

Ovulation-Inducing Drugs Versus Progesterone Therapy for Infertility in Patients with Luteal Phase Defects

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ABSTRACT: The efficacy of ovulation-inducing drugs (OVI) for treating infertility related to luteal phase defects (LPD) was compared with the efficacy of progesterone vaginal suppositories (PVS). Patients were divided into two groups: (1) LPD secondary to immature follicles and (2) pure LPD, in which the follicle was mature. Twenty-four of 31 women (77%) with pure LPD conceived (one aborted) during the first 6 months, compared with only 3 of 27 (11%) treated with OVI—and 2 of 3 aborted. However, in women with LPD secondary to immature follicles, 14 of 20 (70%) treated with OVI and PVS conceived (and one aborted) compared with 7 of 10 conceiving (70%) with OVI only (four aborted), and 3 of 12 conceived (25%) with PVS only (none aborted). Thus, both PVS and OVI are effective in treating LPD; follicular maturation studies help determine the proper choice. PVS appears to decrease the risk of abortion in both categories.

INTRODUCTION

LUTEAL PHASE DEFECT (LPD) IS A KNOWN cause of infertility. The treatment remains controversial, with some physicians recommending ovulation-inducing drugs, e.g., clomiphene citrate,¹⁻⁴ whereas others recommend progesterone.⁵⁻⁷ Theoretically, LPD may be a disorder of follicular maturation, or follicular maturation may be normal, but corpus luteum function may yet be abnormal. A study was performed to determine if the efficacy of therapy of infertility related to LPD could be enhanced by basing therapy on the maturation

of the follicle, i.e., the use of ovulation-inducing drugs (e.g., clomiphene or hMG) if the follicle never reached a minimum size of 18 mm or if serum estradiol (E₂) never reached 200 pg/mL at the time of the maximum-sized follicle; or the exclusive use of progesterone vaginal suppositories (PVS) when the follicle was apparently mature but LPD existed.

MATERIALS AND METHODS

One hundred consecutive patients with LPD, who did not have the luteinized unruptured follicle syn-

drome, were enlisted. All had a minimum of 1 year of infertility, no other apparent infertility problem, and a menstrual cycle that did not vary each month by more than three days. LPD was diagnosed if the late luteal phase endometrial biopsy dated two or more days early.⁸ Those patients diagnosed as having LPD were further subdivided into two groups on the basis of pelvic sonography⁹⁻¹⁰ and serum estradiol (E₂) and progesterone (P) assays. A patient with LPD who in neither of two evaluation cycles formed a "mature" follicle with an 18-24-mm diameter nor had a serum E₂ level over 200 pg/mL was considered as having LPD secondary to an immature follicle. LPD patients producing a mature follicle and demonstrating the rupture of follicles by ultrasound were considered as having "pure" LPD (second group). Patients with the luteinized unruptured follicle syndrome (LUF) would be eliminated from the study.

Patients with immature follicles were treated initially with PVS, clomiphene citrate (CC), or CC and PVS. The CC dosage was started at 50 mg/day for five days and titrated upward until a mature follicle was achieved, or switched to human menopausal gonadotropins (hMG) if CC therapy was complicated by uncorrectable cervical mucus or premature luteinization. The objective, no matter which ovulation drug was chosen, was to try to achieve one (and not more than two) follicle of 18 mm, with a minimum serum E₂ of 200 pg/mL per follicle of 18 mm size or more.

Those patients with LPD and immature follicles were treated with PVS if the first and last digit of their social security number ended in an even number, with clomiphene if the first and last digits were odd numbers, and clomiphene and PVS if the first and last digits were odd and even or vice versa. Those patients diagnosed as having pure LPD were treated with PVS if the last digit of their social security number was even and clomiphene if it was odd.

We had decided that after 6 months we would evaluate the results of the various therapies for the two different types of LPD and treat the women not achieving pregnancies and those having spontaneous abortions with the specific therapeutic regimen that was found to be most effective during the first 6 months.

Those patients using PVS were started on 25 mg twice daily beginning three days after ovulation. The dose was titrated up by 25 mg each cycle until the biopsy in the luteal phase dated appropriately. Because the PVS therapy could delay menses, the

dating was based on the time of ovulation by ultrasound rather than onset of next menses. All other infertility factors were required to be within normal limits.

The serum P level prior to therapy was required to be at least 10 ng/mL 1 week before the expected menses. For this study, a patient with hyperprolactinemia was not treated with bromocriptine.

RESULTS

Fifty-eight women were found to have pure LPD and 42 had LPD secondary to immature follicles. Initially 31 patients with pure LPD were treated with PVS, whereas 27 were treated with clomiphene or hMG. The 42 patients with LPD secondary to immature follicles were initially treated as follows: (1) 20 patients with clomiphene or hMG and PVS; (2) 12 with PVS only; (3) 10 with clomiphene only or hMG only.

The results of the first 6 months of therapy are seen in Table I. Twenty-four of the 31 patients (77%) with pure LPD treated with PVS achieved a pregnancy, and one had a spontaneous first-trimester abortion. However, only 3 of 27 women (11.1%) with pure LPD treated with ovulation-in-

TABLE I
Luteal phase defects divided into categories of immature follicles and mature follicles and the results of different treatment combinations of progesterone vaginal suppositories and ovulation-inducing drugs.

	I		II	
A. Pure LPD-58				
Rx PVS	31(24-1)	Rx OVI & PVS	6(2-0)	
Rx OVI	27(3-2)	Rx PVS	25(16-1)	
B. Immature follicles				
Rx OVI & PVS	20(14-1)	Rx OVI & PVS	5(1-0)	
Rx PVS only	12(3-0)	Rx OVI & PVS	9(7-1)	
Rx OVI only	10(7-4)	Rx OVI & PVS	6(4-0)	

OVI = ovulation-inducing drugs; PVS = progesterone vaginal suppositories.

LPD = luteal phase defect; Rx PVS = treated with progesterone vaginal suppositories; Rx OVI = treated with ovulation-inducing drug clomiphene or human menopausal gonadotropins. The number to the left of the brackets indicates the total number of patients treated with a given therapy. The number on the left in the brackets indicates the number achieving a pregnancy in 6 months and the number to the right in the brackets indicates the number of spontaneous first-trimester abortions. I indicates patients treated during the first 6 months of study. II indicates the patients treated during the second 6 months of study (patients who failed in first 6 months).

Total no. of patients with LPD = 100.

ducing drugs became pregnant, and two had first-trimester spontaneous abortions. The probability that chance alone would have produced these results was quite low by chi-square analysis ($P < .001$).

The pregnancy results in those women with LPD and immature follicles were as follows: 14 of 20 (70%) treated with ovulation-inducing drugs and PVS achieved a pregnancy, and one spontaneously aborted; 7 of 10 (70%) treated with ovulation-inducing drugs alone conceived, but four aborted, whereas only 3 of 12 women treated with PVS alone conceived—but none aborted. The probability that the improved fertility results (counting deliveries only) of ovulation-inducing drugs and PVS were purely due to chance when compared with those treated with ovulation-inducing drugs, or PVS alone when compared with those treated with ovulation drugs or PVS only was as follows: $P < .01$ in the former and $P < .025$ in the latter by the chi-square test. The difference between PVS and ovulation-inducing drugs for LPD with immature follicles was not statistically significant.

There were only 4 spontaneous abortions out of 71 pregnancies (5.6%) in women taking PVS, whereas there were 6 losses out of 10 (60%) in patients conceiving with clomiphene or hMG alone; the difference was highly statistically significant ($P < .001$).

Table I also indicates the results of the second 6 months of therapy given to those women who failed to conceive during the first 6 months. The therapy offered in each of the two categories was the specific therapy demonstrating the best results during the first 6 months.

There were 27 patients with pure LPD treated with ovulation-inducing drugs, and only one had a successful delivery. Twenty-five of the remaining patients were treated with only PVS, and 16 of 25 (62%) became pregnant; only two had first-trimester abortions. There were only six successful deliveries among 22 women with LPD and immature follicles treated with either ovulation-inducing drugs alone or PVS alone. When given both during the next 6 months, 10 of 16 (62%) achieved a pregnancy, with only one abortion. The probability that

TABLE II
Life-table analysis of treatment of luteal phase defect in infertility patients—
first 6 months.

<i>LPD with Immature Follicle (and no other problems):</i>					
<i>Treatment with Ovulation-Inducing Drugs and PVS</i>					
<i># of Cycles</i>	<i># of Pts</i>	<i>Pregnancies Achieved</i>	<i>Pt-months of Treatment</i>	<i>Preg Rate/month</i>	<i>Cumulative Probability of Pregnancy</i>
1	20	4	18	0.22	0.22
2	16	4	14	0.29	0.44
3	12	3	10.5	0.29	0.60
4	9	0	9	0	0.60
5	9	2	8	0.25	0.70
6	7	1	6.5	0.15	0.75
<i>Pure Luteal Phase Defects (and no other problems):</i>					
<i>Treatment with PVS only</i>					
<i># of Cycles</i>	<i># of Pts</i>	<i>Pregnancies Achieved</i>	<i>Pt-months of Treatment</i>	<i>Preg Rate/month</i>	<i>Cumulative Probability of Pregnancy</i>
1	31	6	28	0.21	0.21
2	25	8	21	0.38	0.51
3	17	7	13.5	0.52	0.77
4	10	1	9.5	0.11	0.79
5	9	1	8.5	0.12	0.82
6	8	1	7.5	0.13	0.84

the improved results demonstrated during the last half year were due to chance alone was $P < .001$ using chi-square analysis in the pure LPD category and $P < .005$ in LPD secondary to immature follicles.

A life-table analysis comparing the cumulative probability of pregnancy in patients given the "appropriate" therapy for their type of LPD during the first 6 months with the "normal" pregnancy rate is shown in Table II and Figure 1.¹¹ The normal pregnancy rate was assumed to be between 17 and 25% on the basis of other reports.¹²⁻¹³ The patients with pure LPD treated by PVS exclusively and the women with LPD secondary to immature follicles treated by an ovulation-inducing drug plus PVS had a greater cumulative probability of pregnancy than would be expected for the normal population.

DISCUSSION

A study was designed to determine if an effective therapeutic regime for the treatment of LPD as a cause of infertility could be based on follicular maturation theories. Two separate types of LPD were hypothesized: (1) LPD secondary to release of an ovum from an immature follicle or an insufficient estradiol level to generate adequate progesterone receptors and thus possibly an immature ovum that

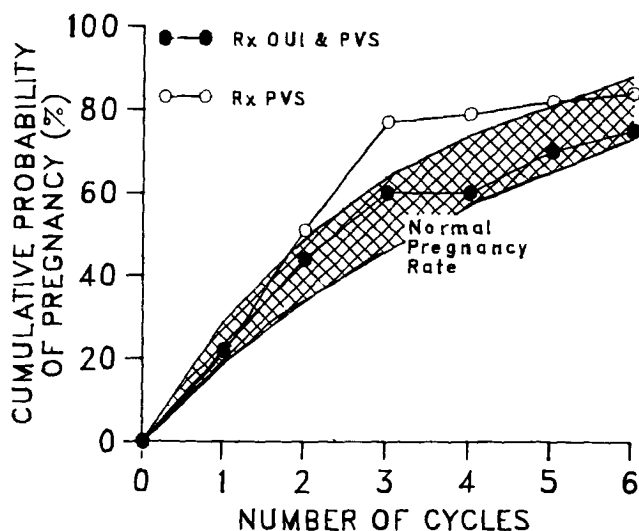


FIG 1: The two groups with the best pregnancy rates compared to the normal pregnancy rate. LPD with immature follicle group treated by ovulation-inducing drugs in follicular phase; progesterone vaginal suppositories (PVS) in luteal phase. Pure LPD group treated by PVS only in luteal phase.

may not be fertilizable, or (2) pure LPD, in which the ovum is mature but the corpus luteum specifically is defective.

The results demonstrated a high success rate using only PVS for pure LPD and ovulation-inducing drugs and PVS for LPD associated with immature follicles. PVS seemed to reduce spontaneous abortions.¹² In fact, despite a minimum of one year of infertility, the cumulative probability of pregnancy was even greater than predicted for a normal fertile population.

Downs and Gibson⁴ found a better success with clomiphene, the worse the mid-luteal phase serum P level and, in addition, greater success with PVS the better the serum P level. We required that there be included in the study a mid-luteal phase serum P level of at least 10 ng/mL. This may account for the higher percentage (52/90 = 58%) of patients with pure LPD in this study than with immature follicles (42%). If one could make the supposition that the more immature a follicle is at the time of ovum release, the less likely the resultant production of P by the corpus luteum would be, then we could well understand from our data how Downs and Gibson were able to reach their conclusions.

Cross-over studies demonstrated a high degree of success in the patients with pure LPD who failed with ovulation-inducing therapy and were now treated with PVS (19 live births out of 26). Similarly, in 16 therapeutic-failure patients with immature follicles now treated for the first time with ovulation-inducing drugs and PVS, 12 of 16 delivered a live baby (75%).

Our definition of a mature follicle was based on evaluating over 1,000 cycles in fertile women. Though somewhat arbitrary, this definition seems to provide a basis for finding a rational approach to determining the appropriate initial therapy for LPD. Nevertheless, though not proven by this study, we feel that should the couple with pure LPD not achieve a pregnancy within 6 months, they should be treated with both an ovulation-inducing drug and PVS, because it is possible that a follicle that is mature for the statistically average woman is not mature for the given individual.

We feel that the results of the cross-over data support the concept of dividing LPD into our two categories for purposes of therapeutic decision between pure LPD and LPD associated with immature follicles.

Possibly all instances of LPD are secondary to releasing an ovum from an immature follicle; but un-

fortunately, present ovulation-inducing drugs do not correct the maturation of the follicle perfectly.

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