Research Article

Effect of Progesterone Supplementation to Prevent Preterm Labor

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ABSTRACT

Preterm birth is the most important problem in maternal and child health throughout the world. It complicates one in eight deliveries and accounts for over 85% of all perinatal morbidity and mortality. On February 3, 2011, the US food and drug administration (FDA) approved the use of progesterone supplementation during pregnancy to reduce the risk of recurrent preterm birth in women without prior spontaneous preterm delivery.

Aim

1. To determine the impact of progesterone therapy in prevention of preterm labor.
2. To measure the maternal and perinatal outcome in those treated by progesterone.

Materials and Methods

Study Design: Randomized control trial
Study Setting: Department of Obstetrics and Gynaecology, Government medical College, Kottayam, Kerala, India
Study Period: March 2012 to March 2014
Methodology: 88 antenatal women with a previous history of spontaneous preterm vaginal delivery were chosen for the study and they were randomly assigned as cases who received progesterone and controls who do not receive progesterone. Natural micronized progesterone is used in this study. There is functional progesterone withdrawal which is a cause for onset and establishment of labor in both preterm and term deliveries. This is the rationale for providing progesterone to prevent preterm labor.

Results: Progesterone is effective in preventing preterm labor in those women with a history of spontaneous preterm labor.

Conclusion: Progesterone supplementation is a very good method to prevent preterm labor and should be continued until 37 weeks. There is significant improvement in neonatal outcome in progesterone users.

Keywords: Vaginal progesterone, Preterm labor, Perinatal outcome.

Introduction

Preterm (premature) birth refers to any delivery occurring prior to 37-0/7 weeks (259 days) of gestation. Preterm birth complicates one in eight births, and accounts for more than 85% of all perinatal morbidity and mortality. (1) On February 3, 2011, the US Food and Drug Administration (FDA) approved the use of progesterone...
supplementation to reduce the risk of recurrent preterm birth in women with a singleton pregnancy who have a history of at least one prior spontaneous preterm delivery. The overall preterm birth rate has been accompanied by an increase in moderately preterm (28-34 weeks) and extreme preterm births (< 28 weeks). In the last two to three years that there has been a decrease in the preterm birth rate. The reason may represent a plateauing of the risk factors for preterm birth (including advanced maternal age and the use of assisted reproductive technology), a systematic change in the management of pregnancies that leads to late preterm births (defined as delivery from 34-37 weeks, which accounts for 75% of all preterm births). Preterm babies contribute maximum to the neonatal and infant mortality all around the world. India is the largest contributor to preterm deliveries and thereby India contributes significantly to the neonatal and maternal deaths. Various studies have found that progesterone is effective in prevention of preterm labor. If progesterone supplementation is successfully implemented and the rate of preterm deliveries decreased, it will help in moulding a healthier generation.

The exact mechanism of preterm labor is largely unknown but is believed to include decidual haemorrhage (eg. Abruption, mechanical factors such uterine over distension from multiple gestation or polyhydramnios), cervical incompetence, uterine distortion, cervical inflammation, maternal infections, hormonal changes (eg. Mediated by maternal and fetal stress) and uteroplacental insufficiency (eg.Hypertension, insulin-dependent diabtetes, drug abuse, smoking, alcohol consumption). Recent data suggest that progesterone may be important in maintaining uterine quiescence in the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhibiting the expression of contraction-associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium. It is now clear that, although levels of progesterone in the maternal circulation do not change significantly in the weeks preceding labor, the onset of labor both at term and preterm is associated with a functional withdrawal of casual role. Several studies have indicated immune regulated genes in potentiating chorioamnion in cases of preterm delivery, due to infection. A history of prior preterm deliveries play an important predictor of recurrent preterm birth, past obstetric history may be one of the strongest predictors of recurrent preterm birth. Given a baseline risk of 10-20%, the risk of recurrent preterm birth after 1, 2 and 3 consecutive preterm births may be increased approximately 15%, 30% and 45% respectively. Preconceptual counselling should help to encourage patients to make informed decisions concerning future pregnancy in light of prematurity risk in the presence of previous preterm delivery. Often the best time to counsel the patient is after 4-6 weeks of her preterm delivery. Accumulating evidence suggests that the myometrial activity associated with preterm labor results primarily from a release of the inhibitory effects of pregnancy on the myometrium rather than an active process mediated through the release of uterine stimulants, and progesterone produced by the corpus luteum is critical to the maintenance of early pregnancy until the placenta takes over this function at 7 to 9 weeks of gestation. Indeed, removal of the source of progesterone (the corpus luteum) or administration of a progesterone receptor antagonist readily induces abortion before 7 weeks (49 days) of gestation. The role of progesterone in later pregnancy, however, is less clear.
progesterone activity at the level of the uterus. This is the rationale behind the use of progesterone supplementation to prevent preterm labor and birth.\(^2\)\(^9\)

Although secondary analyses of clinical trials have suggested that women who benefit most from 17P supplementation are those who experienced a prior spontaneous preterm birth <34 weeks, it is reasonable to offer such prophylaxis to all women with a prior spontaneous preterm delivery. If used, progesterone supplementation should generally be initiated between 16 and 20 weeks of gestation, although patients were enrolled in trials up to 26.9 weeks, and treatment should be continued through 36 weeks of gestation. Indeed, early discontinuation of therapy appears to increase the risk of recurrent preterm birth. Of note, a history of a prior preterm delivery of twins should not be written off to the multiple gestations alone. Women with such a history are at risk of a recurrent preterm birth even if the subsequent pregnancy is a singleton, and should be considered as candidates for progesterone supplementation.\(^2\)

ACOG recommends that progesterone supplementation be restricted to women with a singleton pregnancy and a previous history of spontaneous preterm birth. The major secondary indication is cervical shortening. Women with a shortened cervix (≤1.5 cm) on transvaginal ultrasound in the mid trimester should be considered for progesterone supplementation. Because both clinical trials used vaginal progesterone; it would be reasonable to recommend this route of administration.\(^2\)

Although supplemental progesterone does appear to be effective in preventing preterm birth in some high-risk women, it should not be seen as a panacea. Progesterone supplementation prevents only one-third of recurrent preterm births and the long-term benefits of progesterone supplementation are not yet clear. An analysis of 2002 national birth certificate data demonstrated that, even if all eligible women had received progesterone prophylaxis, it would only have reduced the overall preterm birth rate in the United States by approximately 2% (from 12.1% to 11.8%). This is because only 22.5% of preterm births in 2002 were recurrent and prophylaxis only reduces the incidence of recurrent preterm birth by approximately 33%.\(^2\)

Propagesterone also known as P4 (pregn-4-ene-3,20-dione) is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen.\(^2\)

**Proposed Mechanisms of Progesterone Action**

Although levels of progesterone in the maternal circulation during labor are not different from that measured 1 week prior, there is increasing evidence to suggest that labor, both at term and preterm, is preceded by a function withdrawal of progesterone action at the level of the uterus. A number of mechanisms have been proposed to explain how progesterone may act to maintain uterine quiescence and prevent preterm birth;\(^2\)

At The Level of The Myometrium and Cervix:

Progesterone has numerous effects on the myometrium and cervix. It differentially regulates the expression of the two major isoforms of the progesterone receptor (PR) gene, PR-A and PR-B, leading at term to a PR-A/PR-B ratio that favors myometrial contractility and cervical effacement. It alters the expression of PR coactivators and his tone acetylation within myometrial cells, which are key regulators of myometrial contractility. It interferes with oxytocin binding and signaling in a nongenomic fashion by binding directly with the transmembrane oxytocin receptor. It alters immune function both systemically and at the maternal-fetal interface. And most recently, it has been shown to modulate myometrial expression of a number of miRNA-200 family members and their targets, ZEB1 and ZEB2, which, in turn, directly regulate the expression of key contraction-associated genes, including the oxytocin receptor and connexin-43.
At The Level of The Placenta: Progesterone has been shown to interfere with cortisol-mediated regulation of placental gene expression, the most important of which is placental corticotropin-releasing hormone (CRH), which has been implicated as the "placental clock" regulating the timing of labor.

In Amniotic Fluid: Progesterone has been shown to up regulate an endogenous inhibitor of phospholipase A2, which is present in high concentrations in amniotic fluid. High levels of such an inhibitor would serve to limit the availability of arachidonic acid and thereby the production of prostaglandins.

At The Level of The Fetal Membranes: One third of preterm birth occurs in the setting of PPROM. Recent studies have shown that progesterone is able to inhibit apoptosis (programmed cell death) in term fetal membranes both under basal conditions and in the setting of inflammation. These data suggest that progesterone may block pro-inflammatory cytokine-induced apoptosis within the fetal membrane, thereby preventing PPROM and subsequent preterm birth.

Two major types of progesterone are described:

1. Synthetic Progestins include such as medroxy progesterone acetate and norethindrone acetate. They are typically given by injection, and may have significant androgenic activity.

2. Natural Progesterone: These agents include progesterone powders, capsules, and gels as well as injectable, progesterone in-oil. They can be given vaginally, orally, or by injection. The advantage of vaginal progesterone is its high uterine bioavailability because uterine exposure occurs before the first pass through the liver. It also has fewer systemic side effects, although vaginal irritation can be bothersome. Because vaginal progesterone has a half-life of approximately 13 hours, it should be administered daily. Doses of 90 to 400 mg have been recommended. An oral micronized preparation of natural progesterone also exists, although daily doses of 900 to 1600 mg have to be given. Side effects include sleepiness, fatigue, and headache. (10) (11) The only study to date to investigate the effect of oral micronized progesterone (400 mg daily) on the rate of recurrent preterm birth was underpowered to detect any significant difference, with a total of only 33 study subjects. (12) 17P is a natural progesterone with no androgenic activity that is produced by both the corpus luteum and placenta.

Exogenous 17P is administered intramuscularly. Doses have ranged from 25 mg every 5 days to 1000 mg weekly, beginning as early as 16 weeks of gestation. Because the half-life of 17P is approximately 7 days, (13) weekly dosing would seem most appropriate. Although actively metabolized in the placenta, significant concentrations of exogenous 17P and its metabolites do cross the placenta. (14)

Safety of Progesterone Use in Pregnancy
The safety of 17P in pregnancy has been confirmed by numerous epidemiologic studies and clinical trials. This point was repeated again in the recent FDA statement approving 17P for use in Pregnancy. Several studies have suggested that the risk of miscarriage and stillbirth may be increased in women exposed to progestins, but none of these differences reached statistical significance. Moreover, not all studies were able to confirm this observation, and yet others have suggested that progestins may be protective in this regard. (15) The only concern that persists is a possible increased risk of hypospadias in male offspring exposed to exogenous progestins; even if real, however, this risk is limited to exposure prior to 11 weeks of gestation and, as such, is not relevant to the current discussion. (2)

Aim of Study
1. To determine the impact of progesterone therapy in prevention of preterm labor.
2. To measure the maternal and perinatal outcome in those treated by progesterone.

Materials and Methods
This is a randomized control trial performed in the Department of Obstetrics and Gynaecology, Government Medical College, Kottayam during the period March 2012 – March 2014 after getting the approval from the ethical committee Government Medical College, Kottayam. Proper informed consent was obtained from all the patients after explaining the benefits of the study.

Study Design
Randomized control trial

Study group – women who receive vaginal progesterone therapy

Control group - those who do not receive vaginal progesterone therapy

Study Settings
Department of Obstetrics and Gynaecology, Government Medical College, Kottayam.

Study Duration
March 2012 – March 2014

Inclusion Criteria
- Antenatal women with a history spontaneous preterm delivery
- Singleton pregnancy
- 24 weeks gestation
- Maternal age between 20 to 40 years
- Non anomalous fetus
- Intact membrane at the time of antepartum testing

Exclusion Criteria
- Fetal anomalies
- Intrauterine death
- Multiple pregnancies

Statistical Analysis
The data were collected and tabulated into excel sheet and SPSS software data variable. Chi-square analysis and paired t test were used for qualitative variables and p value less than 0.05 was taken as statistically significant. Qualitative data were expressed as number and percentage and Quantitative data were expressed as mean ±SD.

Results and Observations
A total of 88 antenatal women were selected for the study. 44 women are chosen as cases and 44 as controls.

Table 1: Gestational age

<table>
<thead>
<tr>
<th>Gestational age (First delivery)</th>
<th>Progesterone (n=44)</th>
<th>No Progesterone (n=44)</th>
<th>Statistic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.2±2.7</td>
<td>33.5±2.6</td>
<td>0.18</td>
<td>p&gt;.05</td>
<td></td>
</tr>
<tr>
<td>Gestational age (Subsequent delivery)</td>
<td>37.5±2.2</td>
<td>36.3±2.4</td>
<td>2.4</td>
<td>p&lt;.05</td>
</tr>
</tbody>
</table>

- Use of cervical encirclage
- PPROM
- History of cervical injury / surgery

Sample Size: 88 antenatal women

Randomizing Technique: Random number table

Procedure
- 88 antenatal women, with a previous history of spontaneous preterm labor, satisfying all inclusion criteria; are selected from antenatal OP after getting informed consent. 44 women were chosen as cases and 44 controls.
- They are randomly assorted into case and control groups by using a proforma to collect data.
- A detailed history and examination done meanwhile.
- Those in the case group are advised to insert micronized progesterone capsules vaginally, one per night without fail from 24 weeks to 37 weeks gestation.
- Those in the control group will not receive progesterone therapy.
- Patients are followed up in the OP/labor room/postnatal ward.
- Symptoms suggestive of preterm labor will be carefully looked for.
The statistical analysis of gestational age at first preterm delivery after subdividing them into progesterone and non-progesterone groups. There is a significant increase in the number of term pregnancies in the progesterone group and it shows that progesterone helps in preventing preterm labor. The P value is <.05 which is statistically significant. This table also shows that the gestational age at which previous delivery occurred, is comparable in both groups.

Table 2: Mode of delivery

<table>
<thead>
<tr>
<th>Mode of delivery (Subsequent)</th>
<th>Progesterone (n=44)</th>
<th>No Progesterone (n=44)</th>
<th>Statistic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced</td>
<td>12(27.3)</td>
<td>16(36.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>32(72.7)</td>
<td>28(63.6)</td>
<td>9.2</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Here mode of delivery is compared statistically between two groups to know whether intervention with progesterone is contributing to inductions. The P value is <.05 which is statistically insignificant. So it can be concluded that progesterone has no role in leading to induction. 12 were induced in the progesterone group and 16 in the non-progesterone group which are similar values.

Table 3: Route of delivery

<table>
<thead>
<tr>
<th>Route of delivery (Subsequent)</th>
<th>Progesterone (n=44)</th>
<th>No Progesterone (n=44)</th>
<th>Statistic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>42(95.5)</td>
<td>38(86.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency LSCS</td>
<td>2(4.5)</td>
<td>6(13.6)</td>
<td>2.2</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

The percentage of emergency C S in the intervention group is 4.5% and that in non-intervention group is 13.6%. The overall P value from the chart is >.05 which is statistically insignificant. So from this it can be inferred that route of delivery is not significantly affected by progesterone use. All the C S were emergency C S, various indications being breech, fetal distress etc.

Table 4: Outcome of delivery

<table>
<thead>
<tr>
<th>Outcome (First delivery)</th>
<th>Progesterone (n=44)</th>
<th>No Progesterone (n=44)</th>
<th>Statistic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>34(77.3)</td>
<td>32(72.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NND</td>
<td>10(22.7)</td>
<td>12(27.3)</td>
<td>0.242</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Outcome (Subsequent delivery)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>42(95.5)</td>
<td>40(90.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NND</td>
<td>2(4.5)</td>
<td>4(9.1)</td>
<td>0.71</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

The overall P value is >.05 which is not statistically significant. This table again shows that both the groups of women had comparable neonatal outcome in the first delivery. The percentage of healthy babies in the non-progesterone group is 72 and that in progesterone group is 77. Neonatal mortality in non-progesterone group was 27% and that in progesterone group is 22%.
Table 5: Birth weight of babies

<table>
<thead>
<tr>
<th></th>
<th>Progesterone (n=44)</th>
<th>No Progesterone (n=44)</th>
<th>Statistic</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (First delivery)</td>
<td>2.16±0.6</td>
<td>1.83±0.07</td>
<td>3.6</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Birth weight (Subsequent delivery)</td>
<td>2.7±0.8</td>
<td>2.4±0.5</td>
<td>2.2</td>
<td>p&lt;.05</td>
</tr>
</tbody>
</table>

Statistical analysis of comparison between mean birth weights in both the groups shows:- Mean birth weight in the non-intervention group is 2.4±0.5 and that in intervention group is 2.7±0.8 which is higher. The t value is 2.2 and P value is <.05, both of which are statistically significant. This shows that progesterone helps in increasing birth weight by preventing preterm labor.

Analysis of the Results

At Government Medical College Kottayam, an average of 400-500 deliveries takes place per month. A minimum of 150 antenatal women visit our OPD in a day. The average incidence of preterm delivery is 10% in our hospital. Antenatal women with a history of spontaneous preterm vaginal delivery were randomized evenly into case and control groups. Patients were followed up in OP, labor room and postnatal ward. No maternal or fetal adverse effects were noted during the therapy.

During previous pregnancy, 8 women had vaginal delivery between 24-28 weeks, 7 women delivered between 28-32 weeks and 73 women delivered between 32-37 weeks. In the subsequent pregnancy, no woman delivered between 24-28 weeks. 4 women delivered between 28-32 weeks in the subsequent pregnancy. 27 women delivered between 32-37 weeks with progesterone. 57 women delivered after 37 weeks in progesterone group.

The need for induction in the progesterone and non-progesterone group was compared. 16 were induced in non-progesterone group and 12 in the progesterone group. 28 had spontaneous labour in non-progesterone group and 32 in progesterone group. The overall p value is 0.36. Hence the change seen is not statistically significant.

The non-progesterone group had 38 vaginal deliveries i.e. 86% and 6 LSCS contributing to 13.1%. In progesterone group 42 had vaginal delivery (95%) and 2 underwent LSCS (4%). The overall p value is >0.05 which is not significant. So the route of delivery is not significantly altered by progesterone.

The outcome of pregnancy i.e. whether the baby was healthy or died in the neonatal period was unaltered. The progesterone users group did not have a significant improvement in outcome in terms of this. The number of healthy babies in the non-progesterone group in the first pregnancy was 32, where as in the subsequent pregnancy it was 40. 12 were NND in the first pregnancy in the non-progesterone group and 4 NND in the subsequent pregnancy. The number of healthy babies in the progesterone group in the first pregnancy was 34 and that in subsequent pregnancy is 42. NND in the same group in the first pregnancy was 10 and after using progesterone, it was 2.

The birth weight of babies born in the subsequent pregnancy was charted after dividing into 3 groups i.e. <1kg, 1-2 kg and >2 kg. In the non-progesterone group <1kg babies were 5, in the progesterone it were 4.1-2 kg babies in the non-progesterone group were 25 and in progesterone group were 12. >2 kg babies in the non-progesterone group were 14 and that in progesterone group were 28 (50% increase). The p value is 0.001 which shows a significant increase in birth weight (by preventing preterm delivery) in the progesterone group. The mean birth weight in non-progesterone group as 2.356 kg and that in progesterone group was 2.66 kg. The p value is <.05 which is statistically significant.

Limitations of the Study

1. Strict compliance to the therapy is an issue as daily vaginal progesterone application may not be a comfortable option for some women.
2. The multitude of factors causing preterm labor often confuses the scenario. Progesterone may be useful in woman with recurrent preterm delivery. But extrapolation of its use in multiple pregnancies or in primigravidae with preterm pain or short cervix is controversial. These aspects are not considered in this study.

Conclusion
1) Progesterone therapy is a very good method to prevent preterm labor.
2) Strict compliance to the therapy is needed.
3) Progesterone therapy should be continued until 37 weeks.
4) There are no maternal or foetal adverse effects for progesterone.
5) There is significant improvement in birth weight and neonatal outcome in progesterone users (as preterm labour is prevented).
6) Even though the incidence of preterm labour is reduced; the outcome, as measured by the number of healthy babies and the babies who died in the neonatal period do not show a significant change in case and control group.
7) The route of delivery is not significantly affected by the use of progesterone.

Recommendations
1) The recommendations put forward as per the results of our research: is to promote the use of natural progesterone from 24-37 weeks of gestation; to prevent preterm labor.
2) Prevention of preterm labor by this simple method helps to reduce neonatal morbidity and mortality to a great extent.
3) It is a cost effective method compared to the huge expenditure required to manage the problems of a preterm baby.
4) Vaginal route of progesterone application is better as it is more bioavailable via this route. Only half the amount of progesterone is required if this route is used.

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Declaration
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Conflict of interest: None declared

Bibliography


