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Original Article

Effectiveness of 17-Alpha-Hydroxyprogesterone in the Prevention of Preterm Labour

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ABSTRACT

Objective: To compare the effectiveness of 17-Alpha- Hydroxyprogesterone in preventing preterm labour.
Study Design: Prospective longitudinal study.
Place and Duration of Study: Department of Obstetrics and Gynecology, Combined Military Hospital, Sakardu Pakistan, from Jun to Dec 2019.
Methodology: A total of 208 patients (104 in each group) were recruited in this study. Group-A 17-alpha-hydroxyprogesterone (250mg) intramuscular injection was given weekly from 20-36 weeks of gestation or delivery, whichever occurred first. Group-B (Control Group) received no treatment except routine antenatal care but was treated actively with tocolytic drugs and corticosteroids if they presented with preterm labour.
Results: Mean age of the patients was 26.1±4.9 and 25.7±4.5 in Group-A and B, respectively. In Group-A (17-alpha-hydroxyprogesterone), the mean gestational age at delivery was 36.8±3.8; in Group-B (control), the mean gestational age was 35.7±1.3. Treatment was efficacious in 82 patients (78.8%) in Group-A and 65(62.5%) in Group-B. The difference was statistically significant between the two groups (p=0.009).
Conclusion: 17 Alpha-Hydroxyprogesterone caproate preventive therapy likely plays an important role in reducing the risk of recurrent preterm birth.

Keywords: Antenatal care, Prevention, Recurrent preterm delivery, 17-Alpha-hydroxyprogesterone, Tocolytic drugs.

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INTRODUCTION

Spontaneous preterm birth occurs due to spontaneous preterm labour or preterm rupture of fetal membranes before the onset of labour and accounts for two-thirds of preterm birth.[1,2] About 15 million pregnancies end up with preterm delivery worldwide.[3] Prematurity is the leading cause of neonatal mortality and morbidity, and affects mostly the neonates borne before 34 weeks of gestation, accounting for 70-80% of perinatal details. In addition, preterm babies are at high risk of birth trauma, fetal intrapartum hypoxia, respiratory distress syndrome, necrotizing enterocolitis, intracranial haemorrhage, convulsions, septicemia, and neurodevelopmental delay.[4,5]

Preterm labour was treated with tocolytic drugs, antibiotics, hydration and bed rest. Trials showed the limited success of tocolytic agents because of multiple maternal and fetal side effects without improved perinatal outcomes.[6] These agents do not alter the fundamental process leading to myometrial activation, so does not prevent preterm birth. It only delays delivery to allow the administration of steroids and patient transfer to a better neonatal care facility.[7] Broad-spectrum antibiotics have no role in the prevention of preterm birth.[8] Cervical cerclage has a role only in patients with a history of cervical incompetence. Prevention of preterm delivery by identification of women at risk of preterm labour is the most effective intervention to prevent prematurity and related complications.[9] Progesterone is now used to prevent preterm birth in high-risk women as it maintains myometrial quiescence. Progesterone has many cellular functions which maintain pregnancy and causes relaxation of myometrial smooth muscles blocking the action of Oxytocin and inhibiting the formation of gap junctions.[10]

The rationale of our study was to assess the effectiveness of 17-alpha-hydroxyprogesterone in preventing preterm labour so that premature births and related complications can be prevented and to reduce perinatal morbidity and mortality.

METHODOLOGY

The prospective longitudinal study was conducted at the Department of Obstetrics and Gynecology, Combined Military Hospital, Sakardu Pakistan, from June to December 2019. The study was conducted after approval from the Hospital Ethical Review committee (ERB 1015/admn). The sample was calculated using the WHO calculator using two proportion formulas;

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P1=34.4%4, P2=19.2%4. The sampling technique used was non-probability consecutive sampling.

Inclusion Criteria: Women with singleton pregnancy at 20 weeks with previous spontaneous preterm delivery were included in the study.

Exclusion Criteria: Patients with multiple gestations, ruptured membranes, McDonald stitch, fetal anomalies, antepartum haemorrhage, painful regular uterine contractions and women with medical illnesses, e.g. diabetes, hypertension, and seizure disorders, were excluded from the study.

Preterm Labour is the onset of regular uterine contractions associated with the progressive cervical change between 28 to 36 completed weeks gestation.[11]

17-Alpha-Hydroxyprogesterone is synthetic progesterone given by intramuscular injections weekly from 20 to 36 weeks of gestation. Efficacy The drug was considered efficacious if the pregnancy lasts 36 weeks. Patients presenting to the outpatient department fulfilling the selection criteria were selected. Informed consent was taken from patients. Detailed obstetrical history was taken. In addition, relevant general physical examination, systemic examination and investigations were done. Gestational age was determined from menstrual history and early first-trimester ultrasonography. Ultrasonography was done between 18-20 weeks to reconfirm gestational age and to exclude fetal anomalies. The patients were randomly divided into two groups by lottery method; Group-A (Study Group), 17-alpha-hydroxyprogesterone (250-mg) intramuscular injection was given weekly from 20-36 weeks of gestation or delivery, whichever occurred first. Group-B (Control Group) did not receive any treatment except routine antenatal care, but they were treated actively with tocolytic drugs and corticosteroids if they presented with preterm labour. Follow-up was done by the trainee researcher, with frequent visits and noting contact numbers. All the information was recorded on the specially designed proforma.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22:00. Mean and SD was calculated for age, parity, number of previous preterm deliveries, and gestational age at delivery. In addition, frequency and percentages were calculated for the efficacy of the drug. The chi-square test was used to compare efficacy in two groups. The *p*-value of ≤0.05 was taken as significant.

RESULTS

A total of 208 (104 cases in each group) were included in the study. The mean age of the patients was 26.1±4.9 years and 25.7±4.5 years in Group-A and B, respectively. In Group-A (17-alpha-hydroxyprogesterone) mean gestational age at delivery was noted as 36.8±3.8 weeks, and in Group-B (Control) mean gestational age was 35.7±1.3 weeks (Table-I).

Table-I: Distribution of Cases (n=208)

Parameters	Group-A (n=104) 17-Alpha-Hdroxyprogesteron	Group-B (n=104) (Control Group)
Age (year) of patient		
20-25	51(49%)	57(54.85%)
26-30	30(28.9%)	27(25.9%)
31-35	23(22.1%)	20(19.3%)
Mean Gestational Age at Delivery	36.8±3.8	35.7±1.3
Parity		
Para 1-2	35(33.6%)	33(31.7%)
Para 3-4	55(52.9%)	56(53.9%)
Para >5	14(13.5%)	15(14.4%)

Parity distribution showed that 35 patients (33.6%) in group-A and 33 patients (31.7%) in Group-B belong to para 1-2, in Group-A 55 patients (52.9%) and Group-B, 56 patients (53.9%) belong to para 3-4, similarly 14 patients (13.5%) and 15 patients (14.4%) in Group-A and B, respectively belong to para >5. Treatment was efficacious in 82 patients (78.8%) in group-A and 65(62.5%) in Group-B. The difference was statistically significant between the two Groups (p=0.009), shown in Table-II.

Table-II: Treatment Efficacy (n=208)

Treatment Efficacy	Group-A (n=104) 17-Alpha-Hdroxyprogesteron)	Group-B (n=104) (Control Group)	*p*-value
Yes	82(78.8%)	65(62.5%)	0.009
No	22(21.2%)	39(37.5%)	

DISCUSSION

Management of preterm labour should be directed towards establishing the cause, ensuring delivery under optimal conditions, and considering the pros and cons of delaying delivery to increase gestational age. In practice, this means that women admitted in threatened preterm labour should be appropriately assessed to determine the optimal time for delivery.[11,12] For example, the presence of fetal compromise or intrauterine infection can hinder the prolonging of the pregnancy. In contrast, early gestational age and uncomplicated preterm labour with intact membranes can mitigate a delay in delivery. The decision should be based on a riskbenefit analysis for each individual. The main pharmacological considerations are whether to administer antibiotics, steroids or tocolytics. [13]

Meis *et al*.[14] reported the results of a large multicenter trial of 17P conducted by the Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. The study enrolled women with a documented history of a previous spontaneous preterm delivery, which resulted from either spontaneous preterm labour or premature rupture of the fetal membranes. After receiving an ultrasound examination to rule out major fetal anomalies and to determine gestational age, the subjects were offered the study and given a test dose of the placebo injection to assess compliance. If they chose to continue, they were randomly assigned, using a 2:1 ratio, to weekly injections of 250mg 17P or a placebo injection. Treatment was begun between 16 and 20 weeks of gestation and was continued until delivery, or 37 weeks of gestation, whichever came first. The study planned to enrol 500 subjects, a sample size estimated to be sufficient to detect a 37% reduction in the rate of preterm birth. However, enrollment was halted at 463 subjects, 310 in the treatment group and 153 in the placebo group, following a scheduled evaluation by the Data Safety and Monitoring Committee, which found that the evidence of efficacy for the primary outcome was such that further entry of patients would not be ethical.

Gonzalez-Quintero *et al*. examined whether the efficacy of 17-alpha hydroxy-progesterone depends upon the earliest gestational age (GA) at prior SPTB 15. Data were divided into three groups according to the earliest GA of prior SPTB (20-27.9, 28-33.9, and 34-36.9 weeks). GA at delivery of current pregnancy and incidence of recurrent SPTB were compared between women enrolled in outpatient progesterone is dependent upon the earliest gestational age (GA) at administration program (n=2978) and women receiving other outpatient services without progesterone is dependent upon the earliest gestational age (GA) at (n=1260).[15]

The current study is comparable with the study of Jaiman *et al.* regarding the age of the patients.[16] There was no patient below 20 years of age. The mean age in the present study was observed at 26.1±4.9 & 25.7±4.5 years in Group-A (17-alpha-hydroxyprogesterone) and Group-B (Control group), respectively, which is consistent with a study carried out by Ghazi *et al.*[17] However, our study disagrees with the study by Lockwood *et al*. who found the increased risk of preterm delivery in women <20 years and over 35 years of age.[18] This may be due to the lack of knowledge about the ages of females in our setup.

Our study compared 17-alpha hydroxy-progesterone (Group-A) with controls (Group-B) to prevent preterm delivery. Group-A proved more efficacious in reducing preterm delivery (p=0.009). Meis *et al.* demonstrated that the baseline characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. However, treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3% in the progesterone group vs. 54.9% in the placebo group. In addition, infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular haemorrhage, and the need for supplemental oxygen.[14]

CONCLUSION

17 Alpha-hydroxyprogesterone caproate preventive therapy likely plays an important role in reducing the risk of recurrent preterm birth. Weekly injections of 17P resulted in a substantially reduced rate of recurrent preterm delivery among women at particularly high risk for preterm delivery. In addition, they reduced the likelihood of several complications in their infants.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

UU & SK: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

SP & SAS: Conception, study design, data interpretation, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFRENCES

1. Elovitz MA, Gajer P, Riis V, Brown AG, Humphrys MS, Holm JB, et al. Cervicovaginal microbiota and local immune response modulate the risk of spontaneous preterm delivery. Nature Communicat 2019: 21; 10(1): 1-8.doi:10.1038/s41467-019-09285-9.
2. Samejima T, Nagamatsu T, Iriyama T, Nakayama T, Seyama T, Sayama S, et al. Impact of additional risk factors on the incidence of preterm delivery among pregnant women diagnosed with short cervix. Taiwan J Obstet Gynecol 2020; 59(2): 195-199. doi: 10.1016/j.tjog.2020.01.005.
3. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fetal Neonatal Med 2016; 21(2): 74-79. doi: 10.1016/ j.siny. 2015.12.007.
4. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007; 357(5): 462-469. doi: 10.1056/ NEJMoa067815.

5. Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. Semin Perinatol 2017; 41(7): 387-391. doi:10.1053/j.semper. 2017.07.009.
6. Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, Chauhan SP, Hughes BL, Louis JM, et al. 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial. Am J Perinatol 2020; 37(2): 127-136. doi: 10.1055/s-0039-3400227.
7. Lamont CD, Jørgensen JS, Lamont RF. The safety of tocolytics used for the inhibition of preterm labour. Expert Opin Drug Saf 2016; 15(9): 1163-1173. doi: 10.1080/14740338.2016.1187128.
8. Gilman-Sachs A, Dambaeva S, Salazar Garcia MD, Hussein Y, Kwak-Kim J, et al. Inflammation induced preterm labor and birth. J Reprod Immunol 2018; 129: 53-58. doi: 10.1016/j.jri. 2018.06.029.
9. Rundell K, Panchal B. Preterm Labor: Prevention and Management. Am Fam Physician 2017; 95(6): 366-372.
10. Garry DJ, Baker DA, Persad MD, Peresleni T, Kocis C, Demishev M. Progesterone effects on vaginal cytokines in women with a history of preterm birth. PLoS One 2018; 13(12): e0209346. doi: 10.1371/journal.pone.0209346.
11. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. Obstet Gynecol 2016; 128(4): e155-64. doi: 10.1097/AOG.0000000000001711.
12. Medley N, Poljak B, Mammarella S, Alfirevic Z. Clinical guidelines for prevention and management of preterm birth: a systematic review. BJOG 2018; 125(11): 1361-1369. doi: 10.1111/1471-0528.15173.
13. Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17alpha-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med 1975; 293(14): 675-680. doi: 10.1056/NEJM197510022931401.
14. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348(24):2379-2385. doi: 10.1056/NEJMoa035140. Erratum in: N Engl J Med 2003; 349(13): 1299-1302.
15. González-Quintero VH, de la Torre L, Rhea DJ, Tudela CM, Vazquez-Vera E, Desch C, et al. Impact of prior gestational age at preterm delivery on effectiveness of 17-alpha-hydroxypro-gesterone caproate in practice. Am J Obstet Gynecol 2010; 203(3): 257.e1-5. doi: 10.1016/j.ajog.2010.06.020.
16. Jaiman S, Romero R, Bhatti G, Jung E, Gotsch F, Suksai M, et al. The role of the placenta in spontaneous preterm labor and delivery with intact membranes. J Perinat Med 2022; 50(5): 553-566. doi: 10.1515/jpm-2021-0681.
17. Ghazi A, Jabbar S, Siddiq NM. Preterm labour–still a challenge! Pak J Surg 2006; 22(3): 222-226.
18. Lockwood CJ, Kuczynski E. Risk stratification and pathological mechanisms in preterm delivery. Paediatr Perinat Epidemiol 2001; 15 (Suppl 2): 78-89. doi: 10.1046/j.1365-3016.2001.00010.x.