presently accepted criteria of LPD, however, are low progesterone, discordant endometrial dating and infertility. Whether or not a diagnosis of luteal phase deficiency has any important impact on future fertility or whether therapy of the disorder increases the chances for conception and normal delivery are too early to answer and needs long term studies.

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