Vaginal Progesterone Pessary for Preterm Labor Prevention in Women with a Short Cervix Early in The Second Trimester

Enas A.A. Khazaali FICMS (OG), CABOG
Dept. of Obstetrics and Gynecology, College of Medicine, Al-Nahrain University, Baghdad, Iraq

Abstract

Background
The prevention of preterm birth is a major health care priority.

Objective
To evaluate the efficacy of vaginal progesterone pessary in reducing the rate of preterm delivery and subsequent neonatal morbidity and mortality events in pregnant women with a short cervical length early in the 2nd trimester.

Methods
Women with a singleton pregnancy without a history of preterm labor nor a history of second trimester miscarriage, underwent cervical length measurement at 14+0 to 15+6 weeks of gestation. Women found to have a cervical length less than 30 mm received vaginal progesterone pessary (400 mg per pessary) on daily basis, or no treatment. Primary outcome was preterm delivery rate before 37 weeks gestation. Secondary outcome includes neonatal morbidity and mortality events.

Results
From the 7725 pregnant women screened between the period from April 2015 to January 2017, 613 were found to have a cervical length less than 30 mm and only 518 pregnant women met the inclusion criteria and agreed to participate in this study. However, only 492 were followed up till the time of delivery. From those 252 women administered 400 mg vaginal progesterone pessary once daily at night and the remaining 240 women did not receive any form of progesterone and served as control. There was a significant reduction in preterm delivery rate less than 37 weeks gestation among women receiving progesterone vaginal pessary compared to the control group 11 (4.4%) vs 38 (15.8%), p value < 0.001. Regarding neonatal outcome, there were significant reduction in the frequency of respiratory distress syndrome, low birth weight neonates and admissions to neonatal intensive care unit in women taking vaginal progesterone pessary compared to the control. While other neonatal morbidity and mortality events, incidence of neonatal congenital anomalies were not significantly different between the two groups.

Conclusion
Vaginal progesterone pessaries in women with a cervical length less than 30 mm early in the second trimester are found to be effective in reducing the rate of preterm birth and some of the prematurity related morbidity events.

Keywords
preterm labor, vaginal progesterone pessaries, short cervix, premature delivery

Citation
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List of abbreviations: BMI = Body mass index, BPD = Bronchopulmonary dysplasia, CNS = Central nervous system, 17-OHPC = 17 hydroxy progesterone caproate, LMP = Last menstrual period, PTB = Preterm birth, RDS = Respiratory distress syndrome, TVU = Transvaginal ultrasound

Introduction
The definition of preterm birth (PTB) is delivery of a baby before 37 completed weeks of pregnancy (1). About one-quarter of PTB are iatrogenic usually for pre-eclampsia, fetal growth retardation or maternal disease. The remainder is due to spontaneous preterm labor and delivery (2). There was steady improvement in the survival rates of preterm babies over the past two decades, mainly due to the introduction of surfactant therapy, wider spread use of antenatal steroids and improvement in neonatal respiratory management (2).
PTB is a leading cause of neonatal and infant mortality as well as short- and long-term disability. In developed countries, rates for PTB range between 6% and 12% and are generally higher in developing countries (3,4).

Premature delivery in an under-resourced setting, place the baby at extremely high risk of death in the early neonatal period. The lower the gestational age at birth, the greater the need for more expensive interventions and support to improve the chances of infants' survival. In developing countries, the absence of skilled maternity care, leads to high rates of neonatal morbidity and mortality for premature babies. Despite increasing incidence of prematurity in both developed and developing countries, no significant advances have been made in the prevention or treatment of preterm delivery (3,4).

It has been found that progesterone plays a major role in the maintenance of pregnancy and in the majority of mammals, labor is preceded by a decline in circulating progesterone levels (5).

In the human, there is no systemic withdrawal of progesterone prior to labor, although there is an increase in the expressions of genes formerly repressed by progesterone (6).

It has been widely thought that progesterone inhibits contractions principally by repressing contraction-associated proteins such as oxytocin, gap-junction proteins, prostaglandin receptors and prostaglandin-metabolizing enzymes (7,8).

Preterm labor cannot be considered as a single disease entity, but it is a syndrome or symptom that may have one or more causes (3).

Because of multifactorial (social, behavioral and biological) causes in preterm delivery, efforts in prevention measures have not been successful so far (9).

Early identification of woman at risk and the use of prophylactic therapies are one of the most important strategies to reduce perinatal morbidity and mortality associated with PTB. Initial identification of women at high risk of preterm labor is based on their past obstetric history (10).

A single previous preterm delivery increases the risk of preterm delivery in the next pregnancy by four folds compared with a previous delivery at term. However, the large majority of spontaneous preterm delivery occurs in nulliparous women, and progesterone has not been widely assessed in those women (11).

Although women with of previous history PTB and those with multiple gestation are at the highest risk of preterm delivery (12,13), the majority of spontaneous PTB occur in women with low risk (14).

There is good evidence that support the use of transvaginal sonographic measurement of cervical length to predict the risk of preterm labor in both low- and high-risk pregnancies and in symptomatic women (15).

Currently, there are two strategies in common use: a single measurement of cervical length usually at the time of the routine ultrasound scan at 18-22 weeks of gestation or a serial measurement of cervical length throughout the 2nd and early 3rd trimester of pregnancy. There is a direct relationship between cervical length and preterm delivery risk at any given gestational age, example, a cervical length of 15 mm or less at 20-24 weeks predicts a 50% risk of preterm delivery prior to 34 weeks in a low risk population. However, identification of a risk of preterm labor as late as 23 weeks may be too late for any potential prophylactic therapies to be beneficial (16).

There is currently no effective method for the prediction of preterm labor in prime gravid women with no other significant risk factors for preterm delivery. However, it is possible to identify a subgroup of women who can be identified as being at risk of PTB depending on the use of screening tests e.g. measurement of cervical length, detection of fetal fibronectin in vaginal secretions and the presence of abnormalities of the genital tract.
Commonly used therapies include cervical cerclage, non-steroidal anti-inflammatory drugs (NSAIDs) and progesterone. The weight of both clinical evidence and basic science currently points to progesterone being potentially beneficial in women at high risk of preterm delivery, except those with multiple gestation and there appear to be few if any side effects.

The efficiency and safety of progestogens are related to individual pharmacologic properties of each drug within this class of medication and characteristics of the population that is treated.

Research among exposed women and controls showed no difference with respect to the occurrence of abnormalities of the central nervous system (CNS), limbs and joints, urogenital tract and circulatory tract between treated and untreated programs, even when 17 hydroxy progesterone caproate (17-OHPC) was administered in early pregnancy. Manuck et al. demonstrated a variable response to 17-OHPC exposure, based on the progesterone receptor genotype.

The recommendation of the American College of Obstetrics and Gynecology about the use of antenatal progesterone to prevent preterm delivery is that: its use should be restricted to women incidentally found to have a short cervix (less than 15 mm), or to women with a documented history of prior spontaneous preterm delivery at less than 37 weeks gestation.

Methods

The present study was conducted from April 2015 to January 2017 in the ultrasound outpatient department at Al-Imamein Al-Kadhimein Medical City and in 5 ultrasound private clinics operated by an ultrasound specialist, and it was approved by the Institutional Review of the Iraqi Board of the participating center.

A verbal informed consent was taken from all the eligible participants before study entrance. This trial enrolled 518 low risk asymptomatic women with a singleton pregnancy who were nulliparous or multiparous without a history of spontaneous PTB less than 37 weeks gestation nor 2nd trimester miscarriage and who were found to have a cervical length < 30 mm on transvaginal ultrasound scan at 14+0 to 15+6 weeks gestation.

Gestational age was estimated based on the last menstrual period (LMP), which was reported by the participants and was confirmed by ultrasound or ultrasound alone when LMP was unknown.

After emptying the urinary bladder, transvaginal measurement of cervical length was performed. The name of the ultrasound machine used is Voluson E6 ultrasound machine GE health care, the transvaginal probe used is IC5-9-D Micro Convex Endocavitary Probe. The cervical length was measured from the internal os to the external os along the endocervical canal.

All participating sonographers were experienced.

For each participant, baseline demographic data including maternal age, body mass index (BMI), level of education were collected. BMI was calculated around the time of the transvaginal scan, using the following formula: weight in kilograms (Kg) divided by the height in meters squared (Kg/m^2). Obstetric and medical history were taken and physical examination was done.

Exclusion criteria include women less than 18 years of age, women with a history of previous preterm delivery and 2nd trimester miscarriage, vaginal bleeding, fetal congenital malformation or suspected chromosomal abnormalities (from the increased nuckal translucency thickness measurement above 2.9 mm), cervical or abdominal cerclage in situ or planned cerclage.
uterine anomalies e.g. bicornuate uterus or septate uterus, current or recent progesterone therapy within the previous 4 weeks, allergy to any ingredient of the pessaries, cervical dilatation, chronic maternal medical condition e.g. diabetes mellitus, chronic hypertension, liver disease, psychiatric disorders, epilepsy, porphyrias, known or suspected progesterone-sensitive tumors e.g. breast cancer, deep venous thrombosis, pulmonary embolism, thrombophlebitis, heart attack or stroke.

All the participants were randomly allocated to receive either vaginal or rectal progesterone pessaries (trade name: cyclogest, company’s name: Actavis, Barnstaple EX328NS, UK) 400 mg daily or no treatment till 36+6 weeks gestation.

Progesterone pessaries were self-administered vaginally using the 400 mg formulation, on daily basis at night. Those who had vaginal infection e.g. moniliasis and in those with recurrent cystitis the pessaries were applied rectally. However, in the presence of colitis or fecal incontinence, it was applied vaginally.

The treatment was initiated between 14+0 and 15+6 weeks of gestation and continued until 36+6 weeks gestational age, rupture of membranes or delivery, whichever occurred first.

All the participants were followed-up every 3 weeks and were interviewed to determine the occurrence of any adverse events and to ensure about the compliance with the treatment in those who receive the progesterone pessaries.

Women who developed 2nd trimester miscarriage (one) and those who were lost to be followed up (twenty-three) were excluded from the study as well as those who needed an emergency cerclage (two) which was done if cervical dilatation exceeds 1 cm, in the presence of an intact membranes and in the absence of uterine contractions, significant vaginal bleeding and clinical or subclinical (increased c-reactive protein, increased white blood cell count) evidence of chorioamnionitis.

Progesterone pessaries were stored below 25 °C in a dry place.

Maternal outcome was preterm birth prior to 37 weeks gestation.

Neonatal outcome was recorded after delivery and up to the first 28 days of life and it included fetal death, neonatal death, or neonatal morbidity in the form of grade III or IV intraventricular hemorrhage, periventricular leukomalacia, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), proven sepsis, necrotizing enterocolitis.

According to radiological appearance, intraventricular hemorrhage was classified as followed: (22)

Grade three intraventricular hemorrhage: the blood filling and distending the ventricular system. Dilated ventricles which are more than 50% full of blood

Grade four intraventricular hemorrhage: parenchymal involvement of hemorrhage, also known as periventricular venous infarction.

Periventricular leukomalacia is a form of white-matter brain injury, characterized by the necrosis (more often coagulation) of white matter near the lateral ventricles (23).

RDS was defined as need for artificial ventilation and an x-ray meeting RDS criteria (24).

BPD was defined as need for supplemental O2 during at first 28 days after birth (25).

Analysis was by an intention to treat.

Statistical analysis

With using the Microsoft excel 2016 and GraphPad Prism version 6 software, most of data was categorical and presented as frequency and percentage, the comparison of these data between the two groups of study was done Using chi square test and Fisher exact test. Only age and body mass index were presented as mean ± standard deviation and comparison done by an unpaired t-test. P value less than 0.05 was considered significant.

Results

From the 7725 women scanned, 613 found to have a cervical length less than 30 mm; and from the 613 women, 575 met the inclusion criteria. However, only, 518 pregnant women agreed to participate in this study.
From the 518 women who participated in this study, 492 were followed-up till the time of delivery. Of the remaining 26 women, 23 women were lost to follow-up and 3 were excluded from the study because one of them miscarried at 17+3 weeks of gestation and two needed emergency cerclage for cervical dilatation one at 17+6 weeks gestation and the other at 21+2 weeks gestation. From the 492 participants who were followed up; 252 women administered 400 mg progesterone pessary once daily at night and the remaining 240 women did not receive any form of progestogens and served as control. Thus, this study included two groups; pregnant women receiving vaginal or rectal progesterone pessaries, the study group n=252 and the control group n=240. The two study groups were matched regarding maternal age (26.34±3.62 for women taking cyclogest and 26.44±3.63 for control) p value = 0.759. Likewise, for the body mass index, no significant difference was found between the two groups (28.49±2.34 for women taking cyclogest and 28.6±2.28 for control) p value = 0.577 (table 1).

There was no significant difference between the two groups in other maternal related data including obstetric history, method of delivery, history of infertility ± assisted reproductive technologies, cervical length and higher professional education as shown in table (2). The frequency of preterm delivery was significantly less in women receiving cyclogest in comparison with control (11 vs 38), p value <0.001 as shown in table (3). Table (4) shows a significant lower frequency of respiratory distress syndrome in neonates born to women taking progesterone pessary than those born to the controls; (9 vs 32), p value < 0.001. With regard to the frequency of other neonatal morbidity and mortality events (apart from respiratory distress syndrome), no significant difference was shown between the two study groups (2 vs 7), p value = 0.099, as illustrated in table (4) as well. Table (5) demonstrated the presence of significant lower frequency of low birth weight neonates born from women taking progesterone pessary than those born to the controls (5 vs 26), p value < 0.001. Moreover, there was no significant difference regarding the frequency of congenital anomalies in the neonates between the two study groups (one case of ventricular septal defect in women taking progesterone pessary vs one case of cleft lip in control group), p value = 1.000, furthermore, a significant lower frequency of admission of neonates to neonatal intensive care unit (NICU) was shown between women taking progesterone pessary and control group (10 vs 34), p value < 0.001.
Table 2. Comparison of other maternal related data between the two groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women taking progesterone pessary</th>
<th>Control</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=252 No. (%)</td>
<td>N=240 No. (%)</td>
<td></td>
</tr>
<tr>
<td>Obstetric history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>95 (37.7)</td>
<td>93 (38.7)</td>
<td>0.853</td>
</tr>
<tr>
<td>Multiparous</td>
<td>157 (62.3)</td>
<td>147 (61.3)</td>
<td></td>
</tr>
<tr>
<td>Method of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>215 (85.3)</td>
<td>207 (86.3)</td>
<td>0.797</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>37 (14.7)</td>
<td>33 (13.7)</td>
<td></td>
</tr>
<tr>
<td>History of infertility ± ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Negative</td>
<td>252 (100)</td>
<td>240 (100)</td>
<td></td>
</tr>
<tr>
<td>Cervical length</td>
<td>&lt; 20 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>42 (16.7)</td>
<td>39 (16.2)</td>
<td>0.904</td>
</tr>
<tr>
<td></td>
<td>20-30 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>210 (83.3)</td>
<td>201 (83.8)</td>
<td></td>
</tr>
<tr>
<td>Higher professional education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>97 (38.5)</td>
<td>90 (37.5)</td>
<td>0.853</td>
</tr>
<tr>
<td>Absent</td>
<td>155 (61.5)</td>
<td>150 (62.5)</td>
<td></td>
</tr>
</tbody>
</table>

* Fishers' exact test, ART: Assisted reproductive technologies

Table 3. Comparison of preterm delivery between 2 groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women taking progesterone pessary</th>
<th>Control</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=252 No. (%)</td>
<td>N=240 No. (%)</td>
<td></td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>11 (4.4)</td>
<td>38 (15.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Term delivery</td>
<td>241 (95.6)</td>
<td>202 (84.2)</td>
<td></td>
</tr>
</tbody>
</table>

* Fishers' exact test

Table 4. Comparison of respiratory distress syndrome and other neonatal morbidity and mortality events between 2 groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women taking progesterone pessary</th>
<th>Control</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=252 No. (%)</td>
<td>N=240 No. (%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>9 (3.6)</td>
<td>32 (13.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Absent</td>
<td>243 (96.4)</td>
<td>208 (86.7)</td>
<td></td>
</tr>
<tr>
<td>Other morbidity or mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>2 (0.8)</td>
<td>7 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>250 (99.2)</td>
<td>233 (97.1)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

* Fishers' exact test
Table 5. Comparison of neonates’ parameters between the two groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Women taking progesterone pessary N=252</th>
<th>Control N= 240</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Low birth weight neonates</td>
<td>Present 5 (2.0)</td>
<td>26 (10.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Absent 247 (98.0)</td>
<td>214 (89.2)</td>
<td></td>
</tr>
<tr>
<td>Neonates with congenital anomalies</td>
<td>Present 1 (0.4)</td>
<td>1 (0.4)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Absent 251 (99.6)</td>
<td>239 (99.6)</td>
<td></td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>Present 10 (4.0)</td>
<td>34 (14.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Absent 242 (96.0)</td>
<td>206 (85.8)</td>
<td></td>
</tr>
</tbody>
</table>

* Fishers’ exact test, NICU: Neonatal intensive care unit

Concerning incidence of treatment related adverse events, no significant difference was found between women taking cyclogest and control groups (5 vs 0), p value = 0.062 as shown in table (6). Only five patients from the 252 experienced minor side effects in the form of soreness and flatulence with rectal administration and leakage of the pessary with rectal and vaginal administration.

Table 6. Comparison of incidence of treatment related adverse events between the two groups

<table>
<thead>
<tr>
<th>Treatment adverse events</th>
<th>Women taking progesterone pessary N=252</th>
<th>Control N= 240</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>5 (1.98)</td>
<td>0 (0.0)</td>
<td>0.062</td>
</tr>
<tr>
<td>Absent</td>
<td>247 (98.02)</td>
<td>240 (100)</td>
<td></td>
</tr>
</tbody>
</table>

* Fishers’ exact test

**Discussion**

The prevention of preterm birth is a major health care priority. The only class of medication to demonstrate significant reductions repeatedly in the rate of early preterm birth are progestogens, natural progesterone or the synthetic 17-hydroxy progesterone caproate (17-OHPC). The rationale behind the use of progesterone supplantations in reducing the rate of preterm birth is the following fact: although there is no significant change in progesterone concentration in the maternal circulation in the weeks preceding labor, the onset of labor both at term and preterm is associated with a functional withdrawal of progesterone activity.

The vaginal route of drug delivery results in a greater concentration of supplemental progesterone within the uterus and cervix compared to serum (a first uterine pass effect). In 2003, Da Fonseca et al. reported a lower rate of preterm delivery in women at high risk and who receive a 100 mg vaginal suppository daily, 13.8% before 37 weeks compared with the placebo group 28% before 37 weeks. In a similar study, Meis et al. used weekly injections of 250 mg of 17 α-hydroxy progesterone caproate between 16 and 36 and this reduced the preterm delivery rate from 55 to 36% before 37 weeks. In this study, the neonates of mothers treated with progesterone had lower morbidity.

In the current study, there was further reduction in the rate of preterm delivery in the progesterone treated group than in the control group (4.4% versus 15.8%) as well as the findings of our study were translated into a significant reduction in RDS, low birth weight.
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infants and overall neonatal morbidity and mortality events in women who were taken cyclogest vaginal pessary compared to control group.

In agreement with the findings of the current study, a randomized clinical trial of vaginal progesterone capsules to prevent preterm delivery in women with a short cervix (defined as 15 mm or less) on transvaginal ultrasound at 20-25 weeks’ gestation, reported a 44% reduction in the rate of preterm delivery (19.2% vs 34.4%) (34). However, in this study, the reduction in the rate of preterm delivery was 72%. This probably can be explained by earlier gestational age of intervention, which was at 15 weeks gestation as well by the longer cervical length of the women enrolled in our study (less than 30 mm). In addition to the above findings our trial was associated with a significant improvement in neonatal outcome, which was not the case in the study done at 2007 (34).

The above difference in the findings might be explained by the following fact: the risk of preterm birth based on cervical length varies according to the population in which the measurement is obtained and the gestational age in which a short cervix is identified (14,35).

In line with finding of the current study, a large trial done at 2009 (36) measured cervical length at enrollment and at 28 weeks gestation in asymptomatic singletons, there was significantly smaller difference in the measurement of cervical length at these time points and significantly longer cervices at 28 weeks gestation in women who were treated with progesterone.

It has been found that natural progesterone exposure, significantly decrease contraction frequency (32,37).

Another trial that showed findings similar to those found in the current study is that done by Maher et al., who demonstrated a significant reduction in preterm birth at < 34 weeks with supplemental vaginal progesterone (16.6% vs 25.7%) (38), although the reduction in this study is more marked.

Hassan et al. (39) and Romero et al. (40) demonstrated that progesterone treatment indicated for a sonographic short cervix based on a universal screening strategy by TVU scanning can reduce the rate of preterm birth.

In the current study, we extended the upper limit of cervical length to less than 30 mm to explore whether vaginal progesterone pessaries would have a beneficial effect above the limit of cervical lengths included in the previous trials and therefore expand its therapeutic range.

As well our treatment protocol began at earlier gestation (15 weeks) than in the previous studies and continued till the time of delivery or up to 36 weeks + 6 days because it is possible that earlier treatment may confer more beneficial effects and this what has been shown in our results in comparison with the findings of the previous trials.

However, the findings of this study disagree with that shown by Grobman et al. (41) who conducted a randomized trial among nulliparous women with a singleton gestation and mid trimester cervical length < 30 mm, weekly injections with 17 α-hydroxy progesterone caproate or placebo did not alter the frequency of preterm birth less than 37 weeks of gestation or neonatal outcome. Other investigators observed that vaginal progesterone but not 17 α-hydroxy progesterone caproate was associated with beneficial effects (42).

The reason for this discrepancy in the findings between this trial and other trials including ours, may be related to the type, dose and route of administration of progesterone.

With regard to the risk of congenital anomaly in the progesterone treated group, our findings did not show any increase.

There is one concern exist is a possible increased risk of hypospadias in male offspring exposed to exogenous progestins (43) even if this risk is real, it is limited to exposure prior to 11 weeks gestation.

In the current study, there was no report of significant side effects in the progesterone treated group. However, long-term side effects on mothers and infants should be considered in further investigation.

Adverse effects of progesterone suppositories were not mentioned (32,34,44).
The main implication of this study for clinical practice is that universal screening of women with transvaginal ultrasound to measure cervical length early in the second trimester to identify women at risk of preterm labor can now be coupled with an intervention, the administration of vaginal progesterone to reduce the rate of preterm labor and improve neonatal outcome. The limitation of this trial is that it is not double blind and not placebo controlled. This study concluded that vaginal progesterone pessaries in women with a cervical length less than 30 mm early in the second trimester is effective in reducing the rate of preterm birth and some of the prematurity related morbidity and mortality events.

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Conflict of interest
The author declares no conflict of interest.

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References
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