Effect of Vaginal versus Intramuscular Progesterone in Prevention of Recurrent Preterm Labor

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Abstract

Objectives: The aim of this study is to compare between vaginal and intramuscular progesterone in the prevention of recurrent preterm labor.

Study Design: Comparative clinical trial.

Methodology: This study is a comparative clinical trial, which was carried out at Kasr El-Ainy Maternity Hospital during the period between January 2014 and January 2016. One hundred (100) pregnant women who have history of previous spontaneous preterm labor (s) were selected in this study and randomly arranged into three groups [vaginal progesterone Group (A), intramuscular progesterone Group (B) and control Group (C)].

Results: Preterm labor was higher among the control group in comparison to progesterone group also the vaginal progesterone was higher compared to the intramuscular progesterone group in prevention of preterm labor.

Conclusion: Prophylactic use of progesterone reduces the rate of preterm labor in women with history of recurrent spontaneous preterm labors, vaginally administrated progesterone was nearly as equally effective as intra muscular progesterone in the prevention of PTL in women at risk with superior effect with vaginal route.

Key Words: Vaginal progesterone – Intramuscular progesterone – Recurrent preterm labor.

Introduction

PRETERM labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation (before completing 37wks of gestation) [1].

Preterm Labor (PTL) is the leading cause of perinatal and neonatal morbidity and mortality and strongly related to the developmental and neurological disabilities later in life [2].

The incidence of this problem is rising and is reported to be 15% of pregnancies in the developed world. So, its prevention is considered a major challenge for obstetricians.

The obstetric events that precede preterm labor are:
A- Spontaneous preterm labor constitutes 40-45% of all preterm labors.
B- 25-30% of preterm labors occur after premature rupture of membranes.
C- The remainder 30-35% of preterm labors are induced for obstetrical reasons; obstetricians may have to deliver the baby preterm because of a deteriorating intrauterine environment (i.e. infection, intrauterine growth retardation) or significant endangerment of the maternal health (i.e. preeclampsia, cancer) [3].

By gestational age, 5% of preterm labors occur at less than 28 weeks (extreme prematurity), 15% at 28-31 weeks (severe prematurity), 20% at 32-33 weeks (moderate prematurity), and 60-70% at 34-36 weeks (near term) [3].

Complications from preterm birth are not limited to the neonatal period, such as in retinopathy of prematurity, intraventricular hemorrhage, necrotizing enterocolitis, respiratory disorders and sepsis; they can also constitute sequelae such as abnormal neurophysiological development in early childhood and underachievement at school, the early detection of pregnant women at high risk for preterm labor could be the best way to prevent preterm labor [4].

Thereby, bed rest, cervical cerclage, bacterial vaginosis treatment, and prophylactic use of progesterone could be one of the managements in this high-risk population [5].
Labor in sheep is preceded by a decrease in progesterone and an increase in estradiol (E2) plasma concentrations which result from conversion of progesterone to E2, mediated by placental 17α-hydroxylase. 17α-hydroxylase is not present in the human placenta and there is no evidence for a decrease in progesterone or an increase in E2 before the onset of term labor in women, although the concept of 'functional progesterone withdrawal' has been supported by investigations of the progesterone receptor and its isoforms, recent study has shown that frequency and intensity of uterine contractions are increased before the onset of preterm labor than term labor [6].

Most common interventions recommended to prevent preterm birth have been proved to have a little or no benefit. However, bed rest, once universally advocated, is now largely historical, and cerclage, antibiotics or tocolytics may be beneficial only in specific circumstances, progesterone is useful in allowing pregnancy to reach its physiologic term. In animal studies medroxyprogesterone treatment prevented labor and possessed anti-inflammatory activity in vivo [7]. Moreover progesterone antagonists given at term increase the rate of spontaneous labor [8].

Progesterone and 17α-hydroxyprogesterone acetate slow the process of cervical ripening, and this is the rationale for prophylactic long-term progestin supplementation mostly studied so far. However, progesterone (but not 17α-hydroxyprogesterone acetate) also inhibits myometrial activity even after the cervix has already ripened. Moreover, these effects depend greatly on the vehicle used and the route of administration. Understanding different mechanisms of action, as well as the importance of progestin formulation, vehicle and route of administration, is the key to finding the optimal progestin treatment for prevention of preterm birth. Natural progesterone is free of any disturbing teratogenic, metabolic, or hemo-dynamic effects. This is not true for certain synthetic gestagens and 3α mimetics [9].

Progesterone administration was considered to be effective in the prevention of PTL in women at risk, especially women with history of previous spontaneous PTL.

There is still considerable uncertainty regarding the optimal progesterone type, route of administration, dosage and timing of start of therapy to prevent PTL in risky women.

Aim of the work:
The aim of this study is to compare between vaginal and intramuscular progesterone in the prevention of recurrent preterm labor.

Patients and Methods
This study is a comparative clinical trial, which was carried out at Kasr El-Ainy Maternity Hospital during the period between January 2014 and January 2016. One hundred (100) pregnant women who have history of previous spontaneous preterm labor (s) were selected in this study and randomly arranged into three groups [vaginal progesterone Group (A), intramuscular progesterone Group (B) and control Group (C)].

Inclusion criteria:
Women selected for this study who were sought to be at high risk for preterm labor with the following criteria, singleton viable pregnancy, gestational from 20 to 24 weeks, past history of one or more spontaneous preterm labor.

Exclusion criteria:
Women with multi-fetal pregnancy, history of ante partum PROM, cervical incompetence or current cervical cerclage, known fetal anomaly, hypertension requiring medications, progesterone or Heparin treatment in current pregnancy or history of thrombo-embolic disorders, known allergy to progesterone, known liver disease, established preterm labor.

Interventions:
A- At the first antenatal visit:
All these pregnant women were subjected to history, clinical examination, laboratory investigations and ultrasound examinations.

Ultrasound examination:
Trans-abdominal ultrasound to assess the gestational age and to exclude fetal anomalies and trans-vaginal ultrasound every four weeks to assess cervical length and funneling.

Prophylactic medical treatment:
All pregnant women in the study received prophylactic medical treatment for bacterial vaginosis and Chlamydial infection in the form of Azithromycin tablets 500mg. Orally once daily for 3 days and Metronidazole tablets 250mg. Three times per day for 7 days. Medications were given just before starting progesterone therapy, treatment will be started at 20-24 weeks gestation; the first 35 patients (Group A) will be given micronized progesterone tablets vaginally 200mg twice daily and the second
35 patients (Group B) will be given 100mg of intramuscular progesterone every third day while the third group (Group C) included 30 women who had not received any progesterone for prevention of PTL and settled as control group. Treatment will be continued until completed 36 weeks gestation or until occurrence of PROM or delivery.

**B- At the follow-up visits:**

All pregnant women were submitted to uterine contraction monitoring by an external tocodynamometer every other week for 60 minutes by an external monitor from 28 to 36 weeks of gestation while women in left lateral position, we determine the frequency of contractions. A positive test was considered when there were four or more contractions per hour before the 30th week of gestation and from 30 weeks onward, 6 or more contractions per hour [10,11], all pregnant women were asked for symptoms of preterm labor like heaviness, cramps, abdominal colic, and sudden gush of fluid.

**Statistical analysis:**

Results are expressed as mean ± standard deviation or number (%). Comparison between numerical data in three studied groups was performed using one way ANOVA followed by LSD test if significant results were recorded. Comparison between categorical data was performed using Chi square test. SPSS computer program (Version 19 windows) was used for data analysis. $p$-value less than or equal to 0.05 was considered significant and less than 0.01 was considered highly significant.

**Results**

The current study was a comparative clinical trial, which was carried out at Kasr El-Ainy Maternity Hospital during the period between January 2014 and January 2016. One hundred (100) pregnant women who have history of spontaneous preterm labor (s) were selected in this study and randomly arranged into three groups [vaginal progesterone Group (A), intramuscular progesterone Group (B) and control Group (C)].

There is no statistically significant difference between all groups as regards the age, parity and number of previous preterm labors.

There was statistically significant difference between the progesterone groups and the control group as regards GA. At delivery with higher percentage of lower GA at delivery among the control group (32 weeks) compared to the progesterone groups (35 weeks).

Also, there was statistically significant difference between the vaginal progesterone group and the intramuscular progesterone group as regards GA. At delivery with higher percentage of lower GA at delivery among the intramuscular progesterone group (34.5 weeks) compared to the vaginal progesterone group (36 weeks).

**Table (1): Demographic features of different studied groups.**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=30)</th>
<th>Vaginal (n=35)</th>
<th>Intramuscular (n=35)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>26.80±4.26</td>
<td>28.71±4.09</td>
<td>28.23±4.75</td>
<td>0.200 (NS)</td>
</tr>
<tr>
<td>Parity</td>
<td>3.10±0.85</td>
<td>3.14±0.60</td>
<td>2.91±0.56</td>
<td>0.326 (NS)</td>
</tr>
<tr>
<td>No. of PLT</td>
<td>2.40±0.50</td>
<td>2.49±0.51</td>
<td>2.51±0.51</td>
<td>0.645 (NS)</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.
NS $p>0.05$ = Not Significant.

**Table (2): Comparison between mean values of Gestational Age (GA) at delivery in different studied groups.**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=30)</th>
<th>Vaginal (n=35)</th>
<th>Intramuscular (n=35)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (GA)</td>
<td>32.30±2.00</td>
<td>36.03±1.22</td>
<td>34.57±1.09</td>
<td>0.001**</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.
aa $p<0.01$ relative to control group,
bb $p<0.01$ relative to vaginal group.

**Discussion**

The present study showed no statistically significant difference between the three groups as regarding to age, parity, mode of delivery and number of previous preterm labors.

This agreed with the studies of Meis et al., 2003 [12].

In a meta-analysis of RCT by Farine et al., 2008, there is a good evidence to recommend the use of vaginal progesterone 200mg daily in the prevention of PTL in women with short cervix <15 mm detected during TVS scanning at 22-26 weeks.

In the prevention of recurrent PTL in women with previous PTL, vaginal progesterone 100mg daily was advised, or IM 17 alpha hydroxyl progesterone 250mg once weekly. As regards timing of starting progesterone for prevention of PTL, no apparent benefit of early start before 20 weeks and also the use of higher doses is not beneficial.

This study compares vaginal progesterone with IM 17 alpha hydroxyl progesterone for the prevention of PTL, we found that both were effective in the prevention of threatened PTL, PTL <37 weeks and PTL <34 weeks in women at risk with higher efficacy in the vaginal progesterone group running in agreement with many previous studies [14].
On the other hand, one study by J.M. O’Brien et al., [13] concluded that vaginal progesterone did not reduce the rate of early PTL, neonatal morbidity or mortality and this could be explained by performing their study on women with one risk factor (previous PTL) and considering the primary outcome PTL <32 weeks, also, they used progesterone in a dose of 90mg and in the form of vaginal gel.

Some studies found that although progesterone is effective in the prevention of PTL, it was not effective in reducing the rate of hospital admission for PTL (threatened PTL) [12].

No data from RCTs and other studies indicate that progesterone use in the prevention of PTL is not safe apart from a single retrospective study which showed that the incidence of gestational diabetes mellitus was 12.9% in women treated by I.M 17 alpha hydroxyl progesterone 250mg weekly (557 cases) compared to 4.9% in control cases (1524 cases), in this study safety could not be confirmed due to the small number of cases and further large series studies are advocated.

Conclusion:
Prophylactic use of progesterone reduces the rate of preterm labor, prolongs gestational age at delivery, reduces the frequency of uterine contractions, and improves the symptoms of preterm labor in women with history of recurrent spontaneous preterm labors, vaginally administrated progesterone was nearly as equally effective as intra muscular progesterone in the prevention of PTL in women at risk with superior effect with vaginal route.

References
7- ELOVITZ M. and WANG Z.: Elucidating the mechanisms by which gestational diabetes mellitus was 12.9% in women treated by I.M 17 alpha hydroxyl progesterone 250mg weekly (557 cases) compared to 4.9% in control cases (1524 cases), in this study safety could not be confirmed due to the small number of cases and further large series studies are advocated.
البروجسترون المهبلى مقابل العضلى في الوقاية من الولادة المبكرة المتكررة

يعترض المخاط المبكر بوجود إيقافات رحمية ذات معدل وقية كافية لإحداث محو وإنساء في عبر الرحم قبل وصول الحمل إلى الميعاد (أو قبل إكتمال 37 أسبوع من الحمل).

الولادة المبكرة تؤدي إلى زيادة حالات المرض والوفيات وما يتصل بها من الإصابات الشهرية والعصبية في وقت لاحق في الحياة. معدل حدوث هذه المشكلة في إندونيسيا يتراوح بين 15% من حالات الحمل في العالم المتقدم. لذلك تعتبر الوقاية منها تحدياً كبيرًا لطب العناية بالولادة.

المضاعفات الناجمة عن الولادة المبكرة لا تتوقف فقط على فترة ما بعد الولادة، كما هو الحال في إعتلال الشبكية، أو التزيف داخل البطين المخلي، إعتلال الأوعية الدموية، إضطرابات الجهاز التنفسي وتسمم الدم. كما أنها يمكن أن تشكل مضاعفات أخرى مثل تدهور التطور الفيسيولوجي العصبي في مرحلة الطفولة المبكرة، وتشديد التحصيل الدراسي في المدرسة.

الاكتشاف المبكر للنساء الحوامل الأكثر عرضة للمخاط المبكر يمكن أن يكون أفضل الطرق لمنع حدوثه، وعلى ذلك فقد تكون الراحة بالسرير وربط عنق الرحم ومعالجة الإيقافات المهبلية والإستخدام الوقائي للبروجسترون من الوسائل 일بية الفعالة في الوقاية من المخاط المبكر.

هرمون البروجسترون عقار فعالة كبيرة في الحد من المخاط المبكر حيث أنه يمكن إيقاف الرحم، وعندما يصل تركيزها إلى نسبة معينة في عمضة الرحم يمنع تأثير الأوكسيجين الحفز لإيقاف الرحم، وهكذا فإن البروجسترون يؤدي إلى إسترخاء عضلة الرحم ويعيد المخاط المبكر.

خلصت هذه الدراسة أن الإستخدام الوقائي لهرمون البروجسترون يقلل من نسبة الولادة المبكرة، ويطيل عمر الحمل عند الولادة، ويفقل من تأثير تقلبات الرحم، ويحسن أعراض الولادة المبكرة عند النساء نوات التاريخ المتكرر للولادة المبكرة العالية.

كان البروجسترون المهبلى ما يقرب من نفس القدر من الفعالية كما البروجسترون العضلى في الوقاية من الولادة المبكرة في النساء المعرضة للخطر مع تأثير متفوق للبروجسترون المهبلى وكان كلاهما مرتبطًا بانخفاض كبير في معدل المقاومة بالنسبة للدورة الشريان الدماغي الإفستى للجنين، ولكن كان البروجسترون المهبلى فقط حقق حمضًا كبير في معدل المقاومة بالنسبة للسديان الرحمي.