

THE IMPORTANCE OF LUTEAL PHASE DEFICIENCY AS A CAUSE OF INFERTILITY IN PRIVATE PRACTICE—A PRELIMINARY REPORT

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Abstract

The incidence of luteal phase deficiency (LPD) in a series of 100 consecutive patients with regular menses with at least 1 year infertility was determined. 86 patients had LPD and 44 had LPD and no other infertility factor. We required the endometrial biopsy to be out of phase in only 1 of 2 cycles to establish the diagnosis. The patients with pure LPD were divided into those with immature follicles (16) and 14 achieved a pregnancy within 6 months following treatment with ovulation-inducing drugs and progesterone vaginal suppositories (PVS); 3 patients had luteinized unruptured follicle syndrome (LUF) and 2 pregnancies occurred following hCG and PVS; 25 patients had pure LPD and 22 conceived following PVS therapy only. LPD should thus be carefully evaluated in all infertility patients even with other apparent causes since it appears to occur frequently in private practice.

Introduction

The incidence of luteal phase defects (LPD) as a cause of infertility has been approximated at 3.5 percent.¹ Traditionally the standard diagnosis requires that the defect be diagnosed in 2

consecutive cycles. However, there is some question as to how accurate is the biopsy as originally defined- ie. there may be more subtle defects that can be determined by the endometrial biopsy; or in contrast, a slightly out of phase endometrial biopsy may not be associated with infertility.

We decided to test the hypothesis that the treatment of LPD may improve fertility results even if only 1 of 2 endometrial biopsies dated out of phase.

The incidence of LPD as determined by at least one of a potential 2 endometrial biopsies in the late luteal phase to be 2 or more days out of phase was evaluated in 100 patients presenting for evaluation of infertility and the success of therapy as evidenced by achieving a pregnancy as a result of therapy was then determined.

Materials and Methods

One hundred patients were enlisted who had a minimum of 1 year infertility and whose menstrual cycle interval did not vary each month by more than three days.

The endometrial biopsy was dated according to the criteria of Noyes et al.² LPD was diagnosed if the biopsy performed in the 1st cycle dated more than 2 days early. Those patients diagnosed as having LPD were further subdivided into 3 groups on the basis of pelvic sonography³⁻⁴ and serum estradiol (E2) and progesterone (P) assays. A patient with LPD who in neither of 2 evaluation cycles formed a "mature" follicle with an 18-24 mm diameter nor had a serum estradiol over 200 pg/ml was considered as having LPD secondary to an immature follicle. LPD patients forming a mature follicle

but where this follicle enlarged 2-3 days later associated with a drop in the serum E2 level and a rise of P over 1 ng/ml associated with regression of the cervical mucus were considered to have LPD associated with the luteinized unruptured follicle syndrome (LUF). LPD patients making a mature follicle and demonstrating the rupture of follicles by ultrasound findings were considered as having "pure" LPD.

Patients with immature follicles were treated with either bromocriptine if the serum prolactin was elevated, or clomiphene citrate (beginning at 50 mg/day for 5 days titrating until a mature follicle was achieved, or human menopausal gonadotropins (hMG) if clomiphene therapy was complicated by uncorrectable mucus or premature luteinization). The objective, no matter which ovulation drug was chosen, was to try to achieve one (and hopefully not more than 2) follicle of 18 mm size with a serum E2 of a minimum of 200 pg/ml per follicle.

If the LUF syndrome was diagnosed in one cycle they were given one more chance without therapy. If failure to release the ovum occurred in 2 consecutive cycles then hCG 10,000 units was given in the 3rd cycle when the follicle was 18-24 mm, the serum E2 was over 200 pg/ml and the serum P was under 1 ng/ml. If this failed then the next cycle at the same maturation of the follicle a combination of 15,000 units hCG and 150 IU periovulatory was given.

Each patient in the pure LPD group was started on 25 mg two times daily progesterone suppositories beginning 3 days after ovulation. The dose was titrated up by 25 mg each cycle until the

biopsy in the late luteal phase dated appropriately.

Post-coital tests were performed 6-12 hours after intercourse at the time of a mature follicle. An abnormal test was considered if there was less than 5 sperm per high powered field with forward progressive motion. A semen analysis was considered abnormal if there was less than 20×10^6 sperm per cc, or if the motility was less than 60%, grade 3 of 4 quality or a volume under 1 cc. Either a hysterosalpingogram or laparoscopy was performed to exclude a tubal factor or endometriosis.

Results

A total of 86 patients were found to have LPD of which 36 were found to have an abnormal endometrial biopsy on the 2nd but not the 1st one; the 1st biopsy was abnormal in 50 patients. Thirty-two of the 36 patients with immature follicles had LPD diagnosed on the 1st cycle.

Forty-four patients out of 100 consecutive patients were found to have LPD without other associated infertility factors, 42 patients had LPD plus at least one additional infertility factor, 13 patients had some infertility factor other than LPD and in 1 patient the cause for infertility was unknown. Those patients with LPD were further divided into 3 categories of LPD secondary to immature follicles, LPD secondary to LUF syndrome, and pure LPD as seen in Table I. Thirty-six percent (16/44) of women with exclusively LPD problems had immature follicles, 6.8% (3/44) LUF syndrome and 57% (25/44) pure LPD; whereas 47% (20/42) of patients with LPD associated with other infertility factors had immature follicles, 16% (7/42) LUF syndrome and 34% (15/42) pure LPD.

Table I. The distribution of luteal phase defects and success of therapy based on follicular dynamics and estradiol and progesterone levels.

	LPD only	LPD + Other Factor	No LPD, Just other factor	Unexplained	
TYPE OF LUTEAL PHASE DEFECT	Total Patients	44 (38)*	42 (26)	13 (11)	1 (0)
	LPD with immature follicle	16 (14)	20 (14)		
	Pure LPD	25 (22)	15 (9)		

* The number in parenthesis indicated the number pregnant

The patients with LPD conceived as follows: 87% (14/16) of the patients with immature follicles; 88% (22/25) of patients with pure LPD conceived within 6 months; 67% (2/3) of the LUF cases conceived. Eight patients with immature follicles were treated with clomiphene citrate, 6 patients with hMG and 2 patients with bromocriptine. All pure LPD patients were treated with progesterone suppositories only. Life table analysis of the groups with immature follicles is seen in Table 2. The LUF group is not included because of small numbers.

Pregnancies in the 42 patients with LPD and other infertility factors were as follows: 70% (14/20) of patients with immature follicles achieved a pregnancy within 6 months, whereas 43% (3/7) with LUF syndrome conceived and 60% (9/15) of patients with pure LPD conceived. Thirteen patients were found to have other associated infertility factors but no LPD; 84% (11/13) conceived within 6 months

after correcting the other infertility causes. Only 1 patient had unexplained infertility and she did not conceive.

Table II. Life table analysis of treatment of luteal phase defect in infertility patients.

<u>LPD with Immature Follicle</u> (and no other problems)					
# of cycles	# of pts	pregnancies achieved	pt months of treatment	preg rate/ month	cumulative prob. of pregnancy
1	16	4	14	0.29	0.29
2	12	3	7.5	0.4	0.58
3	9	4	7	0.57	0.82
4	5	2	4	0.5	0.91
5	3	0	3	0	0.91
6	3	1	2.5	0.4	0.96

<u>Pure Luteal Phase Defects</u> (and no other problems)					
# of cycles	# of pts	pregnancies achieved	pt months of treatment	preg rate/ month	cumulative prob. of pregnancy
1	25	6	22	0.27	0.27
2	19	6	16	0.37	0.55
3	13	9	8.5	1.0	1.0
4	4	0	4	0	1.0
5	4	0	4	0	1.0
6	4	1	3.5	0.28	1.0

Discussion

The incidence of LPD in this series of 100 infertility patients

was quite high. The group was composed of a predominantly middle-class population. The exact percentage is not so important as the fact that at least in a private environment LPD may be a significant factor in infertility and should be evaluated in all patients with regular menstrual cycles even if there is already discovered some other infertility factors. Our practice co-exists with many other infertility practices in the city and this may have biased patient selection. In fact we calculated that these patients had seen 1.9 previous infertility specialists prior to coming to our office. This may explain our significantly higher frequency of LPD in our infertility population along with our modified definition requiring only 1 of 2 cycles to be abnormal for the diagnosis.

Fifty-five of 100 patients were found to have a problem with either male factor, cervical factor, or tubal factor. However, 76% (42/55) of these patients were found to have LPD coexisting with other infertility factors. The 67% pregnancies (26 + 11/55) achieved in this group in 6 months may have been significantly less had LPD not been identified and treated also. However, since a matched control group treated for all other infertility factors except LPD was not provided, one can only speculate as to whether the percent of conceptions would have been less if LPD was left untreated.

Even though 86% (38/44) of patients with LPD as the exclusive cause of infertility achieved a pregnancy within 6 months, one cannot be sure that a placebo would not have been just as effective. Several studies have indicated that the normal pregnancy rate per month is 17-21%⁵ and with artificial insemination by donor 25%.⁶ The life table analysis seen in Table 2 of patients treated

exclusively for LPD demonstrates a higher pregnancy rate per month than would normally be expected in a "fertile" population and this is illustrated in Figure 1.

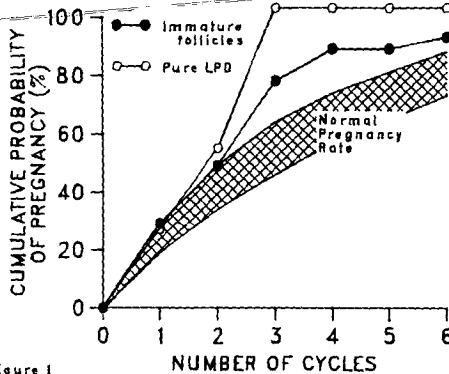


Figure 1

Cumulative probability of pregnancy as determined by life table analysis in patients with immature follicles versus Pure Luteal Phase Defects. The normal pregnancy rate was assumed to be 17-25% on the basis of other reports.⁷

The separation into 3 types of LPD has been an effective means in our practice of deciding who needs an ovulation-inducing drug and who needs human chorionic gonadotropin (hCG) and who only needs progesterone. The somewhat arbitrary definition of an immature follicle as one that never achieves a size of 18 mm or a serum estradiol level of 200 pg/ml was based on studying these levels in a large fertile population. Nevertheless, this study was not designed to demonstrate that this division and subsequent treatment is essential for treating LPD. For example, in a patient with LPD and an immature follicle treated with clomiphene and progesterone suppository (PVS) we cannot categorically state that PVS alone

might not have helped to achieve the pregnancy nor can we say that clomiphene alone might not have helped achieve a pregnancy in the patients labelled as "pure" LPD. Our preliminary data indicates that a randomized study is now needed to determine if treatment based on the division into LPD with immature follicles versus pure LPD is helpful in determining the most effective therapy or would all therapies be effective.

Thirty-six patients had an abnormal biopsy in the 2nd cycle but not the 1st. If one assumes a similar number would have had an abnormal 1st one but not the 2nd (we did not perform a 2nd if the 1st was abnormal) then perhaps only 14% would have been considered as having LPD by normal criteria. Each woman had a minimum of 1 year of infertility and in fact the average years of infertility was 2.4 years.

If an "in phase" biopsy indicates everything normal than those patients with no other factor than LPD as the cause of infertility should have conceived without treatment within a year since theoretically they would have had approximately 6 normal cycles. We hypothesize that the "normal endometrial biopsy" is not sensitive enough to determine subtle abnormalities in the luteal phase which is still sufficient to interfere with conception and may be corrected by supplemental progesterone. Another possible hypothesis is that the outlined treatment of LPD improves fertility by some other means than by correcting LPD. Because of the lack of proper controls in this preliminary report, the possibility of a placebo effect cannot be excluded.

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