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A COMPARATIVE STUDY BETWEEN INTRAMUSCULAR 17 ALPHA-HYDROXYPROGESTERONE AND NATURAL PROGESTERONE SUPPOSITORIES AND DEHYDROGESTRONE TABLETS IN PREVENTING PRETERM LABOR

By

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ABSTRACT

Background: Preterm birth (PTB) is a complex condition leading to neonatal morbidity and mortality. It is the second leading cause of mortality before the age of 5 years. The risk of morbidity also extends to later life. Many efforts have been done to prevent Preterm birth in order to decrease future complications. Dehydrogestrone has a good safety and tolerability profile. It is structurally and pharmacologically similar to natural progesterone and has good oral bioavailability with few side effects. Dehydrogestrone has no androgenic effects on the fetus, and does not inhibit the formation of progesterone in the placenta.

Objective: To evaluate the intramuscular 17 alpha-hydroxyprogesterone, natural progesterone suppositories, and dehydrogestrone tablets in preventing preterm labor.

Patients and Methods: This was a comparative study, involving 300 pregnant women attended outpatient clinic of Al-Hussein University Hospital, and diagnosed at risk of preterm labor. Those patients were allocated into three equal groups: Group (A) received vaginal Progesterone suppositories, Group (B) received intramuscular 17 alpha hydroxyprogesterone Injections, and Group (C) received oral dehydrogestrone tablets, during the period from January 2020 to December 2021.

Results: There was no significant difference between the groups in term of preterm labor, short cervix, and mid-trimestric miscarriage. There was a significant difference regarding middle cerebral artery resistance index before and after treatment as it decreased in Group (C) than Group (A) and Group (B). Regarding middle cerebral artery pulsatility index also there was a decrease after treatment in Group (B) than Group (A) and (C). There was a difference regarding umbilical artery pulsatility index after treatment as it increased in Group (A), Group (B) and Group (C). Moreover, there was a significant increase in umbilical artery resistance index in Group (C) than Group (A) and (B). There was no significant difference between the three groups in term of preterm delivery.

There was no significant difference between the three groups in term of neonatal complications.

Conclusion: Vaginal progesterone suppositories, intramuscular 17-alpha hydroxyprogesterone injections, and oral dehydrogestrone tablets have the same effect on the rate of PTB in asymptomatic women with a sonographically short cervix, and there was no significant difference between the effects of three drugs on the cervical length (CL) changes over time.

Keywords: Preterm Labor, Intramuscular 17 Alpha-Hydroxyprogesterone, Natural Progesterone Suppositories, Dehydrogestrone Tablets.

INTRODUCTION

Preterm labor is defined as delivery before 37 completed weeks of pregnancy and it is the leading cause of perinatal and neonatal morbidity and mortality and strongly related to the developmental and neurological disabilities later in life *(Blencowe et al., 2013a)*. Morbidity and mortality are inversely related to the gestational age at the time of delivery, the most severe consequences occur when delivery is before 34 weeks of gestation *(Klein et al., 2011)*.

Preterm labor prevention is considered a major challenge to obstetricians as it is the leading direct cause of neonatal death (death during the first 28 days of life), its responsible for 27 percent of neonatal deaths worldwide comprising over one million deaths annually *(Blencowe et al., 2013b)*.

Progesterone is an important hormone for the maintenance of pregnancy early as well as later in gestation. In singleton pregnancies, prophylactic progesterone administration during the second and third trimesters has been shown to reduce the rate of preterm deliveries in those with a history of previous spontaneous preterm delivery *(Rode et al., 2010)*.

Progesterone is an endogenous steroid hormone involved in the menstrual cycle, pregnancy and the embryogenesis of humans and other species *(Norman et al., 2016)*. It belongs to a group of steroid hormones called Progestogens and is the major progestogen in the body. Progesterone decreases the contractility of uterine smooth muscles *(Brucker and King, 2016)*. Drop in progesterone levels is possibly one step that facilitates the onset of labor. There is still considerable uncertainity regarding the optimal progesterone type, route of administration, dosage, timing of the start of the therapy to prevent preterm labor in risky women *(Tita and Rouse, 2010)*.

Vaginal progesterone is as effective as cervical cerclage to prevent preterm birth in women with a singleton Gestation, previous spontaneous preterm birth and a short cervix *(Conde-Agudelo et al., 2018)*.

The aim of the present work was to evaluate intramuscular 17 alpha-hydroxyprogesterone, natural progesterone suppositories and dehydrogestrone tablets in preventing preterm labor

PATIENTS AND METHODS

This was a comparative study, involving 300 pregnant women attended outpatient clinic of Al-Hussein University Hospital, and diagnosed at risk of preterm labor. These patients were allocated into three equal groups: Group (A) received vaginal progesterone suppositories, Group (B) received intramuscular 17 alpha hydroxyprogesterone injections, and group (C) received oral dehydrogestrone tablets during the period from January 2020 to December 2021.

Inclusion criteria:

1. Singleton pregnancy.
2. Living fetus with gestational age from 22 th To 37 week of gestation (calculated according to date of last

menstrual period and confirmed by Ultrasound examination).

3. Presence of risk factor for preterm labor: (a) Previous spontaneous preterm labor in previous singleton pregnancy. (b) Previous spontaneous second trimestric miscarriage less than 3 times. (c) Short cervix less than 25mm diagnosed by second trimestric transvaginal ultrasound with or without history of preterm labor.

Exclusion criteria:

1. Multiple pregnancies.
2. Medical or obstetric causes requiring termination of pregnancy.
3. Contraindications to progesterone administration: Known sensitivity to progesterone injection, known sensitivity to sesame oil/seeds, liver dysfunction or disease, known or suspected malignancy of breast or genital organs, and current or past history of thrombophlebitis or thromboembolic disorders.
4. Congenital fetal anomalies.
5. Cervical cerclage in the current pregnancy.
6. Presence of uterine anomalies (unicornate uterus, bicornate uterus, septated uterus, uterine didelphys).
7. History of chronic hypertension and chronic liver or kidney disease.

Women who fulfilled the eligibility criteria were subjected to:

1. History taking with particular emphasis on menstrual history to calculate gestional age, past obstetric history, past history of preterm labor or midtrimestric miscarriage, and past medical history and chronic disorders.
2. General examination.
3. Abdominal examination: to detect the fundal height and presence of uterine contractions.
4. Obstetric ultrasound to confirm gestational age and fetal well-being, and measure cervical length by transvaginal ultrasound.
5. Administration of Selected progesterone according to the groups:

   a. Oral group took oral dehydrogestrone.

   Trade name: Duphastone 10 mg tabs

   Dose: 2 tablets /day.

   b. Intramuscular group took 17 alpha hydroxyprogesterone caproate.

   Trade name: Cidolut depot 250mg ampoules.

   Dose: IM injection once / week.

   C. Vaginal group took progesterone vaginal suppositories.

Trade name: Prontogest 200mg.

Dose: Twice/ day.

6. Duration of the study: Selected women were given the previously mentioned doses starting from 22nd week of pregnancy till the 37^{th} week.

Statistical Analysis:

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$)

and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation). Paired t-test was used to compare between two dependent groups of normally distributed variables. One-way ANOVA test was used to compare between more than two dependent groups of normally distributed variables, while Kruskal-Wallis test was used for non-normally distributed variables. Binary logistic regression analysis using the stepwise method was used to determine the potential risk factors of preterm labor. All statistical comparisons were two tailed with significance level of P-value ≤ 0.05 indicated significant.

RESULTS

There was no significant difference between the groups regarding maternal age, BMI, parity and GA at administration. There was no significant difference between the groups in term of preterm labor, short cervix and mid-trimestric miscarriage **(Table 1)**.

Table (1): Demographic characteristics and clinical data and risk factors among the studied groups

Groups / Parameters	**Group A** (n=100)	**Group B** (n=100)	**Group C** (n=100)	**p**
Age (years) Mean ± SD	28.56 ± 4.73	29.11 ± 4.12	29.7 ± 4.31	0.187
BMI (kg/m^2) Mean ± SD	26.6 ± 2.69	26.29 ± 2.39	27.12 ± 2.84	0.083
Parity Mean ± SD	3.16 ± 1.44	3.43 ± 1.52	3.35 ± 1.24	0.379
GA (weeks) Mean ± SD	18.25 ± 2.41	17.76 ± 2.86	18.31 ± 2.25	0.241
Risk factors:				
Preterm labor history	42 (42%)	35 (35%)	37 (37%)	0.576
Short cervix	36 (36%)	38 (38%)	40 (40%)	0.844
MTA	31 (31%)	28 (28%)	32 (32%)	0.845

There was a significant difference regarding middle cerebral artery resistance index in Group (C) than Group (A) and (B) as it was before treatment was (0.963 ± 0.066) in Group (A), 0.939 ± 0.079 in Group (B) and 0.958 ± 0.041 in Group (C) and after treatment it decreased to 0.781 ± 0.064 in Group (A), 0.811 ± 0.053 in Group (B) and 0.775 ±0.071 in Group (C). Middle cerebral pulsatility index before treatment was 1.74 ± 0.744 in Group(A), 1.92 ± 0.701 in Group (B) and (1.81 ± 0.648) in Group (C) and decreased to 1.41 ± 0.225 in Group (A) , 1.47 ± 0.265 in Group (B) and 1.52 ± 0.155 in Group(C).

Table (2): Indices of the three studied groups before and after treatment

Groups / Parameters	**Group A** (n=100)	**Group B** (n=100)	**Group C** (n=100)	**P**
Middle cerebral artery resistance index before Mean ± SD	0.963 ± 0.066	0.939 ± 0.079	0.958 ± 0.041	**0.021**
Middle cerebral artery resistance index after Mean ± SD	0.781 ± 0.064	0.811 ± 0.053	0.775 ±0.071	**0.0001**
^{pt}P	**<0.001**	**<0.001**	**<0.001**	
Middle cerebral artery pulsatility index before Mean ± SD	1.74 ± 0.744	1.92 ± 0.701	1.81 ± 0.648	0.187
Middle cerebral artery pulsatility index after Mean ± SD	1.41 ± 0.225	1.47 ± 0.265	1.52 ± 0.155	**0.002**
^{pt}P	**0.0003**	**<0.001**	**0.00002**	

There was a difference in umbilical artery pulsatility index as it was (1.19 ± 0.183) in Group (A), 1.17 ± 0.175 in Group (B) and 1.11 ± 0.192 in Group (C) and increased to 1.74 ± 0.087 in Group (A), 1.77 ± 0.085 in Group (B) and 1.72 ± 0.081 in Group (C).

There was a significant increase in umbilical artery resistance index in Group (C) than Group (A) and (B) as it was before treatment 0.687 ± 0.046 in Group (A), 0.692 ± 0.081 in Group (B) and 0.675 ± 0.072 in Group (C) and after treatment it increased to 0.872 ± 0.067 in Group (A), 0.868 ± 0.056 in Group (B) and 0.887 ± 0.062 in Group (C).

Table (3): Umbilical artery Indices of the three studied groups

Groups / Parameters	**Group A** (n=100)	**Group B** (n=100)	**Group C** (n=100)	**P**
Umbilical artery resistance index before Mean ± SD	0.687 ± 0.046	0.692 ± 0.081	0.675 ± 0.072	0.193
Umbilical artery resistance index after Mean ± SD	0.872 ± 0.067	0.868 ± 0.056	0.887 ± 0.062	0.074
^{pt}P	**<0.001**	**<0.001**	**<0.001**	
Umbilical artery pulsatility index before Mean ± SD	1.19 ± 0.183	1.17 ± 0.175	1.11 ± 0.192	0.007
Umbilical artery pulsatility index after Mean ± SD	1.74 ± 0.087	1.77 ± 0.085	1.72 ± 0.081	**0.0002**
^{pt}P	**<0.001**	**<0.001**	**<0.001**	
Middle cerebral/ Umbilical artery resistance index Mean ± SD	0.876 ± 0.093	0.854 ± 0.081	0.978 ± 0.084	**<0.0001**
Middle cerebral/ Umbilical artery resistance index after Mean ± SD	0.633 ± 0.065	0.642 ± 0.073	0.762 ± 0.072	**<0.0001**
^{pt}P	**<0.001**	**<0.001**	**<0.001**	

There was difference between the groups regarding gestational age (GA) at delivery as it was 36.63 ± 1.27 in Group (A), 37.29 ± 1.84 in Group (B) and 36.8 ± 1.62 in Group (C). The Apgar score at 1 min also showed a change as it was 7.32 ± 1.27 in Group (A), 6.49 ± 2.26 in Group (B) and 7 ± 1.54 in Group (C), Apgar score at 5 min was 9.7±1.09 in Group (A), 8.81 ± 2.92 in Group (B) and 9.71 ± 0.499 in Group (C). There was no significant difference between the groups in term of preterm delivery. There was no significant difference between the groups in term of neonatal complications **(Table 4)**.

Table (4): Neonatal characteristics and clinical data, preterm delivery outcome, and neonatal complications and outcome among the studied groups

Groups / Parameters	Group A (n=100)	Group B (n=100)	Group C (n=100)	P
GA at delivery (weeks) Mean ± SD	36.63 ± 1.27	37.29 ± 1.84	36.8 ± 1.62	**0.011**
Birth weight (kg) Mean ± SD	2.97 ± 0.365	2.98 ± 0.338	2.97 ± 0.134	0.963
Apgar at 1 min Mean ± SD	7.32 ± 1.27	6.49 ± 2.26	7 ± 1.54	**0.003**
Apgar at 5 min Mean ± SD	9.7 ± 1.09	8.81 ± 2.92	9.71 ± 0.499	**0.0004**
Preterm delivery outcome:				
Preterm delivery (<37 weeks)	25 (25%)	28 (28%)	35 (35%)	0.281
Early Preterm delivery (<34 weeks)	8 (8%)	2 (2%)	10 (10%)	0.062
Neonatal complications and outcome:				
Admitted to NICU	12 (12%)	18 (18%)	16 (16%)	0.487
Severe jaundice	17 (17%)	26 (26%)	20 (20%)	0.282
Respiratory distress	9 (9%)	5 (5%)	10 (10%)	0.386
Death	1 (1%)	2 (2%)	0	0.364

NICU: Neonatal ICU

There were no changes in age, PTL history, short cervix and BMI (Table 5).

Table (5): Multivariate logistic regression analysis to determine the possible risk factors of preterm labor

Analysis / Risk factors	OR	Wald	Sig.	95% CI
Age	1.215	1.199	0.273	0.139 - 2.679
PTL history	0.465	0.363	0.547	0.039 - 5.592
Short cervix	0.573	0.187	0.666	0.046 - 7.167
BMI	3.725	0.555	0.456	0.117 - 8.321

DISCUSSION

There was no significant difference between the groups regarding maternal age, BMI, parity and GA at administration. Our results were supported by study of *Areeruk and Phupong (2016)* as they reported that, there were no significant differences between the groups in respect to age, gravidity, parity, gestational age, pre-pregnancy body mass index (BMI) and history of preterm birth.

In the study of *Elimian et al. (2016)* on intramuscular progesterone and vaginal progesterone were similar with respect to baseline characteristics.

To the best of our knowledge, this was a novel study to evaluate the intramuscular 17 alpha-hydroxyprogesterone, natural progesterone suppositories and dehydrogestrone tablets in preventing preterm labor.

Etiology of preterm birth is attributed to complex pathological processes. However, the majority of preterm deliveries occur in women without any evident risk factors. Currently, there is no distinct scoring system to predict preterm birth. In addition, the management of ongoing LM (late miscarriage) /PD (preterm delivery) is not sufficiently effective. Beta-mimetics, calcium-channel blockers, inhibitors of prostaglandin synthesis, oxytocin receptor antagonists administered to decrease the probability of delivery within 2–7 days, however, do not affect PD rate. Preventative long-term administration of any tocolytic drugs does not affect the rate of PD *(Neilson et al., 2014).*

The present study showed that as regard risk factors, there was significant difference between the groups in term of preterm labor, short cervix and mid-trimestric miscarriage. Our results were supported by study of *Berghella et al.* (2010) showed no additional benefit of 17α-hydroxyprogesterone caproate for the prevention of PTB in women who had ultrasound-indicated cerclage if their cervical length was <25 mm, but if these women did not have cerclage the drug reduced previable and perinatal mortality. Also, *Bafghi et al. (2015)* as they revealed that the two treatment groups (vaginal progesterone and intramuscular progesterone) showed no significant difference in number of previous preterm labor as risk factor.

The current study showed that there was significant difference between the three studied groups regarding middle cerebral artery resistance index before and after treatment and pulsatility index after treatment. Moreover, there was a significant decrease in middle cerebral artery resistance index and pulsatility index after treatment. There was significant difference between the three studied groups regarding umbilical artery pulsatility index after treatment. Moreover, there was a significant increase in umbilical artery resistance index and pulsatility index after treatment, meanwhile there was a significant decrease in middle cerebral/ umbilical artery resistance index after treatment.

In the study of *Maher et al. (2013),* as regard maternal outcome, adverse effects were reported in 14.1% of patients in the intramuscular group and in 7.5% of patients in the vaginal group. No significant differences in the other parameters were observed between the groups.

Preterm delivery has many negative consequences for newborns, their families, and society, and it is the leading cause of neonatal mortality and long-term morbidity. Thus, in recent years, preventing preterm delivery has become a major priority for healthcare systems in most countries. The first step in preventing preterm delivery is the correct identification of those who are at risk. Several markers could be used as indicators for the prediction of preterm delivery, but the strongest determinants are a history of prior preterm delivery and a short cervix *(Khandelwal, 2012).*

As regard neonatal outcomes, the present study showed that there was significant difference between the groups regarding GA at delivery and Apgar score at 1 min and 5 min. There was no significant difference between the groups

in term of neonatal complications. However, in the study of *Maher et al. (2013)*, the intramuscular progesterone group showed a significantly higher rate of neonatal intensive care unit admission than the vaginal progesterone group. No significant differences were observed between the groups regarding other neonatal outcomes.

In contrary with our results, study of *Areeruk and Phupong (2016)* revealed that neonatal birth weight, low birth weight and Apgar scores <7 at 1 and 5 min did not differ between the groups. Additionally, differences between groups in respect to RDS, IVH, NEC, sepsis, apnea of prematurity, transient tachypnea of new born (TTNB), NICU admission and days of neonatal hospitalization were not significant. There was no neonatal mortality in this study.

In terms of Apgar scores and need for admission to the NICU, their results were similar to those of *Abd El Hameed (2012)*. In the study of *Bafghi et al. (2015)*, the mean Apgar scores of the first and fifth minutes in the two study groups were not significantly different. Also, 28.20% of the infants born to the Cyclogest group and 17.90% of infants born to the hydroxyprogesterone caproate group were admitted to the NICU, but the difference of the length of stay in the NICU between the two groups was not significant. It is notable that the six-day difference between the lengths of the infants' stays in the NICU in the two groups was due to one case in the intramuscular progesterone group. This one case increased the mean and standard deviation of this group with 38 days of hospitalization in the NICU because of sepsis. This infant was born after 31 weeks and four days of pregnancy. When they excluded this case from the data sheet, the length of the NICU stay for the intramuscular group decreased to 7.30 ± 2.86 days.

Also, the studies of *Berghella et al. (2010)* and *Conde-Agudelo et al. (2013)* confirmed the positive effects of progesterone on reducing perinatal mortality and morbidity. Also, *Hassan et al. (2011)* and *Gargari et al. (2012)*, confirmed the positive effects of progesterone on reducing admissions to the NICU. They did not observe any cases of perinatal mortality and birth time abnormalities in their study. But in the studies of *O'Brien et al. (2010)* and *Gargari et al. (2012)* on cyclogest, the rate of infant mortality in the progesterone group was not significantly different from the placebo group.

In the study in our hands, there was no significant difference between the groups in term of preterm delivery. None of studied variable was found to be significant risk factor for preterm labor.

In a study conducted by *Maher et al. (2013)*, no statistically significant difference was observed between the groups regarding deliveries at other weeks of gestation. A significant difference was observed in the probability of delivery among patients who used vaginal progesterone compared those who used intramuscular progesterone.

Our results were supported by study of *Areeruk and Phupong (2016)*, the latency period was not different between the dehydrogestrone and placebo groups.

Furthermore, *Elimian et al. (2016)* revealed that mean length of pregnancy at

delivery did not differ between groups. Similarly, there was no statistically significant between-group difference in the mean birth weight. Delivery before 37 weeks was recorded among 43.9% women in the intramuscular progesterone group, and 37.9% in the vaginal progesterone group. The proportions of women who delivered before 34th weeks and 28th weeks similarly did not differ by group.

CONCLUSION

Vaginal progesterone suppositories, intramuscular 17 alpha hydroxyprogesterone Injections, and oral dehydrogestrone tablets have the same effect on the rate of PTB in asymptomatic women with a sonographically short cervix with no significant difference between the effects of three drugs on the CL changes over time.

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دراسة مقارنة بين الحقن العضلي لـ 17 الفا هيدروكسي بروجستيرون واللبوس المهبلي بروجستيرون وأقراص الديهدروجستيرون في الوقاية من الولاده المبكرة

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خلفية البحث: الولادة المبكرة هي حالة معقدة تؤدي إلى مراضة ووفيات حديثي الولادة، وهو السبب الرئيسي الثاني للوفاة قبل سن 5 سنوات، ويمتد خطر الإصابة بالأمراض أيضًا إلى الحياة اللاحقة. تم بذل العديد من الجهود لمنع الولادة المبكرة لتقليل المضاعفات. ويتمتع الديهدروجستيرون بصفات جينية للسلامة والتحمل، ويشبه من الناحية الهيكلية والصيدلانية البروجسترون الطبيعي، وله توافر بيولوجي جيد عن طريق الفم، وآثار جانبية قليلة. الديهدروجستيرون ليس له تأثير منشط ذكورة على الجنين، ولا يثبط تكوين البروجسترون في المشيمة، ويبدو أن الدواء ليس له آثاراً جانبية على الأم.

الهدف من البحث: تقييم 17 تحاميل ألفا هيدروكسي بروجسترون العضلي والبروجسترون الطبيعي وأقراص ديهدروجستيرون في منع الولادة المبكرة.

المريضات وطرق البحث: هذه دراسة مقارنة أجريت على 300 امرأة من الحوامل التحقن بالعيادة الخارجية في مستشفى الحسين الجامعي، وتم تشخيصهن بأنهن معرضات لخطر الولادة المبكرة وتم تضمينها في دراسة مقارنة. وقد تم تقسيم هؤلاء المريضات إلى ثلاث مجموعات متساوية: المجموعة (أ) تلقين تحاميل البروجسترون المهبلية, والمجموعة (ب) تلقين 17 حقنة ألفا هيدروكسي بروجستيرون عضليًا, والمجموعة (ج) تناولن أقراص ديهدروجستيرون عن طريق الفم. وقد كانت الدراسة خلال الفترة من يناير 2020 حتي ديسمبر 2021.

نتائج البحث: لا يوجد فرق معتد به بين المجموعات من حيث الولادة المبكرة، وقصر عنق الرحم، والإجهاض في منتصف الثلث. هناك فرق معنوي فيما يتعلق بمؤشر مقاومة الشريان الدماغي الأوسط قبل وبعد العلاج حيث انه نقص في

المجموعه (ج) بصوره اكبر من نقصه في المجموعه (أ) والمجموعه (ب). يوجد فرق معنوي فيما يتعلق بمؤشر نبض الشريان السري بعد العلاج حيث اظهر نقص في المجموعه (ج) اكثر من المجموعه (أ) والمجموعه (ب). علاوة على ذلك، كانت هناك زيادة في مؤشر مقاومة الشريان السري ومؤشر النبض بعد العلاج، بينما كان هناك انخفاض كبير في مؤشر مقاومة الشريان الدماغي/ السري الأوسط بعد العلاج. هناك فرق بين المجموعات فيما يتعلق بعمر الحمل عند التسليم ودرجة ابجار في 1 دقيقة و 5 دقائق. لا يوجد فرق كبير بين المجموعتين من حيث الولادة المبكرة. لا يوجد فرق كبير بين المجموعات من حيث مضاعفات الولدان.

الاستنتاج: تحاميل البروجسترون المهبلية، وحقن ألفا هيدروكسي بروجستيرون 17 عضليًا، وأقراص ديدروجيستيرون عن طريق الفم لها نفس التأثير على معدل الولادة المبكرة لدى النساء اللاتي لا تظهر عليهن أعراض مع عنق رحم قصير بالموجات فوق الصوتية، ولا يوجد فرق كبير بين تأثير ثلاثة عقاقير على تغيير طول عنق الرحم بمرور الوقت.

الكلمات الدالة: الولادة المبكرة، الحقن العضلي لـ 17 الفا هيدروكسي بروجستيرون، لبوس بروجستيرون، أقراص الديهدروجستيرون.