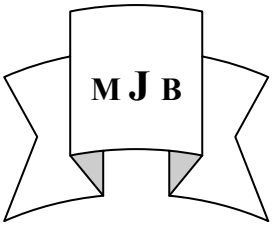
Prophylactic Administration of Vaginal Progesterone Reduces the Risk of Preterm Birth

Huda Mahmood Altemimmi
College of Medicine, University of Babylon, Hilla, Babylon, Iraq.



Abstract

Objective :To evaluate the effects of vaginal progesterone in reducing the risk of preterm delivery in women with short cervix.

Setting :Dept. of Obstet. and Gyncol.,Babylon Maternity Hospital , Ultrasound unit, 2008-2009

Materials and methods: Prospective Follow up study carried for 2 years, cervical length was measured by vaginal ultrasound in 313 women with history of preterm delivery(one or subsequent type),46 women with cervical length of < 28mm was evaluated further and divided in 2 group, study group which include19 pregnant women received 200Mg micronized vaginal progesterone, , daily which is identical to progesterone of ovarian origin. Other control group of 27 pregnant women received no treatment, outcome regarding preterm labor before 32weeks was evaluated, together with neonatal outcome .

Results: the study shows, 1-the incidence of preterm labor was low in progesterone group when compared with the other group. 2- admission to baby care unit was lower in 1st group, with shorter stay.

Conclusion : vaginal progesterone may reduce the risk of preterm labor in women with short cervix.

الخلاصة

دراسة شملت ٣١٣ امرأة حامل مع تاريخ ولادي سابق بولادة مبكرة واحدة اواكثرقبل٣٢ أسبوع من الحمل زرن مستشفى الولادة والأطفال، اجري لهن سونار مهبلى خلال اول زيارة (خلال الأسبوع ١٨ –٢٣) من الحمل وكرر ذلك في ال٢٨ أسبوع من الحمل أخذت عينة بعدد٤٦ حامل ممن لديهن التاريخ الولادي ذاته قسمت العينة الى فئتين ، ١٩ منهن أعطين ٢٠٠ ملغم بروجستيرون تحاميل مهبلية يوميا(تحميلة واحدة بجرعة ١٠٠ ملغم) واستمرت المعالجة حتى وصولهن ال٣٧ أسبوع من الحمل او ولدن تلقائيا قبل هذا التاريخ أو حصل لديهن انفجار في السائل الامنيوسي .والفئة الأخرى وتتضمن ٢٧ امرأة حامل لم تستلم اى دواء بينت الدراسةان النساء اللواتي أعطين البروجستيرون المهبلى لم تحدث لديهن اي ولادة مسبقة بالمقارنة مع المجموعة الأخرى كما ان دخول الأطفال حديثي الولادة الى وحدة رعاية حديثي الولادة كانت اقل فى نفس المجموعة .

Introduction

Despite medical efforts towards its prevention, the rate of preterm birth, defined as birth occurring prior to 37 weeks of gestation, continues to rise among certain populations, occurring in up to 15% of pregnancies in the developed world. The frequency in is even higher in developing countries. Preterm birth is associated with a high prevalence of severe neurological defects and developmental disabilities and is a leading cause of infant and neonatal mortality in the world. Preterm neonates are at increased risk of developing respiratory distress syndrome, sepsis, intra ventricular hemorrhage, necrotizing enteric-olitis and disorders related to gestational age at birth. The incidence of preterm labor is at its lowest in women in their 20s . The risk increased in teenagers and in over 30. There is a higher incidence in first pregnancies. Having had a single previous preterm delivery increases the

risk of preterm delivery in a subsequent pregnancy four times when compared to a women whose previous delivery was at term.[2]

.Preterm labor has been linked to cervical incompetence, more recently it is probable that cervical length and strength together with the quality of the cervical mucus contribute towards the cervix function, both to retain the pregnancy and to exclude potential bacterial pathogen from ascending from the vagina.

A short cervix often occurs when there is cervical ripening; however, not all short cervix are ripened; hence, the observation that some women with short cervix deliver at term. we have proposed that a short cervix is syndromic in nature and can be caused by multiple etiologies,such as :

(1)the loss of connective tissue after a cervical operation as conization or loop electrical excision procedure (LEEP).

(2)a congenital disorders such as cervical hypoplasia after diethylstilbesterol exposure.

(3)intrauterine infection.

(4)a decline in progesterone action.

(5)a cervical disorder that manifestes as the clinical presentation of "cervical insufficiency".

Each of these different causes of the syndrome could be affected by genetic or environmental factors. Morovere, more than one mechanism of disease may be operative in a patient. The possibility of novel and as yet undiscovered mechanisms of disease must be considered.(2)

Numerous studies have demonstrated a strong association between cervical length and the risk of preterm labor.A short or partially dilated cervix may allow bacteria to ascend into the lower pole of the uterus where, acting through the toll- like receptors of the innate immune system, they stimulate production of inflammatory cytokines, prostaglandins and inflammatory response. This leads to cervical ripening and shortening and then decreases the ability of the cervix to act as either a mechanical or a micro-biological barrier and so, ultimately, development of either localized or generalized chorioamnionitis and to preterm labor.Therefor a short or weak cervix may therefore contribute to preterm delivery.[1]

There is now good evidence that trans-vaginal sonographic measurement of cervical length can be used to predict the risk of preterm labor in both low – and high –risk pregnancies and in women who are symptomatic[1].

Two strategies are currently in common use- either serial measurement of cervical length throughout the second and early third trimester of pregnancy or single measurement of cervical length usually at the time of the routine ultrasound between 18 and 22weeks. If a screening strategy using a single ultrasound measurement of cervical length is used, then assessment between 21 and 24 weeks gestation appears to be better than assessment prior to 20 weeks gestation in predicting the risk of preterm labor. Serial measurement of cervical length is more costly but appears to be superior to a single assessment[3].

The precise mechanism by which a blockade of progesterone action may induces cervical changes are complex and poorly understood.A decline in progesterone action probably causes cervical changes by inducing inflammation (leukocyte infiltration and production of chemokines such as interleukin-8, nitric oxide, prostaglandins and matrix –degrading enzymes). It is also possible that cervical remodeling and ripening is influenced by NF-kB(nuclear factor – kappa B), atranscription factor which mediates the effect of certain pro-

inflammatory cytokines such as 1L-1B(interleukin 1B) and TNF-alpha (tumor necrosis factor –alpha. This is important ,because NF-kB can oppose progesterone action. Thus ,NF-kB provides a link between inflammation, a decline in progesterone action and cervical ripening.

Progesterone is thought to inhibit the production of pro- inflammatory cytokines and prostaglandins within the uterus and to inhibit myometrial contractility. Although a meta-analysis by Kierse etal. In 1990 suggested that progesterone may be beneficial in reducing the risk of preterm delivery. It was not until the publication of two trials in 2003 that there was more widespread interest in the possibility that progesterone may be used as prophylactic treatment in women at high risk of preterm delivery.[1]

The use of progesterone to treat all women at risk for preterm birth does not have uniform support at present but it has rapidly become accepted as prophylactic measure to prevent preterm birth in women with a documented history of spontaneous preterm birth.[2]

Materials and Methods

This trial was carried out in the department of obstetric and gynecology, Babylon maternity hospital , women with documented history of spontaneous preterm birth before (34 weeks) in a singleton pregnancy in the immediate preceding pregnancy , regardless of cervical length, and women without a history of preterm birth but with a short cervix ($\leq$ 25mm) in the mid trimester of the current pregnancy were screened by the investigator or study coordinator between 18- 23 weeks of gestation .pregnant women were eligible to enter the trial if they meet the criteria mentioned above. Subjects meeting the study criteria were offered enrollment into the study at 18 -23 weeks of gestation to receive daily treatment with 200 mg of vaginal progesterone in form of soft gelatin capsules (Endogest) containing micronized progesterone , yellow tablet, this progesterone is structurally and biologically identical to progesterone of ovarian origin. Micronization increases the bioavailability of progesterone. All women provide written informed consent demonstrate understanding of the purpose of the study and agree to adhere to the study protocol .Any of these women who gave history of thrombotic disorders (thrombophlebitis, cerebrvascular disorders, pulmonary embolism and retinal thrombosis) are withdrawn from the study.

Cervical length was measured with trans-vaginal ultrasound at enrollment and at 28 weeks of gestation. Treatment was continued until either delivery, 37 weeks of gestation or development of preterm rupture of membranes.

The outcome for this study were the preterm birth before 37 weeks, $\leq$35 weeks,<32 weeks and , $\leq$ 28 weeks, hospital admission for preterm labor, change in cervical length between enrollment and 28 weeks, and neonatal morbidity and mortality.

The baseline demographic and obstetric characteristic of women with short cervix were matched for both groups. Using a cervical length of < 28 mm (the 9^{th} percentile of the population studied (313) to expand the criteria for short cervix which resulted in a cohort of 46 women studied in this trial).

Data were analyzed by Chi –square or fishers exact tests. A p- value of <0.05 was considered statisticall y significant .

Table 1 baseline demographic and obstetric characteristic of women with short cervix

Characteristic	Progesterone (n=19)	control (n=27)	p-Value
_Maternal age (years,mean (SD)	27.4 (4.9)	25.4 (4.8)	O.18
_Body mass index (mean(ED)	28.5(8.3)	26.9(6.7)	0 .52
_Prior preterm births (n,mean (SD)	1.2 (0.5)	1.4 (0.8)	0.26
_ >1prior preterm births (n,mean (SD)	7 (37)	5(19)	0.80
_ prior cervical surgery (n (%))	3 (16)	6 (22)	0.70

Results

The study shows that :

1. The mean gestational age at birth for progesterone treated group was 36.3 while it was 34.6 for the control group and p- value was o.160.
2. The percentage of variable time of occurrence of preterm birth in progesterone group was 42.1%, 36.8% , zero ,zero at <37 weeks , < 35 weeks < 32 weeks , < 28 weeks respectively. The time of preterm birth in control group was 59%, 48.1%,29.6 %,11.1%.
3. The mean cervical length at 28 weeks in progesterone treated group was25mm and it was 22mm at 28 weeks in control group.
4. Admission for preterm labor was 6 patients in progesterone treated group and it was 7 in control group ,the p- value was 1.
5. There was no difference between the vaginal progesterone group with respect to the frequency of adverse effects overall (81.3% vs83.2%).

Table 2 Shows the outcome for both groups

Outcome	Progesterone (n =19)	control (n =27)	P- value
GA at birth (weeks, mean (SD))	36.3(2.4)	34.6(4.6)	0.160
Preterm birth (n(%)) < 37 weeks <35 weeks <32 weeks <28weeks	 8(42.1) 7(36.8) 0 0	 16(59.3) 13(48.1) 8(29.6) 3(11.1)	 0.370 0.551 0.014 0.257
Cervical length at enrollment (mm) Mean (SD) Cervical length at 28 weeks (mm, mean (SD))	24 (0.2) 25(0.8)	22(0.5) 22(0.8)	0.07 0.27
Admission for preterm labor (n (%))	6(31.6)	7(25.9)	0.70

Table 3 Neonatal outcome in women with cervical length <28 mm at enrollment

Outcome	Progesterone (n=19)	control(n= 27)	p-value
Birth weight (g, mean .(SD)	2726 (625)	2290 (937)	0.1
Hospital days (n, mean (SD))	5.8 (9)	18.2 (25.5)	0.055
NICU admission (n(%)	3 (15.8)	14 (51.9)	0.016
Days In NICU per admission (n, mean (SD)	1.1 (2.7)	16.5(24.9)	0.013
Respiratory distress syndrome(n (%))	1 (5.3)	8 (29.6)	0.060
Proven sepsis(n(%))	1 (5.3)	3 (11.1)	1.0

Discussion

This study was conducted to evaluate the efficacy of progesterone for the prevention of preterm birth. Our analysis suggests that progesterone may prevent early preterm birth(< 32 weeks of gestation) and improve neonatal outcome in women with short cervical length ≤28 mm identified between 18 and 22 weeks of gestation.

The study demonstrated that the rate of preterm birth in progesterone treated group was significantly lowered than the control group .The rate was(42.1%,36.8%,0%, 0%) at <37, ≤35, ≤32, ≤28weeks respectively while it was in rate of59%,48.1%,29.6%,11.1% in the control group.[2]

The action of progesterone on the pregnant myometrium include relaxation of myometrial smooth muscle ,blocking of the action of oxytocin, and inhibition of the formation of gap junctions.There is evidence that local changes in the progesterone level or the ratio of progesterone to esterogen in the placenta ,decidua,or fetal membranes may be important in initiation of labor in humans.[2]

Many trials and studies had demonstrated that the use of other type of progesterone as 17 alpha hydroxyl progesterone caproate on weekly basis intramuscular injection ,beginning at 16 to 20 weeks of gestation and continued to delivery or 36 weeks, significantly reduced the rate of preterm delivery before 37 weeks , ,35 weeks, and 32 weeks of gestation among women at high risk for preterm delivery. The rates of several complications of prematurity were correspondingly decreased among infants of women assigned to this therapy.[3,7,18]

Da fonseca et al,enrolled142 women with varied risk factors for spontaneous preterm birth, and found intra-vaginal natural progesterone to be efficacious in reducing the occurrence of preterm birth. In that trial ,the frequency of delivery at <34 weeks was 18.6% in the control group ,and it was 2.8% in the group allocated to daily 100 mg vaginal suppository treatment .The data suggest that intra-vaginal natural progesterone can have a benefit if an appropriate target population is identified .[6]

Indeed, a land-mark study by The Fetal Medicine Foundation recently revealed that intra-vaginal progesterone could reduce the rate of preterm birth in a population with a short cervical length.[19]

If we go back to our study , the trial revealed that the frequency of preterm birth in patients treated with vaginal progesterone at ≤35 was 36.8% and it was 0% at 32 weeks of pregnancy, which indicate a good responders to therapy introduced although the sample size were small .

The efficacy of progesterone in our study population is noteworthy and encouraging..Although we do not believe that every patient will respond identically, in women treated with an short cervix, no treated patients delivered at less than 32 weeks ,8 delivered <37weeks,7 delivered≤ 35weeks, and in the control group there was 8 delivered below≤ 32 weeks,16 delivered<37weeks, 13 delivered ≤ 35weeks of gestation.

Fonseca et al also demonstrated that women with short cervical length identified in mid-trimester by trans-vaginal sonography are less likely to deliver preterm if they were treated with 200mg vaginal progesterone when they were screened between 20 and 25 weeks of gestation, and were found to have very short cervix ≤15mm [16].

Rouse et al. reported amulticenter, placebo- controlled, randomized clinical trial of using 17 alpha

hydroxyprogesterone caproate for prevention of preterm birth .[22]

Several studies have addressed the mechanism with which progesterone might reduce the rate of cervical shortening or ripening[13]. Cervical ripening can be characterized as a reduction in total collagen content by an increase in collagen solubility and collagenolytic activity. Collectively, these activities cause a remodeling of the extracellular matrix of the cervix[14].

A number of hormones, including progesterone, influence this activity .Esterogen stimulates collagen degradation in vitro and progesterone blocks esterogen – induced collagenolysis in vitro [14]. Progesterone also down-regulates interleukin 8 production by the cervix(15). Taken together, these observation suggest that progesterone inhibits the cervical ripening that is known to precede labor.

Regarding neonatal outcome, the study showed that there was a significant improvement in neonatal outcome with intra vaginal progesterone . There was a significant improvement in birth weight , the mean birth weight was 2726 gram in progesterone treated group which is more than the control group .table (3)

The hospital stay days, neonatal care unite admission are recognized measures of infant morbidity, these parameters are greatly reduced in infants of mothers treated with vaginal suppositories , and indicate effectiveness of this trial,

many trials of use of variable routes of progesterone , as weekly intramuscular injection , or vaginal route had greatly reduced the recurrence rate of preterm delivery, and also reduced the likelihood of several complications in their infants.[3]

This analysis provides the first hint that vaginal progesterone adminstration may improve infant outcome in properly selected patients.

Conclusion and Further Recommendation

1.Given the finding of this trial , we suggest that mid-trimester cervical length assessment by trans-vaginal ultrasound Be incorporated into routine clinical practice,as prophylactic vaginal progesterone supplementation benefits asymptomatic high –risk pregnancies with early onset cervical ripening.

2.Other tools may help to refine the estimation of risk; for example, vaginal fibronectin,vaginal fluid analysis for other compounds, the collascope,amniotic fluid analysis ,the presence \absence of amniotic fluid 'sludge ' and even genetic analysis of DNA varients of the progesterone receptor,

3. These may help to discriminate between patients who will respond to progesterone and those who will not.And this could be an important step towards achieving "personalized perinatal medicine" in the 21st century.

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