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# Role of Intramuscular 17-Hydroxyprogesterone Caproate in Prolongation of Pregnancy in Women with Placenta Previa: A Randomized Control Study

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## ABSTRACT

**Background:** Placenta previa is a maternal condition that usually presents as vaginal bleeding without pain within the third phase of pregnancy. It is caused by an aberrant placental insertion near or overlaying the internal os of cervix.

**Objective:** This study aimed to evaluate the place of intramuscular 17-Hydroxyprogesterone Caproate in Prolongation (17-OHPC) therapy in the standard care of patients between 28 and 36 weeks of pregnancy who exhibit symptoms of placenta previa.

**Subjects and methods:** A randomized control investigation that was conducted through the period from June 2023 to June 2024 at Ain Shams University Maternity Hospital (ASUMH). Forty cases with placenta previa who were between 28 and 34 weeks gestation were involved, and they were split into two groups (20 patients each for the research and control).

**Results:** Concerning the frequency of vaginal bleeding episodes, the need for blood, RBCs, and plasma transfusions. There was insignificant distinction between the studied groups. However, there was a highly significant variation when it came to the prolongation of pregnancy to 36 to 37 week + 6 days. Preterm birth was the only area where there was a highly statistically significant variation between the study groups, not birth weight or NICU admission.

**Conclusion:** In placenta previa patients, the administration of progestational drugs and 17α-hydroxyprogesterone caproate enhanced birth weight and decreased the frequency of premature birth. Nevertheless, there was no improvement in the babies' birth weight or requirement for NICU care.

**Keywords:** Placenta previa, Preterm birth, 17α-hydroxyprogesterone, Vaginal bleeding.

## INTRODUCTION

Placenta previa is a maternal condition that usually presents as vaginal bleeding with no pain within the third phase of pregnancy. It is caused by an aberrant placentation near or overlaying the internal cervical os [(1)]. Frequent statistics state that 0.5% of pregnancies are affected by placenta previa. The effect of race on placenta previa is a topic of much discussion. Additionally, there is a strong correlation between older moms and a higher incidence of placenta previa [(2)]. When the placenta locates completely or incompletely in the lower uterine area, it might cause a condition called placenta previa. Maternal death and neonatal mortality rates in the industrialized world are about 0.03% and 8.1%, respectively. This percentage is larger in underdeveloped countries [(3)].

Upon being confirmed with placenta previa, the patient has a planned Cesarean procedure set for 36 to 37 weeks from now. Some cases with placenta previa who arrive in emergency may call for urgent Cesarean surgeries at a lower gestational age [(4)].

Females who experienced previous vaginal bleeding and placenta previa should have their vital signs taken and have automated fetal heart monitoring started. The individual should have 2 wide-bore IV lines inserted, a complete blood count, type, and screen performed, and capillaries should be taken. If she is bleeding heavily, two to four units of blood should be checked and matched [(5)].

Should the patient satisfy the requirements, they ought to be admitted to the hospital and administered $MgSO_4$ for fetal neurological protection and steroids to encourage fetal lung development. The advantages of the frequently enforced rules, which include bed rest, reduced exercise, and refraining from sexual engagement, are not entirely evident. If the fetus is declared healthy and the vaginal bleeding ceases for > 48 hours, inpatient observation is maintained, if not, the patient may be discharged for outpatient treatment. The patient's stability, the amount of hemorrhage episodes, the hospital's distance, and compliance all have a role in selecting amongst inpatient and outpatient care [(6)].

The administration of corticosteroids prior to an expected premature delivery is one of the most important prenatal medications known for boosting newborn outcomes. Resuscitation may also be taken in account starting at 23 0/7 weeks of gestation who are at risk of an early delivery within 7 days, whatever the number of babies or their degree of membrane rupture. This will rely on the family's desire [(7)].

Progesterone is essential for maintaining the integrity of pregnancy and aids in its extension. As a metabolic link between corticosteroids and other innate steroids, including sex hormones, progesterone is essential. As a neural protection, they have a major effect on brain function [(8)].

Delaying delivery is necessary to reduce the rate of chronic diseases and to give vital organs time to mature [(9)]. Progesterone primarily functions by promoting uterine resistance to oxidation and maintaining a steady length of the cervix. It minimizes the impact of oxytocin on the myometrium and suppresses the immune system [(10)].



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**Aim of the work:** The present investigation aimed to test the place of intramuscular 17α-hydroxyprogesterone caproate medication in the standard management of patients between 28 and 36 weeks of gestation who have symptomatic placenta previa.

## METHODS

This study was a prospective randomized controlled clinical trial. It was performed in ASUMH for one year from June 2023 to June 2024. It included 40 women in gestational age from 28 to 34 weeks with placenta previa who were randomized using a computer-generated sequence 1:1 into two equal groups: **Group A (study)** that received 17α-hydroxyprogesterone caproate injection 250 mg, IM, once per week till delivery or 37 weeks of gestation. **Group B (control)**, which didn't receive drugs. They only took her routine treatment as vitamins.

**Inclusion criteria:** Patients with singleton pregnancy, estimated gestational age within 28 to 34 weeks and documented placenta previa were included in the study.

**Exclusion criteria:** Patient with PROM as it increases the possibility of delivery, maternal and/or fetal compromise required an immediate termination of pregnancy and women refusing to participate in the study.

All candidates underwent complete history taking, physical examinations, general examination, routine laboratory work-up, radiological investigation with special emphasis on transabdominal ultrasound transvaginal ultrasound and Color Doppler.

**Study procedures and interventions:** Following a thorough history taking, an assessment was carried out, covering all of the important factors. Clinical examination, recorded first trimester ultrasound imaging, or a definitive latest menstrual cycle were the factors that corresponded with the gestational age of both groups. Using a computer-generated pattern, patients with eligibility were allocated 1:1 into two equal groups: Prior to being included in the trial, both groups were administered corticosteroid prophylaxis. The abdomen was examined by a qualified obstetrician in order to evaluate the fetal heart sound, fetal presentation, fundal elevation uterine tone, activity, and tenderness. With the use of ultrasound, the placenta's kind of presentation was identified.

The discovery of placental tissues spreading across the internal cervical os on a second or third trimester ultrasound study (Ideally a transvaginal ultrasound) was the basis for the diagnosis of placenta previa. Notably, the placenta was classified as "low-lying" when the margin was less than 2 cm from the internal os but not above it. Both groups' cases were monitored closely, and any complaints were promptly handled.

The woman was planned for a scheduled Cesarean section delivery at 36 to 37 weeks after it was determined that she had placenta previa. Computerized fetal tracking was started and vitals were taken on patients who had previous experiences of vaginal hemorrhage and placenta previa. Following the insertion of two large-bore intravenous lines, 2-4 units of blood were drawn and matched for the patient. Whatever the gestational age, patients experiencing significant or persistent vaginal hemorrhage were delivered via a Cesarean birth. If the bleeding stops, expecting mothers with gestational ages under 36 weeks may be allowed to manage their pregnancy.

A Cesarean birth was advised if the gestational age was ≥ 36 weeks. After being hospitalized, the patient was given steroids to promote fetal lung maturity and magnesium sulfate to preserve the developing brain. The patient was either sent for treatment at home or hospital surveillance was prolonged if the vaginal bleeding stopped for > 48 hours and the fetus was found to be healthy. The choice between inpatient and outpatient care is based on the patient's stability, the frequency of bleeding episodes, the distance to the hospital, and compliance. Any allergies resulting from progesterone injections were treated right away with antihistaminics or other appropriate antiallergenic medications. In both study groups, the maternal and neonatal outcome was noted.

**Ethical approval:** Before the study began, it was approved by Ain Shams University Faculty of Medicine's Ethics Committee. The Helsinki Declaration was followed throughout the entire research process. Following a thorough description of the goal, scope, and possible results of the clinical trial, all patients provided written informed consents to participate in the study.

### *Statistical analysis*

The Statistical Package for Social Science, version 27, was updated with the collected, revised, and coded data. The mean, standard deviations, and ranges were used where the quantitative data were parametric, and the median and inter-quartile range (IQR) when they were found to be non-parametric. Qualitative attributes were also represented by numbers and percentages. The groups were then compared using the relevant statistical tests. The confidence interval was set at 95%, while the permitted margin of error was set at 5%.

## RESULTS

The trial revealed that, there were no significant statistical difference among study population as regards age, gravity, parity and abortion (Table 1).

**Table (1):** Birth weight of babies, preterm birth, need for NICU admission and neonatal death among the studied patients

| | | Group A<br>No. = 20 | Group B<br>No. = 20 | Test value | P-value | Sig. |
|---|---|---|---|---|---|---|
| Age (years) | Mean ± SD<br>Range | 32.45 ± 5.25<br>20 – 40 | 30.98 ± 4.07<br>24– 38 | 0.989 | 0.328 | NS |
| Gravity | Mean ± SD<br>Range | 4.05 ± 1.47<br>1 – 7 | 3.75 ± 1.68<br>1 – 6 | 0.601• | 0.551 | NS |
| Parity | Median (IQR)<br>Range | 3 (2 – 3)<br>0 – 5 | 2 (1.5 – 3.5)<br>0 – 4 | -0.419≠ | 0.675 | NS |
| Abortion | No<br>Yes | 13 (65.0%)<br>7 (35.0%) | 12 (60.0%)<br>8 (40.0%) | 0.107* | 0.744 | NS |

*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

The trial revealed that, there were insignificant statistical difference among study population as regards gestational age, number of previous CS and previous uterine surgery (Table 2).

**Table (2):** Gestational age, number of previous CS and previous uterine surgery among the studied patients

| | | Group A<br>No. = 20 | Group B<br>No. = 20 | Test value | P-value | Sig. |
|---|---|---|---|---|---|---|
| Gestational age | Mean ± SD<br>Range | 32.53 ± 2.16<br>28 – 35.57 | 33.34 ± 2.33<br>28.71 – 36.43 | -1.129• | 0.266 | NS |
| Number of previous CS | Median (IQR)<br>Range | 2 (0.5 – 3)<br>0 – 3 | 1.5 (0 – 3)<br>0 – 4 | -0.433≠ | 0.665 | NS |
| Previous uterine surgery | No<br>D&C<br>Myomectomy | 16 (80.0%)<br>3 (15.0%)<br>1 (5.0%) | 16 (80.0%)<br>4 (20.0%)<br>0 (0.0%) | 1.143* | 0.565 | NS |

*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

The trial revealed that, there was insignificant statistical variation among study population as regards number of attacks of vaginal bleeding, need for blood transfusion and plasma transfusion, while there was highly significant distinction between studied groups regarding prolongation of pregnancy till 36 to 37 WK + 6 days. Although, number of attacks of vaginal bleeding were not statistically significant in the studied groups but clinically number of attacks decreased in group A when compared to group B (Table 3).

**Table (3):** Prolongation of pregnancy, number of attacks of vaginal bleeding, need for blood transfusion among the studied patients

| | | Group A<br>No. = 20 | Group B<br>No. = 20 | Test value | P-value | Sig. |
|---|---|---|---|---|---|---|
| Prolongation of pregnancy till 36 to 37 WK + 6 days | Mean ± SD<br>Range | 35.91 ± 1.14<br>33.29 – 37.71 | 33.49 ± 2.12<br>28.71 – 36.43 | 4.480• | 0.000 | HS |
| Number of attacks of vaginal bleeding | Median (IQR)<br>Range | 1.5 (1 – 2)<br>0 – 4 | 2 (1.5 – 3)<br>0 – 4 | -1.851≠ | 0.064 | NS |
| Need for blood transfusion | No<br>Yes | 8 (40.0%)<br>12 (60.0%) | 5 (25.0%)<br>15 (75.0%) | 1.026* | 0.311 | NS |
| Plasma | No<br>Yes | 12 (60.0%)<br>8 (40.0%) | 14 (70.0%)<br>6 (30.0%) | 0.440* | 0.507 | NS |

*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

The trial revealed that, there was insignificant statistical variation among study population as regards birth weight of babies and need for NICU admission in which there was clinically increase in group B when contrasted to group A, while there was highly significant variation between studied groups regarding preterm birth as shown in table (4).

**Table (4):** Birth weight, preterm birth, need for NICU admission and neonatal death among the studied patients

| | | Group A | Group B | Test value | P-value | Sig. |
|---|---|---|---|---|---|---|
| | | No. = 20 | No. = 20 | | | |
| Birth weight of babies (gm) | Mean ± SD<br>Range | 2561.05 ± 540.97<br>1400 – 3600 | 2256.75 ± 588.08<br>1355 – 3200 | 1.703• | 0.097 | NS |
| Preterm birth | No<br>Yes | 14 (70.0%)<br>6 (30.0%) | 3 (15.0%)<br>17 (85.0%) | 12.379* | 0.000 | HS |
| Need for NICU admission | No<br>Yes | 13 (65.0%)<br>7 (35.0%) | 8 (40.0%)<br>12 (60.0%) | 2.506* | 0.113 | NS |
| Neonatal death | No<br>Yes | 20 (100.0%)<br>0 (0.0%) | 20 (100.0%)<br>0 (0.0%) | – | – | – |

*: Chi-square test; •: Independent t-test.

## DISCUSSION

In order to assess the place of intramuscular 17α-hydroxyprogesterone caproate treatment in the standard care of cases with manifesting placenta previa between 28 and 36 weeks of pregnancy, the current study was conducted. Forty pregnant women with placenta previa and gestational ages ranging from 28 to 34 weeks participated in the study and were split into two distinct groups. Group A participated in the "study" by receiving a weekly injection of 250 mg of 17α-hydroxy progesterone caproate intramuscularly (IM) until the baby was delivered or 37 weeks gestation. The "control" group, B, wasn't given medication. They merely took vitamins as part of their regular regimen.

Concerning pregnancy delay, the results of this study concurred with those of **Besinger *et al.*** [11] who discovered that tocolytic actions was linked to a clinically significant delay of pregnancy, or being admitted to delivery (39.2 vs. 26.9 days, $p < 0.02$) in cases manifesting symptoms premature previa. **Bose *et al.*** [12] conducted a metanalysis on the data from the single RCT, which demonstrated that pregnancy lasts longer for more than 7 days when tocolytics are maintained (OR 3.10, 95% CI 1.38 to 6.96). In comparison with the cohort of pregnant females given placebo or no therapy, **Singh and Jain** [13] observed significant variations in indices, such as a prolonging of pregnancy, in the IM 17aOHP-C-treated group.

**Morfaw *et al.*** [14] carried out a meta-analysis and systematic review, which stated that the mean number of extra days of pregnancy did not significantly differ across women who took tocolysis and those who did not take treatment (mean difference 11.51 extra days; 95% CI − 1.75 to 24.76; 3 trials, 253 participants; I2 = 82%; low certainty evidence). This discovery was not consistent with the current study's findings. According to **Shaamash *et al.*** [15], the 17aOHP-C effectively prolonged gestation in patients with placenta praevia, as evidenced by the fact that the mean gestational age (36.7 weeks) of the 17aOHP-C group at the time of birth was significantly prolonged than that of the non-17aOHP-C group (34.9 weeks).

In the current study, the likelihood of bleeding from the vagina was evaluated, group A had a clinically lower incidence of vaginal occasions of bleeding than group B, although there was insignificant distinction between the groups. This result was in line with **Besinger *et al.*** [11] who demonstrated that in these situations, tocolytic therapy did not seem to have an influence on the frequency or severity of repeated bleeding from the vagina. **Towers *et al.*** [16] evaluated the utilization of tocolytic medications in preterm individuals who had 3rd trimester bleeding in a controlled tertiary setting and discovered that it was reliable and did not seem to be linked to any serious adverse effects or death. According to **Chattopadhyay *et al.*** [17], recurring bleeding episodes were not statistically significant (p value>0.05). According to **Shaamash *et al.*** [15], the intramuscular 17aOHP-C in placenta praevia women seemed to be helpful in reducing the frequency of bleeding incidents, and the mean number of hemorrhage episodes was much lower.

The current investigation demonstrated that there was an extremely significant variation in premature births between the groups under investigation. This finding is consistent with earlier findings. **Chattopadhyay *et al.*** [17] and **Singh and Jain** [13] evaluated strategies to prevent for premature deliveries in women with a placenta previa and found that the group of females who received intramuscular progesterone had a considerably greater mean gestational age at delivery.
In individuals with placenta praevia, **Saccone *et al.*** [18] demonstrated the beneficial impacts of IM 17aOHP-C, which were linked to numerous therapeutic advantages such a decreased incidence of repeated unexplained PTD and reduced unfavorable adverse effects for the mother. According to **Shaamash *et al.*** [15], the proportion of patients with placenta praevia who experienced PTD in the 17aOHP-C group was considerably lower than that of PTD in the non-17aOHP-C group.

Unlike the current investigation, a meta-analysis by **Goldstein *et al.*** [19] found no evidence of the beneficial impact of progesterone medication on the incidence of premature birth, fetal demise miscarriage, or newborn death. The proportions of PTB prior to 37, 32, and 28 weeks of pregnancy did not differ

significantly across the groups, according to **Awwad *et al.*** [20]. However, there was an upward trajectory in the 17aOHP-C group (9.3%) towards a lower rate of births before 32 weeks of gestation in contrast to the placebo (16.0%). **Areeruk and Phupong** [21], discovered that there was no variation in the lag period between the dehydrogestrone and control groups.

**Elimian *et al.*** [22] also found no difference in the mean period of pregnancy at birth among the groups. In a comparable manner the mean birth weight did not differ between the groups in a way that was statistically significant. 43.9% of the women in the intramuscular progesterone group and 37.9% of the women in the vaginal progesterone group had deliveries before 37 weeks. By group, the percentages of women who gave birth before 34 weeks and 28 weeks were likewise equal.

Other significant outcomes, such as premature birth at < 37 weeks, premature birth less than 28 weeks, or infant birth weight < 2500 g , did not show any discernible differences between women obtaining progesterone or a placebo, according to **Dodd *et al.***'s study [23]. According to **Manuck** [24] only a small percentage of women will benefit from 17aOHP-C, and up to 30–40% will still have recurring SPTB after therapy.

When administered to women with singleton pregnancy and previous episodes of SPTB, a weekly intramuscular injection (IM injection) of 250 mg of 17aOHP-C (from 16 to 36 weeks of gestation) did not reduce the risk of recurrent PTB or neonatal mortality as opposed to a placebo in a double-blind, placebo-controlled, international trial (PROLONG, Blackwell et al., 2019). **Mohammed *et al.*** [26] also discovered that 37.9% of women in the vaginal progesterone group and 43.9% of women in the injectable progesterone group had deliveries before 37 weeks. By group, the percentages of women who gave birth before 34 weeks and 28 weeks were likewise equal.

According to the current investigation, there was a lack of statistical significance in necessity for NICU admission across the analyzed groupings. This outcome is consistent with earlier findings of **Meis *et al.*** [27] who discovered a positive correlation with noteworthy reductions in newborn problems and global PTB. According to **Shaamash *et al.*** [15], the IM 17aOHP-C in placenta praevia mothers seems to help reduce the number of newborns admitted to the NICU.

According to **Chattopadhyay *et al.*** [17], there was a noteworthy distinction between the study and control groups with respect to NICU admissions and infant death. On the other hand, compared to the vaginal progesterone group, the intramuscular progesterone group in **Maher *et al.*** [28] investigation revealed a noticeably greater rate of newborn critical care unit hospitalization. Regarding other newborn outcomes, there were no notable variations among the groups.

**Dodd *et al.*** [23] discovered that in contrast to babies delivered to mothers who were not given IM progesterone, babies born to women who did had a higher likelihood needing hospitalization to the NICU. In the PROLONG study, **Blackwell *et al.*** [25] reported that giving women with singleton pregnancy and previous episodes of SPTB a weekly intramuscular injection of 250 mg of 17aOHP-C (during gestation from 16 to 36 weeks) did not reduce infant morbidity in comparison with a placebo. In a new Egyptian research, **Mohammed *et al.*** [26] found that the mean birth weight did not differ across the groups in a way that was statistically significant. Additionally, their research revealed that there was no discernible variation in newborn problems across the groups.

**Limitation:** Due to many drawbacks, including the very small sample size, we suggest conducting additional clinical trials to validate our findings.

## CONCLUSION

In placenta previa patients, the administration of progestational drugs and 17α-hydroxyprogesterone caproate enhanced birth weight and decreased the frequency of premature birth. Nevertheless, there was no improvement in the babies' birth weight or requirement for NICU care.

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## REFERENCES

1. **Pluym I, Han C (2020):** Third-Trimester Bleeding. Protocols for High-Risk Pregnancies: An Evidence-Based Approach., 493-505.
2. **Bereczky L, Kiss S, Szabó B (2015):** Increased frequency of gestational and delivery-related complications in women of 35 years of age and above. Journal of Obstetrics and Gynaecology, 35 (2): 115-20.
3. **Durukan H, Durukan Ö (2019):** Planned versus urgent deliveries in placenta previa: maternal, surgical and neonatal results. Archives of Gynecology and Obstetrics, 300 (6): 1541-9.
4. **ACOG Committee Opinion No. 764 (2019):** Medically Indicated Late-Preterm and Early-Term Deliveries. Obstet Gynecol., 133 (2): e151-e155.
5. **Yeo L, Ananth C (2018):** Management of Uteroplacental Bleeding Disorders. InPrenatal Assessment of Multiple Pregnancy, 4 (32): 728-735.
6. **Silver R (2015):** Abnormal placentation: placenta previa, vasa previa, and placenta accreta. Obstetrics & Gynecology, 126 (3): 654-68.
7. **ACOG Committee on Obstetric Practice. Committee opinion no. 713 (2017):** Antenatal corticosteroid therapy for fetal maturation. Obstetrics and gynecology, 130 (2): e102-9.
8. **Lim M, Ku C, Tan T, Lee Y, Allen J *et al.* (2020):** Characterisation of serum progesterone and progesterone-

induced blocking factor (PIBF) levels across trimesters in healthy pregnant women. Scientific reports, 10 (1): 1-9.

9. **Agnew E, Ivy J , Stock J, Chapman K (2018):** Glucocorticoids, antenatal corticosteroid therapy and fetal heart maturation. Journal of molecular endocrinology, 61 (1): R61-73.
10. **Yulia A, Varley A, Singh N, Lei K, Tribe R *et al.* (2020):** The interaction between protein kinase A and progesterone on basal and inflammation-induced myometrial oxytocin receptor expression. Plos one, 15 (12): e0239937.
11. **Besinger R, Moniak C, Paskiewicz L, Fisher S *et al.* (2019):** The effect of tocolytic use in the management of symptomatic placenta previa. American Journal of Obstetrics and Gynecology, 172 (6): 1770–1778.
12. **Bose D, Assel B, Hill J, Chauhan S (2018):** Maintenance tocolytics for preterm symptomatic placenta previa: A review. American Journal of Perinatology, 28 (1): 45–50.
13. **Singh P, Jain S (2015):** Evaluation of the effect of progesterone and placebo in parturient of symptomatic placenta praevia: a prospective randomised control study. Int J Sci Stud., 3: 69–72.
14. **Morfaw F, Fundoh M, Bartoszko J, Mbuagbaw L, Thabane L *et al.* (2018):** Using tocolysis in pregnant women with symptomatic placenta praevia does not significantly improve prenatal, perinatal, neonatal and maternal outcomes: a systematic review and meta-analysis. Systematic Reviews, 7: 1-1.
15. **Shaamash A, Ali M, Attyia K (2020):** Intramuscular 17α-hydroxyprogesterone caproate to decrease preterm delivery in women with placenta praevia: a randomised controlled trial. Journal of Obstetrics and Gynaecology, 40 (5): 633-8.
16. **Towers C, Pircon R, Sheppard M, Parer J, Laros J *et al.* (2021):** Is tocolysis safe in the management of third-trimester bleeding? American journal of obstetrics and gynecology, 180 (6 Pt 1): 1572–1578.
17. **Chattopadhyay S, Roy A, Mandal A, Basu D, Bandyopadhyay S *et al.* (2021):** Randomised control study of use of progesterone v / s placebo for management of symptomatic placenta previa before 34 weeks of gestation in a tertiary care centre. Journal of Evolution of Medical and Dental Sciences, 4 (28): 4862–4867.
18. **Saccone G, Schoen C, Franasiak J, Scott R, Berghella V *et al.* (2017):** Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials. Fertility and Sterility, 107 (2): 430-8.
19. **Goldstein P, Berrier J, Rosen S, Sacks H , Chalmers T *et al.* (2016):** A meta-analysis of randomized control trials of progestational agents in pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology, 96 (3): 265-74.
20. **Awwad J, Usta M, Ghazeeri G, Yacoub N, Succar J, Hayek S *et al.* (2019):** A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity. *BJOG:* An International Journal of Obstetrics & Gynaecology, 122 (1): 71–79.
21. **Areeruk W, Phupong V (2021):** A randomized, double blinded, placebo controlled trial of oral dydrogesterone supplementation in the management of preterm labor. Scientific reports, 6 (1): 20638.
22. **Elimian A, Smith K, Williams M, Knudtson E, Goodman J *et al.* (2019):** A randomized controlled trial of intramuscular versus vaginal progesterone for the prevention of recurrent preterm birth. International Journal of Gynecology & Obstetrics, 134 (2): 169-72.
23. **Dodd J, Grivell R, Obrien C, Dowswell T *et al.* (2017):**Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy. The Cochrane Database of Systematic Reviews, 3 (10): 233-243.
24. **Manuck T, Gyamfi-Bannerman C, Saade G (2023):** What now? A critical evaluation of over 20 years of clinical and research experience with 17-alpha hydroxyprogesterone caproate for recurrent preterm birth prevention. American Journal of Obstetrics & Gynecology MFM, 5 (10): 101108.
25. **Blackwell S, Chauhan S, Gyamfi-Bannerman C, Biggio J, Hughes B, Louis J *et al.* (2020):**17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial. American Journal of Perinatology, 37 (2): 127–136.
26. **Mohammed M, Ali A, Abd A, Al-Tabakh E (2022):** A comparative study between intramuscular 17 alpha-hydroxyprogesterone and natural progesterone suppositories and dehydrogestrone tablets in preventing preterm labor. Al-Azhar Medical Journal, 51 (3): 1361–1374.
27. **Meis P, Klebanoff M, Thom E, Dombrowski M, Sibai B, Moawad A *et al.* (2021):**Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate. New England Journal of Medicine, 348 (24): 2379–2385.
28. **Maher M, Abdelaziz A, Ellaithy M, Bazeed M (2018):** Prevention of preterm birth: a randomized trial of vaginal compared with intramuscular progesterone. Acta obstetricia et gynecologica Scandinavica, 92 (2): 215-22.