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Research Article

The Use of Vaginal Progesterone in Risk Reduction of Preterm Birth in Pregnant Women with Short Cervix

Sana Monem[1] and Chro Najmaddin Fattah[2]*

[1]*Diploma in Obstetrics and Gynecology, Sulaimani Maternity Teaching Hospital, Sulaimani, Kurdistan Region, Iraq*

[2]*Assistant Professor, Head of Department, Obstetrics and Gynaecology, Medical School, University of Sulaimani, Kurdistan Region, Iraq*

***Corresponding Author:** Chro Najmaddin Fattah, Assistant Professor, Head of Department, Obstetrics and Gynaecology, Medical School, University of Sulaimani, Kurdistan Region, Iraq.

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Abstract

Background: Preterm labour is a major health challenge in obstetrics. Many risk factors being identified, the most common one is short cervical length, can be diagnosed by transvaginal ultrasound scan after 13 weeks of pregnancy. Vaginal progesterone is the most bioavailable form of progesterone that have effect on uterine and cervix. Progesterone is thought to inhibit the production of proinflammatory cytokines and prostaglandins within the uterus and to inhibit myometrial contractility

Objectives: The objective of this study is to assess the usefulness of vaginal progesterone suppositories in reduction of preterm birth in asymptomatic singleton pregnancy women with short cervix.

Patients and Methods: This is a study on the daily use of (100mg or 200mg) of vaginal progesterone by 79 women in a prospective Randomized Controlled study. Between 24-34 weeks of gestation with short cervix of <29mm confirmed by transvaginal ultrasound and followed prospectively.

Result: Preterm labour among vaginal progesterone group were less but statistically nonsignificant. The preterm labour among who received 100 mg was significantly lower than other 200mg.

Conclusion: The study found the advantage of progesterone pessary in a women with short cervical length <25 mm in mid-trimester of pregnancy with no history of preterm labour.

Keywords: Preterm Birth; Progesterone; Short Cervix; Cervical Length (CL)

Introduction

Definition of preterm birth

Preterm birth is described as when a baby is delivered before 37 weeks of pregnancy, Preterm parturition is a syndrome caused by multiple etiological factors, In United Kingdom, and preterm birth includes all deliveries between 24+0 and 36+6 weeks. Many developed countries now officially register all deliveries with a birth weight above 500 g, in United States in 2014, 5863 live births <500g were recorded [1].

Classification of preterm birth: depend on gestational age are:

- Extremely preterm (less than 28 weeks)
- Very preterm (28 to 32 weeks)
- Moderate to late preterm (32 to 37 weeks) [2].

Etiological factors

Cervical incompetence, abnormalities of hemostasis, placental abruption or decidua hemorrhage, multiple pregnancy, intraamniotic infection, extra-uterine infections, a decline in progesterone action, uterine over-distension, marital status, cigarette smoking, poor nutrition, environmental stress ,use of alcohol, caffeine and street drugs (especially cocaine) have all been associated to increase risk of preterm birth [3]. The risk is also high in teenagers and in women over the age of 30. However, the risk is lower with each successive term pregnancy.

Incidence

The rate of preterm birth is on the increase internationally; about 15 million babies are born preterm every year. The incidence is variable of about 10% in most developed countries. The rate in UK is around 7% and in the USA is varies according to geographical and interstate vibration between 9% to 12%. And higher in most African country. The Largest number of preterm birth occurs in India, China, Nigeria, Pakistan, Indonesia and the USA [4]. The incidence is more extreme of in first pregnancies.

Complications: the most common cause of death among children under age of 5 is due to preterm birth and it caused approximately 1 million deaths in 2015) [5]. With recent advance in health sector and current cost-effective interventions three quarter of these death can be prevented. in extreme preterm labour at 24-26 weeks gestation Neurodevelopmental impairment, intellectual disabilities, cerebral palsy, blindness, seizure and spastic quadriparesis are especially significant, may need life time medical care [1].

Cervical weakness

The most objective and effective method for evaluating the cervix is by transvaginal Ultrasound, cervical length ≤25 mm in around 24 weeks regarded as a very strong risk factor for preterm delivery and has a high predictive value for spontaneous preterm birth <34 weeks of gestation and a moderate to low predictive accuracy for spontaneous preterm birth <37 weeks of gestation in both singleton and twin gestations [6].

Cervical incompetence based on clinical diagnosis, characterized by recurrent painless dilation of cervix and spontaneous second trimester loss and preterm delivery, one of the other risk factors is exposure to diethylstilbestrol (DES) before birth [7].

Diagnosis of cervical weakness

Cervical length can be diagnosed by transabdominal (TAS) or transvaginal (TVS) ultrasound. TVS is more producible than TAS because TAS needs full maternal bladder that interfere with accurate calculation of cervical length, Also there is high false rate with (TAS), pregnant women can be reassured that (TVS) is safe, and minimally invasive [8]. TVS a useful screening tool for low-risk pregnant women.

Treatment of cervical weakness

Traditionally cervical cerclage and progesterone used for correction of cervical weakness. There is good evidence that the women with a history of spontaneous second-trimester loss or preterm delivery who have short cervix are at an increased risk of subsequent second-trimester loss/preterm birth may gain benefit from cervical cerclage while those whose normal length cervix remains at low risk. In Low-risk pregnancy short cervix can be diagnosed in mid-trimester of pregnancy (18-24weeks) unlike to high risk patient with prior history of preterm labour may not benefit from cervical cerclage, however vaginal progesterone may be beneficial. Pregnant women with previous LLETZ procedure on cervix may benefit from cervical cerclage [9]. Progesterone: Progesterone is endogenous steroid and sex hormone produced by body in the adrenals, ovary, nervous system, and placenta in pregnancy. Progesterone derives its name from 'progestational related to its fundamental function of preparing and maintaining the uterine endometrium for conception [10]. Early in pregnancy corpus luteum is the primary source of progesterone until the seventh week of gestation, after that the placenta takes over as the main source of progesterone, a transition termed the "luteal-placental shift". The placenta assumes progesterone secretion after approximately 8 weeks of gestation, resulting in gradual increase in maternal serum levels throughout pregnancy [11,12].

The normal daily production for singleton pregnancy is 250mg while for multiple pregnancy may exceed 600 mg [13]. On the bases of this oophorectomy before 8 weeks gestation can lead to miscarriage, but has no effect on the pregnancy if performed after that. Progesterone is synthesized from cholesterol in Mitochondria initially cholesterol is converted to pregnenolone.

In a reaction catalyzed by cytochrome P450 cholesterol side-chain cleavage enzyme. Then progesterone is produced by convert-

ing Pregnenolone when it leaves the mitochondria. Progesterone is released immediately through a process of diffusion [13]. The trophoblast preferentially uses LDL cholesterol for progesterone biosynthesis [13].

When the level of progesterone came down it induce cervical changes through pro-inflammatory mediators including IL-8, nitric oxide, PGs and matrix-degrading enzymes [14]. Beside that the uterine decidua natural killer (NK) cells are affected by progesterone too, these cells have a role in promoting blastocyst implantation and maintenance of pregnancy [15,16].

Progesterone therapy: currently the use of progesterone therapy is utilized to women with singleton pregnancies. Accordingly, both American College of Obstetricians and Gynecologists (2016) and the society for Maternal-Fetal Medicine (2017) approve the use of progesterone therapy for prevention of preterm birth in select women with singleton pregnancies. These Criteria include are a prior preterm birth or no prior preterm birth but a sonographically identified short cervix [17].

Vaginal progesterone pessary has been prescribed for patients with a singleton gestation and a short cervix also by the International Federation of Gynecology and Obstetrics [18], and the National Institute for Health and Care Excellence [19]. The vaginal route is better because it is rapid absorption and avoiding the first-pass hepatic metabolism, resulting in sustained plasma concentrations, and high bioavailability in the in the uterus. This effect has been seen on the endometrium in spite of low serum progesterone level [20,21].

The use of vaginal progesterone was associated with a less admission to the neonatal intensive care unit (NICU), respiratory distress syndrome (RDS) [22], and comparable neonatal morbidity and mortality , and birthweight <1500 g [22].

Aims of the Study

- To assess the usefulness of vaginal progesterone in reducing the risk of preterm birth in pregnant women with short cervix (cervical length less than 29 mm).
- Compare the benefit of the doses of (100mg and 200mg) vaginal progesterone, in preventing preterm birth.

Patients and Method

This was an Interventional Randomized Controlled Trial conducted in Sulaimani maternity hospital, from 1st June 2018 until 1st of March 2019, patient were collected from outpatient clinics and emergency department. Full detailed history and examinations including obstetric and gynecological history was taken, questionnaire has been used to record variables. The cervical length estimated by trans-vaginal ultrasound (TVS), the distance between internal and external os was measured. The treatment group included was 46 Singleton pregnant women with CL < 29 mm between 22–28 weeks of gestation with no sign and symptoms, treated with daily vaginal progesterone for up to 10 weeks the doses were 100 mg and 200 mg according to woman's Gynecologist preference and experience. Also a group of 32 women with cervical length of <29 mm between 22–28 weeks gestation were given no treatment and both groups were prospectively observed by investigator until delivery. Primary data and information were collected by phones or personal interview. Inclusion criteria included any singleton pregnancy with or without history of preterm labour that diagnosed with short cervix by transvaginal ultrasound.

Exclusion criteria include; maternal medical diseases, patient in labour, ruptured amniotic membrane (PROM, PPROM), placenta Previa, history of adverse reaction to progesterone, grand multiparous, twin pregnancy , efficient uterine contractions , polyhydramnios , cervical cerclage in current pregnancy, history of cone biopsy, history of treatment of CIN , LLETZ , recurrent APH and uterine abnormalities all were excluded from the review.

Ethical issues

Informed consent was taken verbally from all women. Permission obtained from authorities of health sector in Sulaimani. And scientific committee of the maternity hospital.

Statistical analysis of the review

The questions of study were coded. Statistical analysis was performed by SPSS program, version 21 (IBM SPSS Statistical Package for the Social Sciences). Compliance of quantitative random variables with Gaussian curve (normal distribution) was analyzed using Kolmogorov-smirnov test. The difference in the mean rank between 2 groups was assessed by non-parametric test (Mann-Whitney), while between 3 and more groups Kruskal-Wallis test were used. These two types of variables were described by mean

and SD (standard deviation). The statistical significance of difference in mean between two groups was assessed using independent sample t-test, while between more than 2 groups ANOVA test was used.

Chi-square tests were used to compare the categorical data between these two or three groups of patients in respect to different variables P values of 0.05 were used as a cut off point for significance of statistical test.

Results

In this randomized controlled study seventy-nine women were enrolled in the research and divided into two groups: 47 Singleton pregnant women with CL < 29 mm between 24 – 29 weeks of gestation with no sign and symptoms were given daily vaginal progesterone for up to 10 weeks the doses were 100 mg and 200 mg and a group of 32 women with cervical length of <29 mm between 24-29 weeks of pregnancy were given no treatment, Maximum distribution belongs to age of 19-24 years followed by 30-34 years, no significant difference between those rural and urban area and both belong to medium socioeconomic level , main group of women where nulliparous. Most of women in this study have no history of preterm labour. In those who received vaginal progesterone 5 women had history of two preterm labour and five women in no treatment group. Cervical length in both groups was between 25 – 29 mm and the remaining between 21-24mm.

Socio-demographic	Vaginal progesterone	No treatment	P value
Age (years)			
19 - 24 years	7	16	0.004
25 - 29 years	19	9	
30 - 34 years	20	7	
Mean ± SD	28.2 ± 3.3	25.2 ± 4.4	0.001
Residency			
Inside city	14	16	0.08
Outside city	22	16	
Socioeconomic status			
Low	11	6	0.86
Medium	28	21	
High	7	5	

Table 1: The demographic characteristics of pregnant women in both groups.

Obstetric history	Vaginal progesterone	No treatment	P value
Parity			
Nulliparous	23	20	0.29
Para 1	13	7	
Para 2	6	5	
Para 3	4	0	
Previous preterm labor			
None	30	23	0.42
One	11	4	
Two	5	5	
Cervical length (mm)			
21 - 24	11	13	0.12
25 – 29	35	19	
Mean ± SD	25.5 ± 1.6	24.8 ± 1.8	0.08 *
Median (mean rank)	26 (42.7)	25 (34.9)	0.13 **
Gestational age			
24 - 25 weeks	45	21	< 0.001
26 - 29 Weeks	1	11	
Mean ± SD	24.3 ± 0.5	25.1 ± 1.0	< 0.001*

Table 2: Compare parity, obstetric history, cervical length and gestational age between both groups.

* t test

** Mann – Whitney test.

Pregnancy outcome (weeks)	Cases	Control	P value
Preterm (28 - 33 weeks)	7 (15.2%)	9 (28.1%)	0.17
Late preterm (34 - 37 weeks)	39 (84.8%)	23 (71.9%)	
Mean ± SD	35.1 ± 2.2	34.0 ± 2.7	0.06*
Median (mean rank)	36.0 (43.6)	35.0 (33.6)	0.052**

Table 3: Shows gestational age at delivery for both groups.

* t test

** Mann – Whitney test.

Pregnancy outcome (weeks)	No treatment (n = 32)	Progesterone 100 mg (n= 31)	Progesterone 200 mg (n= 15)	P value
Preterm (28 - 33 weeks)	9 (28%)	1 (3%)	6 (40%)	0.01
Late preterm (34 - 37 weeks)	23 (72%)	30 (97%)	9 (60%)	
Mean ± SD	34.0 ± 2.7	36.0 ± 1.2	33.1 ± 2.6	< 0.001 *
Median (mean rank)	35.0 (33.6)	36.0 (52.8)	34.0 (24.6)	< 0.001 **

Table 4: Compare gestational age at time of delivery among no treatment group, group of 100 mg vaginal progesterone and the group of 200 mg vaginal progesterone.

* ANOVA test

** Kruskal – Wallis test.

Figure 1: A line graph shows that larger number of cases (who received 100 mg progesterone) reached 37 weeks of gestation.

Discussion

Our findings suggest that the percentage of preterm birth among women attending our hospital is about 7-10% among 11000 delivery in study period, study confirmed that preterm birth in group that received vaginal progesterone were less than those who received no treatment, but this difference was statistically not significant, this findings defeated by Meena Khandelwal., *et al.* study that conducted in Cooper University Hospital in USA in 2012 [23]. Short cervical length belonged majorly to younger age group in our study this finding agreed with Heath., *et al.* study conducted in fetal medicine in Harris Birthright Research Centre.

King's College Hospital Medical School, London, UK, shows that maternal age (<20 years; >35) years are associated with a risk of short cervix [24]. The percentage of preterm birth in women receiving vaginal progesterone was less than no treatment group, specifically the frequency of preterm labor among those women who received 100 mg were significantly lower than other two groups, 84.8% of women using vaginal progesterone delivered between (34 - 37 weeks) and only 15.2% of this group delivered preterm between (28-33 weeks) Mean ± SD 35.1 ± 2.2, and about those women with no treatment group 71.9% delivered after 34 weeks gestations and 28.1% of them were preterm between (28-33 weeks) Mean ± SD 34.0 ± 2.7, Odd's ration 0.45. We divided the women received vaginal progesterone into two groups (one receiving 100 mg of vaginal progesterone and another 200 mg) daily. Vaginal progesterone does not have effect on the risk of preterm labour <32 weeks in patients with cervical length <22mm and previous history of preterm birth regarding the dose of 200mg this agreed with Danish., *et al.* at 2011 [25] in the Department of Obstetrics and Gynecology, Medical University of Vienna, in Austria. The study of pregnancy with high risk of sPTB that showed no benefit from 200 mg vaginal progesterone suppositories.

Vaginal progesterone of 100 mg daily up to 10 weeks appeared to have effect on pregnant women with short cervix <25 mm that delivered after 34 weeks of gestations those pregnant women with no history of preterm birth, It is agreed with the study that done by Romero R., *et al.* [26], showed a 45% reduction in the rate of preterm birth before 33 weeks of gestation with administration of vaginal progesterone to women with a sonographic short cervix in the mid-trimester. Also Hassan., *et al.* in USA in 2016 [27], showed by updated systematic reviewed and meta-analysis confirmed that

the risk of preterm birth and neonatal morbidity and mortality reduced with the use of vaginal progesterone in a singleton pregnancy with short cervix at mid-trimester CL ≤ 25 mm.

Conde-Agudelo., *et al.* at 2013 USA [28], adjusted indirect meta-analyses, either vaginal progesterone or cerclage are both useful in the prevention of preterm birth in women with ultrasound short cervix in the mid trimester in singleton pregnancy, and previous preterm birth.

Conclusion

The use of vaginal progesterone in mid-trimester of pregnancy between 24-28 weeks of gestation may benefit in women with a short cervical length <29 mm in mid-trimester of pregnancy with no history of preterm birth or with previous one history of preterm birth. Also for those women the use of 100 mg vaginal progesterone per day is better than 200 mg vaginal progesterone. In contrast the use of vaginal progesterone has no significant benefit for patient with short cervical length if there was a history of more than one preterm birth.

Recommendations

We recommend cervical length measurement of all pregnant women with singleton gestation at mid-trimester, and offering prophylactic treatment with vaginal progesterone in those with short cervical length.

I preferred further larger studies, use of vaginal progesterone for pregnant women with short cervix < 25 mm.

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Conflict of Interest

The authors declare no conflict of interest in preparing this article.

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