

Late Luteal Phase Progesterone-Dependent Endometrial Protein Levels in Women with In-Phase Biopsies—Can Low Levels Predict a Subfertile Group?

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ABSTRACT: A group of infertile women who had luteal phase defects (LPD), but in whom follicular maturation was deemed normal, were treated with progesterone until the endometrial biopsy was corrected. At the time the corrected biopsy was obtained, serum was taken and the progesterone-dependent endometrial protein (PEP) concentration was determined. Serum PEP concentration in patients who successfully conceived was $102.5 \pm 62.6\%$ units/mL, while PEP concentrations in patients who failed to conceive were $57.9 \pm 34.4\%$ ($P = .003$). In patients whose PEP value was more than two standard deviations below the corresponding mean control PEP, pregnancy was achieved in 6/17 (35.3%). The conception rate was significantly greater (25/35, 71.4%) in patients with values higher than this. Thus, the PEP concentration in serum may identify a group of patients with persistent LPD despite apparent normalization of the morphology of late secretory phase endometrium, which might explain some cases of cryptic, unexplained infertility.

INTRODUCTION

THE HUMAN ENDOMETRIUM synthesizes and secretes a specific protein known as the progesterone-dependent endometrial protein (PEP) [1]. This protein

has been found to rise in plasma from the mid-luteal to late luteal phase of the ovarian cycle [2]. The clinical importance of this protein has been hypothesized, but its clinical significance has not been established. The possibility exists, however, that the PEP assay could substitute for the endome-

trial biopsy, thereby providing clinicians with a potentially more accurate and certainly less invasive method to diagnose luteal phase defects (LPD). Furthermore, the serum PEP results would provide for the determination of another factor responsible for infertility even when the results of the endometrial biopsy are normal.

A study was designed to compare results of the late luteal phase endometrial biopsy and the serum concentrations of PEP using the achievement of pregnancy as the end point in patients believed to have luteal phase defect, i.e., mature ovarian follicles in the cycles that were dated more than two days out of phase by an endometrial biopsy taken in the late luteal phase of the ovarian cycle.

PATIENTS AND METHODS

All patients included in the study had a minimum of one year of infertility. The PEP assay was performed as previously described [3]. Serum values of PEP obtained on patients were normalized to a 28-day ovarian cycle by dividing the results of the assay by the mean PEP value observed on the postovulatory day that the sample was obtained and multiplying by 100. The mean PEP values for days 11, 12, 13, and 14 postovulation in a group of 58 control patients during nonconception cycles not stimulated by follicle maturing drugs were 51.1, 62.0, 67.4, and 79.9 units/mL, respectively [3]. Normalized values are expressed as the percent of control PEP (\pm SD) corresponding to the appropriate postovulation day. PEP values in patients who conceived were compared to values obtained in patients who failed to conceive, using the Mann-Whitney U test. Conception rates for each group were compared using chi-square analysis. A *P* value of $<.05$ was considered to be statistically significant [4].

The endometrial biopsy was performed in two consecutive cycles in the late luteal phase, about 12–14 days after ovulation. Serum for determination of PEP level was obtained on the same day as the biopsy. The day of ovulation was determined by measurement of serum estradiol, progesterone, and pelvic sonography. All patients demonstrated a minimum average ovarian follicular diameter of 18 mm [5] and a serum estradiol level of 200 pg/mL [6]. The luteinized unruptured follicle syndrome was ruled out by sonographic demonstration of shrinkage of the dominant follicle by at least 5 mm

two to three days after maturation of the follicle was demonstrated [7,8]. From the time that a serum estradiol level of 200 pg/mL was obtained, daily serum estradiol and progesterone levels were obtained until ova release was documented by ultrasound. Ovulation was defined as the next day following the serum estradiol peak, and was usually associated with rising serum progesterone and luteinizing hormone levels.

Progesterone suppositories were started at 25 mg twice daily beginning one day following the release of the ovum. The average progesterone dosage employed was 65 mg. The maximum dosage needed for correction was 200 mg/day. In all cases, the biopsies were in phase, or the patient was not included in this study. Once corrected, the biopsy was repeated in 4 months on the same therapy if no pregnancy had occurred. An average of 1.8 cycles was needed to correct the biopsy [9].

The recorded PEP level was the one obtained at the same time as the corrected biopsy. Thereafter, the patients were followed for a 6-month period, and the number of pregnancies achieved during this interval was recorded. Informed consent was obtained for these procedures from the 52 patients entered into the study.

Minimum acceptable semen analysis for patients entered into the study included a concentration of 20×10^6 /cc, 60% motility, with progressive forward motion and 60% normal forms. In addition, a postcoital test was done six hours following intercourse, and was considered to be acceptable if at least five sperm per high-power field with progressive forward motion were noted. Laparoscopy was performed on 80% of the patients who did not conceive.

RESULTS

The mean values obtained for PEP levels in patients who successfully conceived was $102.5 \pm 62.6\%$ units/mL, while those obtained in patients who failed to conceive was 57.9 ± 34.4 units/mL. These differences were statistically significant (*P* = .003). There was considerable overlap in the concentrations of PEP normalized to the day of ovulation among patients who conceived and those who did not (Figure 1). In patients whose PEP concentrations were more than two standard deviations below the corresponding mean control PEP, preg-

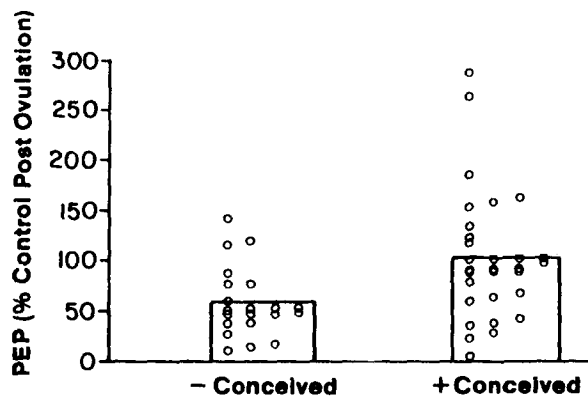


FIG. 1: Comparison of serum PEP levels in patients who conceived versus those who did not conceive. Each circle represents the PEP level as the percent of the control for the appropriate number of days post-ovulation.

nancy was achieved in 6/17 (35.3%). The conception rate was significantly greater, 25/35 (71.4%), in patients with values higher than this.

DISCUSSION

We have demonstrated previously that correcting the endometrial biopsy with supplemental progesterone therapy in women with normal follicular maturation resulted in at least 70% pregnancy rate within 6 months [10,11]. There was a 60% pregnancy rate in the present study in the progesterone-treated women.

We have previously demonstrated a poor correlation with the late luteal phase PEP level and the dosage of progesterone used in therapy ($r = 0.07$) [12]. The effect of progesterone was minimal in raising the serum PEP level. Similarly, no correlation was found between late luteal phase PEP levels and the endometrial biopsies [$P = 0.127$ using the Kruskal-Wallis one-way analysis of variance] [12]. PEP values were also grouped by the number of days the endometrial biopsy was out of phase. Nonparametric values could only be integers (not continuous). The correlation coefficient was 0.17 by linear regression [12].

The reported incidence of retarded endometrial development among women with infertility varies from 4 to 86% [6,13]. Not surprisingly, there is also a lack of a consensus on whether treatment of

retarded endometrial development successfully improves fertility rate. One possible explanation may be that correction of endometrial morphology may not correlate directly with improvement in endometrial function. The results of the present study suggest that there are some women in whom progesterone therapy results in improvement in endometrial histology without normalization of endometrial physiology. Patients in whom endometrial histology is normalized but who manifest a low serum PEP value had a significantly lower pregnancy rate than those patients who developed normal endometrium and achieved normal concentrations of PEP.

Owing to the significant overlap of PEP values between conceiver and non-conceivers the power of prediction is low; therefore, we are unsure that the serum PEP levels alone should be used to determine clinically whether a given patient would conceive after correction of LPD. It is a useful measurement in populations, but not in individual patients. We believe, however, that PEP remains a very important research probe into the physiology of the endometrium.

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