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Effect of Vaginal Versus Intramuscular Progesterone on the Uterine and Fetal Blood Flow in Patients with History of Recurrent Preterm Labor

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Abstract

Objectives: The aim of this study is to compare between effect of vaginal and intramuscular progesterone on the uterine and fetal circulations and on serum progesterone level in patients with history of recurrent spontaneous 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 with 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: Fetal MCA-PI and RI, uterine artery RI and lower birth weight, were higher among the control group in comparison to progesterone group and serum progesterone was higher among progesterone group compared to control group.

Conclusion: Vaginally administrated progesterone and intra muscular progesterone were associated with significant reduction in fetal MCA-PI and RI, but vaginal progesterone only had significant reduction in uterine artery RI and PI.

Key Words: *Vaginal progesterone – Intramuscular progesterone – Uterine blood flow – Fetal blood flow – 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]**.

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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, thereby, bed rest, cervical cerclage, bacterial vaginosis treatment, and prophylactic use of progesterone could be one

of the managements in this high-risk population [4].

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 17 a hydroxylase. 17 a 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, 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 [5].

Moreover progesterone antagonists given at term increase the rate of spontaneous labor [6].

Progesterone and 17 a -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 17 (x -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 hemodynamic effects. This is not true for certain synthetic gestagens and 0 mimetics [7].

The vasodilator effect of progesterone on uterine circulation in the non-pregnant female [8] and during the first trimester of pregnancy is well known [9], but little information is available on its effect on uterine and fetal circulation later in gestation. In one study performed by Barda et al., it showed that vaginal micronized progesterone used for the prevention of PTL was associated with a significant reduction in the fetal Middle Cerebral Artery (MCA) Pulsatility Index (PI) but with no effect on uterine circulation [10].

Aim of the work:

The aim of this study is to compare between effect of vaginal and intramuscular progesterone on the uterine and fetal circulations and on serum progesterone level in patients with history of recurrent spontaneous 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 were thought to be at high risk for preterm labor with the following criteria, singleton viable pregnancy, gestational age from 20 to 24 weeks, with 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.

A- *At the first antenatal visit:*

All these pregnant women were subjected to history, clinical examination, laboratory investigations and ultrasound examination.

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 started at 20-24 weeks gestation; the first 35 patients (Group A) were given micronized progesterone tablets vaginally 200mg twice daily

and the second 35 patients (Group B) were given 100mg of intramuscular progesterone every third day While the third group (Group C) included 30 women who did not receive 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.

Doppler examination of fetal middle cerebral artery, umbilical artery and uterine artery was done one week before and one week after progesterone administration, progesterone was continued till 36 weeks pregnancy or delivery.

Serum progesterone monitoring was done before progesterone administration and again in the late second/early third trimester.

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 30 th week of gestation and from 30 weeks onward, 6 or more contractions per hour **[11,12]**, 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 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)].

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

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

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

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

Table (2): Comparison between mean values of birth weight in different studied groups.

Control (n=30)	Vaginal (n=35)	Intramuscular (n=35)	p-value
1.94±0.34	2.87±0.29aa	2.32±0.36aa bb	0.001 **

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

There was statistically significant difference between the progesterone groups and the control group as regards mean values of birth weight with higher percentage of lower birth weight among the control group (1.94kg) compared to the progesterone groups (2.6kg).

Also, there was statistically significant difference between the vaginal progesterone group and the intramuscular progesterone group as regards mean values of birth weight with higher percentage of lower birth weight among the intramuscular progesterone group (2.32kg) compared to the vaginal progesterone group (2.87kg).

Table (3): Comparison between mean values of five minutes APGAR score in different studied groups.

Control (n=30)	Vaginal (n=35)	Intramuscular (n=35)	p-value
6.33±1.32	8.40±1.12aa	7.51±0.74aa bb	0.001 **

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

There was statistically significant difference between the progesterone groups and the control group as regards mean values of five minutes APGAR score with higher percentage of lower five minutes APGAR score among the control group (6.33) compared to the progesterone groups (7.95).

Also, there was statistically significant difference between the vaginal progesterone group and the intramuscular progesterone group as regards mean values of five minutes APGAR score with

higher percentage of lower five minutes APGAR score among the intramuscular progesterone group (7.5) compared to the vaginal progesterone group (8.4).

Table (4): Mode of delivery in different studied groups.

	Control (n=30)	Vaginal (n=35)	Intramuscular (n=35)	*p*-value
CS	10 (33.3%)	12 (34.3%)	12 (34.3%)	0.996 (NS)
Vaginal	20 (66.7%)	23 (65.7%)	23 (65.7%)	

Data are expressed as number (%).
NS = p>0.05 = Not Significant.

There is no statistically significant difference between all groups as regards the mode of delivery.

Table (5): Neonatal Intensive Care Unit (NICU) admission in different studied groups.

	Control (n=30)	Vaginal (n=35)	Intramuscular (n=35)	*p*-value
No	11 (36.7%)	31 (88.6%)	21 (60.0%)	0.001 **
Yes	19 (63.3%)	4 (11.4%)	14 (40.0%)	

Data are expressed as number (%).
p<0.01= Highly Significant.

There was statistically significant difference between the progesterone groups and the control group as regards NICU admission with higher percentage of NICU admission among the control group (63.3%) compared to the progesterone groups (25.2%).

Also, there was statistically significant difference between the vaginal progesterone group and the intramuscular progesterone group as regards NICU admission with higher percentage of NICU admission among the intramuscular progesterone group (40%) compared to the vaginal progesterone group (11.4%).

Table (6): Comparison between mean values of MCA RI measured before and after progesterone administration in different studied groups.

	Control (n=30)	Vaginal (n=35)	Intramuscular (n=35)	*p*-value
Before	0.88±0.03	0.87±0.02	0.85±$^{0.03aa\ bb}$	0.001 **
After	0.88±0.04	0.79±0.02aa	0.79±0.02aa	0.001 **
p-value	0.580 (NS)	0.001 **	0.001 * *	

Data are expressed as mean ± SD.
NS = p>0.05 = Not Significant.
**: p<0.01= highly significant.
aa: P<0.01 relative to control group.

There was statistically significant difference between both progesterone groups before and after progesterone administration as regards mean values of MCA RI with higher MCA RI before progesterone administration (0.86) than after (0.79).

Table (7): Comparison between mean values of UA RI measured before and after progesterone administration in different studied groups.

	Control (n=30)	Vaginal (n=35)	Intramuscular (n=35)	*p*-value
Before	0.75±0.02	0.75±0.03	0.73±0.03	0.067 (NS)
After	0.75±0.02	0.75±0.03	0.73±0.03	0.067 (NS)
p-value	–	–	–	

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

There was no statistically significant difference between both progesterone groups before and after progesterone administration as regards mean values of UA RI.

Comparison between both progesterone groups before and after progesterone administration as regards mean values of Uterine Artery Doppler (UA RI):

Table (8): Comparison between mean values of Ut. A RI measured before and after progesterone administration in different studied groups.

	Control (n=30)	Vaginal (n=35)	Intramuscular (n=35)	*p*-value
Before	0.75±0.02	0.75±0.03	0.73±0.03	0.067 (NS)
After	0.75±0.03	0.64±$^{0.02aa}$	0.74±0.03bb	0.001 **
p-value	0.118 (NS)	0.001 * *	0.124 (NS)	

Data are expressed as mean ± SD.
NS = p>0.05 = Not Significant.
**: p<0.01= Highly significant.
aa: P< 0.01 relative to control group.
bb: P< 0.01 relative to vaginal group.

There was statistically significant difference in Vaginal progesterone group only before and after progesterone administration as regards mean values of Uterine Artery Doppler with higher Ut. A RI Before (0.75) than after progesterone administration (0.64).

Table (9): Comparison between mean values of serum progesterone measured before and after progesterone administration in different studied groups.

	Control (N=30)	Vaginal (n=35)	Intramuscular (n=35)	*p*-value
Before	49.53±2.35	50.00±1.91	49.40±1.65	0.415 (NS)
After	82.97±1.73	100.00±1.96aa	92.91±$^{1.52aa\ bb}$	0.001 **
p-value	0.001 **	0.001 * *	0.001 **	

Data are expressed as mean ± SD.
NS = p>0.05 = Not Significant.
**: p<0.01= Highly Significant.
aa: P<0.01 relative to control group.
bb: P<0.01 relative to vaginal group.

There was statistically significant difference in different studied groups before and after progesterone administration as regards mean values of serum progesterone.

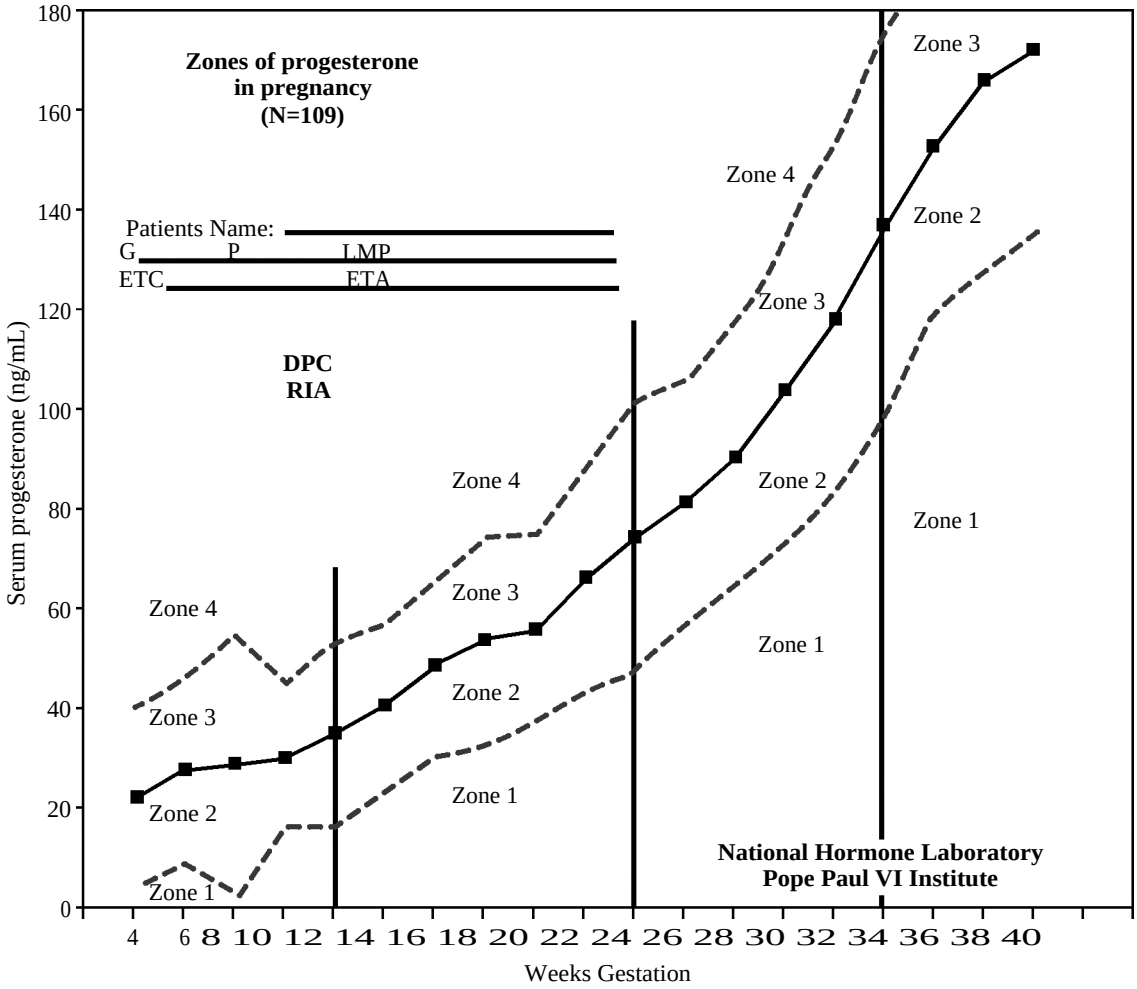

Fig. (1): P. 731 from the NaPro textbook. The four zones of progesterone shown using the DPC-RIA assay.

Discussion

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

Our results showed that the ratio of neonatal ICU admission to neonatal mortality was reduced in both groups that had received progesterone in relation to the control group **[16]**.

On the other hand, two other studies reported that the ratio of neonatal admission to ICU was significantly lower in women who had received progesterone but without changes in the neonatal deaths **[13,14]**.

The vasodilator effect of progesterone on fetal cerebral circulation may be supported by animal studies that showed that the brain is sensitive to progesterone during critical periods of development and maturation and presence of progesterone receptors in the brain also progesterone reduces brain edema in animal models **[17]**.

In this study we observed a significant reduction in MCA-PI and RI with no significant change in UA Doppler indices with the vaginally administered progesterone running in accord with Barder et al., 2010. In disaccord with the same authors we found a significant reduction in Ut. A-RI and PI after vaginal progesterone administration, this, could be explained by the difference in the timing of Doppler reexamination (24h after the first dose vaginal progesterone in their study and after one week of vaginal progesterone administration in this study, also, they included cases with GA 24-32 weeks with effect of different gestational ages on Doppler examination.

Intramuscular progesterone produces the same effect of vaginal progesterone on fetal MCA and UA blood flow, but no significant change in Ut. A blood flow was observed in this study, this may be explained by the higher bioavailability after vaginal progesterone than after intramuscular progesterone administration despite lower serum levels with the former **[15]**.

This could be attributed to the uterine first pass effect with direct transport of progesterone from vagina to uterus.

As regards serum progesterone level before and after progesterone administration, our study revealed that it was below the normal level at 24wks measuring approximately 50ng/ml compared to the average normal level at this gestational age 73ng/ml.

Six weeks after progesterone administration (at thirty weeks gestation), serum progesterone level was approaching the average normal level at this age (100ng/ml) in both progesterone groups with higher average level in the vaginal group (100ng/ml) than the intramuscular group (92.9ng/ml) while in the control group, serum progesterone level was still away from the average normal levels at this gestational age (82ng/ml) augmenting the need for progesterone support in this high risk population with the need for further studies regarding when to start treatment, mode and dose of progesterone.

Here, we study the short term effect of progesterone but long term effect was not studied as some cases had received medications other than progesterone such as betamethasone and some tocolytic drugs with their vasodilator effect.

Conclusion:

Vaginally administrated progesterone and intramuscular progesterone were associated with significant reduction in fetal MCA-PI and RI, but vaginal progesterone only had significant reduction in uterine artery RI and PI.

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تآثير البروجسترون المهبلى مقابل العضلى على تدفق الدم الرحمى والجنينى فى الوقاية من الولادة المبكرة المتكررة

يعرف المخاض المبكر بوجود إنقباضات رحمية ذات معدل وقوة كافية لإحداث محو وإتساع فى عنق الرحم قبل وصول الحمل إلى الميعاد (آى قبل إكتمال ٣٧ آسبوع من الحمل).

الولادة المبكرة تؤدى إلى زيادة حالات المرض والوفيات وما يتصل بها من الإعاقات النمائية والعصبية فى وقت لاحق فى الحياة. معدل حدوث هذه المشكلة فى إزدياد وتفيد تقارير بآنها تمثل ١٥٪ من حالات الحمل فى العالم المتقدم. لذلك تعتبر الوقاية منها تحديا كبيرا لآطباء التوليد.

المضاعفات الناجمة عن الولادة المبكرة لا تقتصر فقط على فترة ما بعد الولادة، كما هو الحال فى إعتلال الشبكية، آو النزيف داخل البطين المخى، إلتهاب الآمعاء الناخر، إضطرابات الجهاز التنفسى وتسمم الدم. كما آنها يمكن آن تشكل مضاعفات آخرى مثل تدهور النمو الفيسيولوجيى العصبى فى مرحلة الطفولة المبكرة، وتدنى التحصيل الدراسى فى المدرسة.

الإكتشاف المبكر للنساء الحوامل الآكثر عرضة للمخاض المبكر يمكن آن يكون آفضل الطرق لمنع حدوثه، وعلى ذلك فقد تكون الراحة بالسرير وربط عنق الرحم ومعالجة الإلتهابات المهبلية والإستخدام الوقائى لهرمون البروجستيرون من الوسائل الفعالة للوقاية من المخاض المبكر.

هرمون البروجستيرون عقار له فاعلية كبيرة فى الحد من المخاض المبكر حيث آنه يمنع إنقباض الرحم، وعندما يصل تركيزة إلى نسبة معينة فى عضلة الرحم يمنع تآثير الآوكسيتوسين المحفز لإنقباض الرحم.

التآثير الموسع للدورة الدموية لهرمون البروجسترون على رحم الآنثى غير الحامل وخلال الآشهر الثلاثة الآولى من الحمل هو تآثير معروف جيدا، ولكن القليل من المعلومات متاح فى تآثيره على الرحم والدورة الدموية للجنين فى وقت لاحق من الحمل. فى دراسة واحدة يؤديها باردا وآخرون: آنها آظهرت آن البروجستيرون المهبلى المستخدم للوقاية من الولادة المبكرة كان ولكن PI مرتبطا مع إنخفاض كبير فى مؤشر (معدل) المقاومة للشريان الدماغى الآوسط للجنين مع عدم وجود تآثير على الدورة الدموية فى الرحم.

خلصت هذه الراسة آن للبروجسترون المهبلى ما يقرب من نفس القدر من الفعالية كما البروجسترون العضلى فى حدوث إنخفاض كبير فى معدل المقاومة بالنسبة لدوبلر الشريان الدماغى الآوسط للجنين، ولكن كان للبروجسترون المهبلى فقط خفض كبير فى معدل المقاومة بالنسبة للشريان الرحمى.