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Comparison of First Trimester Serum Estradiol Levels in Aborters versus Nonaborters during Maintenance of Normal Progesterone Levels

Key Words

Estradiol levels
First trimester abortion
Progesterone therapy

Abstract

This study was designed to measure the average serum estradiol (E_2) levels in the first trimester for women whose serum progesterone (P) levels were carefully maintained at normal levels by the use of exogenous P, and to compare the mean serum E_2 levels in women who aborted with those in women who did not. The study group consisted of 94 pregnant women supported with exogenous natural P therapy from the luteal phase through the first trimester. Beginning at week 5, and continuing through the first trimester, the mean serum E_2 levels for nonaborters were significantly higher than those for aborters.

Introduction

Studies on the prediction and prevention of spontaneous abortions (SPAB) in the first trimester have centered around the hormones progesterone (P) and estradiol (E_2) produced by the corpus luteum. E_2 during the early first trimester is produced partly in the corpus luteum and partly in the placenta [1]. Jones and Delfa [2] have estimated that inadequate functioning of the corpus luteum may be responsible for 35% of all recurrent abortions. Most experts agree that if P drops too low, SPAB is likely to occur [3]. Witt et al. [4] have shown that although P is the single most reliable predictor of outcome in high- and low-risk pregnancy, serum E_2 levels are also likely to be lower in aborters. Low first trimester E_2 levels in aborters have also been reported by Miyakawa et al. [5], Hertz et al. [6] and Yuen et al. [7].

Despite findings of low serum E_2 levels in aborters, the modern treatment of an inadequate luteal phase, to prevent SPAB, has centered on supplementing P during the first trimester. Our group has previously published data showing reduced SPAB rates with P supplementation in anovulatory women [8, 9], in women who are habitual aborters [10] and in those with threatened abortion and low serum P levels [11].

The possibility exists that P deficiency is the main hormone deficiency leading to SPAB, and that low serum E_2 levels merely indicate waning corpus luteum function with subsequent low P levels. The study presented here was designed to measure the average serum levels of E_2 in the first trimester of pregnancy for women whose serum P levels were carefully maintained at normal levels by the use of exogenous P. We were also interested in determining if women treated with exogenous P and who still

aborted during the first trimester, had different E₂ levels compared to the women treated with exogenous P who did not abort.

Materials and Methods

The study group consisted exclusively of new patients in our infertility practice presenting either with (1) a history of infertility related to anovulation, (2) a history of two or more previous abortions, or (3) for infertility related to luteal phase deficiency (LPD) as diagnosed by a late luteal phase biopsy being out of phase by more than 2 days in 2 consecutive cycles [12]. The first 100 consecutive patients with the above diagnoses who became pregnant were prospectively enlisted in the study. A progressively increasing human chorionic gonadotropin (hCG) level up to 500 mIU/ml was required to confirm the pregnancy. Three patients were unable to return for serial hormone assays and (3) refused P therapy; these 6 were eliminated, leaving a total of 94 patients in the study.

The 94 patients were classified as follows: 24 with anovulation, 28 with recurrent abortions and 42 with LPD. All were treated in the luteal phase initially with P therapy using P vaginal suppositories 25 mg twice daily. If the repeat biopsy was still out of phase by more than 2 days, the patients were instructed not to conceive until their biopsy was in phase and the dose of P was adjusted higher. Dosages were adjusted through the first trimester to keep the serum P levels between 30–45 ng/ml.

Additionally, ovulation-inducing drugs (OVID) were prescribed for 39 women in the cycle of conception with 26 taking human menopausal gonadotropins (hMG) and 13 using clomiphene citrate (CC). HMG was used in 18 of the 24 anovulatory women and in 8 of the 42 with LPD [13]. CC was administered to the remaining 6 of the anovulatory women and in 7 with LPD but who released oocytes from immature follicles (as determined by a peak serum E₂ level in the cycle not reaching 200 pg/ml) [13].

A β-hCG level was obtained 16 days from the most mature follicle. Maturity was determined using a sonographic measurement of average follicle diameter of 18–24 mm and serum E₂ levels of at least 200 pg/ml. With the establishment of a positive pregnancy test, the P dose was doubled and the patient was requested to have a serum P, E₂ and β-hCG level measured weekly from week 4 postconception up to the first pelvic sonogram performed at 7–8 weeks. Women with viable fetuses were to continue with weekly E₂ and P monitoring until 12 weeks postconception, but the β-hCG level would no longer be obtained. If viability was not confirmed, the ultrasound was to be repeated 1 week later at which time the last E₂, P and β-hCG values would be obtained. Nonaborters had an average of 5.91 serum samples drawn, aborters an average of 4.2.

Serum E₂ measurements were performed by solid-phase radioimmunoassay (Diagnostic Products, Los Angeles, Calif., USA). The serum P and β-hCG testing was done by radioimmunoassay techniques based on enhanced luminescence (Amersham, Arlington Heights, Ill., USA). Ultrasound for follicle diameter and fetal viability was performed by one of three experienced sonographers using an ATL Ultramark 4 (Advanced Technology Laboratories, Bothell, Wash., USA) with a 5 MHz vaginal transducer.

The mean weekly serum E₂ levels were calculated and presented by pregnancy outcome (aborters and nonaborters) and by drug therapy administered in addition to P (none vs. hMG or CC).

Table 1. Patient characteristics by pregnancy outcome

	Nonaborters	Aborters
<i>Infertility factor</i>		
Anovulatory	16 (21.6)	8 (40)
LPD	35 (47.3)	7 (35)
Previous abortions	23 (31)	5 (25)
<i>Age, years</i>		
21–25	2 (2.7)	1 (5)
26–30	25 (33.8)	5 (25)
31–35	22 (29.7)	7 (35)
36–40	25 (33.8)	7 (35)
<i>Mean P dosage administered, mg</i>		
Luteal phase	68.4	65.5
First trimester	465	530
<i>OVID therapy</i>		
None	42 (56.7)	13 (65)
CC	10 (13.5)	1 (5)
hMG	22 (29.8)	6 (30)
Values in parentheses are percentages.		

Since the distribution of E₂ levels in the OVID group had a larger variance than the distribution of E₂ levels in the nonOVID group during weeks 4 and 5 postconception, and the number of serum samples drawn varied from patient to patient, an Anova model to compare mean E₂ levels over time by drug and pregnancy outcomes was deemed inappropriate. Comparisons of mean E₂ levels for each week by pregnancy outcome were made within each drug therapy group using Student's t test for independent groups with a probability level of 0.05.

Results

There were 74 women (78.8%) who successfully completed their first trimester, and 20 aborters (21.2%). A comparison of the distribution of infertility factor, age, and P dosage administered to aborters and nonaborters is presented in table 1.

In the analysis, 7 patients were identified whose data were atypical of the distribution of serum E₂ levels in the remaining sample, i.e. these 7 patients had elevated initial serum E₂ levels (> 700 pg/ml). These patients' data were not included in the calculation of mean E₂ levels for this study. In addition, it was determined that the distribution of serum E₂ levels in the OVID and nonOVID groups

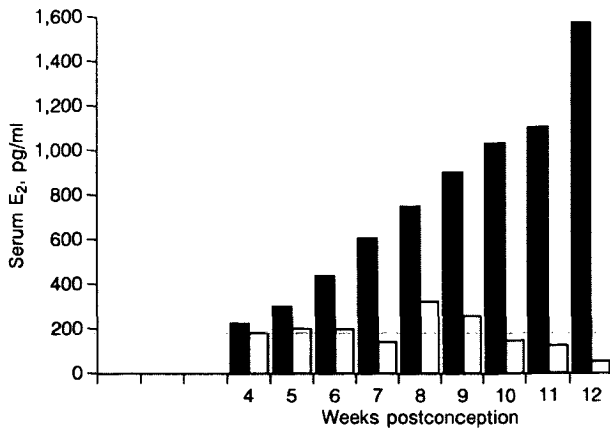


Fig. 1. Mean serum E₂ levels by pregnancy outcome in patients treated with exogenous P only. ■ = Nonaborters; □ = aborters.

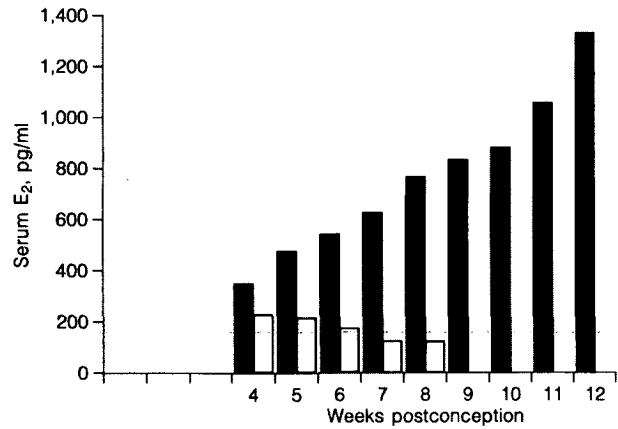


Fig. 2. Mean serum E₂ levels by pregnancy outcome in patients treated with exogenous P and OVID. ■ = Nonaborters; □ = aborters.

Table 2. Comparison of first trimester serum E₂ levels by pregnancy outcome in patients treated with exogenous P only

Weeks post-conception	Serum E ₂ , pg/ml	
	nonaborters	aborters
4	212.8 ± 71.5 (13)	175.3 ± 89.9 (10)
5	287.5 ± 111.5 (28)	195.8 ± 157.4 (12)**
6	421.8 ± 216.8 (34)	189.1 ± 126.9 (8)**
7	587.8 ± 302.2 (30)	139.1 ± 88.4 (8)**
8	734.3 ± 442.9 (35)	311.3 ± 184.2 (7)**
9	888.6 ± 445.2 (33)	246.5 ± 130.6 (4)**
10	1,018.9 ± 562.8 (30)	142.0 ± 117.0 (3)**
11	1,096.3 ± 576.1 (24)	116.0 ± 98.9 (2)**
12	1,569.6 ± 865.1 (23)	52.0 (1)

Results are presented as the mean ± SD. Values in parentheses represent the number of cases sampled. ** p < 0.05 (t test comparing mean E₂ in aborters vs. nonaborters).

Table 3. Comparison of first trimester serum E₂ levels by pregnancy outcome in patients treated with exogenous P and OVID

Week post-conception	Serum E ₂ , pg/ml	
	nonaborters	aborters
4	348.6 ± 148.4 (13)	230.8 ± 54.1 (4)
5	480.6 ± 240.9 (22)	215.6 ± 78.7 (5)**
6	545.7 ± 227.3 (24)	173.9 ± 34.9 (4)**
7	624.6 ± 282.3 (23)	126 (1)
8	762.9 ± 393.1 (21)	126 (1)
9	835.8 ± 399.1 (18)	
10	885.0 ± 430.3 (19)	
11	1,062.2 ± 438.6 (13)	
12	1,340.8 ± 490.8 (9)	

Results are presented as the mean ± SD. Values in parentheses represent the number of cases sampled. ** p < 0.05 (t test comparing mean E₂ in aborters vs. nonaborters).

were not the same. The variance of serum E₂ levels is greater in the OVID groups than in the nonOVID groups in weeks 4 and 5 postconception. These groups were therefore analyzed separately.

The average weekly serum E₂ levels for the P treated group not taking ovulation drugs is presented in table 2. Mean serum E₂ levels were significantly lower in the

aborters than in the nonaborters from week 5 to week 12 (fig. 1). In fact, 61.3% of the serum E₂ levels measured for aborters were at least 1 SD below the corresponding weekly mean for nonaborters.

There was no difference in the mean serum E₂ levels in patients taking hMG as compared to patients taking CC. These patients were therefore combined into one OVID

group. The average weekly serum E₂ levels for the OVID group are presented in table 3.

The aborters taking OVID all aborted by week 8 post-conception so the data on which to base our conclusions is more limited. At week 4 postconception, the aborters and nonaborters had the same mean serum E₂ levels, but from week 5 the aborters have lower mean serum E₂ levels similar to the trend for the nonOVID group (fig. 2). 73.3% of the individual serum E₂ levels measured for aborters were at least 1 SD below the corresponding weekly mean for nonaborters.

Discussion

It is hard to compare the 21.1% abortion rate of this study with the standard 15% level, since pregnancy is not normally established in the general population as early as 4 days after the missed menses (a 500 mIU/ml β -hCG level was used to approximate this time). Thus, this study may have included early aborters who would not have been included in general population studies, because without early β -hCG measurements and a delay in menses due to P therapy they would not have known that they were pregnant.

In the first few weeks of pregnancy, there was little difference in the serum E₂ levels between aborters and nonaborters but the differences increased weekly. The data presented here suggest that the failure of the corpus luteum may occur during the pregnancy and loss of hormones, including E₂, may account for pregnancy losses despite in-phase endometrial biopsies and maintenance of normal serum P levels.

The data presented here do not allow us to draw any definite conclusions about the efficacy of hormonal therapy in preventing SPAB. Rather, these findings stimulate speculation and allow more insight into the hypotheses that still need to be tested to resolve the conflict over the importance of corpus luteum failure and its treatment to inhibit pregnancy loss. There are several possibilities. (1) Corpus luteum failure may occur in early pregnancy despite a normal late luteal phase endometrial biopsy. (2) Correction of the out of phase endometrial biopsy without further maintenance of P and E₂ at proper critical levels during the pregnancy may still result in fetal wastage. (3) P therapy alone without E₂ therapy may be insufficient to correct LPD and provide maximum prevention of SPAB. Previous studies have also found a lower mean 17-hydroxy progesterone level in exogenous-P-maintained aborters versus nonaborters, suggesting a need for

some other initial corpus luteum hormone and perhaps this was E₂ [14]. (4) P supplementation is not necessary to prevent spontaneous abortions, but E₂ maintenance is. (5) Some other essential hormone or substance made by the corpus luteum is still missing, and supplementing E₂ and P would not prove effective in lowering the abortion rate. For example, Critchley et al. [15] found a promising substance made by the corpus luteum that allows the endometrium to respond to P in the production of placental protein 14. (6) The assumption that the rising hCG level will maintain the corpus luteum during pregnancy and thus preclude the need for hormone treatment is erroneous. (7) Placental failure is the cause of low E₂ levels, not the failure of the corpus luteum. Using donor oocytes, Devroey et al. [16] concluded that the placenta begins making E₂ between 6 and 7 weeks, so damage to the early placenta rather than to the corpus luteum is possible.

Previously, the only available norms for serum E₂ levels during the first trimester were those published by Miyawaka et al. [5]. Our data provide more exact serum E₂ levels for weeks 4 through 12 based on significantly more data, and for both the infertile patient treated with just exogenous P and for those treated with exogenous P and OVID.

Hopefully, the average E₂ levels for nonaborters presented in this study can be used in properly randomized studies in both women at risk for SPAB or women with normal risks to address some of the hypotheses proposed here.

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