

# 17-Hydroxyprogesterone Level as a Marker for Corpus Luteum Function in Aborters Versus Nonaborters

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**ABSTRACT:** Weekly serum levels of 17-hydroxyprogesterone (17-OHP) levels and serum progesterone (P) levels were measured in 378 pregnant women. Normal levels of 17-OHP were established in women taking ovulation-inducing drugs (OVID) versus those conceiving on normal cycles. Weekly levels of 17-OHP were measured in women who aborted and were compared with the established norms. The levels of 17-OHP in aborters were lower than in normals for their specific category established in nonaborters. These results suggest that a failing corpus luteum may contribute to some abortions. Careful attention to 17-OHP levels dropping below normal during the first trimester may alert the clinician to the need to increase progesterone exogenously and possibly prevent an abortion.

## INTRODUCTION

**T**HE SECRETION OF 17-HYDROXYPROGESTERONE (17-OHP) is a function of the corpus luteum, and not the placenta. The possibility exists that a subnormal level of 17-OHP during the first trimester might be an indicator of decreasing corpus luteum function, which could serve as an indicator to the physician to add, or increase, progesterone (P) therapy.

Previous normal levels of 17-OHP in pregnancy based on levels in a small number of cases have been established.<sup>1,2</sup> However, women taking ovulation-inducing drugs (OVID), for example, clomiphene citrate or human menopausal gonadotropins (hMG), may have multiple corpora lutea. Thus, the

serum 17-OHP levels could be increased above normal in women conceiving with OVID.

A study was designed, in which 17-OHP levels were obtained weekly during the first trimester and average levels were calculated for women conceiving without OVID and also for those conceiving with OVID. The serum 17-OHP levels were then evaluated in women who aborted; the mean levels were then compared with the mean levels of 17-OHP in their comparable groups.

## PATIENTS AND METHODS

All patients included in the study sought help in either achieving a pregnancy or helping to prevent a spontaneous abortion. Only those receiving proges-

terone therapy were evaluated in this study since the frequent weekly monitoring of serum P and 17-OHP levels could only be justified in this group. Prophylactic use of progesterone vaginal suppositories (PVS) had been initiated in the luteal phase shortly after ovulation. The details were as follows. A mature graafian follicle was defined as one of 18 mm diameter associated with a serum estradiol level of over 200 pg/mL per mature follicle. If it was determined that the woman did not produce a mature follicle prior to the release of the ovum, she was treated with bromocriptine, 2.5 mg daily, if the prolactin level was elevated, and the dose was increased to 2.5 mg twice daily if the smaller dose did not correct the follicular maturation. Otherwise the patient was given clomiphene citrate and switched to hMG if the clomiphene was associated with hostile cervical mucus uncorrectable even with the addition of supplemental estrogen.

After maturation of the follicle, release of the ovum was next established by sonography. PVS was now initiated after ovum release and four days from the demonstration of a mature follicle, at a dose of 25 mg twice daily. The day of ovulation was assumed to be one day after the LH surge was noted and the serum progesterone level approached 1 ng/mL.

An endometrial biopsy was performed 12–14 days from the assumed day of ovulation, and the dating established from the time of ovulation rather than the time of the next ensuing menses, because the PVS might delay menstruation. If the biopsy dated out of phase more than two days early, the dose of PVS was titrated upward until a correctly dated biopsy was achieved. Thus, the biopsy would be repeated on consecutive cycles until the dating was correct.

Seventeen days from the attainment of a mature follicle, an hCG beta-subunit assay was obtained, as well as a rapid serum P level. If negative, the woman stopped the suppositories. A positive hCG level would prompt the suggestion to double the dose of the PVS, and the patient would be seen again five days later, when another rapid serum P measurement would be made. A level of 35 ng/mL or higher at this time, without bleeding or significant cramping, was taken to indicate that no increase in PVS was needed. A level over 30, but under 35, would prompt a mild increase, of 50 mg PVS daily; a level under 30, but over 25, would prompt a 100-mg increase; and a level under 25 ng/mL would prompt

a 200–300-mg increment. A patient with a low level of serum P would be evaluated again five days later to see if the new increment adequately corrected the serum P level; and if not, the PVS dosage would be adjusted upward. Some women failed to absorb the vaginal suppositories properly, so that an adequate level was not achieved despite 400 mg PVS. The patient would then be started on progesterone-in-oil injections, 100 mg every other day.

Once the appropriate serum P level was obtained, the patient was evaluated at 1-week intervals and the dosage maintained until 12 weeks from conception, when the dosage was tapered, usually by 50 mg/week. The patient was evaluated every 1 to 2 weeks, and progesterone was measured. All PVS was stopped if the patient demonstrated a level over 40 ng/mL 1 week after stopping all PVS therapy. However, if the level dropped under 40 ng/mL during the time of decreasing PVS dosage or stopping, or if there was a significant increase of clinical symptoms of vaginal bleeding or cramping, the full maximum dosage that the patient had taken was resumed for one more month, when another attempt would be made to wean the patient from PVS. Failure to wean the patient successfully after another month of therapy would then generally lead to the suggestion to remain on PVS until 1 month prior to the due date. Levels of serum progesterone over 70 ng/mL during the first trimester were countered by a reduction in the dosage of the PVS.

Quantitative serum progesterone levels were measured by solid-phase  $^{125}\text{I}$  radioimmunoassay (Diagnostic Products Corp., Los Angeles). Quantitative serum 17-OHP levels were measured by double-antibody  $^{125}\text{I}$  radioimmunoassay (Pantex Division of Bio-Analysis, Santa Monica, CA).

The program SYSTAT (Systat, Inc., Evanston, IL) was utilized for all statistical computations. Serum P and 17-OHP concentrations among patient groups were compared using analysis of variance with Bonferroni's correction for multiple comparisons. A *P* value  $<0.05$  was considered to be statistically significant. P and 17-OHP concentrations are expressed as mean  $\pm$  SD.

Pelvic sonography for fetal viability was performed beginning 5 weeks from ovulation and continued weekly to 12 weeks unless spontaneous abortion had taken place. 17-OHP levels were recorded only when fetal viability was seen or, prior to five weeks, with an appropriate hCG beta-subunit level.

**TABLE I**  
**17-Hydroxyprogesterone and progesterone concentrations in aborters vs. nonaborters, with and without use of ovulation-inducing drugs.**

Week From Conception	Group A (Aborters Using OVID)		Group B (Nonaborters Using OVID)		Group C (Aborters Without OVID)		Group D (Nonaborters Without OVID)	
	Serum P	Serum 17OHP	Serum P	Serum 17OHP	Serum P	Serum 17OHP	Serum P	Serum 17OHP
2	60.2 ± 15.8	667 ± 243	64.4 ± 35.6	1020 ± 734	16.9 ± 7.9	248 ± 86	36.7 ± 31.7	429 ± 244
3	40.8 ± 15.6	616 ± 211	60.2 ± 35.6	1170 ± 682	22.1 ± 10.0	272 ± 126	30.9 ± 11.2	426 ± 140
4	35.4 ± 14.2	412 ± 113	54.3 ± 37.2	879 ± 599	30.0 ± 14.6	344 ± 179	28.4 ± 7.3	384 ± 91
5	31.5 ± 13.7	335 ± 131	50.2 ± 24.9	728 ± 495	29.0 ± 14.1	254 ± 197	29.2 ± 8.1	359 ± 79
6	30.2 ± 11.2	352 ± 14	48.2 ± 24.3	639 ± 327	27.8 ± 10.0	180 ± 62	32.3 ± 9.3	317 ± 130
7	20.6 ± 9.2	275 ± 176	43.7 ± 17.7	483 ± 252	32.6 ± 9.8	238 ± 137	31.5 ± 9.8	294 ± 110
8	19.0 ± 7.6	192 ± 89	40.0 ± 15.5	366 ± 190	38.7 ± 9.0	254 ± 84	31.4 ± 9.1	274 ± 109
9			46.3 ± 18.7	371 ± 226			34.0 ± 11.4	297 ± 100
10			43.4 ± 13.5	352 ± 151			34.1 ± 10.9	248 ± 57
11			52.6 ± 24.5	403 ± 268			39.5 ± 10.5	279 ± 81
12			50.5 ± 14.2	358 ± 194			41.2 ± 9.9	281 ± 75

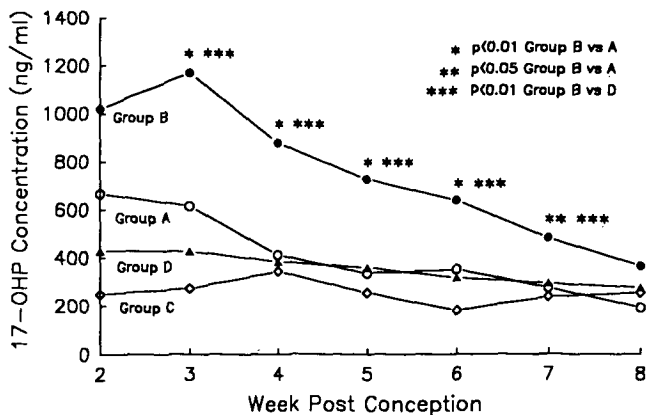
**RESULTS**

A total of 378 women were followed in this study. Patients were retrospectively divided into four groups: A—taking OVID, aborter; B—taking OVID, non-aborter; C—not taking OVID, aborter; D—not taking OVID, non-aborter. Serum P and 17-OHP concentrations during the second through the twelfth week of gestation are presented in Table I.

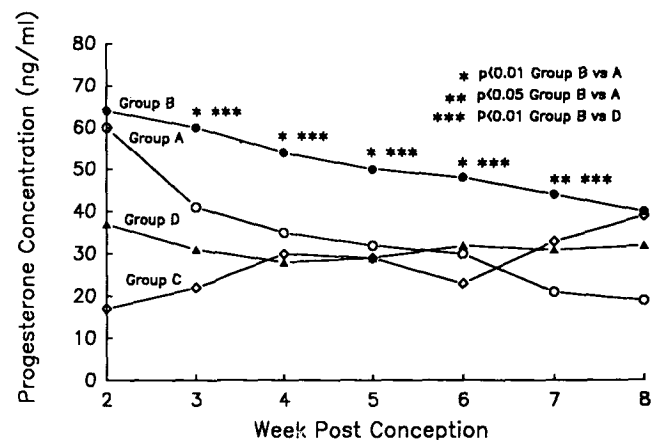
Differences in serum 17-OHP concentrations among the four groups during the first 8 weeks of gestation were highly significant ( $p < 0.01$ ). 17-OHP

levels in non-aborting patients taking OVID were significantly higher than aborting patients taking OVID during weeks 3 to 7 (Figure 1). There were no statistically significant differences in 17-OHP concentrations between non-OVID-taking aborters and non-aborters. Serum 17-OHP concentrations were significantly higher in OVID-taking non-aborters than in non-OVID-taking non-aborters during weeks 3 to 7 of gestation (Figure 1).

Differences in serum P concentrations among the four groups during the first 8 weeks of gestation were also significant ( $p < 0.05$ ). P levels in OVID-taking non-aborters were significantly higher than



**FIG. 1:** Serum 17-hydroxyprogesterone (17-OHP) concentrations following conception. Groups are as follows: A, taking OVID, aborter; B, taking OVID, nonaborter; C, not taking OVID, aborter; D, not taking OVID, nonaborter.



**FIG. 2:** Serum progesterone concentrations following conception. Groups are as listed in Figure 1.

both OVID-taking aborters and non-OVID-taking non-aborters during weeks 3 to 7 (Figure 2). Serum P concentrations were not different in non-OVID-taking aborters and non-aborters.

The hCG beta subunit concentrations were over 10,000 MIU/mL at seven and eight weeks from conception in all patients.

## DISCUSSION

Since the hCG beta-subunit levels were all maintained above 10,000 MIU in the patients, the dropping 17-OHP levels in the aborting patients compared with nonaborting patients suggests a failing corpus luteum of pregnancy. One may question which comes first, the low 17-OHP as a reflection of a failing pregnancy or the low 17-OHP levels along with a drop in the serum P level as a cause of spontaneous abortion. The maintenance of the hCG level may favor the latter hypothesis. Patients aborting despite normal serum P and 17-OHP levels may have aborted from other causes, for example, genetic abnormalities. All patients in this study were supplemented with progesterone vaginal suppositories, up to 400 mg/day.

The abortion incidence was low, but the possibility exists that in some instances the P supplementation was inadequate to maintain the pregnancy. Thus, it is possible that by being even more aggressive with the P supplementation an even lower abortion incidence could be achieved, perhaps by parenteral P. The signal for switching to paren-

teral P therapy may be subnormal 17-OHP levels.

The goal was to try to maintain a serum P level above 35 ng/mL. However, the statistical difference in P level in aborters versus nonaborters suggests that once the corpus luteum begins to fail it may be difficult to maintain adequate serum P levels merely by using progesterone vaginal suppositories. Indeed, the differences in P levels between aborters and nonaborters would have been even greater had supplementation not been given.

## ACKNOWLEDGMENT

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