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# Perinatal outcome in women treated with progesterone for the prevention of preterm birth: a meta-analysis

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**KEYWORDS:** neonatal outcome; preterm birth; progesterone

## ABSTRACT

***Objective*** *To quantify the effect on perinatal outcome in women treated with progesterone for the prevention of preterm birth.*

***Methods*** *MEDLINE and SCOPUS searches, including references of the retrieved articles and additional automated search using the 'search for related articles' PubMed function, were used. Randomized controlled trials assigning women at risk for preterm birth to progesterone or placebo were included (both singleton and multiple pregnancies). Outcomes were neonatal and perinatal death, respiratory distress syndrome (RDS), retinopathy, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) Grade 3–4, sepsis, admission to the neonatal intensive care unit (NICU) and composite adverse outcome.*

***Results*** *Sixteen studies (singletons,* n = *7; twins,* n = *7; triplets,* n = *2) were included in the meta-analysis. For singleton pregnancies, progesterone reduced the rates of neonatal death (risk ratio (RR) 0.487 (95% CI, 0.290–0.818)), RDS (RR 0.677 (95% CI, 0.490–0.935)), NICU admission (RR 0.410 (95% CI, 0.204–0.823)) and composite adverse outcome (RR 0.576 (95% CI, 0.373–0.891)). No favorable effect was observed in twins; in fact, progesterone was associated with increased rates of perinatal death (RR 1.551 (95% CI, 1.014–2.372)), RDS (RR 1.218 (95% CI, 1.038–1.428)) and composite adverse outcome (RR 1.211 (95% CI, 1.029–1.425)). No significant effect was observed in triplet pregnancies.*

***Conclusion*** *Progesterone administration in singleton pregnancies at risk for preterm birth improves perinatal outcomes, but may actually have adverse effects in multiple pregnancies.* Copyright © 2012 ISUOG. *Published by John Wiley & Sons, Ltd.*

## INTRODUCTION

Accumulating evidence over the last 15 years has shown that screening of pregnant women for preterm birth, based mainly on obstetric history and measurement of the length of the uterine cervix, can identify more than 50% of those who will deliver before 34 weeks' gestation[1]. At almost the same time, two large randomized studies[2,3], soon followed by more, showed that administration of progesterone in women with a singleton pregnancy at risk can significantly reduce the rates of preterm birth both in cases of previous history and in cases with a short cervix.

Therefore, having both a reliable screening tool and a treatment option for women identified as being at highest risk, it may be that 'doing nothing is no longer an option' in singleton pregnancies[4]. Progesterone has been used for decades in reproductive medicine without any documented effect on the risk for congenital abnormalities[5], and the allegedly increased risk for fetal hypospadias does not appear to be confirmed in currently used progestogens[6]; the United States Food and Drug Administration has recently approved the use of hydroxyprogesterone caproate for the prevention of prematurity in women with a previous history of preterm birth[7].

However, although progesterone prophylaxis clearly reduces the risk of preterm birth in women at risk, its effects on the actual perinatal and long-term consequences of prematurity are more difficult to assess. This is because these events are relatively uncommon even in preterm births, with the exception of extremely preterm births, and therefore individual studies are usually underpowered for these outcomes because of small sample size. As a result, existing randomized controlled trials (RCTs), and to some extent systematic reviews as well, have so far focused mainly on the primary outcome of reduction of preterm birth rates.

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The aim of this meta-analysis was to systematically review published evidence and pool data on the perinatal outcome in women treated with progesterone for the prevention of preterm birth.

## METHODS

We searched the literature (last update December 2011) for clinical trials in which progesterone was given for the prevention of preterm birth in pregnant women at risk compared to placebo. MEDLINE and SCOPUS searches used combinations of the terms 'progesterone' AND 'preterm'. These searches were complemented by perusal of the references of the retrieved articles and additional automated search using PubMed's 'search for related articles' function. All studies were carefully compared to ensure avoidance of duplicate or overlapping samples. In case of overlap, the study with the largest number of cases was included.

### Study selection

*Inclusion criteria*. Type of studies: RCTs; intervention: progesterone *vs* placebo for the prevention of preterm birth in women at risk; type of participants: women with singleton pregnancy at risk for preterm birth owing to previous history or short cervix during the second trimester or multiple pregnancies; language: no language restrictions.

*Exclusion criteria*. Studies were excluded if there was no adequate randomization or no placebo group, the administration of progesterone was done in women with symptoms of preterm labor, bleeding or rupture of membranes, or if they did not provide data on neonatal outcomes. Cases with fetal structural defects responsible for perinatal complications in the studies included in the meta-analysis were identified when possible, and were excluded from the analysis.

Data extraction and study quality assessment were independently performed by two authors (S.P. and A.S.); in case of disagreement a consensus was reached after discussion between the two authors or after evaluation by the third author (G.M.).

### Quality assessment of the included studies

The CONSORT statement was used for addressing the reporting quality of the RCTs included in our meta-analyses[8]. The risk of bias in the randomized trials was assessed with the 'Risk-of-bias' tool from the Cochrane Collaboration[9]. This is an assessment of the internal validity of each study and is based on six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other sources of bias'.

Both methods of quality control were assessed independently by two reviewers (S.P. and A.S.) and any discrepancies were resolved by discussion between the two and if this was not possible, after evaluation by G.M.

### Quantitative data synthesis

The primary outcome was the rate of neonatal mortality, meaning the number of deaths from birth to under the age of 28 days, and perinatal mortality. Perinatal deaths refer to fetal deaths and live births with only brief survival (days or weeks) and are grouped on the assumption that similar factors are associated with these losses. There are three definitions of perinatal death in use: infant deaths that occur at less than 7 days of age and fetal deaths following a stated or presumed period of gestation of 28 weeks or more; infant deaths that occur at less than 28 days of age and fetal deaths following a stated or presumed period of gestation of 20 weeks or more; and infant deaths that occur at less than 7 days of age and fetal deaths following a stated or presumed gestation of 20 weeks or more. Although there is no consensus regarding the use and interpretation of these definitions, the second is more inclusive and, hence, more appropriate for monitoring perinatal deaths throughout gestation, because most fetal deaths occur before 28 weeks of gestation[10]. The rates of perinatal complications (respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) Grade 3–4, sepsis, necrotizing enterocolitis (NEC), sepsis and retinopathy), admission to the neonatal intensive care unit (NICU) and composite adverse outcome were assessed as secondary outcomes. In general, composite adverse outcome was defined as the presence of *any* perinatal morbidity *or* mortality. The definitions of composite adverse outcome across studies are presented in Appendix S1 (online).

Descriptive statistics are given as proportions, together with their 95% CIs. Comparisons were made using the risk ratio (RR), which is the probability that a member of an exposed group will develop a disease relative to the probability that a member of an unexposed group will develop that same disease. We also calculated the number needed to treat, which is defined by the inverse of the absolute value of the risk difference, and shows the number of patients who need to be treated with one intervention rather than its comparator to have one more event of interest. The equivalent indicator in case of harmful effect of the treatment is the number needed to harm.

We used random effects models (DerSimonian and Laird) for data synthesis. Fixed effects models assume that differences in the results of studies are due to sampling error alone. Random effects allow for between-study differences, and incorporate an estimate of the between-study variance in the calculations. In the absence of between-study heterogeneity, the two approaches coincide; otherwise random effects usually give wider confidence intervals. Unless stated otherwise, random effects estimates are presented in the text. Between-studies heterogeneity was assessed using the $I^2$ statistic, which is

the ratio of between-study variance over the sum of the within- and between-study variances and describes the percentage of variation that is due to heterogeneity rather than chance (range, 0–100%). A simplistic grouping would tentatively assign descriptions of low, moderate and high heterogeneity to $I^2$ values of 25, 50 and 75%[11].

We ran separate analyses for singleton and multiple pregnancies. When the proportion of twin pregnancies in a study was < 20% and separate data were not provided, the study was grouped together with the singleton-pregnancy studies. Planned subgroup analyses were carried out according to the indication (short cervix *vs* history) for and route (local (vaginal) *vs* systemic (intramuscular or oral)) of progesterone administration, in order to explore whether these factors affected the perinatal outcome.

## RESULTS

### Study selection

Of the 628 items retrieved from our electronic search, 458 were excluded based on the title and/or abstract. The remaining 170 articles were retrieved for screening in full text. A flow chart of the selection procedure is shown in Figure 1. In total, 17 RCTs on progesterone in asymptomatic women in order to prevent preterm birth, which provided data on perinatal mortality and/or morbidity, were eligible for inclusion in our meta-analysis[2,3,12–26]. One of them (Cetingoz *et al.*[13]), including both singleton and twin pregnancies, was finally excluded because it was not possible to split the results accordingly, although we contacted the authors for clarification. Therefore, 16 studies were included in our meta-analysis (Figure 1). One study[16] is a subset of a larger study[17]; the smaller study was used only in subgroup analysis for which the larger study was not eligible.

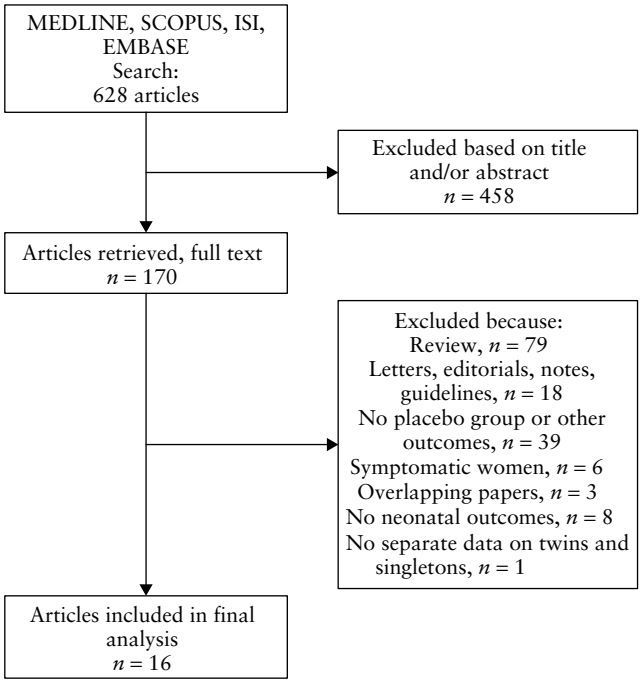


**Figure 1** Flowchart of included studies.

Descriptive characteristics of the included studies are shown in Supplementary Table S1 online.

### Quality assessment

Overall reporting of the studies included in the meta-analysis was good. Only a study that was conducted in 1980 and provided data on twin pregnancies did not follow the guidelines of reporting as expected[24]. The

**Table 1** Summary of bias risk in the 16 papers included in the study

| | *Risk of bias* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Selection bias* | | | | | | |
| *Study* | *Random sequence generation* | *Allocation concealment* | *Performance bias** | *Detection bias†* | *Attrition bias‡* | *Reporting bias§* | *Other bias* |
| Briery *et al.* 2009[21] | Low | Low | Low | Unclear | Low | Low | None |
| Caritis *et al.* 2009[26] | Low | Low | Low | Low | Low | Low | None |
| Combs *et al.* 2010[25] | Low | Low | Low | Low | Low | Low | None |
| Combs *et al.* 2011[18] | Low | Low | Low | Low | Low | Low | None |
| Fonseca *et al.* 2007[3] | Low | Low | Low | Low | Low | Low | None |
| DeFranco *et al.* 2007[16] | Low | Low | Low | Low | Low | Low | None |
| Hartikainen-Sorri *et al.* 1980[24] | High | Unclear | Unclear | Unclear | Low | Low | None |
| Hassan *et al.* 2011[12] | Low | Low | Low | Low | Low | Low | None |
| Ibrahim *et al.* 2010[14] | Unclear | Low | High | High | Low | Low | None |
| Lim *et al.* 2011[19] | Low | Low | Low | Low | Low | Low | None |
| Meis *et al.* 2003[2] | Low | Low | Low | Low | Low | Low | None |
| Norman *et al.* 2009[22] | Low | Low | Low | Low | Low | Low | None |
| O'Brien *et al.* 2007[17] | Low | Low | Low | Low | Low | Low | None |
| Rai *et al.* 2009[15] | Low | Low | Low | Low | Low | Low | None |
| Rode *et al.* 2011[20] | Low | Low | Low | Low | Low | Low | None |
| Rouse *et al.* 2007[23] | Low | Low | Low | Low | Low | Low | None |

*Participants and personnel blinded. †Blinding to outcome assessment. ‡Incomplete outcome data. §Selective reporting.

**Table 2** Perinatal outcomes in singleton pregnancies in the study set (all indications – all progestogens)

| *Outcome* | *Studies* | *Subjects* (n) | *Controls* (n) | $I^2$ (%) | *Risk ratio (95% CI)* | *NNT* |
|---|---|---|---|---|---|---|
| Neonatal death | Meis *et al.*[2]<br>Fonseca *et al.*[3]<br>Hassan *et al.*[12]<br>Ibrahim *et al.*[14]<br>Rai *et al.*[15]<br>O'Brien *et al.*[17] | 23/1085 | 39/915 | 0.0 | 0.487 (0.290–0.818) | 57 (32–1000) |
| Perinatal death | Meis *et al.*[2]<br>Fonseca *et al.*[3]<br>Hassan *et al.*[12] | 25/677 | 30/514 | 0.0 | 0.602 (0.354–1.023) | N/A |
| RDS | Meis *et al.*[2]<br>Fonseca *et al.*[3]<br>Hassan *et al.*[12]<br>O'Brien *et al.*[17] | 81/985 | 95/815 | 18.4 | 0.677 (0.490–0.935) | 26 (15–83) |
| IVH Grade 3–4 | Meis *et al.*[2]<br>Fonseca *et al.*[3]<br>Hassan *et al.*[12]<br>O'Brien *et al.*[17] | 3/985 | 2/816 | 0.0 | 0.965 (0.200–4.666) | N/A |
| NEC | Meis *et al.*[2]<br>Fonseca *et al.*[3]<br>Hassan *et al.*[12]<br>O'Brien *et al.*[17] | 8/985 | 14/815 | 19.5 | 0.569 (0.202–1.606) | N/A |
| Retinopathy | Meis *et al.*[2]<br>Fonseca *et al.*[3] | 7/441 | 5/290 | 48.4 | 1.034 (0.125–8.549) | N/A |
| Sepsis | Meis *et al.*[2]<br>Fonseca *et al.*[3]<br>Hassan *et al.*[12]<br>DeFranco *et al.*[16] | 20/695 | 23/541 | 25.9 | 0.735 (0.339–1.162) | N/A |
| NICU admission | Fonseca *et al.*[3]<br>Ibrahim *et al.*[14]<br>Rai *et al.*[15]<br>DeFranco *et al.*[16] | 49/254 | 103/264 | 72.0 | 0.410 (0.204–0.823) | 4 (2–15) |
| Composite adverse outcome | Fonseca *et al.*[3]<br>Hassan *et al.*[12] | 29/371 | 49/361 | 0.0 | 0.576 (0.373–0.891) | 17 (10–77) |
| Birth < 34 weeks | Fonseca *et al.*[3]<br>Rai *et al.*[15] | 46/199 | 80/199 | 0.0 | 0.577 (0.427–0.779) | 6 (4–13) |
| Birth < 32 weeks | Meis *et al.*[2]<br>Rai *et al.*[15]<br>O'Brien *et al.*[17] | 86/689 | 82/529 | 42.9 | 0.814 (0.563–1.117) | N/A |
| Birth < 28 weeks | Hassan *et al.*[12]<br>Rai *et al.*[15]<br>O'Brien *et al.*[17] | 22/618 | 35/599 | 31.4 | 0.633 (0.307–1.304) | N/A |

IVH, intraventricular hemorrhage; N/A, not applicable; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NNT, number needed to treat; RDS, respiratory distress syndrome.

risk-of-bias tool from the Cochrane Collaboration did not reveal significant sources of bias in most of the studies (Table 1), so we present our results in a single meta-analysis and not separate analyses stratified according to the risk of bias.

### Singleton pregnancies

Seven studies provided data on the impact of progesterone on perinatal mortality and morbidity[2,3,12,14–17]. Pooling all studies that provide such data (Table 2), we found that progesterone administration in women at risk for preterm birth (either because of a short cervix or obstetric history) significantly decreased the risk for composite adverse outcome (RR 0.576 (95% CI, 0.373–0.891)) (Figure 2a), neonatal death (RR 0.487 (95% CI, 0.290–0.818)) (Figure 2b), RDS (RR 0.677 (95% CI, 0.490–0.935)) (Figure 2c) and admission to the NICU (RR 0.410 (95% CI, 0.204–0.823)). No significant difference was found in the rates of perinatal death, Grade 3–4 IVH, NEC, retinopathy or sepsis.

Three studies tested vaginal progesterone in women with a short cervix during the second trimester[3,12,16]. Pooling the relevant data, local progesterone in asymptomatic women with a short cervix appeared to significantly decrease the rate of composite adverse outcome (RR 0.576 (95% CI, 0.373–0.891)) and RDS (RR 0.464 (95% CI, 0.275–0.786)), but failed to reach statistical significance regarding the rates of neonatal death, perinatal death, Grade 3–4 IVH, NEC, sepsis or admission to the NICU (Table S2).

Three studies[2,14,15] tested systemic progesterone (Rai *et al.*[15] used oral administration) in women with a singleton pregnancy and a history of preterm birth. Pooling

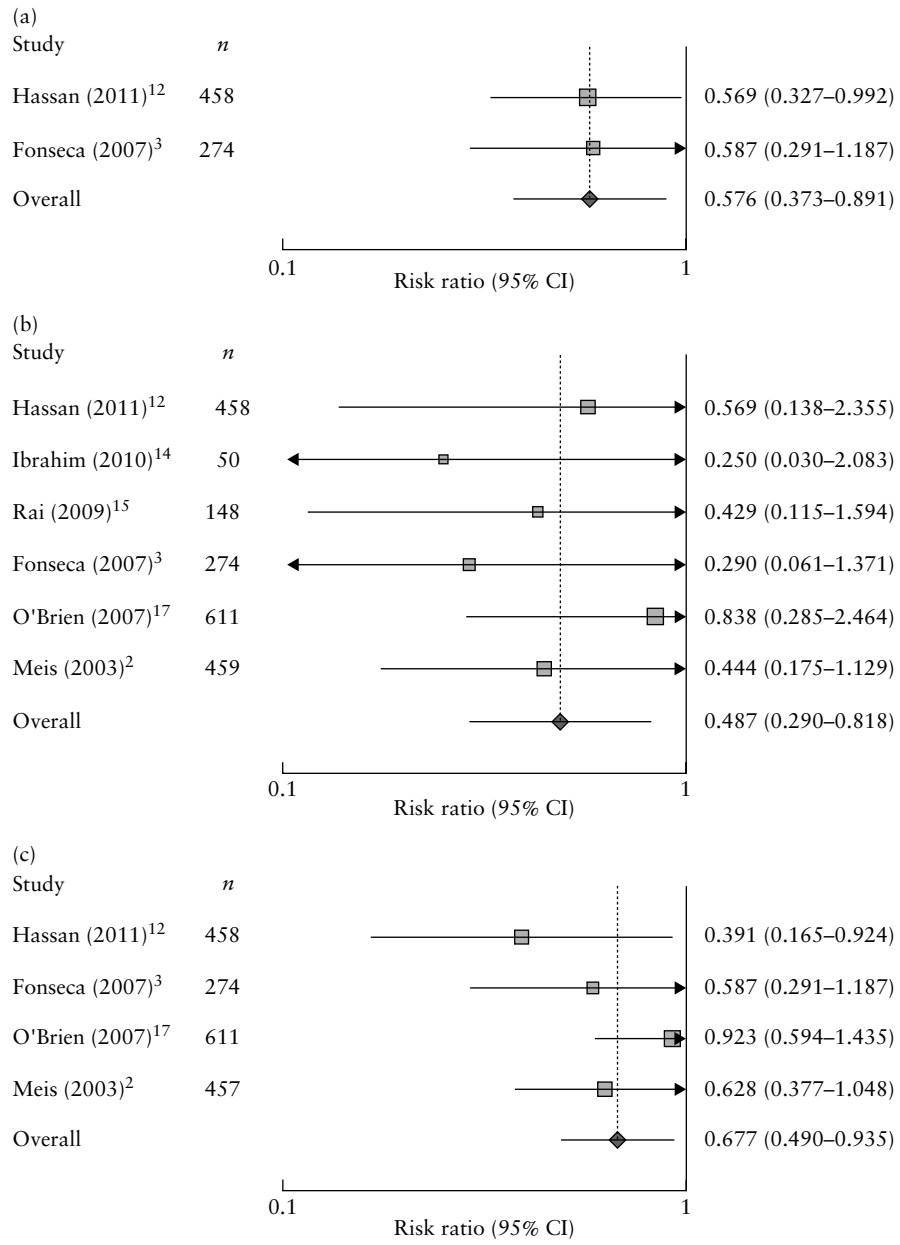


**Figure 2** Forest plot for composite adverse outcome (a), neonatal death (b) and respiratory distress syndrome (c) in singleton pregnancies (all indications, all progestogens). In (a), both studies used local progesterone for women with a short cervix. Only the first author of each study is given.

relevant data, progesterone was found to significantly decrease the rates of neonatal death (RR 0.412 (95% CI, 0.201–0.842)) and NICU admission (RR 0.277 (95% CI, 0.160–0.479)) (Table S3).

## Twin pregnancies

Seven RCTs reported on the effect of progesterone administration in women with twin pregnancies[18–24]. The pooled results showed that progesterone administration did not significantly affect the rates of neonatal death, Grade 3–4 IVH, NEC, retinopathy, sepsis or NICU admission. In fact it was found to significantly increase the rates of composite adverse outcome (RR 1.211 (95% CI, 1.029–1.425)) (Figure 3a), perinatal death (RR 1.551 (95% CI, 1.014–2.372)) (Figure 3b) and RDS (RR 1.218 (95% CI, 1.038–1.428)) (Figure 3c; Table 3).

Subgroup analysis was carried out for women treated with vaginal (Table S4) and systemic (Table S5) progesterone, but there were too few studies to obtain data on most of the outcomes.

## Triplet pregnancies

Two recent RCTs examined the administration of progesterone in asymptomatic women with triplets[25,26]. The pooled data did not show significant differences in the rates of composite adverse outcome, neonatal death, RDS, Grade 3–4 IVH, NEC or sepsis (Table 4).

 

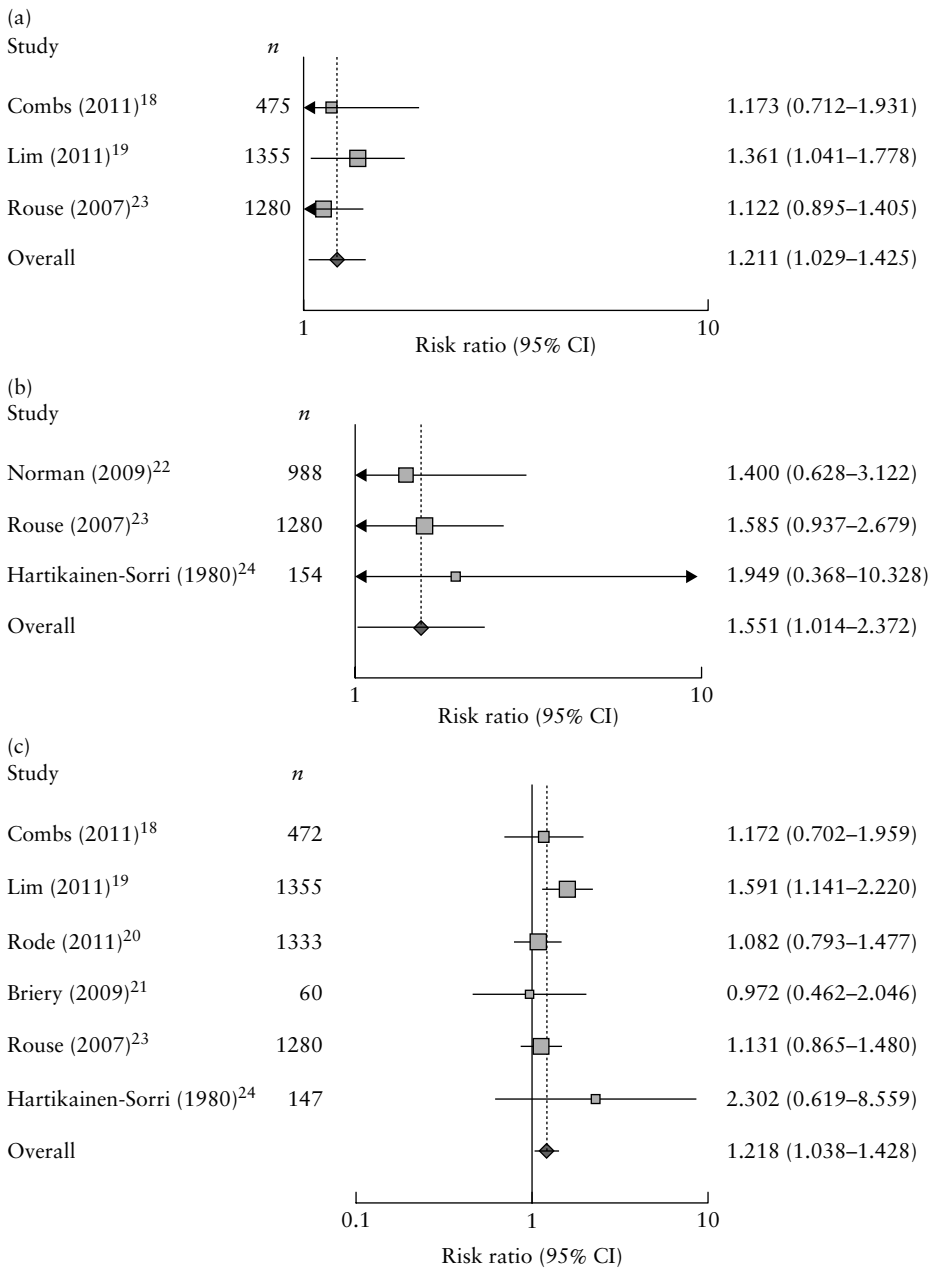


**Figure 3** Forest plot for composite adverse outcome (a), perinatal mortality (b) and respiratory distress syndrome (c) in twin pregnancies (all progestogens). In (a), all three studies used systematic (injectable) progestogen (17 alpha-hydroxyprogesterone caproate). Only the first author of each study is given.

## DISCUSSION

Preterm birth has always been a major cause of perinatal mortality and morbidity with long-term consequences[27–31]. However, it is only in the last decade that progesterone has been successfully shown to prevent preterm birth in singleton (but not in multiple) pregnancies at risk, either because of a short cervix[32] or previous history of preterm birth[2].

As the impact of progesterone treatment in the reduction of prematurity rates has been extensively quantified (level-1 evidence), in this meta-analysis we focused on the effects of progesterone on the actual perinatal outcomes of treated pregnancies. We found that prophylactic progesterone administration in singleton pregnancies at risk reduces rates of neonatal mortality, RDS, admission to the NICU and composite adverse outcome. In contrast, current data fail to support the presence of a beneficial effect of progesterone in multiple pregnancies and, in fact, the rates of perinatal death, RDS and composite adverse outcome may even be increased in twins.

In singleton pregnancies, we found that progesterone decreased the risk for neonatal mortality and common morbidity, when all data were pooled. We furthermore planned to run subgroup analyses based on the indication for progesterone treatment and the type of progestogen used. The design of available studies allowed for only two groupings, i.e. local (natural) progesterone for women

 

**Table 3** Perinatal outcomes in twin pregnancies in the study set (all progestogens)

| *Outcome* | *Studies* | *Subjects* (n) | *Controls* (n) | $I^2$ (%) | *Risk ratio (95% CI)* | *NNH* |
|---|---|---|---|---|---|---|
| Neonatal death | Combs *et al.*[18]<br>Lim *et al.*[19]<br>Rode *et al.*[20]<br>Briery *et al.*[21]<br>Norman *et al.*[22]<br>Rouse *et al.*[23] | 47/2832 | 43/2678 | 24.4 | 1.117 (0.662–1.884) | N/A |
| Perinatal death | Norman *et al.*[22]<br>Rouse *et al.*[23]<br>Hartikainen-Sorri *et al.*[24] | 52/1204 | 34/1218 | 0.0 | 1.551 (1.014–2.372) | 71 (36–1000) |
| RDS | Combs *et al.*[18]<br>Lim *et al.*[19]<br>Rode *et al.*[20]<br>Briery *et al.*[21]<br>Rouse *et al.*[23]<br>Hartikainen-Sorri *et al.*[24] | 312/2397 | 237/2250 | 0.0 | 1.218 (1.038–1.428) | 39 (23–125) |
| IVH Grade 3–4 | Combs *et al.*[18]<br>Lim *et al.*[19]<br>Rouse *et al.*[23] | 14/1629 | 8/1474 | 0.0 | 1.497 (0.625–3.583) | N/A |
| NEC | Combs *et al.*[18]<br>Lim *et al.*[19]<br>Rode *et al.*[20]<br>Briery *et al.*[21]<br>Hartikainen-Sorri *et al.*[24] | 12/2319 | 11/2176 | 0.0 | 1.124 (0.509–2.481) | N/A |
| Retinopathy | Combs *et al.*[18]<br>Rode *et al.*[20]<br>Rouse *et al.*[23] | 6/1604 | 4/1467 | 0.0 | 1.165 (0.352–3.857) | N/A |
| Sepsis | Combs *et al.*[18]<br>Lim *et al.*[19]<br>Rode *et al.*[20]<br>Rouse *et al.*[23] | 70/2291 | 56/2151 | 1.1 | 1.228 (0.861–1.749) | N/A |
| NICU admission | Lim *et al.*[19]<br>Rode *et al.*[20]<br>Norman *et al.*[22] | 627/1834 | 628/1842 | 81.2 | 1.053(0.846–1.312) | N/A |
| Composite adverse outcome | Combs *et al.*[18]<br>Lim *et al.*[19]<br>Rouse *et al.*[23] | 284/1633 | 216/1477 | 0.0 | 1.211 (1.029–1.425) | 31 (17–167) |
| Birth < 34 weeks | Combs *et al.*[18]<br>Rode *et al.*[20]<br>Norman *et al.*[22] | 143/741 | 123/676 | 57.4 | 1.101 (0.766–1.582) | N/A |
| Birth < 32 weeks | Combs *et al.*[18]<br>Rode *et al.*[20]<br>Rouse *et al.*[23] | 142/1155 | 117/1081 | 17.3 | 1.160 (0.890–1.513) | N/A |
| Birth < 28 weeks | Combs *et al.*[18]<br>Lim *et al.*[19]<br>Rode *et al.*[20]<br>Rouse *et al.*[23] | 57/1155 | 46/1167 | 0.0 | 1.244 (0.850–1.817) | N/A |

IVH, intraventricular hemorrhage; N/A, not applicable; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NNH, number needed to harm; RDS, respiratory distress syndrome.

with a short cervix and systemic (essentially 17 alpha-hydroxyprogesterone caproate (17-OHPC)) progestogen for women with previous preterm birth. For the latter pair, data could be pooled only for neonatal mortality and NICU admission; progesterone prevented one death per 24 women treated and one NICU admission per three women treated. For local progesterone in women with a short cervix, 17 women needed to be treated in order to prevent one perinatal death or complication. However, statistical significance was not reached for most of the other outcomes, although the direction of effect was usually in favor of progesterone. For the outcome of neonatal mortality, 829 infants per arm would be needed based on our pooled results, in order for the effect to reach significance. In addition, we were not able to reach any conclusions about the most clinically relevant question, i.e. whether local or systemic progesterone is better for women with a short cervix.

Studies and systematic reviews on twins have shown that progesterone fails to reduce the rate of preterm birth[33]. Two commonly cited hypotheses for this are (1) that the doses used in singleton pregnancies may be insufficient in twin pregnancies and (2) that the mechanisms underlying spontaneous preterm delivery in twins are different from those in singletons[18,21,33]. It is difficult to prove or discard these hypotheses but, at

 

**Table 4** Perinatal outcomes in triplet pregnancies in the study set

| *Outcome* | *Studies* | *Subjects* (n) | *Controls* (n) | $I^2$ (%) | *Risk ratio (95% CI)* | *NNT* |
|---|---|---|---|---|---|---|
| Neonatal death | Combs *et al.*[25] Caritis *et al.*[26] | 11/367 | 4/258 | 0.0 | 1.759 (0.567–5.458) | N/A |
| RDS | Combs *et al.*[25] Caritis *et al.*[26] | 109/367 | 78/258 | 57.8 | 0.940 (0.643–1.374) | N/A |
| IVH Grade 3–4 | Combs *et al.*[25] Caritis *et al.*[26] | 6/367 | 7/258 | 0.0 | 0.552 (0.182–1.674) | N/A |
| NEC | Combs *et al.*[25] Caritis *et al.*[26] | 10/366 | 8/258 | 35.7 | 0.736 (0.204–2.661) | N/A |
| Sepsis | Combs *et al.*[25] Caritis *et al.*[26] | 24/366 | 17/258 | 40.7 | 0.964 (0.385–2.411) | N/A |
| Composite adverse outcome | Combs *et al.*[25] Caritis *et al.*[26] | 141/380 | 96/258 | 0.0 | 0.984 (0.801–1.210) | N/A |
| Birth < 32 weeks | Combs *et al.*[25] Caritis *et al.*[26] | 48/127 | 32/88 | 75.8 | 0.949 (0.464–1.992) | N/A |
| Birth < 28 weeks | Combs *et al.*[25] Caritis *et al.*[26] | 16/127 | 9/88 | 0.0 | 1.149 (0.506–2.608) | N/A |

No studies on triplet pregnancies reported outcomes of perinatal death, retinopathy, admission to neonatal intensive care unit or birth < 34 weeks. IVH, intraventricular hemorrhage; N/A, not applicable; NEC, necrotizing enterocolitis; NNT, number needed to treat; RDS, respiratory distress syndrome.

least for the first hypothesis, maternal body mass did not have significant impact on the effectiveness of 17-OHPC in a study of singletons[34], and its half-life and plasma levels were not found to be affected by parity and the number of fetuses[35]. Therefore, a threshold effect for 17-OHPC has not been proposed so far, and we would expect it to have some effect on preterm labor rather than none. As for the second hypothesis, accepting that infection would be the main cause for preterm birth in singletons *vs* uterine stretch in twins, the effectiveness of progesterone would depend on its ability to reduce uterine excitability. Many[36,37], but not all[38], studies indicate that progesterone may indeed induce uterine quiescence through a multitude of mechanisms, from alteration of the electrical activity of the uterine muscle to alteration of gene expression and peripheral leukocyte activation.

Nevertheless, if the only problem was lack of effectiveness, increasing the dose or selectively treating women with twin pregnancy and a short cervix might be a viable alternative; however we found that progesterone may actually increase the risk of adverse outcome in twin pregnancies. According to our pooled results, there may be one additional case of perinatal death per 71 fetuses, one additional case of RDS per 39 fetuses and one additional case of composite adverse outcome (perinatal death or complication) per 31 fetuses treated. It is not clear why this happens, but it appears to be independent of the rates of preterm birth, which did not differ between treated women and controls for the cut-off of 34 weeks (pooled rates)[18,20,22], 32 weeks (pooled rates)[18–20,23] or 28 weeks (pooled rates)[18–20,23]. The relatively small number of triplets prevented our achieving statistically significant results in this group; however one should still be cautious as the study of Combs *et al.*[25] indicated an increased risk for fetal death in treated women.

A weakness of meta-analyses in general is that pooled studies cannot have identical inclusion criteria, as well as treatment and reporting protocols. This problem is addressed by subgroup and sensitivity analysis, at the cost of reducing the sample size. Indeed, when analyzing predefined groups, statistical significance was lost for many of the perinatal outcomes. However, in our case there was marked consistency in the results across studies for most outcomes, even before subgroup analysis. This was true even for the composite adverse outcome, despite its being defined differently in different studies. The lack of heterogeneity increases the strength of the results and may indicate that the number of fetuses is a more significant predictor of the effectiveness of progesterone treatment than the type of progesterone used (and the indication for treatment in singleton pregnancies). The outcome for which the highest variation was recorded was NICU admission, which may reflect the diversity in defining neonatal special care needs, together with different admission criteria across studies.

The next step after testing the effects of progesterone treatment on the rates of preterm birth and immediate perinatal complications is to examine its impact on the longer-term neurodevelopment of treated children. At the moment there has only been one study assessing neurodevelopment in twins up to 18 months of age; the authors report almost identical results in terms of Ages and Stages Questionnaire mean scores and rates of low scores[20].

Based on current data, it appears that progesterone treatment in women with a singleton pregnancy at risk succeeds in reducing the rates of neonatal mortality, some of the common perinatal complications and composite adverse outcome (perinatal death or complications), in contrast to the case with twins, in which it may even exert an adverse effect.

Among ongoing studies, one will address the impact of cervical length screening and progesterone treatment for length $\leq 30$ mm on perinatal outcomes and cost[39], an individual patient data meta-analysis in twin pregnancies will focus on the effect of progesterone treatment on perinatal mortality and morbidity[40], while another prospective follow-up study will evaluate the differences in developmental outcomes of children aged 23–25 months, born to mothers who participated in a trial of the efficacy of 17-OHPC[41].

## REFERENCES


1. Celik E, To M, Gajewska K, Smith GC, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Cervical length and obstetric history predict spontaneous preterm birth: development and validation of a model to provide individualized risk assessment. *Ultrasound Obstet Gynecol* 2008; **31**: 549–554.
2. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, Spong CY, Hauth JC, Miodovnik M, Varner MW, Leveno KJ, Caritis SN, Iams JD, Wapner RJ, Conway D, O'Sullivan MJ, Carpenter M, Mercer B, Ramin SM, Thorp JM, Peaceman AM, Gabbe S; 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**: 2379–2385.
3. 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**: 462–469.
4. Campbell S. Universal cervical-length screening and vaginal progesterone prevents early preterm births, reduces neonatal morbidity and is cost saving: doing nothing is no longer an option. *Ultrasound Obstet Gynecol* 2011; **38**: 1–9.
5. Norwitz ER, Caughey AB. Progesterone supplementation and the prevention of preterm birth. *Rev Obstet Gynecol* 2011; **4**: 60–72.
6. Elizur SE, Tulandi T. Drugs in infertility and fetal safety. *Fertil Steril* 2008; **89**: 1595–1602.
7. FDA. FDA statement on Makena. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm249025htm) 2011; Assessed 25/03/2012.
8. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med* 2010; **7**: e1000251.
9. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928.
10. Barfield WD; Committee on Fetus and Newborn. Standard terminology for fetal, infant, and perinatal deaths. *Pediatrics* 2011; **128**: 177–181.
11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
12. Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, Vijayaraghavan J, Trivedi Y, Soma-Pillay P, Sambarey P, Dayal A, Potapov V, O'Brien J, Astakhov V, Yuzko O, Kinzler W, Dattel B, Sehdev H, Mazheika L, Manchulenko D, Gervasi MT, Sullivan L, Conde-Agudelo A, Phillips JA, Creasy GW; PREGNANT Trial. 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.
13. 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**: 423–429.
14. 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.
15. 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**: 40–43.
16. DeFranco EA, O'Brien JM, Adair CD, Lewis DF, Hall DR, Fusey S, Soma-Pillay P, Porter K, How H, Schakis R, Eller D, Trivedi Y, Vanburen G, Khandelwal M, Trofatter K, Vidyadhari D, Vijayaraghavan J, Weeks J, Dattel B, Newton E, Chazotte C, Valenzuela G, Calda P, Bsharat M, Creasy GW. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2007; **30**: 697–705.
17. O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, Soma-Pillay P, Porter K, How H, Schackis R, Eller D, Trivedi Y, Vanburen G, Khandelwal M, Trofatter K, Vidyadhari D, Vijayaraghavan J, Weeks J, Dattel B, Newton E, Chazotte C, Valenzuela G, Calda P, Bsharat M, Creasy GW. 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**: 687–696.
18. Combs CA, Garite T, Maurel K, Das A, Porto M; Obstetrix Collaborative Research Network. 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial. *Am J Obstet Gynecol* 2011; **204**: 221.e1–8.
19. Lim AC, Schuit E, Bloemenkamp K, Bernardus RE, Duvekot JJ, Erwich JJ, van Eyck J, Groenwold RH, Hasaart TH, Hummel P, Kars MM, Kwee A, van Oirschot CM, van Pampus MG, Papatsonis D, Porath MM, Spaanderman ME, Willekes C, Wilpshaar J, Mol BW, Bruinse HW. 17alpha-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlled trial. *Obstet Gynecol* 2011; **118**: 513–520.
20. Rode L, Klein K, Nicolaides KH, Krampl-Bettelheim E, Tabor A; PREDICT Group. 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**: 272–280.
21. Briery CM, Veillon EW, Klauser CK, Martin RW, Chauhan SP, Magann EF, Morrison JC. Progesterone does not prevent preterm births in women with twins. *South Med J* 2009; **102**: 900–904.
22. Norman JE, Mackenzie F, Owen P, Mactier H, Hanretty K, Cooper S, Calder A, Mires G, Danielian P, Sturgiss S, MacLennan G, Tydeman G, Thornton S, Martin B, Thornton JG, Neilson JP, Norrie J. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. *Lancet* 2009; **373**: 2034–2040.
23. Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, Varner M, Malone F, Iams JD, Mercer BM, Thorp J, Sorokin Y, Carpenter M, Lo J, Ramin S, Harper M, Anderson G; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007; **357**: 454–461.
24. Hartikainen-Sorri AL, Kauppila A, Tuimala R. Inefficacy of 17 alpha-hydroxyprogesterone caproate in the prevention of prematurity in twin pregnancy. *Obstet Gynecol* 1980; **56**: 692–695.
25. Combs CA, Garite T, Maurel K, Das A, Porto M; Obstetrix Collaborative Research Network. 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.


 

26. Caritis SN, Rouse DJ, Peaceman AM, Sciscione A, Momirova V, Spong CY, Iams JD, Wapner RJ, Varner M, Carpenter M, Lo J, Thorp J, Mercer BM, Sorokin Y, Harper M, Ramin S, Anderson G; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Maternal-Fetal Medicine Units Network (MFMU). Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. *Obstet Gynecol* 2009; **113**: 285–292.
27. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics* 2000; **106**: 659–671.
28. Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med* 2005; **352**: 9–19.
29. Larroque B, Bréart G, Kaminski M, Dehan M, André M, Burguet A, Grandjean H, Ledésert B, Lévêque C, Maillard F, Matis J, Rozé JC, Truffert P; Epipage study group. Survival of very preterm infants: Epipage, a population based cohort study. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: F139–144.
30. Ancel PY, Livinec F, Larroque B, Marret S, Arnaud C, Pierrat V, Dehan M, N'Guyen S, Escande B, Burguet A, Thiriez G, Picaud JC, André M, Bréart G, Kaminski M; EPIPAGE Study Group. Cerebral palsy among very preterm children in relation to gestational age and neonatal ultrasound abnormalities: the EPIPAGE cohort study. *Pediatrics* 2006; **117**: 828–835.
31. Larroque B, Ancel PY, Marret S, Marchand L, André M, Arnaud C, Pierrat V, Rozé JC, Messer J, Thiriez G, Burguet A, Picaud JC, Bréart G, Kaminski M; EPIPAGE Study group. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet* 2008; **371**: 813–820.
32. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration 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.
33. Klein K, Rode L, Nicolaides KH, Krampl-Bettelheim E, Tabor A. Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis. *Ultrasound Obstet Gynecol* 2011; **38**: 281–287.
34. Ventolini G, Duke J, Po W, Barhan S, Rhea D, Desch C, Istwan N, Stanziano G. The impact of maternal body mass on the effectiveness of 17 alpha-hydroxyprogesterone caproate. *J Reprod Med* 2008; **53**: 667–671.
35. Caritis SN, Sharma S, Venkataramanan R, Rouse DJ, Peaceman AM, Sciscione A, Spong CY, Varner MW, Malone FD, Iams JD, Mercer BM, Thorp JM Jr, Sorokin Y, Carpenter M, Lo J, Ramin S, Harper M; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Pharmacokinetics of 17-hydroxyprogesterone caproate in multifetal gestation. *Am J Obstet Gynecol* 2011; **205**: 40.e1–8.
36. Soloff MS, Jeng YJ, Izban MG, Sinha M, Luxon BA, Stamnes SJ, England SK. Effects of progesterone treatment on expression of genes involved in uterine quiescence. *Reprod Sci* 2011; **18**: 781–797.
37. Norman JE, Yuan M, Anderson L, Howie F, Harold G, Young A, Jordan F, McInnes I, Harnett MM. Effect of prolonged in vivo administration of progesterone in pregnancy on myometrial gene expression, peripheral blood leukocyte activation, and circulating steroid hormone levels. *Reprod Sci* 2011; **18**: 435–446.
38. Lei K, Chen L, Cryar BJ, Hua R, Sooranna SR, Brosens JJ, Bennett PR, Johnson MR. Uterine stretch and progesterone action. *J Clin Endocrinol Metab* 2011; **96**: E1013–1024.
39. van Os MA, van der Ven JA, Kleinrouweler CE, Pajkrt E, de Miranda E, van Wassenaer A, Porath M, Bossuyt PM, Bloemenkamp KW, Willekes C, Woiski M, Oudijk MA, Bilardo KM, Sikkema MJ, Duvekot JJ, Veersema D, Laudy J, Kuiper P, de Groot CJ, Mol BW, Haak MC. Preventing preterm birth with progesterone: costs and effects of screening low risk women with a singleton pregnancy for short cervical length, the Triple P study. *BMC Pregnancy Childbirth* 2011; **11**: 77.
40. Schuit E, Stock S, Groenwold RH, Maurel K, Combs CA, Garite T, Spong CY, Thom EA, Rouse DJ, Caritis SN, Saade GR, Zachary JM, Norman JE, Rode L, Klein K, Tabor A, Cetingöz E, Morrison JC, Magann EF, Briery CM, Serra V, Perales A, Meseguer J, Nassar AH, Lim AC, Moons KG, Kwee A, Mol BW. Progestogens to prevent preterm birth in twin pregnancies: an individual participant data meta-analysis of randomized trials. *BMC Pregnancy Childbirth* 2012; **12**: 13.
41. KV Pharmaceutical Company R-M. A Prospective, Non Intervention Follow-Up Study of Children Aged 23 to 25 Months, Born to Mothers Who Received Hydroxyprogesterone Caproate Injection, 250 mg/mL, or Vehicle for Prevention of Preterm Birth. In: Clinical Trials gov [Internet] Bethesda (MD): National Library of Medicine (US) 2000-(cited 2012 Mar 25) Available from: http://clinicaltrialsgov/ct2/show/NCT01146990 NLM identifier: NCT01146990 2012.


## SUPPORTING INFORMATION ON THE INTERNET

**Appendix S1** and **Tables S1–S5** may be found in the online version of this article.

This article has been selected for Journal Club.

A slide presentation, prepared by Dr Aly Youssef, one of UOG's Editors for Trainees, is available online.