Use of hydroxyprogesterone caproate injection for prevention of preterm labor in women with different risk factors: a mini review

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Received 21 March 2019
Revised 06 April 2019
Accepted 27 November 2019
Published 10 August 2020

Journal of Current Medical Research and Practice
2020, 5:237–240

Preterm birth is delivery before 37 weeks of gestation it remains a global challenge with an incidence of 11.1% (1). Progestogens are the only medications that their use showed reduction in incidence of preterm birth (2.3) they are used in asymptomatic women who are at increased risk of preterm birth based on their history and ultrasound finding of short cervical length, their use is supported and guideline recommendation published by Society for Maternal Fetal Medicine publications committee 2012 ,American collage of Obstetricians and gynecology committee on practice bulletin 2012 and European Association of PerinatalMedicine.

Keywords:
17α-hydroxyprogesterone caproate, preterm labor, risk factors

J Curr Med Res Pract 5:237–240

2357-0121

Introduction

Preterm birth is delivery before 37 weeks of gestation; it remains widely challenged with an incidence of 11.1% [1].

Progestogens are the only medications that showed a decrease in the incidence of preterm births [2,3]. They are used in asymptomatic women with increased risk of preterm birth regarding their history and ultrasound finding of short cervical length. Their use is supported and guideline recommendation was published by the Society for Maternal Fetal Medicine Publications Committee 2012, American College of Obstetricians and Gynecology Committee on Practice Bulletin 2012, and European Association of Perinatal Medicine [4].

Progestogens are either natural or synthetic [5]. Natural compounds are those similar to those produced by living organisms. In contrast, synthetic progestogens are made in the laboratory and their structures have been modified and are not like natural progestogen [6].

Progesterone and its metabolite 17 hydroxyprogesterone are largely produced during human pregnancy. On the other hand, 17 α-hydroxyprogesterone caproate is a synthetic compound and it is formed by acetylation of 17 α-hydroxyprogesterone with caproate (Attardi *et al.*, 2007). [7] The formula of 17 α-hydroxyprogesterone caproate is displayed in the following figure.

Mechanism of action

Progestogen hypothesis

Results from a study by Meis and colleagues encouraged many to study the effect of additional progestogens on the function of one tissue or several tissues in the reproductive tract to prolong pregnancy. The response to progestogens is incremental instead of being an all or none phenomenon and is affected by how advanced gestation is and by the count of fetuses [4].

The mechanism of 17 α-hydroxyprogesterone caproate in reducing preterm labor is not entirely understood [3], but progesterone supplementation therapy exhibits its action in maintaining pregnancy by closely interlinked pathways:

(1) Maintenance of uterine quiescence, progesterone has been shown to possess tocolytic action on the myometrial smooth muscle either *in vitro* or *in vivo* during pregnancy. It has been demonstrated that adequate concentrations of progesterone in the myometrium are able to antagonize the stimulatory effect of both prostaglandins and oxytocin as it decreases the number of myometrial oxytocin receptors and also the number and activity of gap junctions. Moreover, it exhibits its effects through interactions between nuclear and membrane progesterone receptors [8].

(2) Modulation of immune response [9].
(3) Cervical performance is improved as shown by the decreased cervical change during the second and third trimesters [4].
(4) In all species studied to date including humans, administration of progesterone antagonists (mifepristone) promotes parturition [10].

Use of 17 α-hydroxyprogesterone caproate in the prevention of preterm birth due to different risk factors

Short cervix

It is assumed that 17 α-hydroxyprogesterone caproate is effective in recurrent preterm birth and vaginal progesterone is effective in preterm birth related to short cervical length [11].

Recent randomized, controlled trial involving nulliparous women with a singleton gestation of between 16 and 22 + 3/7 weeks with cervical length less than 30 mm were assigned to weekly intramuscular injections of 250 mg of 17 α-hydroxyprogesterone caproate through 36 weeks or an identical placebo and concluded that no significant difference in the rate of preterm birth between study groups and weekly intramuscular 17 α-hydroxyprogesterone caproate cannot be recommended for nulliparous women with a short cervix [12].

Recurrent spontaneous preterm birth and intact membranes

Randomized, controlled trial by Meis and colleagues involved women with a history of spontaneous preterm birth. Women were recruited from 19 clinical centers at 16–20 weeks, and were randomized to receive either weekly intramuscular 17 α-hydroxyprogesterone caproate or inert oil placebo; injections were given till delivery or 36 weeks. The study concluded that 17 α-hydroxyprogesterone caproate resulted in a significant decrease in the rate of preterm birth and its associated complications [3]. This study is criticized because of problems in efficacy and safety. For example, the results show a high rate of preterm birth in the placebo group (54.9%) compared with in the treatment group (36.3%) [13]. The other concern is of safety as the study shows increased rate of miscarriage and still birth in 17 α-hydroxyprogesterone caproate group. This was first issued by the Food and Drug Administration medical officer in 2006 and the Food and Drug Administration produced a slide indicating the higher rate of neonatal death in the first 66 days when administrated in mid-trimester compared with the placebo group. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommended that patients be counseled and sign an informed consent when receiving 17OHP-C [6].

Preterm rupture of membranes

Recent randomized, controlled trial involving women with documented rupture of membrane and no contraindication to expectant management. Singleton pregnancies with gestational ages from 23 weeks 0/7 days to 30 weeks 6/7 days were enrolled and randomized to receive weekly intramuscular injections of 17 α-hydroxyprogesterone caproate (250 mg) or placebo continued until reaching 34 weeks 0/7 of gestation or evidence of fetal lung maturity at 32 (0/7) to 33 (6/7) weeks. The study concluded that 17 α-hydroxyprogesterone caproate injection did not prolong pregnancy or decrease perinatal morbidity [14].

Another recent study aiming to study the inhibitory effect of 17 α-hydroxyprogesterone caproate on tumor necrosis factor α and thrombin induced membrane weakening *in vitro*. In this study, human fetal membrane fragments from uncomplicated term repeated cesarean section were cultured with/without 17 α-hydroxyprogesterone caproate and it concluded that 17 α-hydroxyprogesterone caproate is not the optimal progestogen to prevent preterm rupture of membranes and speculated that progestogens other than 17 α-hydroxyprogesterone caproate may be more efficacious [15].

Multiple gestation

Either twin gestation or triplet gestation are risk factors for preterm birth [16], so it was logical to study the effect of 17 α-hydroxyprogesterone caproate on preventing preterm birth in multiple gestation pregnancy. A randomized trial (PROGESTWIN) in which unselected women with twin pregnancies were enrolled and randomized to receive weekly injections of 17 α-hydroxyprogesterone caproate (250 mg) or placebo starting from 16 to 20 weeks of gestation till 36 weeks or delivery and it concluded that there is no significant difference in gestational age at the time of delivery between the study groups, but on the other hand 17 α-hydroxyprogesterone caproate significantly reduced neonatal morbidity parameters and increased the birth weight [17]. Another randomized, controlled trial by Di Renzo and colleagues concluded that 17 α-hydroxyprogesterone caproate may decrease gestational age at delivery in women with twin pregnancy; It showed that women with higher levels of 17 α-hydroxyprogesterone caproate delivered at earlier ages than women with lower levels.

Regarding triplet pregnancies, a double-blinded, randomized clinical trial enrolling women carrying

trichorionic triamniotic triplets were randomized to receive 17 α-hydroxyprogesterone caproate vs placebo concluded that prophylactic 17 α-hydroxyprogesterone caproate treatment did not decrease neonatal morbidity or prolong pregnancy, but it was related to increased fetal loss [18].

Management of placenta previa

A recent randomized, controlled trial addressing the impact on and relation between placenta previa and preterm birth provide an approach for prophylaxis against premature uterine contraction preceding attacks of antepartum hemorrhage in women with placenta previa. The study by Singh and Jain [19] in 2015 involved 80 pregnant women, singleton pregnancy, of maternal age of over 18 years, gestational age at third trimester, and with placenta previa was located ultrasonographically around 5 cm of internal os. The patients were randomized into two groups. The first group (40 patients) received placebo twice weekly and the second group (40 patients) received injections of 17 α-hydroxyprogesterone caproate (500 mg). Either placebo or 17 α-hydroxyprogesterone caproate was continued till delivery or 37 weeks of gestation. This study concluded that 17 α-hydroxyprogesterone caproate inclines to be valuable than placebo, but further research is needed.

Another study by Anjula [20] issuing the same problem. In this study, there were 60 symptomatic pregnant women with placenta previa who had bleeding before 34 weeks of gestation. Patients were randomized into 30 pregnant women in each group to receive either placebo or intramuscular 17 α-hydroxyprogesterone caproate 500 mg twice weekly until 37 weeks or till delivery, whichever is first, and concluded that 17 α-hydroxyprogesterone caproate in expectant management of symptomatic placenta previa tends to be effective than placebo in prolongation of pregnancy.

Safety of 17 α-hydroxyprogesterone caproate during pregnancy (Food and Drug Administration recommendation)

17 Aα-hydroxyprogesterone caproate crosses the placenta, so the drug is detectable in both maternal and fetal blood for at least 44 days after last injection. This is because the drug is slowly released from castor oil depot and maternal fat. The therapeutic concentrations of 17 α-hydroxyprogesterone caproate has not been determined [21].

The primary reviewing medical officer for Makena (commercial 17 α-hydroxyprogesterone caproate in USA) application recommended approval under the subpart H regulation. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit [22].

Congenital anomalies

Progestogens in utero exposure is not likely related to increased risk of congenital anomalies, with exception of hypospadias. This relation is reported in general to progestins but not specifically to 17 α-hydroxyprogesterone caproate, The risk is increased with exposure before 11 weeks' gestation and thus it is not related to the use of 17 α-hydroxyprogesterone caproate for preterm birth after 16 weeks of gestation [21].

A 2- to 5-year follow-up [23] study for the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network arrived at the following:

(1) Fetal exposure to 17 α-hydroxyprogesterone caproate initiated at 16–20 weeks' gestation had no long-term detrimental effect on child neurodevelopment, as measured by Ages and Stages Questionnaire.
(2) The overall incidence of reproductive or genital anomalies was not significantly different between 17 α-hydroxyprogesterone caproate and placebo group.

Potential side effects of the use of 17 α-hydroxyprogesterone caproate

Cholestasis of pregnancy

Elevation of levels of progesterone metabolites plays a role in the pathogenesis of intrahepatic cholestasis of pregnancy as it is caused by impaired biliary excretion and piling up of bile salts. Compared with oral progestins, vaginal and intramuscular progesterone bypass the hepatic metabolism effect and so it is related to less hepatic impairment [21].

Gestational diabetes

The risk of women developing gestational diabetes during pregnancy may be increased with the use of intramuscular 17 α-hydroxyprogesterone caproate, according to data from a large retrospective study that used compounded 17 α-hydroxyprogesterone caproate [24]. Among women with a singleton pregnancy and a history of preterm delivery, there was a significant increase of gestational diabetes incidence in those who received 17 α-hydroxyprogesterone caproate 250 mg once weekly between 16.0 and 20.9 weeks' gestation than in those not treated with the drug. The

manufacturer's prescribing information warns that reductions in glucose tolerance have been seen with progestins and recommends that prediabetic and diabetic women are carefully monitored during treatment with Makena (AMAG Pharaceutical company,headquartered in Waltham, Massachusetts, USA).

Drug interactions

(1) BMI may affect 17 α-hydroxyprogesterone caproate pharmacokinetics. Population pharmacokinetic model data demonstrated significant variation (>twofold) in plasma concentrations of 17 α-hydroxyprogesterone caproate across BMIs of 18–45 kg/m^2 (*P* value not reported) [25].

(2) Race had no significant impact on plasma concentrations of 17 α-hydroxyprogesterone in women with twin gestations, although during the population pharmacokinetic model-building process, median plasma clearance of the drug was found to be significantly ($P < 0.05$) greater in African Americans than Caucasians [25].

(3) The potential impact of renal or hepatic impairment on the pharmacokinetic profile of 17 α-hydroxyprogesterone caproate has not been studied [26].

(4) Use of 17 α-hydroxyprogesterone caproate at therapeutic concentrations is unlikely to inhibit the activity of CYP enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, according to in-vitro data. However, the drug resulted in an ~80–150% increase in the metabolic rate of CYP1A2, CYP2A6, and CYP2B6 *in vitro*, although the clinical implications of this finding are poorly understood [26]. The potential for 17 α-hydroxyprogesterone caproate to induce drug metabolism has not been assessed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Chang HH, Larson J, Blencowe H, Spong CY, Howson CP, Cairns-Smith S, *et al*. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. Lancet 2013;

2 Da Fonseca EB, Bittar RE, Carvalho MHB, Zugaib M. Prophylacticadministration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419–424.

3 Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, *et al*. Prevention of recurrent preterm delivery by 17 α-hydroxyprogesterone caproate. N Engl J Med 2003; 349:1299.

4 O'Brien JM. Medication safety is still an issue in obstetrics 50 years after the Kefauver-Harris amendments: The case of progestogens. Ultrasound Obstet Gynecol 2013; 42: 247–253.

5 Romero R, Stanczyk FZ. Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice. Am J Obstet Gynecol 2013. 421–426.

6 Romero R, Yeo L, Miranda J, Hassan SS, Conde-Agudelo A, Chaiworapongsa T. A blueprint for the prevention of preterm birth: vaginal progesterone in women with a short cervix. J Perinat Med 2013.

7 Attardi j, Zeleznik j, Chiao P,Mattison R, Caritis N et al. Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17-alpha hydroxyprogesterone caproate, and related progestins. American Journal of Obstetrics and Gynecology 2007599.e1-e7.

8 Ashoush S, El-Kady O, Al-Hawwary G, Othman A. The value of oral micronized progesterone in the prevention of recurrent spontaneous preterm birth: a randomized controlled trial. Acta Obstet Gynecol Scand 2017.

9 Di Renzo GC, Giardina I, Clerici G, Mattei A, Alajmi AH, Gerli S. The role of progesterone in maternal and fetal medicine. Gynecol Endocrinol 2012.

10 Facchinetti F, Vergani P, Tommaso M, Marozio L, Acaia B, Vicini R, *et al*. Progestogens for maintenance tocolysis in women with a short cervix: a randomized controlled trial. Obstet Gynecol 2017.

11 Elimian A, Smith K, Williams M, Knudtson E, Goodman JR, Escobedo MB. A randomized controlled trial of intramuscular versus vaginal progesterone for the prevention of recurrent preterm birth. Int J Gynecol Obstet 2016.

12 Grobman W. 532: Short cervix and activity restriction. Am J Obstet Gynecol 2012.

13 Keirse MJNC. Progesterone and preterm: seventy years of 'Deja Vu' or 'Still To Be Seen'?. Birth 2004.

14 Combs CA, Garite TJ, Maurel K, Abril D, Das A, Clewell W, *et al*. 17-hydroxyprogesterone caproate for preterm rupture of the membranes: a multicenter, randomized, double-blind, placebo-controlled trial. Am J Obstetr Gynecol 2015.

15 Kumar D, Moore RM, Mercer BM, Mansour JM, Mesiano S, Schatz F, *et al*. In an in-vitro model using human fetal membranes, 17-α hydroxyprogesterone caproate is not an optimal progestogen for inhibition of fetal membrane weakening. Am J Obstet Gynecol 2017. E1-E14.

16 Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Williams obstetrics. 23rd ed. In: *Williams Obstetrics*. 2001

17 Awwad J, Usta IM, Ghazeeri G, Yacoub N, Succar J, Hayek S, *et al*. 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 Int J Obstet Gynaecol 2015.

18 Combs CA, Garite T, Maurel K, Das A, Porto M. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. Am J Obstet Gynecol 2010;203:248.e1–9.

19 Singh P., Jain SK. Evaluation of the effect of progesterone and placebo in parturient of symptomatic placenta praevia: a prospective randomised control study. Int J Sci Stud 2015; 3:69–72.

20 Anjula B. Study of use of progesterone for symptomatic placenta in a tertiary care teaching hospital. Indian J Basic Appl Med Res 2013; 3:340–345.

21 Vidaeff AC, Belfort MA. Critical appraisal of the efficacy, safety, and patient acceptability of hydroxyprogesterone caproate injection to reduce the risk of preterm birth. Patient Preference Adherence 2013;20:683–691.

22 Barbara W. Clinicalreview, NDA 21-945,17-α- hydroxyprogesterone caproate, 3 February 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000MedR.pdf.

23 Northen AT, Norman GS, Anderson K, Moseley L, DiVito M, Cotroneo M, *et al*. Follow-up of children exposed in utero to 17 α-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol 2007;110:865–872.

24 Rebarber A, Istwan NB, Russo-Stieglitz K, Cleary-Goldman J, Rhea DJ, Stanziano GJ, *et al*. Increased incidence of gestational diabetes in women receiving prophylactic 17α-hydroxyprogesterone caproate for prevention of recurrent preterm delivery. Diabetes Care 2007.

25 Shringi S, Ellis ECS, Dorko K, Zhang S, Mattison DR, Caritis SN, *et al*. Metabolism of 17α-hydroxyprogesterone caproate, an agent for preventing preterm birth, by fetal hepatocytes. Drug Metab Dispos 2010;38:723–727.

26 Makena prescribing information, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021945s000lbl.pdf