

Serum Progestagen-Associated Endometrial Protein (PEP) Levels in Conception Versus Nonconception Cycles Following In Vitro Fertilization–Embryo Transfer

JEROME H. CHECK,^{1,3,4} KOSROW NOWROOZI,¹⁻³ JEFFREY S. CHASE,¹⁻³ MILIND VAZE,¹ SHARAD JOSHI,¹ and AMY F. BAKER³

Submitted: October 16, 1989
Accepted: February 6, 1990

The human endometrium synthesizes a specific protein known as the progestagen-dependent endometrium protein (PEP) which rises from early to late luteal phase. The PEP levels follow the pattern of the endometrial biopsy more than the serum progesterone (P) levels (4). Late luteal-phase serum PEP levels were evaluated as well as serum P in mid-luteal phase in patients undergoing IVF-ET. Comparisons were made between conceiver and nonconceivers and between aborters and nonaborters. Both serum PEP and late luteal P levels were significantly higher in pregnant patients but no differences in mid luteal P levels were seen. No difference was seen in aborters vs nonaborters. It is still inconclusive whether the higher late luteal PEP levels contribute to the greater likelihood of pregnancy or are a result of the pregnancy.

KEY WORDS: progestagen-associated endometrial protein (PEP); spontaneous abortion; fertility rate.

INTRODUCTION

The human endometrium synthesizes and secretes a specific protein known as the progestagen-associated endometrial protein (PEP) (1). This protein rises in plasma concentration from early to late

luteal-phase parallel to endometrial development (2) and continues to rise during early pregnancy. Although the clinical significance of PEP has not yet been determined, the measurement of this protein could prove to be a noninvasive assessment of corpus luteal function. We initiated a study to determine whether there is a correlation between the late luteal-phase PEP levels and the establishment of clinical pregnancies during in vitro fertilization embryo transfer (IVF-ET). We also evaluated the mid and late luteal-phase progesterone (P) levels to see if a similar correlation could be found.

MATERIALS AND METHODS

Sixty-five consecutive patients (aged 23–44 years; median, 34 years) participating in the IVF program were enrolled in this study. Included were 7 patients with proximal tubal occlusion, 2 with distal tubal occlusion, 4 with bilateral fimbrial occlusion, 4 with unilateral fimbrial occlusion, 3 with mild peritoneal adhesions, 7 with moderate peritoneal adhesions, 11 with extensive peritoneal adhesions, 9 with bilateral tubal ligation, 2 with unilateral tubal occlusion or tubal removal, 2 with stage 1 endometriosis, 1 with stage 3 endometriosis, 1 with stage 4 endometriosis, 2 with oligospermia (fewer than 10×10^6 motile sperm/ml), 3 with a male immunological factor directed against spermatozoa, and 7 classified as unexplained infertility.

Patients followed a stimulation protocol starting with 1 mg daily of leuprolide acetate (LA) administered subcutaneously on day 21 of their cycle. Eleven days after LA was started (and running par-

¹ The UMDNJ, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department OB/GYN, Division of Reproductive Endocrinology & Infertility, Camden, New Jersey.

² Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, The Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania.

³ Endocrine Histology Associates, P.C., Melrose Park, Pennsylvania.

⁴ To whom correspondence should be addressed at 1015 Chestnut Street, Suite 1020, Philadelphia, Pennsylvania 19017.

allel with LA), human menopausal gonadotropin (hMG) was administered intramuscularly (IM) at a dosage of 150 IU twice daily for 3 days and then reduced to 225 IU per day for 1 day. At this point, vaginal ultrasound was utilized to monitor the developing follicles and measurement of serum estradiol (E₂): LA and hMG were continued until the patient measured an E₂ of at least 600 pg/ml and at least 3 follicles over 16 mm. Human chorionic gonadotropin (hCG) was then administered at a dosage of 10,000 IU, im, 30–32 hr before the aspiration of ovum.

The follicles were aspirated using a 16-gauge needle ultrasonically guided with a transvaginal transducer (GE RT3600, 5 mHz).

The retrieved oocytes were inseminated with 5–10 × 10⁴ motile sperm (for severe oligospermia 25 × 10⁴ motile sperm were used). One to five embryos were transferred on the second day after the oocytes were aspirated. Extra embryos were cryopreserved using a modification of the one-step method (3).

All study patients received supplemental progesterone (25 mg in oil, im) daily. Each had a serum progesterone (P) test 7 days after oocyte retrieval. The amount of progesterone was increased by 25 mg in cases where the mid-luteal P level was below 12 ng/ml. The serum PEP, P, and B-hCG were measured 13 days after retrieval. The PEP assay was performed as described by Joshi *et al.* (4).

All calculations were performed on an IBM computer using the EPISTAT statistical program. The statistical results were analyzed using the independent Student *t* test.

RESULTS

Sixty-five patients were enrolled in this study. Of the 65 patients, there was a total of 17 pregnancies. Ten patients delivered normal neonates and seven aborted. The results are presented in Tables I, II, and III. In Table I, the mean serum PEP and serum progesterone levels are calculated for the late luteal phase (13 days after ovum aspiration). The mean serum progesterone level is also calculated for the mid luteal phase (7 days after ovum aspiration). All means are shown for conception versus nonconception cycles. The late luteal serum PEP level was significantly higher for pregnant patients (*P* < 0.001). The mean mid luteal-phase serum progesterone level was found not to differ significantly for conception versus nonconception cycles (*P* =

Table I. Serum PEP Levels (Late Luteal Phase) and Mid and Late Luteal-Phase Serum P Levels in Conception vs Nonconception Cycles in Women Undergoing IVF-ET

	Mean late luteal serum PEP level (U/ml)	Serum P level (ng/ml)	
		Mean late luteal	Mean mid luteal
Conception cycles (n = 17)	80.2	56.8	74.3
Nonconception cycles (n = 48)	35.5	13.4	60.8
	<i>P</i> < 0.001 ^a	<i>P</i> < 0.001	<i>P</i> = 0.19 NS

^a *P* values were determined using the two-tailed independent *t* test.

0.19). The late luteal-phase serum P was significantly greater in conception versus nonconception cycles. (*P* < 0.001). As noted in Fig. 1, only 5 of 48 (10.4%) of nonconceivers had a PEP level above the mean for conceiver. Also, only 3 of 17 (17.6%) of the conceiver had a PEP level below the mean for nonconceivers. As noted in Fig. 2 none of the 48 nonconceivers had a progesterone level above the mean of the conceiver. Also, only 4 of 17 (23.5%) had a progesterone level below the mean of nonconceivers.

Table II compares the mean number of follicles, mean number of eggs retrieved, and mean number of embryos transferred in conception versus nonconception cycles. There was no significant difference in any of the three categories for conception versus nonconception cycles.

Table III compares the serum PEP, late luteal-phase serum P, and mid luteal-phase serum progesterone for aborters versus all conception cycles. There was no significant difference between aborters and all conceiver for any of the three serum levels.

DISCUSSION

The study demonstrated significantly higher mean late luteal-phase PEP levels and progesterone

Table II. IVF Data on Conception vs Nonconception Cycles

	Mean number		
	Follicles	Eggs retrieved	Embryos transferred
Conception cycles (n = 17)	13.3	8.4	3.2
Nonconception cycles (n = 48)	12.3	7.5	2.9

Table III. Serum PEP and P Levels in IVF Aborters vs All Conceiving IVF Patients^a

	Nonaborters (n = 12)	Aborters (n = 5)	All conceivers (n = 17)
Serum PEP	66.9 U/ml	83.3 U/ml	80.2 U/ml
	<i>P</i> = 0.91 for aborters vs all conceivers		
	<i>P</i> = 0.58 for aborters vs nonaborters		
Serum P, late luteal phase	45.4 ng/ml	64.6 ng/ml	56.8 ng/ml
	<i>P</i> = 0.73 for aborters vs all conceivers		
	<i>P</i> = 0.61 for aborters vs nonaborters		
Serum P, mid luteal phase	74.5 ng/ml	83.7 ng/ml	74.3 ng/ml
	<i>P</i> = 0.72 for aborters vs all conceivers		
	<i>P</i> = 0.73 for aborters vs nonaborters		

^a *P* values were determined using the two-tailed independent *t* test.

levels in pregnancy cycles. It is not clear, however, whether the pregnancy causes the higher level or these superior levels are intrinsic to the achievement of a successful pregnancy. We feel that if the former hypothesis is correct, the pregnancy factor is something other than hCG, since we have not been very successful in raising PEP levels by supplemental luteal-phase hCG injections (unpublished

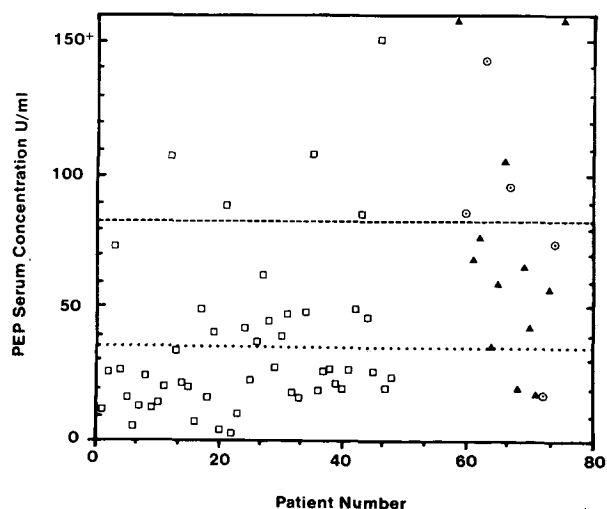


Fig. 1. PEP levels for conception vs nonconception cycles. (□) Nonconceivers, *n* = 48; (▲) conceivers, *n* = 12; (○) Aborters, *n* = 5. (· · · ·) \bar{X} = 35.5 U/ml for nonconceivers, SE = 4.3; (----) \bar{X} = 80.2 U/ml for conceivers, SE = 13.6. Only 5 of 48 (10.4%) of nonconceivers had a PEP level above the mean for conceivers. Only 3 of 17 (17.6%) of conceivers had a PEP level below the mean for nonconceivers.

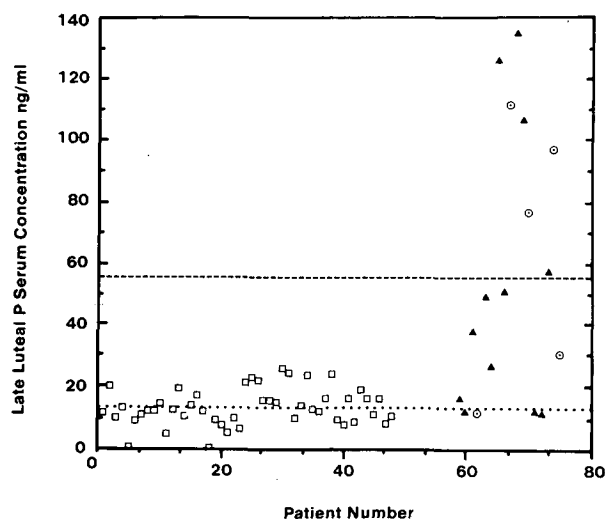


Fig. 2. Late luteal-phase progesterone (P) levels for conception vs nonconception cycles. (□) Nonconceivers, *n* = 48; (▲) conceivers, *n* = 12; (○) aborters, *n* = 5. (· · · ·) \bar{X} = 13.4 ng/ml for nonconceivers, SE = 0.84; (----) \bar{X} = 56.8 ng/ml for conceivers, SE = 10.4. None of the 48 nonconceivers had a progesterone level above the mean of the conceivers. Four of 17 (23.5%) had a progesterone level below the mean of nonconceivers.

data). Mid luteal-phase progesterone levels did not reflect successful outcome. Unfortunately PEP levels were not obtained in the mid luteal phase.

From a practical standpoint, if the late luteal-phase P or PEP is to be used for prediction of pregnancy, the commercially available P assay would be more easily obtained.

Nevertheless, more extensive studies of PEP should be continued to see if a dichotomy between PEP and P would be predictive of a unique clinical circumstance.

REFERENCES

- Joshi SG, Ebert KM, Swartz DP: Detection and synthesis of a progestagen-dependent protein in the human endometrium. *J Reprod Fertil* 1980;59:273-285
- Joshi SG, Henriques ES, Smith RA, Szarowski DH: Progestagen dependent endometrial protein in women. Tissue concentration in relation to development stage and to serum human hormone levels. *Am J Obstet Gynecol* 1980; 138:1131-1136
- Leibo SP: A one-step method for direct non-surgical transfer of frozen thawed bovine embryos. *Therio* 1984;212:5, 767-773
- Joshi SG, Bank JF, Henriques ES, Makarachi A, Matties G: Serum levels of a progestagen associated endometrial protein during the menstrual cycle and pregnancy. *JCE* 1982;55:642-648