Serum progesterone distribution in normal pregnancies compared to pregnancies complicated by threatened miscarriage from 5 to 13 weeks gestation

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Introduction

- Threatened miscarriage is common
  - 15 – 20% of pregnancy\(^1\)
- 15% – 25% of women with threatened miscarriage progress to spontaneous miscarriage\(^2\)
- Progesterone is a critical hormone during implantation\(^3\)
  - Sustains decidualization
  - Controls uterine contractility
  - Promotes maternal immune tolerance to the fetal semi-allograft

Measurement of serum progesterone

- One of the earliest studies of plasma progesterone, showing an *increasing* trend in pregnancy

![Graph showing plasma levels of progesterone in peripheral venous blood during pregnancy of 62 women (× singles; • twins)](image)

Rise in serum progesterone throughout pregnancy

- Increase in maternal serum progesterone (green line) throughout pregnancy

Serum progesterone in early pregnancy

- There are very few studies that show the distribution of serum progesterone in early pregnancy.

- Our group has shown that a single serum progesterone cutoff of 35 nmol/L can differentiate women with a threatened miscarriage who will go on with an ongoing pregnancy or spontaneous miscarriage.

- Hypothesis: Women with low risk pregnancy have a different serum progesterone distribution compared to women with threatened miscarriage.

Objectives

- To establish the *distribution of maternal serum progesterone* in normal *low risk pregnancies* and pregnancies complicated by *threatened miscarriage* from 5 to 13 weeks gestation.
Methods

- This is a single tertiary centre, **prospective cohort study** of 929 patients from 2013 to 2016.
- Women from the normal pregnancy cohort were recruited from antenatal clinics undergoing routine screening and those in the threatened miscarriage cohort were recruited from emergency walk-in clinics.
- Women with previous episodes of per vagina bleeding or those treated with progesterone for previous per vagina bleeding in the current pregnancy, IVF, or women diagnosed with inevitable miscarriage, missed miscarriage, blighted ovum or planned termination of pregnancy were excluded.
Methods

- Quantile regression was used to characterize serum progesterone levels in the normal and threatened miscarriage cohorts by estimating the 10th, 50th and 90th percentiles from 5 to 13 weeks gestation.
- Pregnancy outcome was determined at 16 weeks of gestation.
- Subgroup analysis within the threatened miscarriage cohort, to compare progesterone levels of women who subsequently miscarried with those who had ongoing pregnancies at 16 weeks of gestation.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Risk (n=450)</th>
<th>High Risk (n=479)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage rate (%)</td>
<td>5.4</td>
<td>21.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maternal Age (yr)</td>
<td>30.9 (4.0)</td>
<td>30.6 (4.5)</td>
<td>0.058</td>
</tr>
<tr>
<td>Serum Progesterone (nmol/L)</td>
<td>71.8 (27.2)</td>
<td>53.6 (25.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gestational Age (wk)</td>
<td>8.4 (2.1)</td>
<td>7.3 (1.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>22.9 (4.2)</td>
<td>23.1 (4.6)</td>
<td>0.459</td>
</tr>
<tr>
<td>Fetal Heart (%)</td>
<td>87.6</td>
<td>85.8</td>
<td>0.442</td>
</tr>
<tr>
<td>Previous Miscarriage (%)</td>
<td>18.7</td>
<td>23.0</td>
<td>0.107</td>
</tr>
<tr>
<td>DM (%)</td>
<td>0.21</td>
<td>0.23</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*a Mean (SD)*
Distribution of serum progesterone across gestation weeks 5-13 amongst women with low risk pregnancy vs threatened miscarriage.

- **Low risk cohort**
  - Linearly increasing trend from 60 nmol/L to 80 nmol/L ($p<0.0001$)

- **Threatened miscarriage cohort**
  - Linearly increasing trend from 40 nmol/L to 80 nmol/L ($p<0.0001$)

- Median progesterone levels were uniformly lower in the threatened miscarriage cohort by approximately 10 nmol/L, converging towards the end of the first trimester with similar values at 13 weeks gestation.
Women who progress to spontaneous miscarriage have much lower serum progesterone, with marginal increase across gestations.
Clinical implication

- This is one of the first studies describing the distribution of serum progesterone in low risk pregnancies compared to those with threatened miscarriage.
- This study highlights the **pivotal role of progesterone in supporting early pregnancy**, where a lower serum progesterone is associated with threatened miscarriage and subsequent complete miscarriage at 16 weeks gestation.
- The different distribution curves may potentially be used as a reference range for women who present with low risk pregnancies or threatened miscarriage.
Limitations

- The distribution of serum progesterone across gestations is not taken from the same patient, so it may be affected by inherent biological variation amongst patients.
- Further studies need to be conducted to evaluate the underlying pathophysiology of low progesterone and miscarriage, and examine the role of progestogens in the management of women with threatened miscarriage.
Thank You!

- Any questions?

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