

**FERTILITY BETTER CORRELATES WITH HIGHER  
LEVELS OF PROGESTOGEN-DEPENDENT  
ENDOMETRIAL PROTEIN**

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*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 results of endometrial biopsy were normal. At the time of the normal biopsy, serum was obtained and the progestogen-dependent endometrial protein (PEP) concentration was determined. Serum PEP concentration in patients who successfully conceived*

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was  $102.5 \pm 62.6\%$ , 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 of 17 (35.3%) cases. 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).<sup>1</sup> This protein has been found to rise in plasma from the midluteal phase to the late luteal phase of the ovarian cycle.<sup>2</sup> The clinical importance of this protein has been hypothesized, but its clinical significance has not been established.

However, the possibility exists that the PEP assay could replace the endometrial biopsy thereby providing clinicians with a potentially more accurate and less invasive method to diagnose LPD. Furthermore, the results of the assay of PEP in serum could 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 an endometrial biopsy, taken in the late luteal phase of the ovarian cycle, dated more than 2 days out of phase.

## Materials and Methods

All patients included in the study had a minimum of 1 year of infertility. The PEP assay was performed as previously described.<sup>3</sup> 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 unstimulated by follicle maturing drugs were 51.1, 62.0, 67.4, and 79.9 units/ml, respectively.<sup>3,4</sup> Normalized values are expressed as the percentage of control PEP ( $\pm 1$ -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 the chi square test. A *p* value  $< .05$  was considered to be statistically significant.

The endometrial biopsy was performed in two consecutive cycles in the late luteal phase, about 12 to 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 pelvic sonography and the measurement of serum estradiol ( $E_2$ ) and progesterone (P). All patients demonstrated a minimum average ovarian follicular diameter of 18 mm<sup>5</sup> and a serum estradiol of 200 pg/ml.<sup>6</sup> The luteinized unruptured follicle syndrome was ruled out by sonographic demonstration of shrinkage of the dominant follicle by at least 5 mm 2 to 3 days after maturation of the follicle was demonstrated.<sup>7,8</sup> From the time that a serum  $E_2$  of 200 pg/ml was obtained, daily serum  $E_2$  and P levels were obtained until ova release was documented by ultrasound. Ovulation was defined as the next day following the serum  $E_2$  peak and was usually associated with rising serum P and luteinizing hormone (LH) levels.

Progesterone suppositories (25 mg) were started twice daily beginning one day after the release of the ovum. The average progesterone dosage used 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 the study. Once corrected, the biopsy was repeated in 4 months with the patient on the same therapy if pregnancy had not occurred. An average of 1.8 cycles was needed to correct results of the biopsy.<sup>9</sup>

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

Minimal acceptable semen analysis for patients entered into the

study included a concentration of  $20 \times 10^6/\text{cc}$ , 60% motility, with progressive forward motion and 60% normal forms. In addition, a postcoital test conducted 6 hours after intercourse was considered acceptable if at least five sperm per high-powered 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 were  $102.5 \pm 62.6\%$  while those obtained in patients who failed to conceive were  $57.9 \pm 34.4\%$ . These differences were statistically significant ( $p = 0.003$ ). There was considerable overlap in the concentrations of PEP normalized to the day of ovulation among patients who conceived and those who did not (Fig. 1). In patients whose PEP concentrations were more than

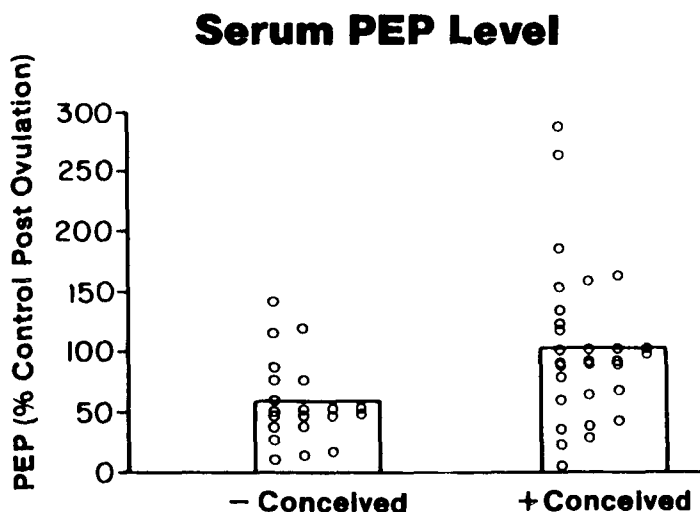


FIGURE 1 Comparison of serum PEP levels in patients who conceived versus those who did not conceive. Each circle represents the PEP level as the percentage of the control for the appropriate number of days postovulation. The black line represents the mean of the PEP levels in those who conceived versus those who did not conceive.

two standard deviations below the corresponding mean control PEP, pregnancy was achieved in 6 of 17 cases (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 results of the endometrial biopsy with supplemental progesterone therapy in women with normal follicular maturation resulted in a pregnancy rate of at least 70% within 6 months.<sup>10,11</sup> There was a 60% pregnancy rate in the present study in the progesterone-treated women.

The reported incidence of retarded endometrial development among women with infertility varies from 4% to 86%.<sup>6,12</sup> Not surprisingly, there is also a lack of a consensus on whether treating retarded endometrial development successfully also improves the fertility rate. One possible explanation may be that correction of endometrial histology 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 who developed normal endometrium and achieved normal concentrations of PEP.

The PEP measurement thus appears to be a potentially useful adjunct to the endometrial biopsy for determining adequacy of luteal function. Because a few patients with low PEP concentrations did become pregnant, it is likely that secretion of PEP by endometrial cells is representative of only one action of normal endometrium. It is reasonable to assume that determination of serum PEP concentrations may provide yet another method for evaluating endometrial function. The present study was not designed to see if quantitation of serum PEP concentrations could replace endometrial biopsy as a method for diagnosing luteal phase dysfunction. However, we suggest that determination of serum concentrations of PEP may serve as a diagnostic tool to evaluate patients in whom the diagnosis of luteal phase defect is based on abnormal endometrial

biopsy, who when treated with progesterone developed normal endometrium, but who thereafter failed to conceive. It is possible that time will show that correction of a low PEP concentration may result in an improved fertility in these patients.

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