Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis

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Background In twin pregnancies, the rates of adverse perinatal outcome and subsequent long-term morbidity are substantial, and mainly result from preterm birth (PTB).

Objectives To assess the effectiveness of progestogen treatment in the prevention of neonatal morbidity or PTB in twin pregnancies using individual participant data meta-analysis (IPDMA).

Search strategy We searched international scientific databases, trial registration websites, and references of identified articles.

Selection criteria Randomised clinical trials (RCTs) of 17–hydroxyprogesterone caproate (17Pc) or vaginally administered natural progesterone, compared with placebo or no treatment.

Data collection and analysis Investigators of identified RCTs were asked to share their IPD. The primary outcome was a composite of perinatal mortality and severe neonatal morbidity. Prespecified subgroup analyses were performed for chorionicity, cervical length, and prior spontaneous PTB.

Main results Thirteen trials included 3768 women and their 7536 babies. Neither 17Pc nor vaginal progesterone reduced the incidence of adverse perinatal outcome (17Pc relative risk, RR 1.1; 95% confidence interval, 95% CI 0.97–1.4, vaginal progesterone RR 0.97; 95% CI 0.77–1.2). In a subgroup of women with a cervical length of ≤25 mm, vaginal progesterone reduced adverse perinatal outcome when cervical length was measured at randomisation (15/56 versus 22/60; RR 0.57; 95% CI 0.47–0.70) or before 24 weeks of gestation (14/52 versus 21/56; RR 0.56; 95% CI 0.42–0.75).

Authors' conclusions In unselected women with an uncomplicated twin gestation, treatment with progestogens (intramuscular 17Pc or vaginal natural progesterone) does not improve perinatal

outcome. Vaginal progesterone may be effective in the reduction of adverse perinatal outcome in women with a cervical length of ≤25 mm; however, further research is warranted to confirm this finding.

Introduction

In Europe and the USA about 3% of all pregnancies are twin pregnancies.[1,2] In twin pregnancies, the rates of stillbirth, neonatal death, preterm birth, (very) low birthweight, and subsequent long-term morbidity are substantially higher than in singletons.[3] Preterm birth is the principal factor contributing to these adverse outcomes, with 50% of twin pregnancies delivering before 37 weeks of gestation and 9% delivering before 32 weeks of gestation.[4] Improving outcomes in twin pregnancies is a goal in modern obstetrics, but as yet no interventions have been proven to be of benefit in this group.

Randomised clinical trials (RCTs) have shown that antenatal progestogen therapy (vaginally administered natural progesterone and semi-synthetic progestogens such as intramuscular 17–hydroxyprogesterone caproate, 17Pc) reduces the rate of preterm delivery in women with singleton pregnancies who are at high risk because of preterm birth in a previous pregnancy,[5–8] or because of a short cervix, measured sonographically, in the current pregnancy.[9–11]

There has been extensive international interest in determining whether the benefits of progestogens extend to twins: that is, whether these agents reduce the rate of preterm birth and thereby reduce perinatal morbidity. Two aggregated data meta-analyses (ADMA) have examined published trials of progestogens in twin pregnancies. One of these did not differentiate between 17Pc and vaginal progesterone.[12] The other had too little information to investigate relevant subgroups.[13] This is a common limitation of ADMA. Individual participant data meta-analysis (IPDMA) is a more robust design that more easily allows for subgroup analysis.[14,15] A recent IPDMA focused on women with a short cervix and found that vaginal progesterone reduced the rate of early preterm birth and the rate of composite neonatal morbidity/mortality in singleton pregnancies.[11] Based on the small number of twins in that analysis, there was a trend towards reduction of early pre-

term birth with progesterone and a significant reduction of neonatal morbidity/mortality. That meta-analysis did not include any studies with 17Pc. Moreover, none of the three previous meta-analyses of the effect of progestogens in twins included all published studies.[11–13]

The aim of the current study was to perform an IPDMA to investigate the effects of progestogens in women with a twin pregnancy and in prespecified subgroups. Analysis was performed separately for intramuscular 17Pc and vaginally administered natural progesterone.

Methods

The reporting of the IPDMA was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] The study was conducted based on a previously published protocol.[17]

Trial search and selection strategy

Trials were identified by searching the electronic databases Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, Embase, ClinicalTrials.gov, and controlled-trials.com (all from inception until 1 March 2013). We used the following search strategy: preterm birth AND (progesterone OR 17–hydroxyprogesterone caproate OR progestogen OR 17P) AND (pregnancy multiple OR pregnancy multifetal OR pregnancy twin) AND (randomised controlled trial OR randomized controlled trial OR randomised trial OR randomized trial) AND human. The principal investigators, regarded as experts in their field, were contacted to identify further studies. No language restrictions were used.

We included RCTs that investigated the effectiveness of vaginally administered progesterone or intramuscular 17Pc, each versus placebo or non-intervention in the second or third trimester in women with a twin pregnancy, in the reduction of either preterm birth or adverse perinatal outcome. Trials that investigated the effectiveness in specific subgroups (e.g. women with a short cervix) were

also eligible for inclusion. Two investigators (ES and SS) independently reviewed the identified papers for eligibility. Any disagreement was solved by a third reviewer (BWJM).

The risk of bias was assessed by two independent reviewers (ES and SS) using a risk-of-bias tool developed by the Cochrane collaboration, which contains specific items that assess random sequence allocation bias, allocation concealment, incomplete outcome data, selective reporting, other bias, blinding of participants and personnel, and blinding of outcome assessment.[18] According to the Cochrane Handbook, each item of bias was scored as low, high, or unclear. All the items were scored twice, once based on the published paper or protocol and once by the principal investigator of the included study.

The principal investigators of all eligible RCTs were contacted to participate and were requested to provide individual participant data. The principal investigators had the choice to either complete an EXCEL or SPSS data sheet or to send their data accompanied by a document clearly stating the definitions used. The data collected included relevant baseline characteristics and outcomes of interest, described in the following subsection. Data quality was assessed by comparison of the numbers published and the data shared by the principal investigator. In case of discrepancies the principal investigator was contacted and corrections were made if necessary. If any questions were raised, the authors were contacted for clarification.

Outcomes and subgroups

The primary outcome of this IPDMA was a composite of adverse perinatal outcome and was defined differently for 17Pc and vaginal progesterone, based on the availability of different components of perinatal outcome in the individual studies. In the 17Pc analysis, the composite outcome included perinatal death, defined as intrauterine fetal death (IUFD) at any gestational age or neonatal death before discharge from the hospital, or significant neonatal morbidity, defined as one or more of the following: respiratory distress syndrome (RDS), requiring oxygen for ≥24 hours; bronchopulmonary dysplasia (BPD); intraventricular haemorrhage (IVH), grades III or IV; necrotising enterocolitis (NEC), grade II or more; or culture-proven sepsis. In the vaginal progestogen analysis the composite outcome included perinatal death, RDS, IVH, and NEC. Secondary outcomes included the individual neonatal morbidities listed above, IUFD, or preterm birth at <37, <35, <32, and <28 weeks of gestation, as well as time to delivery or death.

Secondary objectives were to assess the effect of progestogens in different prespecified subgroups, which were based on the results of included studies or previous studies.

1 Chorionicity, as assessed by ultrasonography and defined as mono- or dichorionic.[19,20]

2 Cervical length at randomisation of ≤25 mm (yes/no).[9,11]

3 Cervical length before 24 weeks of gestation ≤25 mm (yes/no).[9,11]

4 Prior spontaneous preterm birth <37 weeks of gestation (yes/no).[5–8]

The subgroup effects were investigated for the primary outcome, adverse perinatal outcome, and time to delivery or death. Dosage of vaginal progesterone was not prespecified as a separate subgroup analysis, as there is sufficient evidence that dosage does not affect results in twin pregnancies.[21,22]

Analysis

All analyses were performed on an intention-to-treat basis for 17Pc and vaginal progesterone, as compared with control, separately.

The effectiveness of progestogen treatment was estimated using mixed models for binomial outcomes with a log link, thus resulting in risk ratios (RRs) with 95% confidence intervals (95% CIs). A random intercept (to account for differences in prevalence between studies) and a random slope (to account for differences in treatment effect between studies) was included in these models. In the analysis on child level, we incorporated a compound symmetric residual error variance to account for the clustering of children with one shared mother.[23]

Heterogeneity across trials was assessed using the I^2 measure and the values were interpreted as follows: 0% indicates no observed heterogeneity; 25, 50, and 75% indicate low, moderate, and high heterogeneity, respectively.[24] The number needed to treat (NNT) calculation was planned when an association was found to be statistically significant.

As the interest of the effectiveness of progestogen is mainly focused on preterm birth and not necessarily on overall gestational age at delivery, we applied a two-part model to estimate the effect of progestogen on the combined end point of preterm birth (i.e. birth before 37, 35, 32, and 28 weeks of gestation), and gestational age at delivery for those who are born preterm.[25] A two-part model combines the probability of preterm birth (estimated by a mixed log-binomial regression model) with the median gestational at delivery in those with a preterm birth, estimated using a mixed linear quantile regression model.[26] Confidence intervals were constructed with bootstrapping (10 000 samples).

Subgroup effects were investigated using an interaction term between the subgroup of interest and treatment in the regression model. When the interaction was found to be statistically significant ($P < 0.05$), a stratified analysis was performed to investigate the effect of progestogen treatment in different strata of the subgroups.

Two *post-hoc* sensitivity analyses were performed: one in which we excluded all non-blinded studies, and one in which studies that included <100 participants were excluded. Statistical analyses were performed using R 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute Inc., Cary, NC, USA, 2010).

Results

Included studies

Thirty-nine studies were identified through database searching (Figure 1). Thirteen studies met all of the inclusion criteria (Figure 1; Table 1; Appendix S1).[5,9,19,20,22,27–34] The other studies identified from the literature search (*n* = 20) did not investigate twins, described a study protocol, or were not expecting to complete the study within the next year.[35] Data sets containing IPD were obtained for all 13 RCTs. All studies had institutional review board approval and informed consent from all participants.

The studies randomised women to either 17Pc[20,28–31,33] or vaginal progesterone,[5,9,19,22,27,32,34] each versus placebo or non-intervention. The characteristics of the 17Pc and vaginal progesterone included in this IPDMA are shown in Table 1. Eleven studies were placebo-controlled double-blind RCTs,[5,9,19,20,22,28–32,34] one was an open-label trial of 17Pc versus no treatment,[33] and one was a placebo-controlled trial in which participants were not blinded to their treatment (Figure 2).[27]

In general, all studies enrolled twin pregnancies with a gestational age between 16^{+0} and 23^{+6} weeks of gestation at randomisation. Several studies had additional inclusion criteria: three studies included only women with a dichorionic twin pregnancy,[22,27,29] one vaginal progesterone study included women with a cervical length of <15 mm at 20–25 weeks of gestation,[9] and one 17Pc study included women between 20 and 32 weeks of gestation with a cervical length of ≤25 mm.[33] Two trials allowed randomisation of women who had a prophylactic (history-indicated) cerclage *in situ*.[29,32] The exclusion criteria of the studies were similar with most of the studies eliminating twin pregnancies with suspected major fetal abnormalities, suspected twin-to-twin transfusion, serious maternal medical disease, cerclage in place or planned, contraindication to progestogens, or twin gestations that were the result of intentional fetal reduction
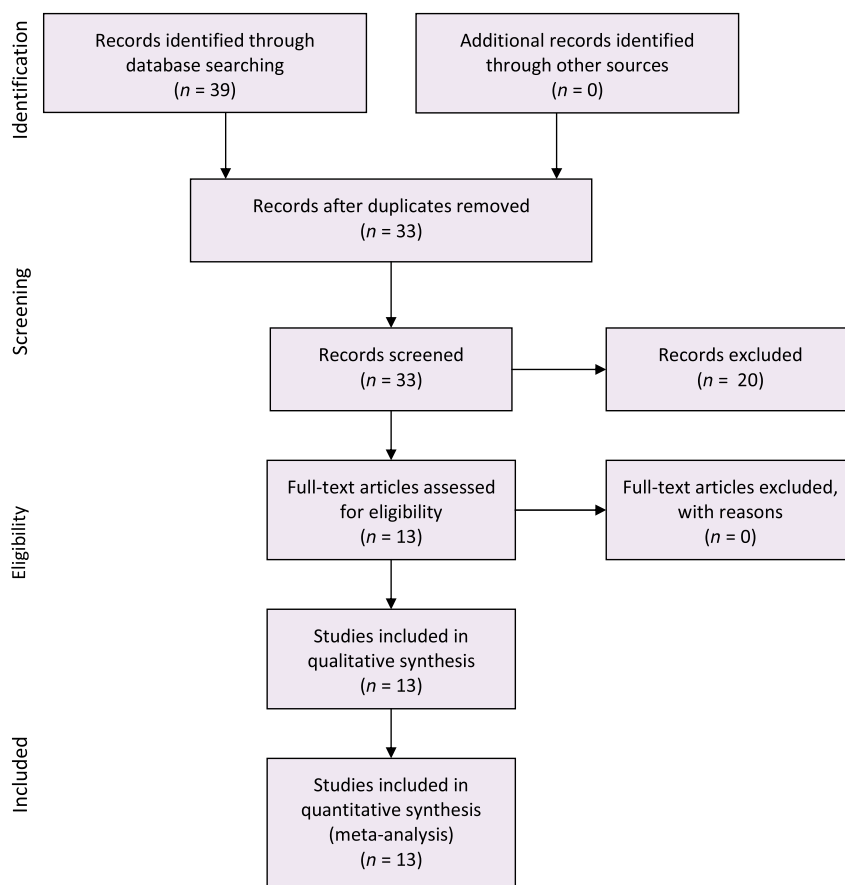

Figure 1. Flow of study identification.

Table 1. Overview of the studies investigating progestogen treatment included in the IPDMA

Type of progestogen	Study	Type of study	n	Inclusion criteria	Dosage
17Pc, weekly	Rouse[20]	Placebo-controlled double-blind RCT, multicentre	661	Women carrying twins with a gestational age of 16^{+0}–20^{+3} weeks	250 mg
	Lim[30]	Placebo-controlled double-blind RCT, multicentre	650	Women with a twin pregnancy and a gestational age between 15 and 19 weeks, with chorionicity assessed by ultrasonography	250 mg
	Nassar[31]	Placebo-controlled double-blind RCT, single centre	286	Viable twin pregnancy between 16 and 20 weeks of gestation	250 mg
	Combs[29]	Placebo-controlled double-blind RCT, multicentre	240	Women with a dichorionic diamniotic twin pregnancy at 15–23 weeks of gestation with an ultrasound examination showing no major fetal anomalies	250 mg
	Senat[33]	Open-label RCT, single centre	165	Women carrying twins with cervical length of ≤25 mm between 20 and 32 weeks of gestation	500 mg
	Briery[28]	Placebo-controlled double-blind RCT, single centre	30	Twin pregnancy between 20 and 30 weeks of gestation with intact membranes	250 mg
Vaginal, daily	Rode[32]	Placebo-controlled double-blind RCT, multicentre	677	Women with a live, diamniotic twin pregnancy and with chorionicity assessed by ultrasound before 16 weeks of gestation	200–mg pessaries
	Norman[19]	Placebo-controlled double-blind RCT, multicentre	500	Women carrying twins with gestation and chorionicity established by scan before 20 weeks of gestation	90 mg of gel
	Serra[22]	Placebo-controlled double-blind RCT, multicentre	290	Dichorionic diamniotic twin pregnant women	1× or 2× 200–mg pessaries
	Aboulghar[27]	Placebo-controlled RCT, single centre	92	Nulliparous women who conceived after IVF or ICSI with a dichorionic twin between 18 and 24 weeks of gestation	2× 200–mg suppositories
	Wood[34]	Placebo-controlled double-blind RCT, single centre	81	Women with a multifetal pregnancy between 16^{+0} and 20^{+6} weeks of gestation and ultrasound-confirmed minimum of two live fetuses	90 mg of gel
	Cetingoz[5]	Placebo-controlled double-blind RCT, single centre	67	Women carrying twins	100–mg suppositories
	Fonseca[9]	Placebo-controlled double-blind RCT, multicentre	24	Women carrying twins who were undergoing routine ultrasonography at 20–25 weeks of gestation and had a cervical length of <15 mm	200–mg capsules

ICSI, intracytoplasmatic sperm injection; IVF, *in vitro* fertilisation.

(Appendix S1). Several studies used stratified randomisation (e.g. by centre,[19,20,29,32] chorionicity,[19,30,32] or parity[30]). One study was excluded from the analysis of the primary outcome, i.e. adverse perinatal outcome (but not the other outcomes), because only two components of the composite were registered.[27] The availability of other data of interest in the individual studies is listed in Appendix S2.

One study found that progestogens (vaginal progesterone) significantly reduced the rate of preterm delivery before 37 weeks of gestation,[5] and one study found that that progestogens (17Pc) reduced composite neonatal morbidity,[31] results that were not repeated in the other 11 trials. Four out of six 17Pc studies and one out of seven vaginal progesterone studies showed that progestogens were

	random sequence allocation bias (selection bias)	allocation concealment (selection bias)	incomplete outcome data (attrition bias)	selective reporting (reporting bias)	other bias	blinding of participants and personnel (performance bias)	blinding of outcome assessment (detection bias)	remark
Rouse 2007	+	+	+	+	+	+	+	
Lim 2011	+	+	+	+	+	+	+	
Nassar 2014	+	+	+[3]	+[3]	+[3]	+	+	1
Combs 2011	+	+	+	+	+	+	+	2
Senat 2013	+	+	+	+	+	–	+	2
Briery 2009	+	+	+[3]	+	+	+	+	
Rode 2011	+	+	+	+	+	+	+	
Norman 2009	+	+	+	+	+	+	+	
Serra 2012	+	+	+	+	+	+	+	
Aboulghar 2012	+	+	+	–	+[3]	–	+	2,4
Wood 2012	+	+	+	+	+	+	+	
Cetingoz 2011	+	+	+	+	+[3]	+	+	
Fonseca 2007	+[3]	+	+	+	+[3]	+	+	

[1] study not yet published, but judgment based on study protocol

[2] participants not blinded for allocation

[3] unclear from paper/protocol but risk of bias judged as low by the principal investigator

[4] neonatal morbidity not presented

Figure 2. Risk of bias for each included study.

associated with a non-significant increase in preterm births.[19,20,28–30] Furthermore, one (17Pc) study found a significant decrease in median gestational age at delivery,[29] and two (vaginal progesterone) studies showed a non-significant reduction in preterm birth in the progestogen group.[9,32] In addition, two studies (one 17Pc, one vaginal progesterone) showed a non-significant increase in IUFD.[19,20]

The overall quality of the included studies was good. A summary of the risk of bias assessment can be found in Figure 2. Selective outcome reporting was assessed but not considered an issue because IPDMA relies on IPD rather than reported outcomes.

In this IPDMA we included individual data of 3768 women with a twin pregnancy, of which 2006 women were allocated to progestogen treatment (1089 to 17Pc and 917 to vaginal progesterone) and 1762 were allocated to control. The baseline characteristics of the women administered 17Pc or placebo and vaginal progesterone or placebo are presented separately in Table 2. Baseline characteristics for the progestogen-treatment groups and their control groups were comparable, although assisted conception occurred more often in those treated with 17Pc, whereas in the vaginal progesterone studies women in the control group drank more alcohol.

17Pc

Overall effects of 17Pc treatment

The overall effects of treatment with 17Pc are depicted in Appendix S5. The primary outcome, i.e. adverse perinatal outcome, occurred in 423 (20%) children in the 17Pc group and 318 (17%) children in the control group (RR 1.2; 95% CI 0.87–1.5). The rates of the individual components of the composite outcome did not differ significantly between the two groups, although it should be noted that there was a trend towards an increased risk for the majority of adverse perinatal and neonatal outcomes in those treated with 17Pc.

For IUFD or delivery before 37, 35, 32, and 28 weeks of gestation, and the other secondary outcomes no substantial differences were found between 17Pc treatment and control. All results were similar when corrected for stratified randomisation.

Heterogeneity amongst studies was low for retinopathy of prematurity (ROP), moderate for RDS and a delivery or death before 35 weeks of gestation, and moderate to high for adverse perinatal outcome, perinatal death, sepsis, and delivery or death before 32 weeks of gestation

Table 2. Baseline characteristics of the participants of the IPDMA according to type of progestogen and allocation

Characteristics	17Pc				Vaginal progesterone			
	17Pc n = 1089	Control n = 944	Available from how many studies	Available for (%)	Vaginal progesterone n = 917	Control n = 818	Available from how many studies	Available for (%)
Maternal age: years (±SD)	31.6 (5.6)	31.4 (5.8)	5/6	1976 (97)	32.2 (5.0)	32.2 (5.0)	7/7	1714 (99)
Body mass index: kg/m² (±SD)	25.8 (6.1)	25.7 (6.3)	4/6	1688 (83)	24.6 (4.8)	24.6 (5.3)	4/7	1033 (60)
Gestational age at randomisation: weeks (±SD)	19.0 (3.0)	19.0 (2.9)	6/6	1977 (97)	20.1 (3.1)	20.6 (2.7)	7/7	1720 (99)
Cervical length at randomisation: cm (±SD)*	2.3 (1.5)	2.5 (1.4)	3/6	258 (13)	3.8 (0.9)	3.7 (0.9)	5/7	907 (52)
Cervical length before 24 weeks of gestation: cm (±SD)**	4.1 (1.1)	4.2 (1.1)	4/6	552 (27)	3.9 (0.8)	3.8 (0.9)	5/7	890 (51)
Nulliparous: n (%)	526 (48)	449 (48)	6/6	2032 (100)	549 (60)	488 (60)	7/7	1729 (100)
Race			5/6	1841 (91)			5/7	514 (30)
Black	106 (11)	103 (12)			3 (1)	3 (1)		
White	773 (78)	665 (78)			279 (90)	185 (90)		
Asian	44 (4)	20 (2)			4 (1)	7 (3)		
Other	69 (7)	61 (7)			23 (7)	10 (5)		
Smoking: n (%)	95 (9)	80 (9)	6/6	2016 (99)	117 (14)	88 (12)	6/7	1617 (93)
Alcohol: n (%)	65 (7)	45 (5)	4/6	1817 (89)	179 (37)	177 (48)	3/7	854 (49)
Assisted conception: n (%)	493 (50)	355 (42)	4/6	1831 (90)	366 (62)	311 (59)	5/7	1120 (65)
Monochorionic twin: n (%)	139 (14)	120 (14)	5/6	1844 (91)	97 (11)	111 (15)	6/7	1622 (93)
Previous preterm delivery: n (%)	84 (8)	87 (10)	6/6	1933 (95)	24 (3)	21 (3)	5/7	1630 (94)

Data are presented as means ± standard deviations (SDs) or n (%). All numbers are based on the data as shared by the individual research groups.

*Cervical length measurement is on the same day or before the moment of randomisation. Number of cervical length measurements at or before randomisation in the 17Pc studies of Lim, Senat, and Briery was 91, 165, and 2, respectively, and in the vaginal progesterone studies of Cetingoz, Serra, Rode, Fonseca, and Aboulgar was 67, 284, 445, 24, and 87, respectively.

**The number of cervical length measurements before 24 weeks of gestation in the 17Pc studies of Lim, Combs, Senat, and Briery was 513, 20, 17, and 2, respectively, and in the vaginal progesterone studies of Cetingoz, Serra, Rode, Fonseca, and Aboulgar was 67, 284, 445, 13, and 81, respectively.

(Appendix S5). For all other outcomes no heterogeneity was observed.

There was one study in which participants and clinicians were not blinded to treatment.[33] Exclusion of all participants from this particular trial did not lead to different results (data not shown). The second sensitivity analysis focused on the analysis of IPD from studies that included 100+ participants,[20,29–31,33] and showed similar results to the main IPDMA (data not shown).

Subgroup analyses in 17Pc treatment
17–Hydroxyprogesterone caproate (17Pc) had a statistically significant interaction with the following subgroups: women with a cervical length at randomisation of ≤25 mm ($P = 0.0098$), and those with a cervical length of ≤25 mm before 24 weeks of gestation ($P = 0.0027$). Stratified subgroup analyses for adverse perinatal outcome according to cervical length indicated no benefit of 17Pc over control in women with a cervical length of ≤25 mm, either at randomisation or before 24 weeks of gestation (Appendix S3). Instead, 17Pc led to an increase in adverse perinatal outcome in women with a cervical length of >25 mm at randomisation (14/78 versus 8/88; RR 2.1; 95% CI 1.9–2.2) and before 24 weeks of gestation (82/518 versus 60/512; RR 1.4; 95% CI 1.26–1.5). Cervical length measurements were available from four studies.[28–30,33] 17Pc did not have a significant effect on adverse perinatal outcome, time to delivery, or death when subgroup analysis was performed according to chorionicity ($P = 0.32$) and prior spontaneous preterm birth <37 weeks of gestation ($P = 0.52$).

Vaginal progesterone

Overall effects of vaginal progesterone treatment
The overall effects of vaginal progesterone treatment are shown in Appendix S6. Adverse perinatal outcome occurred in 219 (13%) children in the vaginal progesterone group and in 201 (13%) children in the control group (RR 0.96; 95% CI 0.83–1.1). The rates of the individual components of the composite outcome did not differ significantly between both groups. Women treated with vaginal progesterone had a lower gestational age at delivery when delivered before 28 weeks of gestation than those in the control group (median difference −1.6 weeks of gestation; 95% CI −2.7 to −0.43 weeks of gestation); however, the combined end point based on the proportion of delivery or death before 28 weeks of gestation and the difference in gestational age at delivery or death for those who were preterm was similar for the two groups (median difference 0.049; 95% CI −0.034 to 0.10). For delivery before 37, 35, 32, and 28 weeks of gestation, and the other secondary outcomes, no substantial differences were found between vaginal progesterone treatment and control. All

results were similar when corrected for stratified randomisation.

Heterogeneity amongst studies was low for BPD, and for delivery or death before 37 and 32 weeks of gestation (Appendix S6). For all other outcomes no heterogeneity was observed.

There was one study in which participants were not blinded to the treatment.[27] Exclusion of the participants of this study did not lead to different results (data not shown). An analysis on IPD from studies that included 100+ participants only did not alter the presented results (data not shown).[19,22,32]

Subgroup analyses in vaginal progesterone treatment
Vaginal progesterone had a statistically significant interaction with the following subgroups: women with a cervical length of ≤25 mm at randomisation ($P = 0.0060$); women with a cervical length of ≤25 mm before 24 weeks of gestation ($P = 0.0055$), and women with a prior spontaneous preterm birth <37 weeks of gestation ($P = 0.0013$).

Stratified subgroup analyses for adverse perinatal outcome according to cervical length indicated a benefit of vaginal progesterone over control in women with a cervical length of ≤25 mm at randomisation (15/56 versus 22/60; RR 0.57; 95% CI 0.47–0.70; NNT 10) and before 24 weeks of gestation (14/52 versus 21/56; RR 0.56; 95% CI 0.42–0.75; NNT 9.5, Appendix S4). No difference between vaginal progesterone and controls was found for women with a cervical length of >25 mm at randomisation or before 24 weeks of gestation. Cervical length measurements were available from five studies,[5,9,22,27,32] of which four had data on women with a cervical length of ≤25 mm.[5,9,22,32]

Stratified subgroup analysis according to prior preterm birth <37 weeks of gestation showed no difference in adverse perinatal outcome when comparing the vaginal progesterone group with controls in those with a prior preterm birth (12/48 versus 9/42; RR 2.0; 95% CI 0.93–4.2) and in those without a previous preterm birth (187/1566 versus 160/1372; RR 1.02; 95% CI 0.96–1.09).

Vaginal progesterone did not have a significant effect on adverse perinatal outcome, time to delivery, or death when subgroup analysis was performed according to chorionicity ($P = 0.46$).

Discussion

Main findings
This meta-analysis based on individual participant data from 13 RCTs of progestogen treatment for the prevention of preterm birth in unselected women with an uncomplicated twin pregnancy shows that progestogen treatment, regardless of type, did not reduce the risk of adverse perinatal outcome, compared with control; however, in a

subgroup of women with a short cervical length, vaginal progesterone treatment was beneficial.

Interpretation

A recent study investigating the relationship between 17Pc concentration and gestational age at delivery showed that 17Pc may reduce gestational age at delivery.[36] This result could not be repeated in this study; however, given the general trend of increased incidence of adverse perinatal outcomes, the increased incidence of adverse perinatal outcomes in a subgroup of women with a cervical length >25 mm, and the ineffectiveness to prolong pregnancy, we conclude that 17Pc is contraindicated in twin pregnancies.

Two recent meta-analyses suggested that women with a twin pregnancy and a short cervical length might benefit from treatment with vaginal progesterone.[12,13] In our IP-DMA we found similar results. The effect estimate was similar to that previously found in an IPDMA in singletons (RR 0.57; 95% CI 0.40–0.81) and twins (RR 0.56; 95% CI 0.30–0.97) versus twin pregnancies with a cervical length of ≤25 mm at randomisation (RR 0.57; 95% CI 0.47–0.70) and before 24 weeks of gestation (RR 0.56; 95% CI 0.42–0.75).[11] The narrower confidence interval in our study may be attributable to our inclusion of a more recent study that was not included in the earlier meta-analysis.[22] The potential effectiveness of vaginal progesterone in twin pregnancy with short cervix may have biological plausibility, as short cervix might be an early sign of the onset of parturition. Nonetheless, these results should be interpreted with caution because they are derived from a *post hoc* analysis of relatively small subgroups, which can lead to spurious conclusions. These findings should stimulate further research on progesterone in twin pregnancies with a short cervix.

Two individual studies previously reported a non-significant trend towards a benefit from vaginal progesterone in monochorionic twin pregnancies.[19,32] One study showed that vaginal progesterone reduced the number of IUFDs or deliveries before 34 weeks of gestation in monochorionic twins by 48%, whereas these were increased by 73% in dichorionic twins, both compared with the placebo group.[19] We did not find a significant interaction between vaginal progesterone treatment and chorionicity. We conclude that progestogens are not effective in a subgroup of women based on chorionicity.

Strengths and limitations

An IPDMA has several distinct advantages over ADMA. IPDMA involves the synthesis of individual-level data from the individual trials, and therefore allows for the verification of published results. As IPD are available, an IPDMA allows for more flexibility regarding the inclusion and

exclusion of individuals,[14] and the choice of end points and subgroups,[15,37] compared with ADMA. Furthermore, an IPDMA allows for more options to perform subgroup analyses and time-to-event analysis, as it can take account of the time between the initiation of treatment and the outcome of interest.[38] This is important because most published trials have reported a non-significant trend towards a shorter duration of pregnancy after the use of progestogens in women with twin pregnancies.[19,20] A final advantage of IPDMA is that IPD from unpublished studies can be included in the analysis. It is, however, important to contact the primary investigators and ask for the study protocol in order to assess the risk of bias, which is normally assessed using the published article. Although the results found in this study are similar to two previous AD-MAs,[12,13] we can be more confident in our findings given our rigorous approach using IPD.

Other strengths of the study are that this is the largest meta-analysis so far conducted on the effects of progestogens in twins and that it includes all currently published studies on this topic, in contrast to previously published meta-analyses.[11–13] Furthermore, our study is strengthened by the low influence of publication bias. Indeed, publication bias is a potential problem in meta-analysis, and can be investigated using funnel plots. Given the low number of included studies we were not able to reliably construct funnel plots. Instead, studies were identified through trial registries, from which we were able to identify continuing as well as terminated studies. Moreover, most of the trials included in this IPDMA failed to show a benefit of progestogens, but were included in a formal trials register, and published according to good practice.

Heterogeneity in the primary outcome between the six 17Pc studies was moderate to high (I^2 64%; 95% CI 14–85%). This heterogeneity is likely to result from the different directions of the effect of 17Pc in the individual studies. In the seven vaginal progesterone studies no heterogeneity was observed for the primary outcome (I^2 0%; 95% CI 0–65%).

The sensitivity analyses performed in blinded studies, and in studies that included 100+ participants, did not lead to different results than are presented here. This shows the robustness of the results of our study.

The number of women with missing primary outcome data was very low (0.0–6.7%). Consequently, it was not likely that these missing values would influence the final conclusions. Therefore, a complete case analysis was considered appropriate.

There are several deviations from our published protocol that must be discussed.[17] First, the cut-off of cervical length was changed from <25 mm to ≤25 mm to allow for a better comparison with another meta-analysis.[11] Second, periventricular leucomalacia and retinopathy of prematurity were excluded from the composite outcome because this

information was not registered in the majority of studies. We would like to emphasise that both changes were made before we investigated treatment effects. Furthermore, the conclusions of our study were similar when using the cut-off of cervical length as previously published in the protocol of this IPDMA.

Conclusion

In conclusion, this IPDMA has shown that in unselected women with uncomplicated twin pregnancies, treatment with progestogens does not prolong pregnancy or improve perinatal outcome. In a subgroup of women with a short cervical length vaginal progesterone treatment did improve perinatal outcome.

Disclosure of interests

None of the authors has any financial, personal, political, academic, or other relationships that could lead to a conflict of interest relevant to this article.

Contribution to authorship

ES, ACL, and BWJM were involved in the concept and the design of the study. ES performed the analyses in collaboration with NPAZ, RHHG, and BWJM. ES, SS, LR, DJR, ACL, JEN, AHN, VS, CAC, CV, SW, EÇ, CMB, EBF, EAT, SNC, KK, AT, JA, IMU, AP, JM, KM, TG, SR, CC, AKa, JCM, EFM, KHN, RHHG, KGMM, AKw, and BWJM participated in face-to-face meetings, teleconferences and/or e-mail conversations to discuss the article, the design of the meta-analysis, the choice of outcome measures, and analysis strategies. SS, LR, DJR, ACL, JEN, AHN, VS, CAC, CV, MMA, SW, EÇ, CMB, EBF, EAT, SNC, KK, AT, JA, IMU, AP, JM, KM, TG, MAA, YMA, SR, CC, AKa, JCM, EFM, KHN, and BWJM were involved in the construction and design of one of the trials included in the meta-analysis. ES wrote the initial article, with significant contributions by RHHG, AK, KGMM, and BWJM. All authors critically reviewed the subsequent versions of the article and approved the final version.

Details of ethics approval

All studies had institutional review board approval and informed consent from all participants.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Exclusion criteria included studies.
Appendix S2. Data availability in the included studies.
Appendix S3. Short cervical length at randomisation and before 24 weeks of gestation in relation to adverse perinatal outcome in the 17Pc studies.
Appendix S4. Short cervical length at randomisation and before 24 weeks of gestation in relation to adverse perinatal outcome in the vaginal progesterone studies.
Appendix S5. Effects of 17Pc on primary and secondary outcomes.
Appendix S6. Effects of vaginal progesterone on primary and secondary outcomes.
Data S1. Powerpoint slides summarising the study. ■

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