

The Efficacy of Progesterone in Achieving Successful Pregnancy: II. In Women with Pure Luteal Phase Defects

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ABSTRACT: Controversy still exists as to the proper therapy of luteal phase defects. Some advocate using drugs to improve follicular dynamics, e.g., clomiphene citrate, while others treat luteal phase defects with progesterone. The possibility exists that in some cases the luteal phase defect is secondary to failure to produce a mature follicle, the better drug then being an ovulation-inducing drug, e.g., clomiphene. However, if the follicle is mature, then progesterone may be the best treatment. We defined a mature follicle as one between 18 and 24 mm while the serum estradiol (E_2) level is over 200 pg/mL. The efficacy of exclusive P therapy was evaluated in 50 women, all with a minimum of 1½ years infertility and with no obvious fertility problems other than luteal phase defect. Seventy percent of the women conceived within 6 months. The abortion rate was 14.7%. The average period of infertility was 2.8 years in the 35 patients who conceived within 6 months. These data suggest that determining the degree of follicular maturation by serum E_2 and pelvic sonography plus excluding the luteinized unruptured follicle syndrome by pelvic sonography helps determine the proper therapy for luteal phase defect.

INTRODUCTION

THE PROPER TREATMENT OF LUTEAL phase defects still remains confusing and controversial. Clomiphene citrate has been found by some to improve fertility, with varying degrees of success in achieving pregnancy within six cycles (Quagliarello and Weiss—87.5%,¹ Hammond and Talbert—45%,² Downs and Gibson—40.9%,³ Jones—19.3%⁴). The abortion rate varied from zero among the seven pregnancies reported by Quagliarello and Weiss to 23% in Hammond and Talbert's 31 pregnancies and 60% of Jones' five pregnancies.

Progesterone treatment of luteal phase defects has

also proven effective therapy, and rates have varied from 80% as reported in 15 cases by Jones and Poumand⁵ down to 50% in 16 cases reported by Soules et al.⁶ Wentz et al⁷ stated that the efficacy of progesterone therapy had been difficult to evaluate because previous studies had not employed uniform criteria for the diagnosis of luteal phase defects and because the studies used relatively small numbers of patients. However, they failed to use as part of their criteria whether the patient produced a mature follicle or released the egg from the follicle. We have recently demonstrated the need for determining whether a mature follicle is produced,⁸ and the egg

released from the follicle⁹ in determining the proper therapy of luteal phase defect.

In fact, we feel that the criterion for "pure" luteal phase defect should be a menstrual cycle date more than two days early, on the basis of endometrial biopsy taken one or two days premenstrually, coupled with the production of a mature follicle and release of the egg from the follicle. A mature follicle we define as one that attains a size of 18 to 24 mm by sonography, with the serum estradiol level at that time greater than 200 pg/mL and serum progesterone under 1.5 ng/mL. We consider a follicle unruptured if we find an increase in size of a mature follicle two or three days later, with a drop in the estradiol level and a rise in progesterone above 1.5 ng/mL. If the reason for the poor luteal phase is related to lack of production of mature follicles, the case should be considered as immature follicle syndrome; and, similarly, if there is failure to release the egg, it should be labeled luteinized unruptured follicle syndrome.

Keeping in mind the objections of Wentz et al⁷ to previous studies, we initiated a study aimed at determining, in a large series of cases, the efficacy of progesterone therapy to achieve pregnancy, with adherence to the uniform criteria demanded by the above definition of pure luteal phase defect.

MATERIALS AND METHODS

Fifty patients were chosen, and met the following criteria: (1) a minimum of 18 months' infertility history (primary or secondary); (2) luteal phase defect diagnosed by demonstrating that an endometrial biopsy obtained one to three days before the expected menses dated over two days early in two consecutive cycles; (3) male partner with a minimum sperm concentration of 30×10^6 /mL, with 60% linear progressive motility, under 25% abnormal forms, and a minimum volume of 2 mL; (4) tubal factor excluded by hysterosalpingogram and/or laparoscopy; (5) finally, the demonstration in two consecutive cycles of the formation at midcycle of a follicle between 18 and 24 mm in diameter, with a serum estradiol level over 200 pg/mL. Release of the egg from the follicle was determined by demonstrating shrinkage of the follicle by at least 5 mm two to three days later.

Progesterone vaginal suppositories, 25 mg twice a day, were started four days after formation of a mature follicle. A repeat endometrial biopsy was performed 12 to 13 days after formation of a mature follicle. If the biopsy was found still to be too early

by three days or more, the progesterone was increased by 25 mg and a repeat biopsy was obtained.

RESULTS

Thirty-five of 50 patients studied conceived within 6 months. Five patients had a first-trimester spontaneous abortion, and one patient had an ectopic pregnancy. Thus, 70% conceived within 6 months and 58% delivered a normal baby. The spontaneous abortion rate was 14.7%.

Five patients had a history of previous spontaneous abortions; all others had primary infertility. The range of ages was 18 to 39, with an average of 31. Their average period of infertility was 2.8 years in the 35 patients who conceived, and 2.7 years for the entire group.

Forty-one of the 50 patients yielded endometrial biopsies that lagged more than 5 days; three of the 15 patients who failed to conceive were in this category. Twelve patients required more than 50 mg/day of vaginal progesterone to attain correctly-timed endometrial biopsy.

There were no birth defects among any of the 29 babies delivered.

DISCUSSION

The varying success of therapy of luteal phase defect with either progesterone or ovulation-inducing drugs (e.g., clomiphene citrate) may be partially explained by varying patient selection in different studies and by relatively small samples in some of the studies. Downs and Gibson³ demonstrated that the best response to clomiphene occurs in women who lag more than five days by endometrial biopsy. In view of our previous experience with ultrasound in the diagnosis and therapy of luteal phase defect, we feel the best explanation to explain Downs and Gibson's observation is that if an immature follicle is formed, then the resulting luteal phase is likely to be more inadequate than when the problem is due strictly to a defective corpus luteum. Thus, a drug like clomiphene might be effective in maturing a follicle in the former instance, but ineffective in correcting luteal phase progesterone production from a follicle that is already mature. A patient population with a relatively high proportion of mature follicles and pure luteal phase deficiencies could account for the finding of Cook et al¹⁰ that clomiphene normalized the endometrial biopsy in patients with luteal phase defects in only 25% of cases.

We have tried to define a "pure" luteal phase defect by eliminating patients who have luteal phase defect secondary to failure to form a mature follicle or to release an ovum from a follicle; more rigid criteria for what constitutes a mature follicle have been provided by requiring a minimum level of serum estradiol and a maximum level of serum progesterone.

We cannot speculate meaningfully as to what percentage of patients would have conceived had they been treated with clomiphene citrate. Our study merely demonstrates that when one selects patients with luteal phase defect who have mature follicles and ovum release as defined above, a majority can achieve pregnancy (70%) within 6 months through the use of progesterone therapy in the luteal phase. Perhaps, some of our failures might have been due to the absence of a mature follicle in certain cases, despite their fulfilling the criteria that we have set for a mature follicle. Therefore, we recommend that if no conception occurs after six cycles of progesterone therapy, one should consider trying an ovulation-inducing drug, e.g., clomiphene citrate, plus luteal phase progesterone.

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