

Measurement of Placental Protein 14 (PP14) Not Helpful in Predicting Infertility or Spontaneous Abortion

*Jerome H. Check, M.D.**
*Milind M. Vaze, M.D.**
Beth Vetter, M.L.T.

*University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School at Camden
Cooper Hospital/University Medical Center
Department of Obstetrics and Gynecology
Division of Reproductive Endocrinology & Infertility
Camden, New Jersey

ABSTRACT: Placental protein 14 (PP14) can be measured in the serum by radioimmunoassay. The level rises from mid to late luteal phase in a manner similar to the endometrial biopsy. A study was initiated to determine if a clinical association could be found between the late luteal phase serum PP14 level and subsequent pregnancy and spontaneous abortion rate. No difference was found in the preconception PP14 level in patients conceiving versus those not conceiving, nor in those aborting versus those not aborting. A trend toward higher levels in conception versus non-conception cycles was noted, but a large patient group will be needed to demonstrate statistical significance.

INTRODUCTION

THE LUTEAL PHASE DEFECT (LPD) AS A cause of infertility is determined by the endometrial biopsy [1,2]. Treatment may be with ovulation-inducing drugs or progesterone [3]. However, it is important to repeat biopsies following therapy to see if the LPD has been corrected; but, unfortunately, the discomfort associated with the endometrial biopsy, even with new instrumentation, frequently precludes repetition of the procedure [4].

Placental protein 14 (PP14) is secreted by the secretory endometrium and the decidua. It has been found to be immunologically indistinguishable from the progestagen-associated endometrial protein (PEP)

[5]. This protein was found to rise from the mid to late luteal phase of the ovulatory cycle, similar to the increasing progesterone effect seen in the endometrial biopsy [6]. Thus, in contrast to serum progesterone, which peaks at mid luteal phase and then drops, PP14 continues to rise, and therefore appears to reflect the cumulative progesterone effect. More evidence that this is truly a progesterone-dependent protein was provided by demonstrating that micronized oral progesterone increased the circulating level [7]. These data led Joshi et al [8] to suggest that the measurement of this endometrial protein could be used to replace the more invasive endometrial biopsy.

The possibility exists that though both the endometrial biopsy and the PP14 level demonstrate

peak progesterone effect in the late luteal phase, they may reflect different aspects of anatomy and physiology; the biopsy may reflect the structural integrity of the endometrium, while the PP14 level represents the functional integrity of the endometrial glands. We speculated that possibly the failure to conceive despite correcting an out-of-phase endometrial biopsy may be related to failure to normalize the serum PP14 level. The study presented herein evaluates the late luteal phase serum PP14 (PEP) levels in patients with documented luteal phase defects after the endometrium was normalized to see if failure to conceive might be related to inadequate PP14 levels.

PATIENTS AND METHODS

Seventy-eight consecutive patients, each with a minimum of 1 year of infertility and a diagnosis of luteal phase defect (LPD), were enrolled in the study. The LPD was diagnosed by two consecutive late luteal phase endometrial biopsies; the histological dating was according to the method of Noyes et al [1]. The time of ovulation was determined by a combination of pelvic sonography and serum estradiol, progesterone, and luteinizing hormone assays [9,10]. Follicular maturation criteria also determined whether the patient was treated by progesterone exclusively or by the use of ovulation-inducing drugs plus progesterone [3]. Each patient was given 6 months to achieve a pregnancy from the time that the endometrial biopsy was deemed in phase. Other infertility factors were concomitantly corrected as well as possible; the patients, however, did not have to be fully normalized to be included in the study.

The PP14 assay (PEP) was performed by a radioimmunoassay technique and conducted under non-equilibrium conditions to improve the sensitivity of the procedure [6]. The serum PP14 drawn during the cycle in which the endometrial biopsy was normalized was the value used for this study. During the biopsy cycle, the patients were asked to use mechanical contraception. Each patient then had another late luteal phase serum PP14 level obtained the next cycle. The initial PP14 level was obtained the same day as the biopsy.

Pregnancies were diagnosed by β -hCG subunit levels and were followed during the first trimester with serial beta β -hCG subunit levels and pelvic sonography.

PP14 levels between groups were compared using an unpaired *t* test, with a *P* value $<.05$ considered to be statistically significant. PP14 concentrations are presented as mean \pm SD.

RESULTS

After the initial studies were performed, 2 of the 78 patients discontinued their visits, leaving 76 patients for the study. Thirty-three patients conceived during the 6 months, and 43 did not. The pre-conception mean PP14 level was 50.9 ± 30.8 U/mL in those conceiving, versus 46.9 ± 39.9 U/mL in those not conceiving (no statistically significant difference). The PP14 levels ranged from 10.4 to 137.3 U/mL in women achieving pregnancies, versus 5.5 to 190 U/mL in nonpregnant patients.

Spontaneous abortions occurred in 9 of 33 (27%) women (including one ectopic pregnancy). This rather high abortion rate may be partially related to the relatively higher mean age of the study group (36.4 years). In fact, five of the nine (55%) abortions occurred in 14 women (36%) aged 40 or older. The pre-conception mean PP14 level in nine aborters was 54.2 ± 41.3 U/mL versus 50.9 ± 30.8 U/mL in non-aborters (NS). The range was 16.1 to 146 U/mL in the former and 10.0 to 137.3 U/mL in the latter.

Of the 33 pregnant women, 12 (36%) conceived during their first cycle of pregnancy attempt after normalizing the biopsy, and maintained fetal viability. PP14 levels were available for comparison of pre-conception versus conception cycle PP14 levels for the same therapy dosage. The mean PP14 level was higher during the conception cycle (43.9 ± 31.4 vs. 31.0 ± 21.5), but the sample size was too small to demonstrate statistical significance. Nevertheless, 10 of the 12 patients (83.3%) exhibited higher PP14 levels on conception versus non-conception cycles. Three patients who subsequently aborted also had PP14 levels measured on both conception and non-conception cycles, and higher PP14 levels were recorded in conception (51 U/mL) than non-conception (39 U/mL) cycles.

DISCUSSION

A study by Bolton et al [11] found that purified PP14 displayed *in vitro* immunosuppressive activity which was removed by an anti-PP14 antibody-based

immunoabsorbent. Thus, the possibility exists that one cause of infertility may be insufficient stimulation of PP14 to prevent immune rejection of the fetus. Theoretically, a dichotomy could exist even in women with normalized biopsies. The data presented herein do not totally negate this idea, since there was at least a trend toward a higher PP14 level (PEP) in conception cycles, and also a statistically significant difference in late luteal levels in a previous study [12] of in vitro fertilization cycles, which would still be consistent with the theory of a possible immunosuppressive role for PP14 in vivo.

However, since conception and abortion rates were similar in conceiver and non-conceivers, and aborters versus non-aborters in pre-conception cycles, attempts to "normalize" PP14 levels with either progesterone or ovulation-inducing drugs as a method of correcting infertility problems do not seem justified.

ACKNOWLEDGMENTS

The authors thank Richard Epstein, M.D. for his help in evaluating and tabulating the data, and Ilene Blumenthal for her help in preparing the manuscript.

REFERENCES

1. Noyes RW, Hertig A, Rock J: Dating the endometrial biopsy. *Fertil Steril* 1:3, 1950.
2. Andrews WC: Luteal phase defects. *Fertil Steril* 32:501, 1979.
3. Check JH, Nowroozi K, Wu CH, et al: Ovulation inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects. *Int J Fertil* 33:252, 1988.
4. Check JH, Chase JS, Nowroozi K, et al: Clinical evaluation of the pipelle endometrial suction curette for timed endometrial biopsies. *J Reprod Med* 34:218, 1989.
5. Julkunen M, Raikar RS, Joshi SG, et al: Placental protein 14 and progesterone-dependent endometrial protein are immunologically indistinguishable. *Hum Reprod* 1:7, 1986.
6. Joshi SG, Ebert KM, Swartz DP: Detection and synthesis of a progesterone-dependent protein in the human endometrium. *J Reprod Fertil* 59:273, 1980.
7. Seppala M, Ronnberg L, Karonen SL, Kauppila A: Micronized oral progesterone increases the circulating level of endometrial secretory PP14/B-lactoglobulin homologue. *Hum Reprod* 2:453, 1987.
8. Joshi S, Rao R, Henriques E, et al: Luteal phase concentrations of a progesterone-associated endometrial protein (PEP) in the serum of cycling women with adequate or inadequate endometrium. *J Clin Endocrinol Metab* 63:1247, 1986.
9. Check JH, Goldberg BB, Kurtz A, et al: Pelvic sonography to help determine the appropriate therapy for luteal phase defects. *Int J Fertil* 29:156, 1984.
10. Check JH, Nowroozi K, Wu CH, et al: The importance of luteal phase deficiency as a cause of infertility in private practice—a preliminary report. *Infertility* 10:111, 1987.
11. Bolton A, Clough K, Stoker R, et al: Identification of placental protein 14 as an immunosuppressive factor in human reproduction. *Lancet* 1:593, 1987.
12. Check JH, Nowroozi K, Chase JS, et al: Serum progesterone-associated endometrial protein (PEP) levels in conception versus nonconception cycles following in vitro fertilization-embryo transfer. *J IVF-ET* 7:134, 1990.

Address reprint requests to:
Jerome H. Check, M.D.
7447 Old York Road
Melrose Park, PA 19126