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Hydroxyprogesterone caproate for preterm birth: A situational analysis from the Indian perspective

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ABSTRACT

Background: Preterm birth can cause morbidity and mortality in addition to trauma or loss to the mother, and present a major financial burden to the family. This risk may be minimized by timely intervention.
Objective: To understand the safety and efficacy of hydroxyprogesterone in decreasing the incidence of preterm birth, neonatal complications, and maternal mortality, based on evidence obtained from the Indian scientific literature.
Methods: Relevant articles were searched for and retrieved from the databases PubMed, medrXiv, Embase, Cochrane, biorXiv, and arXiv.
Results: A total of 62 relevant articles were assessed, and of these, 59 articles did not meet the eligibility criteria. In total, 3 articles which satisfied the criteria and 2 articles sourced from cross references were included in the study. Across these 5 articles, a total of 536 patients received hydroxyprogesterone caproate or placebo for preterm birth.
Conclusion: In all five articles, recurrence rate of preterm birth was reduced in the treated group compared to control group. The safety profile of progesterone tends to be better than that of the placebo. The findings of our analysis of individual patient data (IPD) summarizes various clinical trial data, which can assure clinicians that vaginal progesterone administration is effective and well tolerated.

1. Introduction

Preterm birth increases the risk of complications during perinatal period. Overall global incidence varies between 9.1 and 13.4% and from 10.1 to 13.4% in the south Asian region.[1] The working group of International Federation of Gynaecology and Obstetrics (FIGO) guidelines and the U.S. Food and Drug Administration (FDA) recommends the administration of progesterone to high-risk groups to decrease the incidence of preterm birth.[2] Progesterone is also known as "17 alpha hydroxyprogesterone caproate" or "17 alpha hydroxyprogesterone" or "Makena".

The Centre for Drug Evaluation and Research (CDER), an expert unit under the FDA, recommended withdrawing hydroxyprogesterone caproate (Makena) injection from the market due to lack of efficacy. This decision was based on clinical benefits observed in the post-marketing clinical trials. Earlier, hydroxyprogesterone injection had received marketing permission under the accelerated approval pathway for the prevention of preterm labour in women who have had frequent premature births.[3] Preterm birth is precipitated by multiple factors, which can be categorised as maternal, or foetal, or mixed. Maternal factors include

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short cervix, uterine over-distension, intra-amniotic infection, vascular disorders, pelvic infection, decidual senescence, a decline in progesterone action, or maternal stress.[4] Meis et al., observed that weekly administration of Makena significantly reduces the total number of preterm deliveries and complications in infants.[3] Similarly, a meta-analysis of women with short cervixes (<25 mm) receiving vaginal Makena showed a statistically significant decrease in the incidence of preterm births. In addition, significant reduction in the total number of infants requiring intensive care admission, respiratory distress syndrome (RDS) and birthweight less than 1500 g[5]. However, the OPPTIMUM and PROLONG studies did not observed decreased incidence of preterm births among high-risk pregnant females.[6,7]

The prime objective of this research was to examine the safety and effectiveness of hydroxyprogesterone in decreasing the incidence of preterm birth and complications in infants and total number of maternal deaths, from the literature and Indian clinical trials.

2. Methodology

STUDY SELECTION: We conducted a systematic review of clinical studies and case reports published from January 2000 to January 2021 in PubMed, Embase, Cochrane, biorXiv, medrXiv, and arXiv using the search terms "hydroxyprogesterone" OR "hydroxyprogesterone caproate" AND "India". We included trials in which hydroxyprogesterone caproate was administered during the study period for the treatment of preterm birth. Additionally, we explored the clinical trials registry of India for ongoing studies. The study selection conducted by two authors independently were based on predefined selection criteria. Any

Table 1
Characteristics of the five articles.

Author name and year of publication	Key inclusion criteria	Sample size and basic characteristics	Pregnancy outcomes		Adverse events
Rai P 2009[a]	Asymptomatic 18–35 years women b/n 18 and 24 weeks of pregnancy with h/o - 1 spontaneous preterm delivery and with a singleton live pregnancy.	**T.gr. –**N = 75; Mean age- 26.07 ± 3.24 years, Gestational age- 20.69 ± 2.83, Total number of pregnancy losses 2.61 ± 1.13 **P.gr. –** n = 75; Mean age- 25.72 ± 3.42 years, Gestational age- 20.73 ± 1.78, Total number of pregnancy losses 2.63 ± 1.05	**Maternal** The mean gestational age at delivery between T.gr.and P.gr. was 36.1 ± 2.66 vs 34.0 ± 3.25 weeks, respectively. P < 0.001.	**Neonatal** Neonatal age at delivery (week) in T.gr. was 34.26 ± 2.88 and P.gr. 32.95 ± 3.20 p < 0.001, Birth weight (g) in T.gr.2400 ± 650 and P.gr. 1890 ± 560, p < 0.001.	**T.gr.-:** acne (n = 2), oesophageal reflux (n = 2), and somnolence (n = 1) **P.gr.-:** acne (n = 1), somnolence (n = 1), headache (n = 1), and depression (n = 4).
Majhi P 2009[b]	Asymptomatic 20–30 years women b/n 16 and 24 weeks of pregnancy with h/o - 1 spontaneous preterm delivery and with a singleton infant >20 and < 37 weeks due to spontaneous labour or pre-term rupture of foetal membranes.	**T.gr. –**N = 50; Mean age- 26.56 ± 3.5 years, Mean gestation at previous pre-term birth (weeks) 30.52 ± 3.3, Parity 2.2 ± 1.2 **P.gr. –** n = 50; Mean age- 26.42 ± 3.2 years, Mean gestation at previous pre-term birth- 30.70 ± 3.01, Parity 2.3 ± 1.2	Significantly fewer women in Group 1 (progesterone group) delivered pre-term <37 weeks as compared with Group 2 (12% vs 38%) p = 0.0027.	Birth weight (g) in T.gr. 2813 ± 501 and P.gr. 2599 ± 421 g, p = 0.023.	**T.gr.-:**28% - c/o mild vaginal discharge and irritation. **P.gr.-:** NO AE
Nigar A 2012[c]	Asymptomatic women b/n 16 and 20 weeks of pregnancy with h/o - of previous spontaneous preterm birth.	**T.gr. –**N = 46; Mean gestation at previous pre-term birth (weeks) 29.4 ± 4.3 **P.gr. –** n = 50; Mean gestation at previous pre-term birth (weeks) 30.5 ± 3.6	Deliver at a significantly higher gestational age than the P.gr. with an earlier spontaneous preterm birth at 20–28 weeks.	Infants weighing <2.5 kg was 30.4% in the T.gr. and 44% in the P.gr.	**T.gr.-:**pain (43.4%), swelling at the site of injection (13%), urticaria (4.34%), and injection site nodule (4.34%). **P.gr.-:** No adverse events
Choudhary M 2014[d]	Asymptomatic women b/n 24–34 weeks of pregnancy with h/o - of arrested preterm labour	**T.gr. –**N = 45; Mean age- 24.11 ± 2.39 years, Mean gestation at previous pre-term birth - 31.91 ± 2.09 weeks **P.gr. –** n = 45; Mean age- 23.71 ± 2.93 years, Mean gestation at previous pre-term birth - 32.42 ± 1.65 weeks	The mean gestational age at delivery between T.gr.and P.gr. was 36.79 ± 2.64 vs 35.90 ± 2.00 weeks, respectively. P = 0.076.	Mean birth weight (kg) in T.gr. 2.44 ± 0.58 and P.gr. 2.14 ± 0.47, p = 0.009	In both **T.gr.&P.gr. –** 4 women experienced headache, epigastric pain, and acne.
Shambhavi S 2018[e]	Asymptomatic women b/n 16–24 weeks of pregnancy with h/o - of previous spontaneous preterm birth.	In Group A: N = 50; Mean age- 28.00 ± 4.13 years; gestational age at enrolment- 18.89 ± 2.09 weeks; mean gestation at previous pre-term birth - 29.44 ± 5.19 weeks In Group B: N = 50; Mean age- 26.94 ± 4.02 years; gestational age at enrolment- 18.66 ± 2.12 weeks; mean gestation at previous pre-term birth - 29.9 ± 5.64 weeks	The mean gestational age at delivery between Group A and Group B was 37.44 ± 1.67 36.99 ± 2.78 weeks, respectively. P = 0.33.	Mean birth weight (kg) in group A 2.766 ± 0.558 and group B 2.62 ± 0.661, p = 0.241, NS.	In Group A, 20% reported a mild vaginal discharge. In Group B, 29.2% reported a mild pain at the injection site.

T.gr. – treatment group; P.gr. – placebo group.
[a] 100 mg oral micronized progesterone.
[b] 100 mg natural micronized progesterone intravaginally once daily from 20 to 24 weeks' gestation until 36 weeks.
[c] 250 mg weekly IM injections of 17OHPC starting from 16 to 20 week of pregnancy until 36 weeks.
[d] 200 mg oral micronized progesterone.
[e] Group A: 200 mg micronized progesterone effervescent vaginal tablet daily. Group B: 250 mg IM 17 OHPC weekly.

differences in decision-making between two authors about studies were resolved after discussions with all review authors.

INCLUSION CRITERIA: Clinical trials and case reports conducted in Indian patients who received hydroxyprogesterone caproate during the trial period. In case of multicentre trials, if any centre from India participated, then it was also included in the analysis.

EXCLUSION CRITERIA: Indian writers' remarks, systematic reviews, and meta-analyses were excluded. Studies that examined other uses of hydroxyprogesterone caproate were also rejected.

DATA EXTRACTION (SELECTION AND CODING): From the eligible clinical trials and case reports, study characteristics, including author name, publication year, type of study, number of patients, patient demographics (e.g., age, gender, and ethnicity), comorbidities, sonographic confirmation of small cervix, and adverse events during trials were also collected from the included studies.

STATISTICAL ANALYSIS: Statistical analysis was conducted with Microsoft Excel 2010. Continuous variables were expressed as the mean with standard deviation. Categorical variables were expressed as number of cases and percentages (%).

3. Results and discussion

In this study, a total of 62 articles was screened for admissibility, and 59 of these articles were excluded for various reasons (43 articles were preclinical studies, 16 were studies conducted on other conditions, such as congenital adrenal hyperplasia, polycystic ovarian syndrome, and hirsutism), and 3 were included for final analysis. Two additional articles were sourced from cross referencing the included studies. Overall, 5 clinical trials included 536 patients who received hydroxyprogesterone caproate or placebo for preterm birth.[8–12] Among the included studies, oral micronized progesterone was used in two studies,[8,11] while the other studies examined the effect of intravaginal natural micronized progesterone,[9] micronized progesterone effervescent vaginal tablet,[12] and 17 α hydroxyprogesterone caproate (17OHPC) injection.[10] Details of each study, including study characteristics, key inclusion and exclusion criteria, sample size and basic characteristics of study participants, and overall outcomes and reported adverse events are summarised in Table 1.

Preterm birth remains the single largest risk factor for neonatal morbidity and mortality worldwide.[13] Endogenous progesterone withdrawal is the critical step for initiation of parturition. The biological effects of progesterone are exerted through the uterine myometrium, cervix, and chorioamniotic membranes. Increased uterine muscle contraction at the time of parturition is due to withdrawal of the inhibitory influence of progesterone, which is responsible for relaxation of myometrial smooth muscle due to inhibition of gap junction formation and prostaglandin synthesis by blocking oxytocin action and the inflammatory pathway.[14] Stys et al., conducted an animal study to observe the role of progesterone on parturition, and found that exogenous administration of progesterone during parturition causes inhibition of myometrial contractions and decreases cervical compliance.[15]

A gestational history of previous preterm delivery, short cervix, and infections are considered the strongest determining factors for preterm delivery among singleton pregnancies.[16] Romero et al., advised the use of universal cervical length screening and preventive vaginal progesterone administration in women carrying a singleton pregnancy, which has been shown to reduce the rate of preterm delivery and enhance infant outcomes, including lower intensive care admission and greater birth weight.[5]

The Federation of Obstetric and Gynaecological Societies of India (FOGSI) recommends supplementation of progesterone to women with a history of prior spontaneous preterm birth or with a short cervix. Among women with a history of prior spontaneous preterm birth, weekly 17-hydroxyprogesterone caproate 250 mg intramuscularly injections should be administered. These injections should be started at gestational week 16–20 to and continue to 36 weeks. Among known cases of short cervix, a 100–200 mg progesterone suppository should be administered vaginally every night from the time of diagnosis until 36 weeks gestation.[17] Vaginal and intramuscular progesterone are equally effective in preventing preterm delivery in women with a prior spontaneous PTB/mid-trimester abortion. However, there was a trend favouring vaginal progesterone for preterm births before 34 weeks and 28 weeks gestation.[18]

The positive impact of micronized progesterone on pregnancy prolongation was demonstrated in the current study, which revealed considerably more undelivered women in the progesterone group at each point in time until delivery compared to the placebo group. Five studies found that progesterone has a beneficial influence in extending pregnancy with low or no side effects.[8–12] According to evidence from five randomized, double-blind, placebo-controlled comparison studies, progesterone appears to have a higher safety profile than the placebo. Pain and swelling at the injection site, headache, epigastric pain, and acne are among the potential side effects of progesterone. As administration is at the discretion of the attending physician, there is always a risk of overtreatment or undertreatment. This potential for error necessitates a stronger insight into the medicinal mechanism and long-term effects among physicians. Our research demonstrates, however, that practitioners in the Indian healthcare system are familiar with the use of progesterone.

Although these findings are encouraging, a limited number of studies met criteria for inclusion, narrowing our ability to make strong recommendations. We advise doctors to be cautious while using an understudied medicine and to avoid indiscriminate usage. Because the research community requires a high standard scientific proof from recommendations, quality and amount of data must be required when formulating guidelines. Further studies with larger sample sizes and longer research durations are required to completely describe this medication due to its limited past use in India, and lack of sufficient trials. This necessitates adequate education of medical personnel about the medication and the rationale for its approval. Finally, all healthcare practitioners who choose to use the drug to treat preterm delivery have a responsibility to disclose any and all side effects. This can help in identifying the safety profile of this medicine when used on the Indian subcontinent, anticipating adverse events, and assisting in future drug labelling revisions.

4. Conclusion

All five studies found that hydroxyprogesterone plays a significant impact in reducing preterm births, neonatal morbidity, and mortality. Because this is a less well-studied topic, further multicentric, randomised clinical trials including a greater number of patients and an extended follow-up period are needed to prove its efficacy and safety in women. We specifically focused this article on situational analysis rather than meta-analysis. This limited the scope of our ability to extract additional useful information from the articles. To fully comprehend the role of hydroxyprogesterone caproate in preterm delivery, more research and studies are needed.

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Consent to participate

This article does not contain any research studies with human participants animals performed by any of the authors.

Ethical approval and informed consent

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Consent for publication

All authors has consented for the publication of the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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