

# Threshold progesterone level of 25 ng/ml to sustain pregnancy in first trimester in women with history of infertility or miscarriage

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## Abstract

**Introduction:** The importance of progesterone production by the corpus luteum to maintain pregnancy in the first trimester was first recognized in the 1970s. Since then prophylactic progesterone has been used to decrease the rate of first trimester abortions in women with a history of miscarriage. However, until recently research has failed to establish a target progesterone level at which pregnancy could be sustained in this population.

**Objective:** The objective of the study was to evaluate the effectiveness of a 25 ng/ml serum progesterone threshold to sustain pregnancy in the first trimester in patients with a history of infertility or miscarriage.

**Study design:** In this retrospective chart review, we included 182 female patients (329 pregnancies) aged 22-45 years with at least one pregnancy attempt with a private infertility clinic between 1996-2013. We excluded patients with anatomical defects, ectopic pregnancies, molar pregnancies, blighted ova, abnormal immune levels, or use of donor eggs. All patients received a full work-up including anatomical screening and immune mediators. Progesterone levels were recorded at the initial and 10-week visit. Supplemental progesterone was administered throughout the first trimester of pregnancy if serum levels fell below 25 ng/ml and continued until it was determined that the placenta had taken over progesterone production. Women were stratified based on age into two groups: prime fertility age (22-34 years old) and advanced maternal age (35-45 years old). Chi-squared tests were performed on 329 pregnancies to analyze the association between viable pregnancies in the first trimester and adequate serum progesterone levels ( $\geq 25$  ng/ml at initial and/or 10-week visit) for each age group.

**Results:** A statistically significant difference in viable pregnancy rate in the first trimester and adequate ( $\geq 25$  ng/ml) serum progesterone levels was found for both the prime fertility age group ( $X^2=57.424$ ,  $N=221$ ,  $p<0.0001$ ) and the advanced maternal age group ( $X^2=10.973$ ,  $N=108$ ,  $p=0.001$ ).

**Conclusions:** This study demonstrates that maintaining a serum progesterone level of 25 ng/ml or greater reduces risk of miscarriage in the first trimester in women of all reproductive ages.

## Introduction

Progesterone is considered the “hormone of pregnancy” due to its critical role in preparing the endometrium for implantation and maintaining pregnancy [1]. During the first trimester of pregnancy the corpus luteum is primarily responsible progesterone production. The corpus luteum regresses around 9 weeks, at which point placental progesterone synthesis takes over [2]. The importance of progesterone production by the corpus luteum was first recognized by Csapo who demonstrated that the removal of the corpus luteum before 7-weeks gestational age always results in miscarriage. During this study he observed a continual decline in progesterone, increased intrauterine pressure, and development in cervical dilation before inevitable abortion [3]. Building on this knowledge, he administered supplemental progesterone to prevent miscarriages associated with luteectomy-induced progesterone withdrawal, ultimately leading to sustained pregnancy [4].

Miscarriage is a common complication of early pregnancy with most pregnancy losses occurring before 8 weeks gestation [2,5]. The overall early pregnancy loss rate ( $\geq 12$  weeks) is around 13.5%. This rate rises with maternal age after age 20, increasing from 11.5% in women 20-24 years to 18.6% in women over the age of 30 [6]. In addition, a higher frequency of miscarriages has been observed in women with a history of infertility when compared with the general population [7].

It has been suggested that prophylactic progesterone can be used to decrease the risk of first trimester spontaneous abortions in women with a history of miscarriage [8]. Until recently research has failed to establish a target progesterone level above which pregnancy is most likely to be sustained in this population. McCord *et al.* [9] conducted a retrospective analysis of 3,674 pregnancies to examine the probability of a viable intrauterine pregnancy for a given serum progesterone concentration. The study showed the probability of a viable intrauterine pregnancy as a function of progesterone concentrations increased as a sigmoid shaped curve. This curve leveled off around 25 ng/ml and correlated to a viable intrauterine pregnancy probability of 89%, suggesting 25 ng/ml as important target progesterone concentration for sustaining pregnancy.

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## Objective

We aim to evaluate the effectiveness of a 25 ng/ml threshold progesterone level to sustain pregnancy in the first trimester in women with a history of miscarriage or infertility.

## Materials and methods

A retrospective chart review of patients from a private infertility clinic in Rockford, IL between 1996-2013 was conducted. Women with at least one pregnancy attempt with the clinic were eligible. We excluded patients with anatomical defects, ectopic pregnancies, molar pregnancies, blighted ovums, abnormal immune levels, or use of donor eggs. All other endocrinopathies were addressed and corrected. 182 women between 22-45 years, totaling 329 pregnancies, were enrolled in the study. These patients were stratified into two groups: prime fertility age (22-34 years) and advanced maternal age (35-45 years).

All patients received a full work-up including a full history and physical, transvaginal ultrasound, hysterosalpingogram and/or a saline infusion sonohysterogram. Serum progesterone levels were recorded at the initial visit (2-6 weeks post-conception) and 10-week visit, and monitored every 2 weeks until the transition from ovarian to placental progesterone production was complete. This was determined by examining the trend of serum progesterone throughout the first trimester. Once serum levels had risen to a point where removal of the supplement would still leave patients at or above 25 ng/ml, supplemental progesterone was discontinued. Progesterone levels were checked 2-3 days after discontinuation to ensure levels were at or above 25 ng/ml, confirming transition to placental progesterone production. After progesterone production by the placenta had occurred, patient care was transferred to community obstetricians. Over the years 12 pregnancies required hormonal support the entire pregnancy. For these individuals, patient care was still transitioned to community obstetricians during the second trimester, but we continued to monitor their hormone levels throughout the duration of their pregnancy.

In this study, adequate serum progesterone levels were defined as  $\geq$  25 ng/ml at the initial and/or 10-week visit. Supplemental progesterone was administered to patients if serum progesterone levels fell below 25 ng/ml during the initial or 10-week visit. In cases where patients were already receiving supplemental progesterone, progesterone dose was increased to achieve adequate serum progesterone levels. Method of progesterone supplementation was determined based on patient preference and side effects, and included: oral, vaginal, and intramuscular supplementation. Patients who exhibited poor absorption or tolerance with oral or vaginal progesterone were administered intramuscular progesterone in oil.

The primary outcome was a viable pregnancy in the first trimester. Viable pregnancy was determined by a detailed morphologic ultrasound assessment of the fetus at 11-13 weeks. We did not follow up once the patient was handed off to the community obstetrician, except for the 12 cases described previously that required continuous monitoring during the entire duration of pregnancy. Of note, all 12 pregnancies reached the late third trimester.

Chi-squared tests were performed to analyze the association between viable pregnancies and adequate serum progesterone levels. An *a priori* alpha level of 0.05 was used. SPSS Statistics version 24 was used for all statistical analysis.

## Results

In total, 329 pregnancies were included with 221 in the prime fertility age group (22-34 years) and 108 in the advanced maternal

age group (35-45 years). For women of all ages 287 out of 329 (87%) pregnancies obtained adequate progesterone levels ( $\geq$  25 ng/ml at initial and/or 10-week visit). 188 out of 221 (85%) pregnancies in the prime fertility age group, and 99 out of 108 (92%) in the advanced maternal age group obtained adequate progesterone levels (Table 1).

Viable pregnancy rate was consistently higher in all age groups for those with adequate progesterone levels compared to those with inadequate progesterone levels. In total, 208 out of 287 (72%) pregnancies with adequate progesterone levels resulted in viable pregnancies, while only 5 out of 42 (12%) pregnancies with inadequate progesterone levels resulted in viable pregnancies ( $n=329$ ,  $X^2$  58.883,  $p<0.0001$ ). In the prime fertility age group (22-34 years), 151 out of 188 (80%) pregnancies with adequate progesterone levels resulted in viable pregnancies, while only 5 out of 33 (15%) pregnancies with inadequate progesterone levels resulted in viable pregnancies ( $n=221$ ,  $X^2$  57.424,  $p<0.0001$ ). In the advanced maternal age group (35-45 years), 57 out of 99 (58%) pregnancies with adequate progesterone levels resulted in viable pregnancies, while 0 out of 9 (0%) pregnancies with inadequate progesterone levels resulted in viable pregnancies ( $n=108$ ,  $X^2$  10.973,  $p=0.001$ ) (Table 2).

## Discussion

To the best of our knowledge this is the first study to investigate a threshold progesterone level for sustaining pregnancy. The results show 25 ng/ml is an effective threshold serum progesterone level for sustaining pregnancy in the first trimester in women with a history of miscarriage or infertility in both women of prime fertility age (22-34 years) and advanced maternal age (35-45 years). The data suggest that maintaining a 25 ng/ml progesterone level during the first trimester of pregnancy reduces risk of miscarriage in this population.

This study has several limitations. Because all patients were from a single infertility center, the results may have limited applicability

**Table 1.** Adequate progesterone levels stratified by age group.

Adequate progesterone levels stratified by age group		
	Inadequate serum progesterone levels <sup>a</sup>	Adequate serum progesterone levels <sup>b</sup>
All ages (22-45 years)	42 (13%)	287 (87%)
Prime fertility age (22-34 years)	33 (15%)	188 (85%)
Advanced maternal age (35-45 years)	9 (8%)	99 (92%)

<sup>a</sup>Less than 25 ng/ml at initial and 10-week visit  
<sup>b</sup>Greater than or equal to 25 ng/ml at initial and/or 10-week visit

**Table 2.** Viability pregnancies in first trimester stratified by age group.

Viability pregnancies in first trimester stratified by age group			
	Viable pregnancies in first trimester <sup>a</sup>		Statistical comparison <sup>d</sup>
	Inadequate serum progesterone levels <sup>b</sup>	Adequate serum progesterone levels <sup>c</sup>	
All ages (22-45 years)	5 (12%)	208 (72%)	$p < 0.0001$
Prime fertility age (22-34 years)	5 (15%)	151 (80%)	$p < 0.0001$
Advanced maternal age (35-45 years)	0 (0%)	57 (58%)	$p = 0.001$

<sup>a</sup>Determined by detailed morphologic ultrasound assessment at 11-13 weeks  
<sup>b</sup>Less than 25 ng/ml at initial and 10-week visit  
<sup>c</sup>Greater than or equal to 25 ng/ml at initial and/or 10-week visit  
<sup>d</sup> $X^2$  squared test for categorical values to evaluate association between viable pregnancies and adequate serum progesterone levels

to other populations. Future multicenter studies with a more diverse population and larger sample size would broaden demographic results and allow for further stratification.

In addition, method of conception varied for patients in this study. It has been suggested that previously infertile patients conceived with artificial reproductive technology (ART) have only slightly increased or similar spontaneous abortion rates when compared to naturally conceived pregnancies [10,11]. Because our patient population includes women with a history of infertility, infertile patients conceived via ART may not truly represent the effects of a 25 ng/ml threshold progesterone level of this patient population.

The method of progesterone supplementation was also not controlled for in this study. It has been hypothesized that different routes of progesterone supplementation have different effects on the endometrium, rates of absorption and elimination, and distribution profiles. Oral progesterone, for instance, has been found to be ineffective on endometrial secretory transformation at a serum progesterone level considered adequate for this process. Similarly, vaginal progesterone was observed to exert its action on the endometrium at lower serum concentrations due to its pronounced potency on the uterus, the so-called first uterine pass effect [12]. In our study, it was assumed that a serum progesterone concentration of 25 ng/ml or greater, regardless of avenue of progesterone delivery, was sufficient to exert its effects on the uterus in an intrauterine pregnancy. Future studies controlling for method of progesterone supplementation may reduce inconsistencies in progesterone-induced uterine changes.

Finally, this study did not control for multiple pregnancies (e.g. twins). Studies have advocated that progesterone is the strongest predictor of a viable pregnancy, and have suggested twin pregnancies may require as high as 58 ng/ml serum progesterone level to sustain pregnancy [13,14]. While our study sustained 35 twin and triplet pregnancies in the first trimester with a 25 ng/ml threshold, these pregnancies had an average progesterone level greater than 100 ng/ml, almost twice the average of the viable singleton pregnancies (65 ng/ml). A proportion of the nonviable pregnancies in our study, then, may be due to inadequate progesterone levels in women who were carrying multiples. Further studies would help determine whether different serum progesterone thresholds are needed for singleton versus multiple pregnancies.

Our results also support future studies that aim to establish higher serum progesterone thresholds for women of advanced maternal age. In our study, a large proportion of women with adequate serum progesterone levels in the advanced maternal age group still resulted in miscarriage. Additionally, 0% of women in the advanced maternal age group with inadequate progesterone levels had a viable pregnancy. This suggests that women 35 years and older may require a higher threshold progesterone level than those younger than 35. As more women are delaying pregnancy until after age 35, further investigation into a higher threshold level for women of advanced maternal age would be beneficial [15].

To our knowledge, this is the first study to establish an effective target progesterone level for sustaining pregnancy in the first trimester in women with history of infertility or miscarriage. This study demonstrates the need to be more vigilant in monitoring progesterone levels in the first trimester of pregnancy and intervening if necessary in women with a history of infertility or miscarriage.

## Conflict of interest

The authors report no conflict of interest

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