Review article

Ki Hoon Ahn, Na-Young Bae, Soon-Cheol Hong*, Ji-Sung Lee, Eun Hee Lee, Hee-Jung Jee, Geum-Joon Cho, Min-Jeong Oh and Hai-Joong Kim

The safety of progestogen in the prevention of preterm birth: meta-analysis of neonatal mortality

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Abstract

Background: The safety of preventive progestogen therapy for preterm birth remains to be established. This meta-analysis aimed to evaluate the effects of preventive progestogen therapy on neonatal mortality.
Methods: Randomized controlled trials (RCTs) on the preventive use of progestogen therapy, published between October 1971 and November 2015, were identified by searching MEDLINE/PubMed, EMBASE, Scopus, ClinicalTrials.gov, Cochrane Library databases, CINAHL, POPLINE, and LILACS using "progesterone" and "preterm birth" as key terms. We conducted separate analyses according to the type of progestogen administered and plurality of the pregnancy.
Results: Twenty-two RCTs provided data on 11,188 neonates. Preventive progestogen treatment in women with a history of preterm birth or short cervical length was not associated with increased risk of neonatal death compared to placebo in all analyzed progestogen types and pregnancy conditions. The pooled relative risks (95% confidence interval) of neonatal mortality were 0.69 (0.31–1.54) for vaginal progestogen in singleton pregnancies, 0.6 (0.33–1.09) for intramuscular progestogen in singleton pregnancies, 0.96 (0.51–1.8) for vaginal progestogen in multiple pregnancies, and 0.96 (0.49–1.9) for intramuscular progestogen in multiple pregnancies.
Conclusions: The results of this meta-analysis suggest that administration of preventive progestogen treatment to women at risk for preterm birth does not appear to negatively affect neonatal mortality in single or multiple pregnancies regardless of the route of administration.

Keywords: Neonatal death; preterm birth; progestogen.

***Corresponding author: Soon-Cheol Hong,** Department of Obstetrics and Gynecology, Korea University Anam Hospital, Korea University College of Medicine, 126-1 Anam-dong 5-ga, Seongbuk-gu, Seoul 136-705, South Korea, Fax: +82-2-921-5357, E-mail: novak082@naver.com
Ki Hoon Ahn, Na-Young Bae, Geum-Joon Cho, Min-Jeong Oh and Hai-Joong Kim: Department of Obstetrics and Gynecology, Korea University College of Medicine, Seoul, South Korea
Ji-Sung Lee: Clinical Research Center, Asan Medical Center, Seoul, South Korea
Eun Hee Lee: Department of Pediatrics, Korea University College of Medicine, Seoul, South Korea
Hee-Jung Jee: Department of Biostatistics, Korea University College of Medicine, Seoul, South Korea

Introduction

Preterm birth is the most common cause of perinatal morbidity and mortality [1]. The incidence of preterm birth has increased worldwide to an estimated rate of 11.1%; including important variations in incidence based on geographic location and race, with up to 15 million babies affected by preterm birth in 2010 [2, 3]. Preterm birth causes short-term complications due to developmental immaturity of biological systems, and is a significant risk factor for long-term morbidities, such as neurodevelopmental complications [4]. To avoid serious neonatal complications, early identification of mothers at risk for preterm birth and intervention is crucial.

Preventive progestogen therapy has been recommended for women with identified risk factors for preterm birth, such as a history of spontaneous preterm birth and a short cervix measured by transvaginal ultrasonography [5, 6]. Natural progesterone is known to inhibit cervical ripening and uterine contractility [7]. There is accumulating evidence regarding the role of supplemental progestogen in reducing the rate of preterm birth in the US [5]. However, reports have been issued by the United States Food and Drug Administration (US FDA) linking exposure to progestins, synthetic derivatives of progesterone, to an insignificantly increased risk of perinatal death in singleton and

twin pregnancies [8–10]. However, recently, Romero et al. presented evidence of an overall decrease in the incidence of neonatal morbidity and mortality in a meta-analysis on the use of vaginal progesterone in women with a short cervix [11]. Thus, the effects and safety of progestogen on the neonate remain to be clearly established. The neonatal period is the final period when most obstetricians observe preterm infants, although they may easily neglect the outcomes of infants during hospitalization of mothers and infants. However, neonatal death could be considered a greater mortality issue than fetal death for parents and maternal-fetal physicians in the perinatology field considering the more extensive socioeconomic and emotional communication that occurs among neonates, mothers, and physicians. Therefore, the aim of the present meta-analysis was to specifically evaluate the effect of progestogen therapy on neonatal mortality in the prevention of preterm births. Secondarily, the present study aimed to determine whether the rate of neonatal mortality differs according to the route of progestogen administration and pregnancy type.

Materials and methods

The flow chart for this meta-analysis is shown in Figure 1.

Eligibility criteria, information sources, and search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Published articles included in the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE

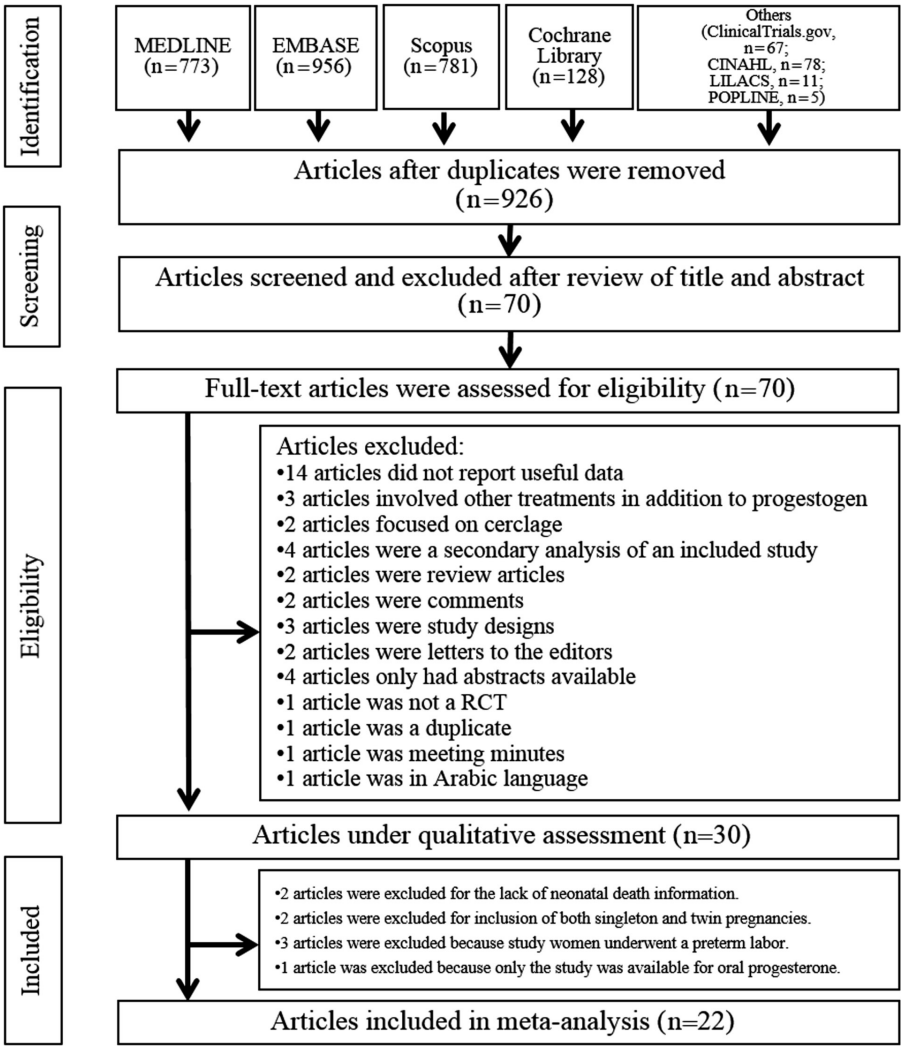

Figure 1: Flow diagram of study identification.

(EMBASE), Scopus, ClinicalTrials.gov, Cochrane Library databases, CINAHL, POPLINE, and LILACS were searched in November 2015 using the search terms "progesterone" and "preterm birth". Articles published from October 1971 to November 2015 were identified and screened by reviewing the title and abstracts for their relevance to this study. There were no language restrictions. Two reviewers (AKH and BNY) independently reviewed the articles for analysis of eligibility.

Study selection

Only randomized controlled trials (RCTs) were included. Articles not reporting human data were excluded. Studies that involved treatments other than progestogen for the prevention of preterm birth, which could have confounded the outcome, were also excluded. Secondary analyses of included studies were excluded as well. When a study included women with singleton and multiple gestations, it was not considered for inclusion in the review unless data for singletons and multiples were extractable separately. Reviews, comments, and study designs were excluded in the study selection.

Data extraction

The reviewers extracted data for statistical analysis. For the data extraction, the definition of "neonatal death" was limited to postnatal infantile death within 1 month of birth, as defined in each of the included studies.

Quality assessment

The reviewers made qualitative assessments of the articles based on the Jadad scale. The appropriateness of randomization, blinding, and withdrawals and dropouts were assessed using a Jadad scale questionnaire for which one point was assigned for each positive response (Table 1). Articles were included in the study if they reported the number of neonatal deaths following preventive treatment for preterm birth in women at risk.

Data synthesis

The extracted data were pooled and analyzed using a fixed- or random-effects model according to the heterogeneity of the data. We chose a random-effects model if heterogeneity (I^2>40%) was evident. A fixed-effects model was used for pooling the data if there was no substantial heterogeneity. Review Manager (RevMan) version 5.3 (Cochrane IKMD, Copenhagen, Denmark) was used for data analysis. Tests of heterogeneity were performed, and Galbraith and L'Abbe plots were also produced to visualize the degree of heterogeneity between studies. Funnel plots and Begg's tests

Table 1: Jadad scores of studies included in the meta-analysis.

Authors	Q1 Randomization	Q2 Description of randomization	Q3 Blinding	Q4 Description of blinding	Q5 Description of withdrawals and dropouts	Total points
Yemini et al.	1	1	1	1	1	5
Meis et al.	1	1	1	1	1	5
Rouse et al.	1	1	1	1	0	4
O'Brien et al.	1	1	1	1	1	5
Norman et al.	1	1	1	1	1	5
Briery et al.	1	1	1	1	1	5
Ibrahim et al.	1	1	1	1	1	5
Combs et al.	1	1	1	1	1	5
Hassan et al.	1	1	1	1	1	5
Rode et al.	1	1	1	1	1	5
Lim et al.	1	1	1	1	1	5
Combs et al.	1	1	1	1	1	5
Tan et al.	1	1	1	1	1	5
Wood et al.	1	1	1	1	1	5
Grobman et al.	1	1	1	1	1	5
Serra et al.	1	1	1	1	1	5
Senat et al.	1	1	1	0	1	4
Awwad et al.	1	1	1	1	1	5
Winer et al.	1	1	1	0	1	4
Brizot et al.	1	1	1	1	1	5
El-Refaie et al.	1	1	0	−1	1	2
van Os et al.	1	1	1	1	0	4

The Jadad scale includes 1 point for each for the following questions: (1) Was the study described as randomized? (2) Was the method of randomization appropriate? (3) Was the study described as blinded? (4) Was the method of blinding appropriate? (5) Was there a description of withdrawals and dropouts?

were used to assess publication bias among the included articles. The population was then divided into four subgroups based on single or multiple gestation and type of progestogen administration (vaginal progesterone or intramuscular 17-hydroxyprogesterone caproate [17OHP-C]) for further analysis. Sensitivity analyses were performed by a statistician (JHJ) to evaluate the methodological quality of the included studies and to remove studies with a poor description of "blinding". Regarding studies with "zero" event, adding 0.5 for each group was performed to avoid computational errors.

Results

Study selection and characteristics

Among the 30 articles screened and assessed for eligibility by the reviewers, 22 were included in the meta-analysis [9, 10, 12–31]. Although the effect size of two studies could not be estimated due to the lack of mortality events in both the intervention (progestogen) and control groups, the studies were nonetheless included in the statistical analysis by adding 0.5 as the number of events to avoid computational errors [30, 31]. Two studies were excluded because no definite information on neonatal death was reported [32, 33]. Two studies were excluded from the analysis because their data did not discriminate between singleton and twin pregnancies [34, 35]. Three studies were excluded because the study participants experienced preterm labor [36–38]. Because only one study evaluating treatment with oral progesterone was available, [39] it was excluded from the final analysis. The characteristics of the included studies are described in Table 2.

Vaginal progesterone in singleton pregnancies

Data from three RCTs comprising 1149 pregnancies were included in the data analysis of vaginal progesterone use in singleton pregnancies (Figure 2) [12, 17, 29]. In this combined pool of data, neonatal death occurred in 10 of 585 pregnancies in the progesterone therapy group, and in 14 of 564 pregnancies in the control group. The pooled relative risk (RR) of neonatal death in the progesterone therapy group compared with the control group among all three studies was 0.69 (95% confidence interval [CI] 0.31–1.54) in a fixed-effects model (Figure 2). The results of chi-square tests of heterogeneity were also not significant (Q=0.29, df=2, I^2=0%, P=0.865). Begg's test was performed for publication bias; however, the bias was not significant (P=0.1172).

Intramuscular 17OHP-C in singleton pregnancies

Six studies reporting 1450 pregnancies in which singleton pregnancy subjects were treated with weekly intramuscular 17OHP-C were included in this meta-analysis (Figure 3) [9, 15, 21, 22, 26, 30]. In the combined pool of data, neonatal death occurred in 17 of 796 subjects in the 17OHP-C therapy group and in 22 of 654 subjects in the control group. The pooled RR of neonatal death in the 17OHP-C therapy group compared with the control groups was 0.6 (95% CI 0.33–1.09) in a fixed-effects model (Figure 3). The results of chi-square tests of heterogeneity were also not significant (Q=2.52, df=5, I^2=0%, P=0.7733). Begg's test was performed for publication bias, but the bias was not significant (P=0.573). Sensitivity analysis was performed after removing a study with non-optimal "description of blinding" domain score [26]. However, the effect of progestogen did not change the risk of neonatal mortality (fixed-effects model, RR=0.58, 95% CI 0.31–1.07; Q=2.27, df=4, I^2=0%, P=0.6857 for heterogeneity test; P=0.6242 for Begg's test).

Vaginal progesterone in multiple pregnancies

In six studies, involving 4275 pregnancies, that were included in this meta-analysis, treatment for multiple pregnancy subjects entailed daily vaginal progesterone (Figure 4) [13, 18, 23, 27, 28, 31]. In the combined pool of data, neonatal death occurred in 59 of 2236 subjects in the progesterone therapy group and in 75 of 2039 subjects in the control group. The pooled RR of neonatal death in the progesterone therapy group compared with the control group was 0.96 (95% CI 0.51–1.8) in a random-effects model (Figure 4). The results of chi-square tests of heterogeneity were significant (Q=9.76, df=5, I^2=48.7%, P=0.0824). Begg's test was performed for publication bias, but the bias was not significant (P=0.573). Sensitivity analysis was performed after excluding a study with non-optimal "description of blinding" domain score [28]. However, the effect of progestogen did not change the risk of neonatal mortality (fixed-effects model, RR=1.37, 95% CI 0.78–2.4; Q=2.11, df=4, I^2=0%, P=0.7157 for heterogeneity test; P=0.6242 for Begg's test).

Table 2: Main characteristics of studies included in the meta-analysis.

Authors	Publication year	Country	Inclusion criteria	n	Administration	Dosage
Yemini et al.	1985	Israel	Women with a history of at least two preterm deliveries or two spontaneous miscarriages or a combination of both	79	Intramuscular 17OHP-C injection, weekly	250 mg
Meis et al.	2003	US	Women with a history of spontaneous preterm delivery in a previous pregnancy and a current pregnancy between 15 and 20 weeks and 3 days of gestation	459	Intramuscular 17OHP-C injection, weekly	250 mg
Rouse et al.	2007	US	Women carrying twins with a GA of at least 16 weeks and no more than 20 weeks 3 days	1310	Intramuscular 17OHP-C injection, weekly	250 mg
O'Brien et al.	2007	US	Women with a history of spontaneous singleton preterm birth in the immediately preceding pregnancy and with pregnancy of GA between 16 weeks 0 days and 22 weeks 6 days	611	Vaginal gel, daily	90 mg
Norman et al.	2009	Multinational	Women with twin pregnancy, with gestation and chorionicity established by scan before 20 weeks of gestation	988	Vaginal gel, daily	90 mg
Briery et al.	2009	US	Women with twin pregnancy between 20 and 30 weeks' gestation with intact membranes	60	Intramuscular 17OHP-C injection, weekly	250 mg
Ibrahim et al.	2010	Egypt	Women with a history of previous preterm labor in their second trimester	50	Intramuscular 17OHP-C injection, weekly	250 mg
Combs et al.	2010	US	Women with trichorionic-triamniotic triplet pregnancy with normal amniotic fluid volume at 15–23 weeks of gestation	230	Intramuscular 17OHP-C injection, weekly	250 mg
Hassan et al.	2011	Turkey	Women without signs or symptoms of preterm labor and carrying singleton of GA between 19 weeks 0 days and 23 weeks 6 days and CL between 10 and 20 mm	458	Vaginal gel, daily	90 mg
Rode et al.	2011	Multinational	Women with a live, diamniotic twin pregnancy and chorionicity assessed by ultrasound before 16 weeks of gestation	1342	Vaginal pessary, daily	200 mg
Lim et al.	2011	Multinational	Women with multiple pregnancy and a GA between 15 and 19 weeks	1355	Intramuscular 17OHP-C injection, weekly	250 mg
Combs et al.	2011	US	Women carrying dichorionic-diamniotic twins at 16–24 weeks	476	Intramuscular 17OHP-C injection, weekly	250 mg
Tan et al.	2012	Malaysia	Women diagnosed with threatened preterm labor between 22 and 35 weeks' gestation	112	Intramuscular 17OHP-C injection, single dose	250 mg
Wood et al.	2012	Canada	Women with multiple gestation	171	Vaginal progesterone gel, daily	90 mg
Grobman et al.	2012	US	Nulliparous women with a viable singleton gestation and had a CL <30 mm between 16 weeks 0 days and 22 weeks 3 days	657	Intramuscular 17OHP-C injection, weekly	250 mg
Serra et al.	2013	Spain	Women with dichorionic diamniotic twin pregnancy diagnosed by ultrasound and written informed consent	575	Vaginal progesterone pessary, daily	200 mg, 400 mg
Senat et al.	2013	France	Women carrying twins, with a CL of 25 mm or less	307	Intramuscular 17OHP-C injection, twice a week	500 mg
Awwad et al.	2015	Lebanon	Women with twin pregnancy	576	Intramuscular 17OHP-C injection, weekly	250 mg
Winer et al.	2015	France	Women with CL <25 mm, history of preterm birth, prior cervical operation, or uterine malformation in singleton pregnancy	93	Intramuscular 17OHP-C injection, weekly	500 mg
Brizot et al.	2015	Brazil	Women with twin pregnancy	760	Vaginal progesterone ovule, daily	200 mg
El-Refaie et al.	2015	Egypt	Women with dichorionic twin pregnancy and CL of 20–25 mm	439	Vaginal progesterone suppository, daily	400 mg
van Os et al.	2015	Netherlands	Women with a CL of 30 mm or less and no history of spontaneous preterm birth <34 weeks	80	Vaginal progesterone capsule, daily	200 mg

17OHP-C=17-alpha-hydroxyprogesterone caproate, CL=cervical length, IVF=*in vitro* fertilization, ICSI=intracytoplasmic sperm injections, GA=gestational age.

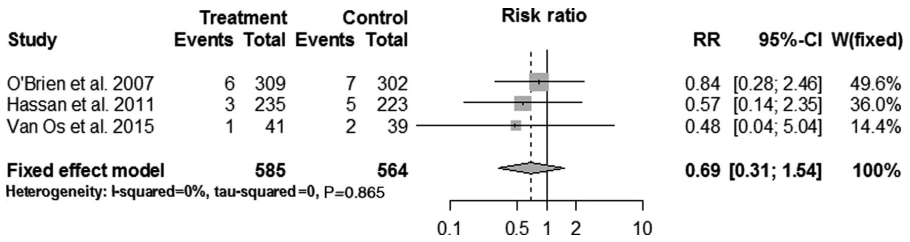

Figure 2: Forest plot of neonatal death in women with singleton pregnancies treated with vaginal progesterone.
The first authors for each study are shown. Progestogen treatments administered to the study populations. The control groups were administered placebos. "Events" refers to the number of neonatal deaths.

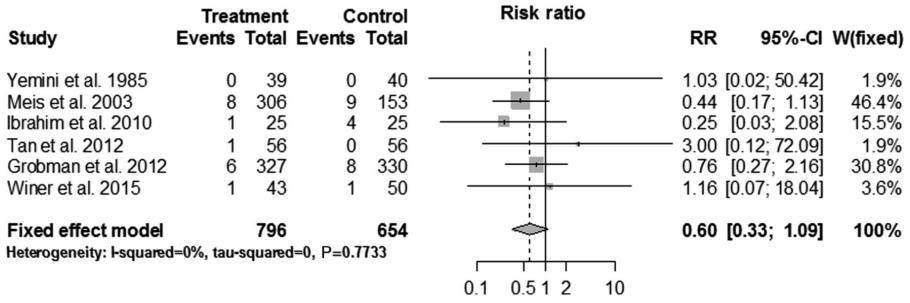

Figure 3: Forest plot of neonatal death in women with singleton pregnancies treated with intramuscular 17-hydroxyprogesterone caproate (17OHP-C).
The first authors for each study are shown. Progestogen treatments were administered to the study populations. The control groups were administered placebos. "Events" refers to the number of neonatal deaths.

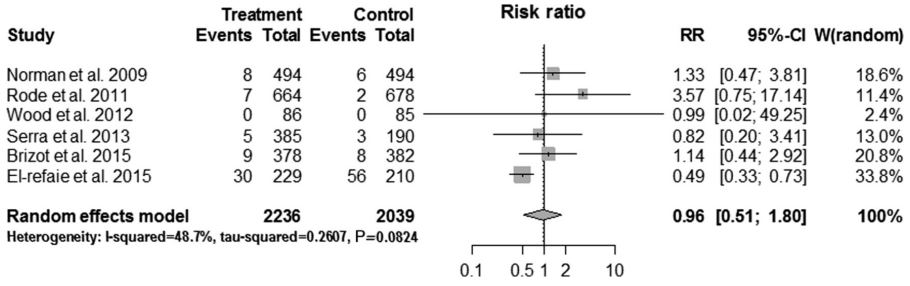

Figure 4: Forest plot of neonatal death in women with multiple pregnancies treated with vaginal progesterone.
The first authors for each study are shown. Progestogen treatments were administered to the study populations. The control groups were administered placebos. "Events" refers to the number of neonatal deaths.

Intramuscular 17OHP-C in multiple pregnancies

Seven studies comprising 4314 pregnancies in which women with multiple pregnancies were administered weekly intramuscular injections of 17OHP-C were included in this meta-analysis (Figure 5) [10, 14, 16, 19, 20, 24, 25]. In the combined data, neonatal death occurred in 46 of 2379 infants in the 17OHP-C therapy group and in 42 of 1935 infants in the control group. The pooled RR of neonatal death in the 17OHP-C therapy group compared with the control group was 0.96 (95% CI 0.49–1.9) in a random-effects model (Figure 5). The results of chi-square tests of heterogeneity were marginally significant (Q=10.49, df=6, I^2=42.8%, P=0.1056). Begg's test was performed for publication bias; however, the bias was not significant (P=0.8806). Sensitivity analysis was performed after removing a study with non-optimal "description

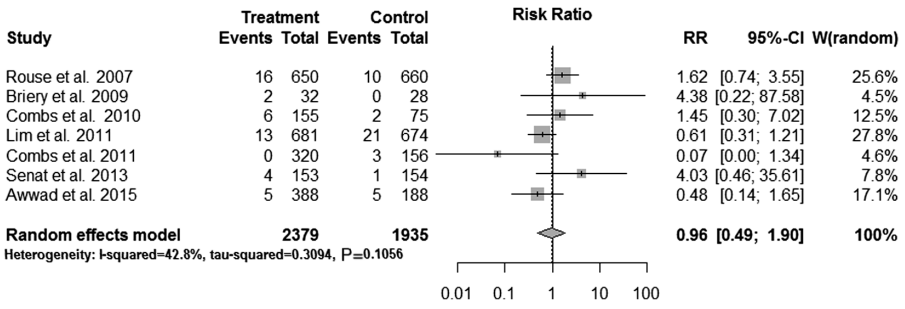

Figure 5: Forest plot of neonatal death in women with multiple pregnancies treated with intramuscular 17-hydroxyprogesterone caproate (17OHP-C).
The first authors for each study are shown. Progestogen treatments were administered to the study populations. The control groups were administered placebos. "Events" refers to the number of neonatal deaths.

of blinding" domain scores [24]. However, the effect of progestogen did not change the risk of neonatal mortality (random-effects model, RR=0.86, 95% CI 0.43–1.69; Q=8.66, df=5, I^2=42.3%, P=0.1234 for heterogeneity test; P=0.851 for Begg's test).

Discussion

In the present meta-analysis, the pooled RR of neonatal death in the progestogen treatment group was not significantly different from that of the placebo groups. In the singleton pregnancy groups, the pooled RR of neonatal mortality associated with progestogen treatment tended to be lower than the risk in controls (0.6 and 0.69), but the difference was not statistically significant. In the multiple pregnancy groups, the risk was essentially the same in the treatment and control groups (0.96). The statistical non-significance was maintained for both vaginal progesterone and intramuscular 17OHP-C.

The strength of this meta-analysis originates from its design to include only RCTs. This study design improved the quality and reliability of the data. Therefore, we are confident in the conclusions derived from the present analyses. Moreover, distinct subgrouping of cases according to singleton or multiple pregnancy and progestogen treatment type avoided any potential confounding effects due to these variables. Performing separate analyses of singleton and multiple pregnancies is reasonable considering that plasma 17OHP-C concentrations in twin pregnancies may be lower than in singleton pregnancies due to the greater volume distribution [40, 41].

These results are clinically meaningful as physicians are provided with concrete evidence that progestogen treatment is a relatively safe option for the prevention of preterm births.

Nevertheless, there might have been bias due to the different inclusion criteria used by the various studies included in this meta-analysis, especially in the studies involving multiple pregnancies, which may limit interpretation of the results. For the potential heterogeneity among studies of multiple pregnancies, we chose to use the random-effects model for calculating the RR of neonatal death in multiple pregnancies. Begg's tests were performed to analyze publication biases and revealed no statistically significant results. The duration and dosage of progestogen treatment varied between the studies, and this may have affected the results. The starting point of progestogen therapy in the included studies varied from 16 weeks to 31 weeks 6 days, and the ending point varied from 34 weeks to 37 weeks. Dosage of vaginal progesterone and 17OHP-C ranged from 90 mg to 400 mg daily and from 250 mg to 1000 mg weekly, respectively. Compounded progestin products of different pharmaceutical companies may also differ from one another in drug efficacy, despite the reported similarity of potency or impurities [42].

Therefore, it may be difficult to directly compare the results of the studies and draw definite conclusions. Genetic variation among the various study populations may also confound the present study results [43]. A recent study showed that patients who responded to 17OHP-C had a higher expression of genes associated with various cell metabolisms [43].

In general, the findings of our study are similar to those of previous reports on neonatal death after administration of progestogen therapies, which also did not indicate a statistically significant increase or decrease in neonatal death rates.

The safety of natural progesterone has been proven by its long-term use in assisted reproductive technology [44];

however, the safety of synthetic progestin, 17OHP-C, is still controversial [45]. The pharmacophysiology of 17OHP-C differs from that of natural progesterone [46]; therefore, although both may have the same progestational role, their effects need to be assessed separately. The present finding that antenatal synthetic 17OHP-C as well as natural progesterone did not change the risk of neonatal mortality is novel, although the result that neither type of progestogen in singleton or multiple pregnancies decreased the risk of neonatal mortality differed from our expectations. As the preventive methods for preterm birth are limited, the present data support antenatal administration of progestogen, consisting of either vaginal progesterone or intramuscular 17OHP-C, for preventing preterm birth in view of preventing neonatal death. However, before antenatal progestogen is safely and freely used, the issue of in utero pregnancy loss should be addressed as it was not an objective of the present analyses. Meis et al. were first concerned about potentially increased antepartum or intrapartum fetal deaths in a group of women treated with 17OHP-C, compared with those in the placebo group (2.0% vs. 1.3%; RR, 1.5, 95% CI 0.31–7.34) [9]. Rouse et al., in their twin pregnancy study, escalated the concern, with a marginally higher fetal death rate (41.5% vs. 37.3%; RR 1.1, 95% CI 0.9–1.3) [10]. Some reviews have pointed out the safety of 17OHP-C in early pregnancy as well. Finally, the potential harmful effects of progestogen therapy, such as androgenic effects, an increased rate of gestational diabetes, and reported cardiovascular, orofacial, and genitourinary anomalies should also be considered during patient counseling before use.

The results of this meta-analysis suggest that preterm birth-preventive progestogen treatment does not change neonatal mortality rates regardless of progestogen origin (natural or synthetic), among singleton or multiple pregnancies at risk of preterm birth in their current pregnancy, including women with a history of preterm birth or those with short cervical length. Therefore, based on our data on neonatal death rates, in order to prevent preterm birth in singleton and multiple pregnancies, vaginal progesterone or intramuscular 17OHP-C can be safely administered antenatally. However, due to the question of the safety of 17OHP-C treatment in the previable period of pregnancy, we propose a limited use of 17OHP-C before 20–24 weeks of gestational age until more RCTs and meta-analyses can evaluate the safety of these treatments during an earlier pregnancy period. We found no evidence to suggest changing current practices regarding the use of vaginal natural progesterone. Proper patient counseling on progestogen safety before use to prevent preterm birth is required.

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References

[1] WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand. 1977;56:247–53.
[2] Steer P. The epidemiology of preterm labour. Br J Obset Gynaecol. 2005;112(Suppl 1):1–3.
[3] Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet. 2012;379:2151–61.
[4] Arpino C, Compagnone E, Montanaro ML, Cacciatore D, De Luca A, Cerulli A, et al. Preterm birth and neurodevelopmental outcome: a review. Childs Nerv Syst. 2010;26:1139–49.
[5] Iams JD. Clinical practice. Prevention of preterm parturition. N Engl J Med. 2014;370:254–61.
[6] Iams JD. Identification of candidates for progesterone: why, who, how, and when? Obstet Gynecol. 2014;123:1317–26.
[7] Ruddock NK, Shi SQ, Jain S, Moore G, Hankins GD, Romero R, et al. Progesterone, but not 17-alpha-hydroxyprogesterone caproate, inhibits human myometrial contractions. Am J Obstet Gynecol. 2008;199:391.e1–7.
[8] Administration FaD. 17α-Alpha hydroxyprogesteronecaproate for prevention of pretermbirth: overview of FDA background document. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4227B1-02-01-FDA-Background.pdf2007.
[9] Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003;348:2379–85.
[10] Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med. 2007;357:454–61.
[11] Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol. 2012;206:124.e1–19.
[12] O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007;30:687–96.
[13] Norman JE, Mackenzie F, Owen P, Mactier H, Hanretty K, Cooper S, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. Lancet. 2009;373:2034–40.

[14] Briery CM, Veillon EW, Klauser CK, Martin RW, Chauhan SP, Magann EF, et al. Progesterone does not prevent preterm births in women with twins. South Med J. 2009;102:900–4.
[15] Ibrahim M, Ramy A, Ramy M, Younis M. Progesterone supplementation for prevention of preterm labor: a randomized controlled trial. Middle East Fertil Soc J. 2010;15:39–41.
[16] 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.
[17] Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2011;38:18–31.
[18] Rode L, Klein K, Nicolaides KH, Krampl-Bettelheim E, Tabor A. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. Ultrasound Obstet Gynecol. 2011;38:272–80.
[19] Lim AC, Schuit E, Bloemenkamp K, Bernardus RE, Duvekot JJ, Erwich JJ, et al. 17alpha-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlled trial. Obstet Gynecol. 2011;118:513–20.
[20] Combs CA, Garite T, Maurel K, Das A, Porto M. 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial. Am J Obstet Gynecol. 2011;204:221.e1–8.
[21] Tan PC, King AS, Vallikkannu N, Omar SZ. Single dose 17 alpha-hydroxyprogesterone caproate in preterm labor: a randomized trial. Arch Gynecol Obstet. 2012;285:585–90.
[22] Grobman WA, Thom EA, Spong CY, Iams JD, Saade GR, Mercer BM, et al. 17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm. Am J Obstet Gynecol. 2012;207:390.e1–8.
[23] Serra V, Perales A, Meseguer J, Parrilla JJ, Lara C, Bellver J, et al. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. Br J Obset Gynaecol. 2013;120:50–7.
[24] Senat MV, Porcher R, Winer N, Vayssiere C, Deruelle P, Capelle M, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2013;208:194.e1–8.
[25] 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. Br J Obset Gynaecol. 2015;122:71–9.
[26] Winer N, Bretelle F, Senat MV, Bohec C, Deruelle P, Perrotin F, et al. 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: a randomized controlled trial. Am J Obstet Gynecol. 2015;212:485.e1–10.
[27] Brizot ML, Hernandez W, Liao AW, Bittar RE, Francisco RP, Krebs VL, et al. Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2015;213:82.e1–9.
[28] El-Refaie W, Abdelhafez MS, Badawy A. Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. Arch Gynecol Obstet. 2015;293:61–7.
[29] van Os MA, van der Ven AJ, Kleinrouweler CE, Schuit E, Kazemier BM, Verhoeven CJ, et al. Preventing preterm birth with progesterone in women with a short cervical length from a low-risk population: a multicenter double-blind placebo-controlled randomized trial. Am J Perinatol. 2015;32:993–1000.
[30] Yemini M, Borenstein R, Dreazen E, Apelman Z, Mogilner BM, Kessler I, et al. Prevention of premature labor by 17 alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985;151:574–7.
[31] Wood S, Ross S, Tang S, Miller L, Sauve R, Brant R. Vaginal progesterone to prevent preterm birth in multiple pregnancy: a randomized controlled trial. J Perinat Med. 2012;40:593–9.
[32] Johnson JW, Lee PA, Zachary AS, Calhoun S, Migeon CJ. High-risk prematurity – progestin treatment and steroid studies. Obstet Gynecol. 1979;54:412–8.
[33] Cetingoz E, Cam C, Sakalli M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. Arch Gynecol Obstet. 2011;283:423–9.
[34] Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007;357:462–9.
[35] Aboulghar MM, Aboulghar MA, Amin YM, Al-Inany HG, Mansour RT, Serour GI. The use of vaginal natural progesterone for prevention of preterm birth in IVF/ICSI pregnancies. Reprod Biomed Online. 2012;25:133–8.
[36] Rozenberg P, Chauveaud A, Deruelle P, Capelle M, Winer N, Desbriere R, et al. Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Am J Obstet Gynecol. 2012;206:206.e1–9.
[37] Choudhary M, Suneja A, Vaid NB, Guleria K, Faridi MM. Maintenance tocolysis with oral micronized progesterone for prevention of preterm birth after arrested preterm labor. Int J Gynaecol Obstet. 2014;126:60–3.
[38] Martinez de Tejada B, Karolinski A, Ocampo MC, Laterra C, Hosli I, Fernandez D, et al. Prevention of preterm delivery with vaginal progesterone in women with preterm labour (4P): randomised double-blind placebo-controlled trial. Br J Obset Gynaecol. 2015;122:80–91.
[39] Rai P, Rajaram S, Goel N, Ayalur Gopalakrishnan R, Agarwal R, Mehta S. Oral micronized progesterone for prevention of preterm birth. Int J Gynaecol Obstet. 2009;104:40–3.
[40] Caritis SN, Simhan HN, Zhao Y, Rouse DJ, Peaceman AM, Sciscione A, et al. Relationship between 17-hydroxyprogesterone caproate concentrations and gestational age at delivery in twin gestation. Am J Obstet Gynecol. 2012;207:396.e1–8.
[41] Usta IM, Usta J, Nassar AH. 17-hydroxy progesterone caproate for preterm labor prevention: final blood levels. Am J Obstet Gynecol. 2013;208:337.
[42] Chang J, Zhao Y, Zhao W, Venkataramanan R, Caritis SN. Quality assessment of compounded 17-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2014;210:47.e1–7.
[43] Manuck TA, Watkins WS, Moore B, Esplin MS, Varner MW, Jackson GM, et al. Pharmacogenomics of 17-alpha hydroxypro-

gesterone caproate for recurrent preterm birth prevention. Am J Obstet Gynecol. 2014;210:321.e1–21.
[44] Posaci C, Smitz J, Camus M, Osmanagaoglu K, Devroey P. Progesterone for the luteal support of assisted reproductive technologies: clinical options. Hum Reprod. 2000;15(Suppl 1): 129–48.
[45] 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: 247–53.
[46] Romero R, Stanczyk FZ. Progesterone is not the same as 17alpha-hydroxyprogesterone caproate: implications for obstetrical practice. Am J Obstet Gynecol. 2013;208:421–6.

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