Journal-club MFM du 26 février 2021 avec Marie Dorey

OBSTETRICS

Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial

Anoop Rehal, MD; Zsófia Benkő, MD; Catalina De Paco Matallana, MD; Argyro Syngelaki, PhD; Deepa Janga, MD; Simona Cicero, MD; Ranjit Akolekar, MD; Mandeep Singh, MD; Petya Chaveeva, MD; Jorge Burgos, MD; Francisca S. Molina, MD; Makrina Savvidou, MD; Maria De La Calle, MD; Nicola Persico, MD; Maria Soledad Quezada Rojas, MD; Ashis Sau, MD; Elena Greco, MD; Neil O'Gorman, MD; Walter Plasencia, MD; Susana Pereira, MD; Jacques C. Jani, MD; Nuria Valino, MD; Maria del Mar Gil, MD; Kate Maclagan, PhD; Alan Wright, PhD; David Wright, PhD; Kypros H. Nicolaides, MD

BACKGROUND: In women with a singleton pregnancy and sonographic short cervix in midgestation, vaginal administration of progesterone reduces the risk of early preterm birth and improves neonatal outcomes without any demonstrable deleterious effects on childhood neurodevelopment. In women with twin pregnancies, the rate of spontaneous early preterm birth is 10 times higher than that in singletons, and in this respect, all twins are at an increased risk of preterm birth. However, 6 trials in unselected twin pregnancies reported that vaginal administration of progesterone from midgestation had no significant effect on the incidence of early preterm birth. Such apparent lack of effectiveness of progesterone in twins may be due to inadequate dosage or treatment that is started too late in pregnancy.

OBJECTIVE: The early vaginal progesterone for the prevention of spontaneous preterm birth in twins, a randomized, placebo-controlled, double-blind trial, was designed to test the hypothesis that among women with twin pregnancies, vaginal progesterone at a dose of 600 mg per day from 11 to 14 until 34 weeks' gestation, as compared with placebo, would result in a significant reduction in the incidence of spontaneous preterm birth between 24^{+0} and 33^{+6} weeks.

STUDY DESIGN: The trial was conducted at 22 hospitals in England, Spain, Bulgaria, Italy, Belgium, and France. Women were randomly assigned in a 1:1 ratio to receive either progesterone or placebo, and in the random-sequence generation, there was stratification according to the participating center. The primary outcome was spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation. Statistical analyses were performed on an intention-to-treat basis. Logistic regression analysis was used to determine the significance of difference in the incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation between the progesterone and placebo groups, adjusting for the effect of participating center, chorionicity, parity, and method of conception. Prespecified tests of treatment interaction effects with chorionicity, parity, method of conception, compliance, and cervical length at recruitment were performed. A post hoc analysis using mixed-effects Cox regression was used for further exploration of the effect of progesterone on preterm birth.

RESULTS: We recruited 1194 women between May 2017 and April 2019; 21 withdrew consent and 4 were lost to follow-up, which left 582 in the progesterone group and 587 in the placebo group. Adherence was good, with reported intake of ≥80% of the required number of capsules in 81.4% of the participants. After excluding births before 24 weeks and indicated deliveries before 34 weeks, spontaneous birth between 24^{+0} and 33^{+6} weeks occurred in 10.4% (56/541) of participants in the progesterone group and in 8.2% (44/538) in the placebo group (odds ratio in the progesterone group, adjusting for the effect of participating center, chorionicity, parity, and method of conception, 1.35; 95% confidence interval, 0.88—2.05; *P*=.17). There was no evidence of interaction between the effects of treatment and chorionicity (*P*=.28), parity (*P*=.35), method of conception (*P*=.56), and adherence (*P*=.34); however, there was weak evidence of an interaction with cervical length (*P*=.08) suggestive of harm to those with a cervical length of ≥30 mm (odds ratio, 1.61; 95% confidence interval, 1.01—2.59) and potential benefit for those with a cervical length of <30 mm (odds ratio, 0.56; 95% confidence interval, 0.20—1.60). There was no evidence of difference between the 2 treatment groups for stillbirth or neonatal death, neonatal complications, neonatal therapy, and poor fetal growth. In the progesterone group, 1.4% (8/582) of women and 1.9% (22/1164) of fetuses experienced at least 1 serious adverse event; the respective numbers for the placebo group were 1.2% (7/587) and 3.2% (37/1174) (*P*=.80 and *P*=.06, respectively). In the post hoc time-to-event analysis, miscarriage or spontaneous preterm birth between randomization and 31^{+6} weeks' gestation was reduced in the progesterone group relative to the placebo group (hazard ratio, 0.23; 95% confidence interval, 0.08—0.69).

CONCLUSION: In women with twin pregnancies, universal treatment with vaginal progesterone did not reduce the incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation. Post hoc time-to-event analysis led to the suggestion that progesterone may reduce the risk of spontaneous birth before 32 weeks' gestation in women with a cervical length of <30 mm, and it may increase the risk for those with a cervical length of ≥30 mm.

Key words: cervical length, preterm birth, twin pregnancy, progesterone, randomized trial

Cite this article as: Rehal A, Benkő Z, De Paco Matallana C, et al. Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial. Am J Obstet Gynecol 2021;224:86.e1-19.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2020.06.050

Preterm birth is the leading cause of neonatal and childhood death and disability, and the incidence of these adverse events is particularly marked in early preterm birth before 34 weeks of gestation.[1,2] In singleton pregnancies, the rate of spontaneous early preterm birth is about 1%, and in twin pregnancies, the rate is 10 times higher.[3] There is strong evidence from randomized trials that in women with a singleton pregnancy and sonographic short cervix in midgestation, vaginal administration of progesterone in doses of 90 to 200 mg daily reduces the risk of early preterm birth and improves neonatal outcomes

AJOG at a Glance

Why was this study conducted?

This randomized controlled trial tested the hypothesis that in women with twin pregnancies, vaginal progesterone at a dose of 600 mg per day from 11 to 14 until 34 weeks' gestation, as compared with placebo, would result in a significant reduction in the incidence of spontaneous preterm birth between 24^{+0} and 33^{+6} weeks.

Key findings

In women with twin pregnancies, universal treatment with vaginal progesterone did not reduce the incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation. Post hoc time-to-event analysis led to the suggestion that progesterone may reduce the risk of spontaneous birth before 32 weeks of gestation in women with a cervical length of <30 mm, and it may increase the risk for those with a cervical length of ≥ 30 mm.

What does this add to what is known?

In women with twin pregnancies, universal treatment with vaginal progesterone does not reduce the incidence of early spontaneous birth.

without any demonstrable deleterious effects on childhood neurodevelopment.[4–7] In contrast, 6 previous trials that recruited between 70 and 675 women with unselected twin pregnancies and used between 90 mg and 400 mg of progesterone daily reported no significant effect on the incidence of early preterm birth.[8–13] One individual participant data meta-analysis in women with unselected twin pregnancies reported that vaginal progesterone from midgestation was not associated with reduction in the rate of adverse perinatal outcome (relative risk [RR], 0.97; 95% confidence interval [CI], 0.77–1.2), but in a subgroup of women with a cervical length of ≤ 25 mm at randomization, progesterone reduced the rate of adverse perinatal outcome (RR, 0.57; 95% CI, 0.47–0.70).[14]

The apparent lack of effectiveness of progesterone in twins may be due to inadequate dosage or treatment that is started too late in pregnancy. The early vaginal progesterone for the prevention of spontaneous preterm birth in twins (EVENTS), a randomized, placebo-controlled, double-blind trial, was designed to test the hypothesis that among women with twin pregnancies, vaginal progesterone at a dose of 600 mg per day from 11 to 14 until 34 weeks' gestation, as compared with placebo, would result in a significant reduction in the incidence of spontaneous preterm birth before 34 weeks' gestation.

Methods

Study design

This was a double-blind, placebo-controlled trial comparing vaginal progesterone at a dose of 300 mg twice per day with placebo from 11 to 14 until 34 weeks' gestation in women with twin pregnancies. We conducted the trial at 22 maternity hospitals in England, Spain, Bulgaria, Italy, Belgium, and France. All women with twin pregnancies with a routine prenatal visit at 11^{+0} to 13^{+6} weeks' gestation in the participating hospitals were assessed for eligibility and were offered to participate in this study. At this visit, first, maternal characteristics, medical history, and obstetrical history were recorded; second, maternal weight and height were measured; third, gestational age was determined from the measurement of the fetal crown-rump length of the larger fetus; and fourth, transvaginal sonography was carried out to determine the cervical length.[15] Quality control of screening and verification of adherence to protocol were performed by the Fundación para la Formación e Investigación Sanitaria for the sites in Spain and by the Fetal Medicine Foundation for the sites in Bulgaria, Belgium, France, Italy, and the United Kingdom. Approval for the study was obtained in each country where the trial was conducted from the relevant research ethics committee and competent authority.

Participants

The following inclusion criteria for the trial were used: age older than 18 years, dichorionic or monochorionic diamniotic twin pregnancy, 2 live fetuses at the 11 to 13 weeks' scan, and fluency in the local language. The following exclusion criteria were used: monoamniotic pregnancies; monochorionic diamniotic pregnancies with early signs of twin-to-twin transfusion syndrome, defined as $>20\%$ discordance in crown-rump length at the 11 to 13 weeks' scan; major fetal abnormality or nuchal translucency thickness of >3.5 mm identified at the 11 to 13 weeks' scan; women who were unconscious or severely ill; those with learning difficulties or serious mental illness; hypersensitivity to progesterone; regular treatment with progesterone within the previous 7 days; severe hepatic dysfunction; mammary or genital tract carcinoma, thrombophlebitis, or thromboembolic disorders; porphyria; cerebral hemorrhage; allergy to sunflower oil, soya lecithin, gelatin, glycerol (E422), or titanium dioxide (E171); and participation in another drug trial within 28 days. Potential trial participants were given written information about the trial, and those who agreed to participate provided written informed consent.

Randomization and masking

Eligible women were randomly assigned, in a 1:1 ratio, with the use of a simple permuted block provided by Besins Healthcare, Brussels, Belgium, to receive either progesterone or placebo, and in the random-sequence generation, there was stratification according to the participating center. The placebo and progesterone capsules were manufactured, packaged, labeled, stored, and distributed by Besins Healthcare, Brussels, Belgium. The placebo capsules were identical to those of the progesterone in

parameters such as size, thickness, physical properties, and appearance. Participants, investigators, pharmacists, and others involved in giving the intervention, assessing outcomes, or analyzing data remained masked to treatment allocation until the end of the study.

Procedures

After randomization, study participants were prescribed the investigational medicinal product and received instructions on the self-administration of 1 vaginal capsule twice daily throughout the study and to stop vaginal insertion of capsules at 34 weeks' gestation or in the event of earlier delivery. Compliance and adverse events were assessed and recorded at follow-up clinical visits at 20 to 22, 24 to 26, 28 to 30, 31 to 33, and 35 to 37 weeks' gestation in dichorionic twin pregnancies and at 16 to 17 weeks and every 2 weeks thereafter in monochorionic twin pregnancies, and in 1 telephonic interview 30 days after the last capsule was taken. Participants were encouraged to record any side effects or adverse events in a diary that was reviewed at each trial visit, and they were specifically asked about such events during the telephonic interview. We assessed adherence by researchers counting the capsules returned by participants at each visit and by the participants themselves during the telephonic interview. The total number of capsules taken was calculated by subtracting the number of capsules returned from the number of capsules prescribed.

Outcome measures

The primary outcome measure was spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation inclusive. In cases in which 1 fetus died (termination, miscarriage, or stillbirth) at a gestational age that was earlier than that of the birth of the second fetus, the gestational age for pregnancy outcome was the one at the birth of the second twin.

Secondary outcomes were spontaneous birth between 24 weeks and <28, <30, <32, and <37 weeks; spontaneous or indicated birth between 24 weeks and <28, <30, <32, <34, and <37 weeks; spontaneous or indicated birth between randomization and <24, <28, <30, <32, and <34 weeks; stillbirth or neonatal death; neonatal complications; neonatal therapy; and poor fetal growth (birthweight below 1500 g, 2000 g, and below the 3rd, 5th, or 10th percentile).[16]

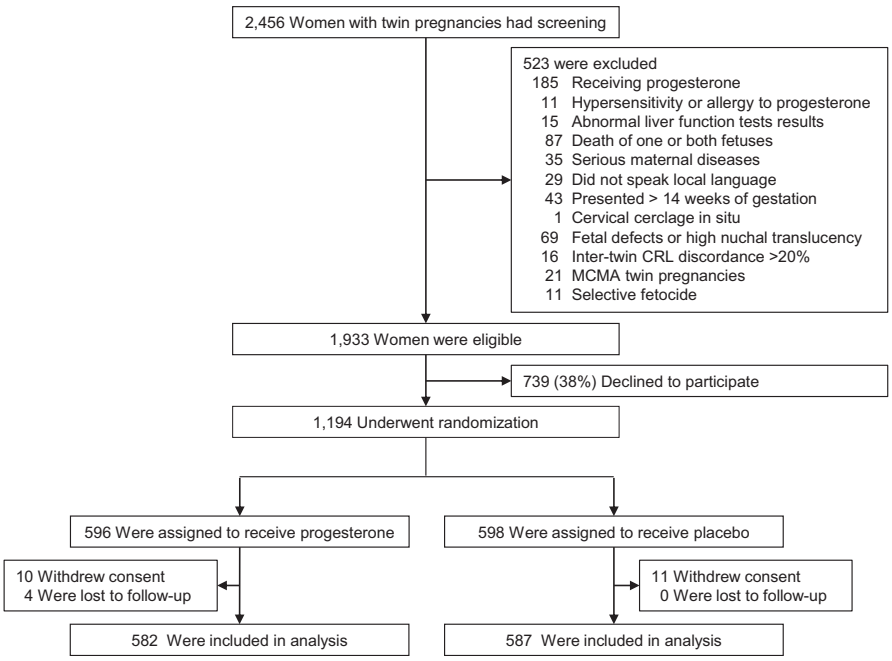
Adherence was considered to be good if the reported use of capsules was ≥80% of the total number participants should have used between the date of randomization and the date of the 34 weeks' visit or delivery if this occurred before 34 weeks.

Statistical analysis

It was hypothesized that vaginal progesterone would reduce the rate of spontaneous birth between 24^{+0} and 33^{+6} weeks of gestation by 40%, from 13% in the placebo group to 7.8% in the progesterone group. We calculated that enrollment of 1080 participants would give the study a power of 80% to show a treatment effect at a 2-sided alpha level of 5%. The target recruitment figure was inflated to 1188 to account for approximately 10% attrition.

Statistical analyses were carried out on an intention-to-treat basis, and no interim analyses were performed. Logistic regression analysis was used to determine the significance of the difference in the incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation between the progesterone and placebo groups, adjusting for the effect of participating center, chorionicity (monochorionic or dichorionic), parity (nulliparous, parous with previous preterm birth, or parous without previous preterm birth), and method of conception (in vitro fertilization, natural conception, or use of ovulation drugs). The treatment effect was quantified as odds ratio (OR) with 95% CI in the progesterone group. We also produced Kaplan-Meier survival estimates of the cumulative incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation according to the trial group, in which births before 24 weeks and indicated births before 34 weeks were treated as censored observations. Cox regression was used to test the effect of treatment, adjusting for parity, chorionicity, and conception.

FIGURE 1
Screening, randomization, and follow-up



CRL, crown-rump length; *MCMA*, monochorionic monoamniotic.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

TABLE 1
Characteristics of the trial participants

Characteristic	Progesterone group (n=582)	Placebo group (n=587)
Gestation at randomization (wk)	13.2 (12.7–13.6)	12.2 (12.7–13.7)
Dichorionic pregnancies	449 (77.1)	453 (77.2)
Monochorionic pregnancies	133 (22.9)	134 (22.8)
Cervical length (mm)	34.4 (31.0–38.0)	34.6 (31.5–38.0)
Cervical length <30 mm	85 (14.6)	70 (11.9)
Age (y)	34.1 (30.3–37.7)	34.0 (30.0–37.6)
Body mass index (kg/m^2)	24.7 (21.9–28.4)	24.3 (22.0–27.9)
Height (cm)	166 (161–170)	165 (160–170)
Weight (kg)	68.7 (59.6–79.0)	66.5 (59.5–76.9)
Race		
White	473 (81.3)	492 (83.8)
Black	69 (11.9)	59 (10.1)
South Asian	18 (3.1)	28 (4.8)
East Asian	8 (1.4)	3 (0.5)
Mixed	14 (2.4)	5 (0.9)
Conception		
Natural	382 (65.6)	380 (64.7)
Assisted by use of ovulation drugs	35 (6.0)	44 (7.5)
In vitro fertilization	165 (28.4)	163 (27.8)
Cigarette smoker	36 (6.2)	39 (6.6)
Medical history		
Chronic hypertension	11 (1.9)	7 (1.2)
Diabetes mellitus type 1 or 2	8 (1.4)	3 (0.5)
Obstetrical history		
Nulliparous	317 (54.5)	326 (55.5)
Parous with preterm birth <37 wk	23 (4.0)	33 (5.6)
Parous without preterm birth <37 wk	242 (41.6)	228 (38.8)

Data are presented as median (25th to 75th percentile) or n (%).

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

Prespecified tests of treatment interaction effects with chorionicity, parity, method of conception, compliance, and cervical length at recruitment were performed. Cervical length was included as a continuous covariate defined as 35 mm minus cervical length for cervical length of <35 mm and 0 for cervical length of ≥35 mm. This choice of transformation was made on the basis of the analysis of data blinded to treatment allocation. To aid interpretation, analyses were performed to examine the effect of treatment by subgroups defined in terms of chorionicity, parity, method of conception, compliance, and cervical length. The findings from the planned analyses led to a post hoc analysis of gestational age at delivery using mixed-effects Cox regression models. The proportional hazards assumption for the treatment effect was clearly inappropriate; the cumulative incidence curves for progesterone and placebo crossed (see Results). This led to stratification according to the gestational age at delivery. We chose to estimate hazard ratios (HRs) with stratification of the gestational age into 2 strata, deliveries before 32 weeks and deliveries between 32^{+0} and 33^{+6} weeks.

Secondary outcomes were compared across treatment groups using mixed-effects logistic regression with fixed effects for treatment, parity, and chorionicity, and random effects for center. Results were presented as forest plots showing estimates and 95% CIs for treatment effects. The results on perinatal and neonatal outcome were examined both at the pregnancy and fetal and neonatal level. For fetal and neonatal outcomes, random effects were included for pregnancy to account for associations between fetuses/neonates of the same mother.

The statistical software package R was used for data analyses.[17–21]

Results

Trial participants

Recruitment to the trial started in May 2017 and was completed in April 2019. A total of 2456 women with twin pregnancies were screened, and 523 (21.3%) of these were excluded from recruitment to the trial because they did not fulfill the eligibility criteria (Figure 1). Of the 1933 eligible women, 1194 (61.8%) agreed to participate in the trial. After randomization, 21 (1.8%) women withdrew consent and 4 (0.3%) were lost to follow-up. The progesterone and placebo groups were well balanced at baseline (Table 1).

In the progesterone group, 15 women delivered before 24 weeks' gestation, including 2 pregnancy terminations (one for fetal abnormalities and another for social reasons); in the placebo group, 26 women delivered before 24 weeks' gestation, including 3 pregnancy terminations (1 for fetal abnormalities and 2 for social reasons). In the progesterone group, 26 women had indicated delivery between 24^{+0} and 33^{+6} weeks' gestation, including 24 for preeclampsia and or fetal growth restriction, 1 for abruption, and 1 for obstetrical cholestasis; in the placebo group, there were 23 indicated deliveries, including 20 for preeclampsia and/or fetal growth restriction, 1 for

al group

	Pregnancy level			Neonatal/fetal level		
	Progesterone group, n/N (%)	Placebo group, n/N (%)	OR (95% CI)	Progesterone group, n/N (%)	Placebo group, n/N (%)	OR (95% CI)
l <34 wk	56/541 (10.4)	44/538 (8.2)	1.35 (0.88–2.05)	—	—	—
<24 wk	15/582 (2.6)	26/587 (4.4)	0.57 (0.30–1.10)	—	—	—
<34 wk	97/582 (16.7)	93/587 (15.8)	1.10 (0.80–1.51)	—	—	—
	82/567 (14.5)	67/561 (11.9)	1.28 (0.90–1.82)	—	—	—
<28 wk	23/582 (4.0)	35/587 (6.0)	0.65 (0.38–1.13)	—	—	—
<30 wk	31/582 (5.3)	49/587 (8.3)	0.63 (0.39–1.01)	—	—	—
<32 wk	53/582 (9.1)	65/587 (11.1)	0.81 (0.55–1.20)	—	—	—
<37 wk	330/582 (56.7)	322/587 (54.9)	1.13 (0.88–1.46)	—	—	—
	8/567 (1.4)	9/561 (1.6)	0.89 (0.34–2.33)	—	—	—
	16/567 (2.8)	23/561 (4.1)	0.70 (0.36–1.34)	—	—	—
	38/567 (6.7)	39/561 (7.0)	0.97 (0.61–1.55)	—	—	—
	315/567 (55.6)	296/561 (52.8)	1.16 (0.90–1.51)	—	—	—
l <28 wk	8/567 (1.4)	7/559 (1.3)	1.15 (0.41–3.21)	—	—	—
l <30 wk	14/565 (2.5)	16/554 (2.9)	0.88 (0.43–1.84)	—	—	—
l <32 wk	25/554 (4.5)	24/546 (4.4)	1.05 (0.59–1.86)	—	—	—
l <37 wk	161/413 (39.0)	137/402 (34.1)	1.36 (1.00–1.83)	—	—	—
	12/582 (2.1)	9/587 (1.5)	1.41 (0.58–3.39)	15/1164 (1.3)	10/1174 (0.9)	1.57 (0.70–3.53)
	n=569	n=565		n=1125	n=1113	
	51/569 (9.0)	50/565 (8.8)	1.03 (0.68–1.56)	75/1125 (6.7)	76/1113 (6.8)	0.93 (0.65–1.32)
	174/569 (30.6)	159/565 (28.1)	1.16 (0.89–1.50)	259/1125 (23.0)	239/1113 (21.5)	1.13 (0.92–1.40)
	272/569 (47.8)	278/565 (49.2)	0.96 (0.75–1.21)	352/1125 (31.3)	369/1113 (33.2)	0.97 (0.80–1.16)
	328/569 (57.6)	319/565 (56.5)	1.07 (0.84–1.36)	443/1125 (39.4)	441/1113 (39.6)	1.05 (0.88–1.25)
	394/569 (69.2)	390/565 (69.0)	1.02 (0.79–1.31)	581/1125 (51.6)	576/1113 (51.8)	1.04 (0.88–1.24)

twin pregnancies. Am J Obstet Gynecol 2021.

(continued)

TABLE 2
Outcomes according to the trial group *(continued)*

Outcome measures	Pregnancy level			Neonatal/fetal level		
	Progesterone group, n/N (%)	Placebo group, n/N (%)	OR (95% CI)	Progesterone group, n/N (%)	Placebo group, n/N (%)	OR (95% CI)
Neonatal therapy	171/569 (30.1)	159/565 (28.1)	1.12 (0.86–1.46)	268/1125 (23.8)	252/1113 (22.6)	1.09 (0.89–1.33)
Admission to NICU	157/569 (27.6)	148/565 (26.2)	1.09 (0.83–1.43)	242/1125 (21.5)	227/1113 (20.4)	1.09 (0.89–1.34)
Need for ventilation	132/569 (23.2)	121/565 (21.4)	1.13 (0.84–1.51)	199/1125 (17.7)	191/1113 (17.2)	1.06 (0.85–1.33)
Neonatal morbidity	56/569 (9.8)	57/565 (10.1)	1.00 (0.67–1.48)	77/1125 (6.8)	85/1113 (7.6)	0.90 (0.65–1.25)
Respiratory distress syndrome	43/569 (7.6)	42/565 (7.4)	1.04 (0.67–1.63)	57/1125 (5.1)	67/1113 (6.0)	0.85 (0.59–1.22)
Intraventricular hemorrhage	8/569 (1.4)	9/565 (1.6)	0.89 (0.34–2.33)	8/1125 (0.7)	10/1113 (0.9)	0.79 (0.31–2.01)
Anemia	20/569 (3.5)	23/565 (4.1)	0.87 (0.47–1.61)	25/1125 (2.2)	29/1113 (2.6)	0.85 (0.49–1.46)
Necrotizing enterocolitis	2/569 (0.4)	3/565 (0.5)	0.70 (0.12–4.23)	2/1125 (0.2)	3/1113 (0.3)	0.69 (0.11–4.17)
Retinopathy	6/569 (1.1)	13/565 (2.3)	0.46 (0.17–1.24)	7/1125 (0.6)	18/1113 (1.6)	0.39 (0.16–0.95)
Sepsis	15/569 (2.6)	16/565 (2.8)	0.95 (0.46–1.96)	17/1125 (1.5)	18/1113 (1.6)	0.95 (0.49–1.86)

CI, confidence interval; *NICU*, neonatal intensive care unit; *OR*, odds ratio.
Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

abruption, 1 for severe maternal hydronephrosis, and 1 for twin anemia-polycythemia sequence.

Primary outcome

After excluding births before 24 weeks and indicated deliveries before 34 weeks, spontaneous birth between 24^{+0} and 33^{+6} weeks of gestation occurred in 10.4% (56/541) of participants in the progesterone group and 8.2% (44/538) in the placebo group (OR in the progesterone group, adjusting for the effect of participating center, chorionicity, parity, and method of conception, 1.35; 95% CI, 0.88–2.05; P=.17) (Table 2).

In the mixed-effects logistic regression model for the primary analysis, the rate of spontaneous birth between 24^{+0} and 33^{+6} weeks was higher in women with monochorionic than dichorionic pregnancies (OR, 1.91; 95% CI, 1.20–3.03; P=.006) and in parous women with previous preterm births than in nulliparous women (OR, 2.631; 95% CI, 1.26–5.48; P=.010), but there was no significant difference between pregnancies conceived by in vitro fertilization and natural conception or those conceived after the use of ovulation induction drugs (OR, 0.81; 95% CI, 0.47–1.37; P=.43) (Supplemental Tables 1 and 2 and Supplemental Figure 1).

Per-protocol analysis in the subgroup of women with adherence of ≥80% demonstrated that the administration of progesterone, compared with placebo, was associated with a significant increase in the rate of spontaneous preterm birth between 24^{+0} and 33^{+6} weeks' gestation, 9.5% (42/443) of participants in the progesterone group and 5.9% (26/443) in the placebo group (OR in the progesterone group, adjusting for the effect of participating center, chorionicity, parity, and method of conception, 1.73; 95% CI, 1.04–2.91; P=.037). Nevertheless, the effect of vaginal progesterone on spontaneous birth between 24^{+0} and 33^{+6} weeks did not differ significantly between women with an adherence of ≥80% and those with an adherence of 60% to 79% and <60% (Supplemental Figure 1).

For the intention-to-treat population, prespecified tests showed no evidence of interaction between the effects of

treatment and chorionicity (P=.28), parity (P=.35), method of conception (P=.56), and adherence (P=.34); however, there was weak evidence of an interaction with the cervical length (P=.08) suggestive of harm to those with a cervical length of ≥30 mm (OR, 1.61; 95% CI, 1.01−2.59) and potential benefit for those with a cervical length of <30 mm (OR, 0.56; 95% CI, 0.20−1.60) (Supplemental Figures 1 and 2).

Secondary outcomes

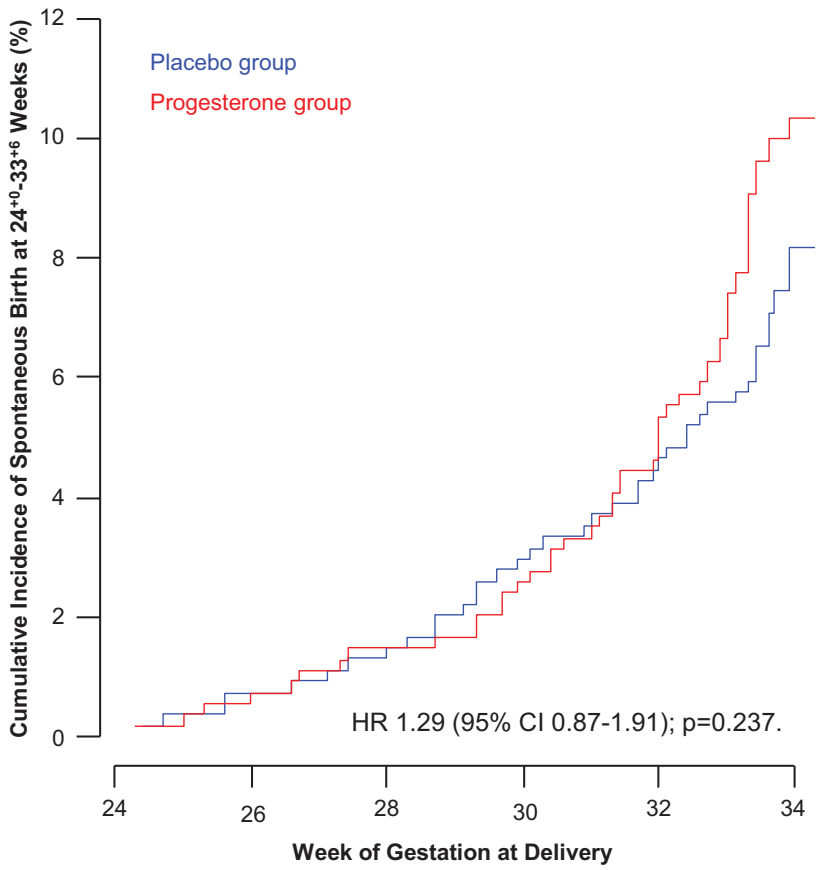
The treatment effect for secondary outcomes, quantified as OR in the progesterone group with 95% CI, is shown in Table 2. There was no significant between-group difference in the incidence of any secondary outcomes. Interclass correlations for neonatal outcomes are calculated in Supplemental Table 3.

Time-to-event analyses

The cumulative incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks of gestation is shown in Figure 2; HR was 1.29 (95% CI, 0.87−1.91). Tests of interactions mirrored those from the logistic regression with no evidence of interaction between the effects of treatment and chorionicity, parity, method of conception, or adherence. There was some evidence of an interaction between the effect of treatment and cervical length (P=.049) (Supplemental Table 4). For those with cervical length ≥30 mm, HR was 1.58 (95% CI, 1.01−2.47), suggestive of harm, whereas for those with a cervical length of <30 mm, there was potential benefit (HR, 0.49; 95% CI, 0.19−1.32). There was also evidence of an interaction between the effect of treatment and cervical length for miscarriage or spontaneous birth from randomization to 33^{+6} weeks (P=.040) but not for all births between randomization and 33^{+6} weeks (P=.45) (Supplemental Tables 5 and 6).

Cumulative incidence stratified by cervical length for spontaneous birth between 24^{+0} and 33^{+6} weeks, miscarriage or spontaneous birth between randomization and 33^{+6} weeks, and all births between randomization and 33^{+6} weeks are shown in Figure 3. It is clear from the cumulative incidence curves that the proportional hazards assumption for the treatment effect is unrealistic because the cumulative incidence curves for progesterone and placebo crossed. This led to the estimation of HRs stratified according to the gestational age at birth, shown in Figure 4 and Supplemental Table 7. The most notable feature of Figure 4 is the relative reduction in risk (progesterone or placebo) of spontaneous births before 32^{+0} weeks in those with a cervical length of <30 mm. For all spontaneous births, HR was 0.23 (95% CI, 0.08−0.69). This can be contrasted with an increase in the rate of spontaneous births between 32^{+0} and 33^{+6} weeks (HR, 1.42; 95% CI, 0.31−6.43), which suggests that in those with short cervical lengths, the effect of progesterone is to delay premature delivery, decreasing risks before 32 weeks but increasing them between 32 and 36 weeks.

FIGURE 2
Kaplan-Meier plot of cumulative percentage of participants who delivered spontaneously between 24^{+0} and 33^{+6} weeks' gestation



No. at Risk

Placebo	538	534	530	522	513	490
Progesterone	541	537	533	527	512	478

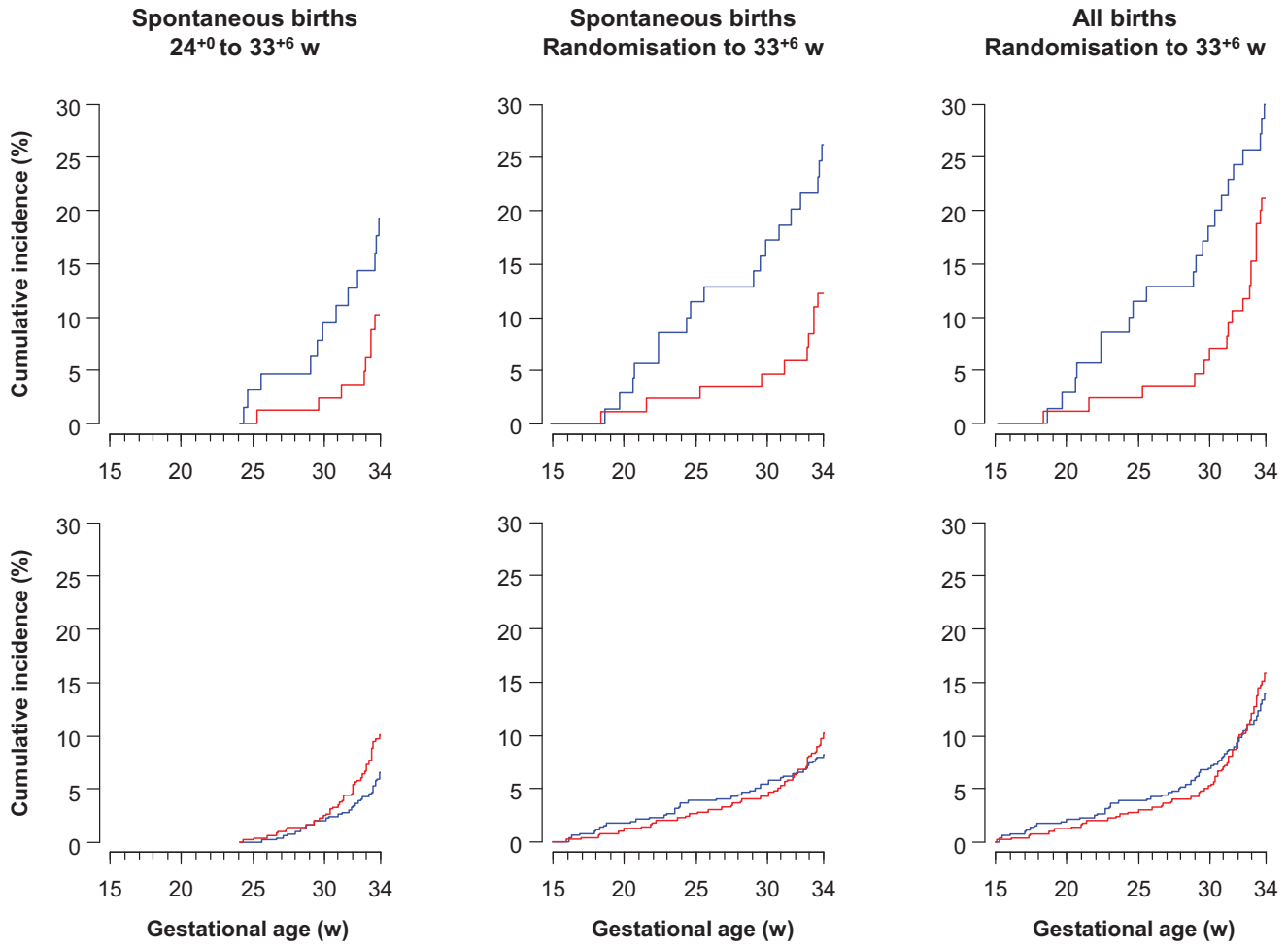
CI, confidence interval; *HR*, hazard ratio.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

Adverse events

In the progesterone group, 1.4% (8/582) of women and 1.9% (22/1164) of fetuses experienced at least 1 serious adverse event; the respective numbers for the placebo group were 1.2% (7/587) and 3.2% (37/1174) (P=.80 and P=.06, respectively) (Table 3). In the

FIGURE 3
Cumulative incidence stratified by cervical length for three outcome measures



The blue curves are for the placebo group and the red ones are for the progesterone group. The top 3 panels are for cervical length <30 mm and the bottom 3 panels are for cervical length ≥30 mm.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

progesterone group, there were 200 (34.4%) women with nonserious adverse events, and the respective value in the placebo group was 186 (31.7%) (*P*=.35) (Supplemental Table 8). There was no significant difference between the 2 groups in the incidence of preeclampsia, gestational hypertension, gestational diabetes mellitus, and intrahepatic cholestasis (Supplemental Table 9).

Adherence

Adherence was ≥80% in 952 (81.4%) participants. There were no significant between-group differences in the degree of adherence (Supplemental Table 10). A sensitivity analysis taking into account adherence to treatment is shown in Supplemental Figure 1.

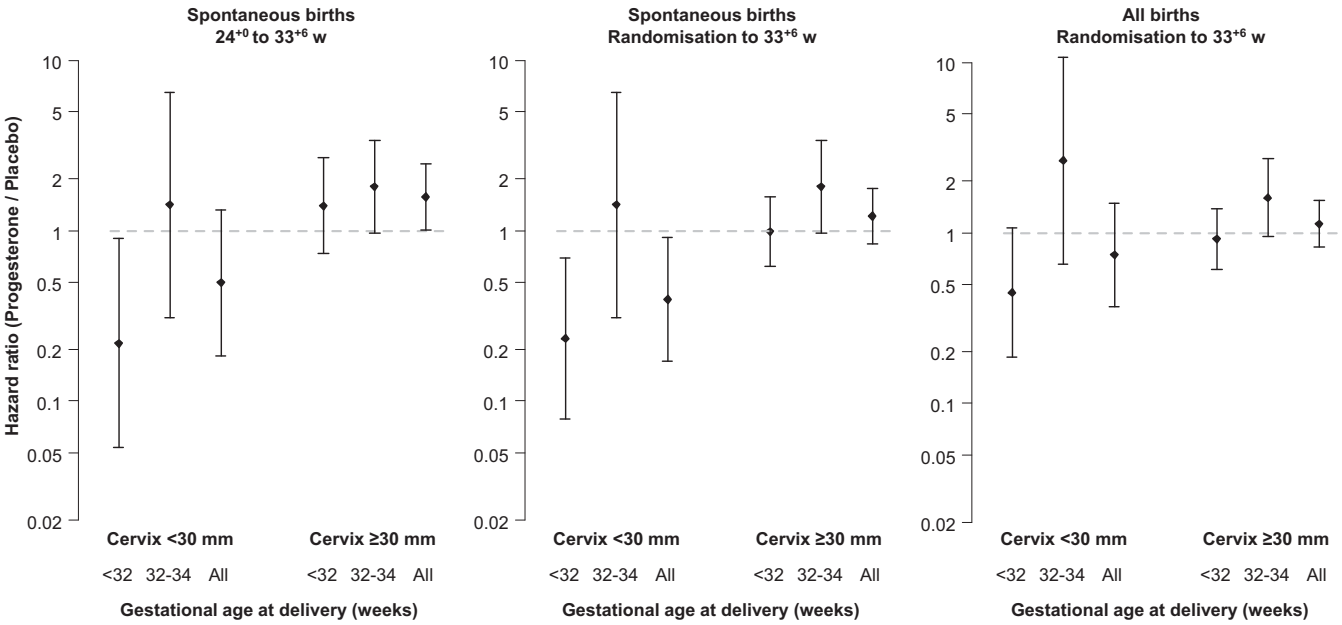
Comment

Main findings of the study

In this large, multicenter, randomized, placebo-controlled trial involving women with twin pregnancies, universal administration of progesterone at a dose of 300 mg twice per day from 11 to 14 until 34 weeks' gestation did not reduce the incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation. There was no evidence of any difference between the groups in the incidence of other pregnancy complications, adverse fetal or neonatal outcomes, and maternal or fetal serious adverse events. Adherence to treatment was good, with >80% of the participants taking ≥80% of their capsules.

In prespecified tests, we found no evidence of interaction between the effects of treatment and chorionicity, parity, method of conception, and adherence, but there was weak evidence of an interaction with cervical length; in the small subgroup of women with a

FIGURE 4
Hazard ratios (progesterone/placebo) for three outcome measures by subgroup according to the cervical length and by gestational age at delivery



Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

cervical length of <30 mm, we could not exclude the possibility of benefit from vaginal progesterone.

The selected primary outcome was spontaneous birth at 24^{+0} to 33^{+6} weeks' gestation, rather than all births between randomization and 34 weeks. We chose spontaneous rather than all preterm births because there is no reason to believe that progesterone would reduce indicated preterm births. As shown in Table 2, we found that the rates of all births at 24^{+0} to 33^{+6} weeks were 14.5% for the progesterone group and 11.9% for the placebo group. We excluded births before 24 weeks to allow comparison with the results of previous trials that recruited patients at midgestation. However, this exclusion could mask an effect of progesterone of converting late miscarriages to early preterm births; birth between randomization and 24 weeks occurred in 2.6% of pregnancies in the progesterone group and in 4.4% in the placebo group, but the rates of all births between randomization and 34 weeks were 16.7% for the progesterone group and 15.8% for the placebo group.

Interpretation of results and comparison with findings of previous studies

The findings of this study, in which progesterone therapy was initiated in early pregnancy, are consistent with those of 6 previous smaller trials in unselected twin pregnancies that investigated the value of prophylactic use of lower doses of vaginal progesterone from midgestation and reported no significant effect on the incidence of early preterm birth.[8–13] Consequently, in twin pregnancies, there is no benefit from universal prophylactic use of progesterone even when the dose is high and the drug is initiated from as early as 11 weeks' gestation. Indeed, our findings that the incidence of spontaneous early preterm birth is increased in women with good adherence to treatment and in those with a cervical length of ≥30 mm suggest that such treatment may actually be harmful. This observation has not been previously identified with a multiple gestation exposed to vaginal progesterone and raises the potential that harm may be related to the high dose, the early onset of therapy, or the duration of high-dose therapy; however, further study is warranted. The identification of potential harm in this lowest-risk subpopulation of women with a multiple gestation exposed to a different progestogen, 17-hydroxyprogesterone caproate (17-OHPC),[22] has also been demonstrated by Schuit et al[14] in an individual participant data meta-analysis; the authors reported that the administration of 17-OHPC in women with a cervical length of >25 mm doubled the risk of a composite of perinatal mortality and serious neonatal morbidity. It was therefore recommended that the use of 17-OHPC should be contraindicated in twin gestations.[23] The results of our study also suggest that vaginal progesterone therapy should be avoided in unselected twin pregnancies because of the evidence of potential harm.

Our finding of possible benefit from vaginal progesterone in the group with short cervix is consistent with the results of 2 individual participant data meta-analyses. One meta-analysis reported that although in women with

TABLE 3
Serious adverse events among trial participants

Serious adverse event	Progesterone group	Placebo group
Number of mothers	596	598
Maternal serious adverse events		
Preeclampsia with prolonged hospital stay (5 d)	3	0
Eclampsia with prolonged hospital stay (10 d)	0	1
Pulmonary embolism with prolonged hospital stay (4 d)	1	0
Postnatal liver rupture with prolonged hospital stay (31 d)	1	0
Obstetrical cholestasis with prolonged hospital stay (2 d)	0	1
Abnormal liver function tests	1	1
Postpartum hemorrhage with 3-L blood loss	1	0
Gastritis with prolonged hospital stay (4 d)	0	1
Dyspnea with prolonged hospital stay (2 d)	1	0
Restrictive cardiomyopathy with prolonged hospital stay (4 d)	0	1
Urinary tract infection with prolonged hospital stay (3 d)	0	1
Maternal mirror syndrome in association with fetal hydrops	0	1
Mothers with at least 1 serious adverse event[a]	8/582 (1.4)	7/587 (1.2)
Number of fetuses	1192	1196
Fetal serious adverse events		
HIV transmission from the mother	2	0
Trisomy 21	1	3
Agenesis of corpus callosum	2	2
Rhomboencephalosynapsis	0	1
Spina bifida	0	1
Ventriculomegaly severe after death of donor in TTTS	0	1
Ventriculomegaly severe and duplex kidneys	1	0
Subependymal cyst	1	0
Cleft lip and palate	1	4
Hypoplastic left heart syndrome	0	1
Dysplastic pulmonary valve	0	1
Coarctation of the aorta	0	2
Pulmonary artery stenosis	0	1
Tetralogy of Fallot	0	1
Right aortic arch	0	1
Ventricular septal defect	2	4
Esophageal atresia	2	0
Exomphalos bowel	1	0
Inguinal bilateral hernia	0	1
Malrotation of the intestine requiring surgery	1	0
Anal atresia	0	1
Renal agenesis unilateral	1	0
Duplex kidneys	1	0

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021. *(continued)*

TABLE 3
Serious adverse events among trial participants *(continued)*

Serious adverse event	Progesterone group	Placebo group
Hypospadias	1	6
Fibular hemimelia bilateral	1	0
Polydactyly bilateral	2	1
Talipes equinovarus bilateral or unilateral	2	3
Hemivertebra	0	1
Hemangioma	1	0
Sacrococcygeal teratoma	2	0
Fetuses with at least 1 serious adverse event[a]	22/1164 (1.9)	37/1174 (3.2)

Data are presented as n or n/N (%).

None of these serious adverse events were considered by the investigators to be associated with progesterone or placebo.

TTTS, twin-twin transfusion syndrome.

[a] Women who withdrew their consent for participation in the study did not allow their data collected before withdrawal to be used in any analysis.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

unselected twin pregnancies, vaginal progesterone from midgestation is not associated with a reduction in the rate of preterm birth or adverse perinatal outcome, in a subgroup with short cervix, progesterone reduces the rate of adverse perinatal outcome.[14] Another individual participant data meta-analysis reported that the administration of vaginal progesterone to asymptomatic women with a twin pregnancy and a midtrimester sonographic short cervix significantly reduced the risk of early preterm birth, neonatal death respiratory distress syndrome, need for mechanical ventilation, composite neonatal morbidity and mortality, and birthweight <1500 g.[24] Consequently, the subgroup of women with short cervix merits further investigation.

Our finding of convergence of the cumulative incidence with gestational age together with the restricted beneficial effect of progesterone to births before 32 weeks' gestation suggests that the effect of progesterone is to delay the gestational age at delivery for those pregnancies destined to deliver before 32 weeks. This is similar to the suggested effect of aspirin in delaying deliveries because of preeclampsia.[25]

Strengths and limitations

The strengths of this study include its large size, high acceptance to randomization and adherence to treatment, and low rates of withdrawal and loss to follow-up. However, the event rates were lower than anticipated so that the primary outcome was somewhat underpowered. Findings from the mixed-effects Cox regression were the result of post hoc analyses and should be considered as exploratory. This is the first phase III study to suggest that first trimester cervical length may be used to discriminate treatment response to vaginal progesterone, and further study is required to validate this observation.

Conclusions

In conclusion, this randomized trial showed that in unselected twin pregnancies, administration of progesterone at a dose of 600 mg per day from 11 to 14 until 34 weeks' gestation did not reduce the incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation. Post hoc time-to-event analysis led to the suggestion that progesterone may reduce the risk of spontaneous birth before 32 weeks in women with a cervical length of <30 mm, and it may increase the risk for those with a cervical length of ≥30 mm. ■

Acknowledgments

We thank all the participants and their attending obstetricians and midwives; Dr George Attilakos, University College London Hospital; Dr Bryony Jones, Imperial College Healthcare NHS Trust; Dr Mark Turner, University of Liverpool; Dr Christina Yu, Imperial College Healthcare NHS Trust; and Ian Bradbury, Statistics at Frontier Science Scotland (all from the United Kingdom); and Dr Anca Panaitescu, Filanthropia Hospital Bucharest from Romania for serving as members of the trial steering committee or independent data monitoring committee; the Clinical Trial Unit-IMIB Arrixaca-SCReN platform of Virgen de la Arrixaca University Clinical Hospital, Murcia, Spain (grant PI18/01027 Instituto Carlos III) for being responsible for the project management and oversight of the trial; and the following medical professionals who helped in the recruitment and follow-up of participants: Jessica Aguilera, Mercedes de Alvarado, Matthew Anderson, Brindusa Cimpoca, Hila de Castro, Mariana Catalano, Carla Coronel, Dejana Dojchinovska, Apostolos Georgantis, Andrea Harrington, Salma Jabak, Konstantinos Maligiannis, Alicia Mazer Zumaeta, Maria Mohova, Aikaterini Papanikolaou, Christina Resta, Angeliki Rouvali, Efsaia Savvoulidou, Maria Tsavdaridou, Theodora Tsokaki, Denisa Vojtassakova, and Emilie Zingler from London, United Kingdom; Vangeliya Atanasova and Cristina Casanova from Madrid, Spain; Juan Luis Delgado, Delia Lopez, and Macarena Quesada Rojas from Murcia, Spain; Carol Diaz and Tania De Ganzo from Granada, Spain; Ana del Campo from Barakaldo, Spain; Vivien Dutemeyer from Brussels, Belgium; Veronica Accurti and Ilma Floriana Carbone from Milan, Italy; and Vasil Kalev from Sofia, Bulgaria. Fundación para la Formación e Investigación Sanitaria in Murcia, Spain represented by the Clinical Trials and Clinical Research Unit, acted as regulatory sponsor of this trial for all sites in Spain and the Fetal Medicine Foundation for sites in Bulgaria,

Belgium, France, Italy, and the United Kingdom.

References

1. UNICEF, World Health Organization, World Bank, UN-DESA Population Division. Levels and trends in child mortality report 2019: estimates developed by the UN Inter-Agency Group for Child Mortality Estimation. New York: United Nations Children's Fund; 2019.
2. Martin JA, Osterman MJK. Describing the increase in preterm births in the United States, 2014-2016. NCHS Data Brief 2018;312:1–8.
3. To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH. Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. Am J Obstet Gynecol 2006;194:1360–5.
4. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462–9.
5. Hassan SS, Romero R, Vidyadhari D, 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.
6. Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol 2018;218:161–80.
7. Likis FE, Edwards DR, Andrews JC, et al. Progestogens for preterm birth prevention: a systematic review and meta-analysis. Obstet Gynecol 2012;120:897–907.
8. Norman JE, Mackenzie F, Owen P, 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.
9. 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;38:272–80.
10. 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.
11. Serra V, Perales A, Meseguer J, et al. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. BJOG 2013;120:50–7.
12. Brizot ML, Hernandez W, Liao AW, 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.
13. Shabaan OM, Hassanin IM, Makhlouf AM, et al. Vaginal progesterone for prevention of preterm delivery in women with twin pregnancy: a randomized controlled trial. Facts Views Vis Obgyn 2018;10:93–8.
14. Schuit E, Stock S, Rode L, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. BJOG 2015;122:27–37.
15. Greco E, Lange A, Ushakov F, Calvo JR, Nicolaides KH. Prediction of spontaneous preterm delivery from endocervical length at 11 to 13 weeks. Prenat Diagn 2011;31:84–9.
16. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. Ultrasound Obstet Gynecol 2018;52:44–51.
17. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. 2011. Available at: http://www.R-project.org/. Accessed January 6, 2020.
18. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Softw 2015;67:1–48.
19. Therneau TM. A package for survival analysis in S. version 3.2-3. 2015. Available at: https://CRAN.R-project.org/package=survival. Accessed January 6, 2020.
20. Therneau TM. Mixed effects Cox models. R package version 2.2-16. 2019. Available at: https://CRAN.R-project.org/package=coxme. Accessed January 6, 2020.
21. Revelle WR. psych: procedures for psychological, psychometric, and personality research. 2017. Available at: https://CRAN.R-project.org/package=psych. Accessed January 6, 2020.
22. Romero R, Stanczyk FZ. Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice. Am J Obstet Gynecol 2013;208:421–6.
23. Romero R, Conde-Agudelo A. Is 17α-hydroxyprogesterone caproate contraindicated in twin gestations? BJOG 2015;122:6–7.
24. Romero R, Conde-Agudelo A, El-Refaie W, et al. Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. Ultrasound Obstet Gynecol 2017;49:303–14.
25. Wright D, Nicolaides KH. Aspirin delays the development of preeclampsia. Am J Obstet Gynecol 2019;220:580.e1–6.

Author and article information

From the Fetal Medicine Research Institute, King's College Hospital, London, United Kingdom (Drs Rehal, Benkő, Syngelaki, and Nicolaides); Hospital Clínico Universitario Virgen de la Arrixaca and Institute for Biomedical Research of Murcia, IMIB-Arrixaca, Murcia, Spain (Dr De Paco Matallana); North Middlesex University Hospital, London, United Kingdom (Dr Janga); Homerton University Hospital, London, United Kingdom (Dr Cicero); Medway Maritime Hospital, Gillingham, United Kingdom (Dr Akolekar); Southend University Hospital, Westcliff-on-Sea, United Kingdom (Dr Singh); Dr Shterev Hospital, Sofia, Bulgaria (Dr Chaveeva); Hospital Universitario Cruces, Biocruces Bizkaia Health Research Institute, UPV/EHU, Bizkaia, Spain (Dr Burgos); Hospital Universitario San Cecilio, Instituto de Investigación Biosanitaria, Granada, Spain (Dr Molina); Chelsea and Westminster Hospital, Imperial College London, London, United Kingdom (Dr Savvidou); Hospital Universitario La Paz, Madrid, Spain (Dr De La Calle); Ospedale Maggiore Policlinico, Milan, Italy (Dr Persico); Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy (Dr Persico); Hospital Universitario "12 De Octubre," Madrid, Spain (Dr Rojas); Lewisham University Hospital, London, United Kingdom (Dr Sau); Royal London Hospital, London, United Kingdom (Dr Greco); Hospital Necker-Enfants Malades, Paris, France (Dr O'Gorman); Hospiten Group, Tenerife, Spain (Dr Plasencia); Kingston Hospital, Kingston upon Thames, United Kingdom (Dr Pereira); University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium (Dr Jani); University Hospital A Coruña, Coruña, Spain (Dr Valino); Hospital Universitario de Torrejón, Madrid, Spain (Dr del Mar Gil); School of Health Sciences, Universidad Francisco de Vitoria, Madrid, Spain (Dr del Mar Gil); Fetal Medicine Foundation, London, United Kingdom (Dr Maclagan); and the University of Exeter, Exeter, United Kingdom (Drs A. Wright and D. Wright).

Received April 16, 2020; revised June 22, 2020; accepted June 23, 2020.

The authors report no conflict of interest.

The study was supported by a grant from the Fetal Medicine Foundation (Charity no: 1037116). The placebo and progesterone capsules were manufactured, packaged, labeled, stored, and distributed free of charge by Besins Healthcare, Brussels, Belgium. These bodies had no involvement in the study design; in the collection, analysis, and interpretation of data; in the preparation, review, or approval of the manuscript; and in the decision to submit the article for publication.

The trial is registered in the European Union Drug Regulating Authorities Clinical Trials database (EudraCT number 2015-005180-16) and with ISRCTN (ISRCTN66445401).

Corresponding author: Kypros H. Nicolaides, MD. kypros@fetalmedicine.com

Appendix

Contents

SUPPLEMENTAL TABLE 1

Regression coefficients from mixed-effects logistic regression model for the incidence of spontaneous delivery between 24^{+0} weeks and 33^{+6} weeks' gestation

Coefficient	Estimate	SE	*P* value	OR	LCL	UCL
Intercept	−2.475	0.234	.000	—	—	—
Monochorionic/dichorionic	0.646	0.237	.006	1.907	1.199	3.033
Parous previous preterm birth/nulliparous	0.967	0.374	.010	2.631	1.263	5.480
Parous previous term birth/nulliparous	−0.464	0.245	.059	0.629	0.389	1.017
IVF conception/non-IVF conception	−0.216	0.271	.425	0.806	0.474	1.371
Progesterone/placebo	0.297	0.215	.167	1.345	0.883	2.049

IVF, in vitro fertilization; *LCL*, lower confidence limit; *OR*, odds ratio; *SE*, standard error; *UCL*, upper confidence limit.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 2
Regression coefficients from mixed-effects logistic regression for the incidence of spontaneous delivery between 24^{+0} weeks and 33^{+6} weeks' gestation incorporating cervical length term and interaction with treatment

Coefficient	Estimate	SE	*P* value	OR	LCL	UCL
Intercept	−2.967	0.295	<.001	—	—	—
Monochorionic/dichorionic	0.599	0.243	.014	1.82	1.13	2.93
Parous previous preterm birth/nulliparous	0.909	0.384	.018	2.48	1.17	5.27
Parous previous term birth/nulliparous	−0.466	0.248	.06	0.63	0.39	1.02
IVF conception/non-IVF conception	−0.199	0.276	.471	0.82	0.48	1.41
35−Cx if Cx <35, 0 if Cx ≥0	0.194	0.057	.001	1.21	1.09	1.36
Progesterone	0.643	0.292	.028	1.90	1.07	3.37
(35−Cx if Cx <35, 0 if Cx ≥0)×progesterone	−0.131	0.075	.08	0.88	0.76	1.02

The fitted treatment effect (log OR) is 0.643−0.131×(35−Cx) if Cx <35 and 0.643 if Cx ≥35. This is shown graphically in Supplemental Figure 1. The fitted treatment effect is 0 when is 0.643 −0.131×(35−Cx)=0, which gives Cx=35−0.643/0.131=30 mm. For Cx <30, the fitted effect is negative (benefit), and for Cx >30, the fitted effect is positive (harm). Supplemental Figure 2 shows subgroup effects determined using a cutoff of 30 mm obtained from the fitted model. This was not prespecified in the statistical analysis plan and should be interpreted as exploratory.

Cx, cervical length; *IVF*, in vitro fertilization; *LCL*, lower confidence limit; *OR*, odds ratio; *SE*, standard error; *UCL*, upper confidence limit.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 3
Interclass correlations among neonatal outcomes

Outcome	Interclass correlation	95% CI	
		Lower	Upper
Birthweight <1500 g	0.691	0.664	0.715
Birthweight <2000 g	0.592	0.560	0.623
Birthweight <3rd percentile	0.226	0.179	0.272
Birthweight <5th percentile	0.239	0.192	0.284
Birthweight <10th percentile	0.274	0.229	0.319
Stillbirth	0.313	0.269	0.356
Neonatal morbidity	0.584	0.551	0.615
Intraventricular hemorrhage	0.104	0.056	0.152
Respiratory distress syndrome	0.619	0.588	0.648
Retinopathy of prematurity	0.475	0.436	0.512
Necrotizing enterocolitis	0.000	-0.049	0.048
Neonatal sepsis	0.266	0.220	0.311
Neonatal anemia	0.423	0.382	0.462
Neonatal therapy	0.654	0.625	0.681
Admission to neonatal intensive care unit	0.621	0.590	0.650
Ventilation	0.645	0.615	0.672

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 4

Regression coefficients from mixed-effects Cox regression for the incidence of spontaneous birth between 24^{+0} and 33^{+6} weeks' gestation incorporating Cx and interaction with treatment

Coefficient	Estimate	SE	HR (95% CI)	*P* value
Progesterone	0.6050	0.2753	1.8313 (1.0677–3.1410)	.028
(35−Cx)×(Cx<35)×progesterone	−0.1308	0.0663	0.8774 (0.7704–0.9992)	.049
Monochorionic	0.4760	0.2242	1.6096 (1.0373–2.4977)	.034
(35−Cx)×(Cx<35)	0.1821	0.0488	1.1997 (1.0902–1.3202)	<.001
Parous with previous preterm birth	0.7506	0.3329	2.1182 (1.1030–4.0678)	.024
Parous with previous term birth	−0.4530	0.2344	0.6357 (0.4015–1.0065)	.053
IVF conception	−0.2173	0.2616	0.8047 (0.4819–1.3437)	.406

CI, confidence interval; *Cx*, cervical length; *HR*, hazard ratio; *IVF*, in vitro fertilization; *SE*, standard error.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 5

Regression coefficients from mixed-effects Cox regression for the incidence of miscarriage or spontaneous birth between randomization and 33^{+6} weeks' gestation incorporating Cx and interaction with treatment

Coefficient	Estimate	SE	HR (95% CI)	*P* value
Progesterone	0.3360	0.2275	1.3993 (0.8959–2.1855)	.140
(35−Cx)×(Cx<35)×progesterone	−0.1125	0.0549	0.8936 (0.8025–0.9951)	.040
Monochorionic	0.6962	0.1829	2.0060 (1.4016–2.8712)	<.001
(35−Cx)×(Cx<35)	0.1544	0.0369	1.1670 (1.0855–1.2546)	<.001
Parous with previous preterm birth	0.5256	0.2929	1.6915 (0.9527–3.0034)	.073
Parous with previous term birth	−0.4657	0.1957	0.6277 (0.4277–0.9211)	.017
IVF conception	−0.0941	0.2141	0.9102 (0.5983–1.3849)	.661

CI, confidence interval; *Cx*, cervical length; *HR*, hazard ratio; *IVF*, in vitro fertilization; *SE*, standard error.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 6
Regression coefficients from mixed-effects Cox regression for the incidence of birth for any reason between randomization and 33^{+6} weeks' gestation incorporating Cx and interaction with treatment

Coefficient	Estimate	SE	HR (95% CI)	*P* value
Progesterone	0.1410	0.1953	1.1515 (0.7852–1.6886)	.470
(35−Cx)×(Cx<35)×progesterone	−0.0352	0.0464	0.9654 (0.8815–1.0573)	.448
Monochorionic	0.8341	0.1566	2.3028 (1.6941–3.1301)	<.001
(35−Cx)×(Cx<35)	0.1211	0.0338	1.1287 (1.0564–1.2059)	<.0001
Parous with previous preterm birth	0.5083	0.2646	1.6625 (0.9898–2.7924)	.055
Parous with previous term birth	−0.3989	0.1677	0.671 (0.4831–0.9321)	.017
IVF conception	0.0680	0.1809	1.0703 (0.7509–1.5258)	.707

CI, confidence interval; *Cx*, cervical length; *HR*, hazard ratio; *IVF*, in vitro fertilization; *SE*, standard error.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 7
Hazard ratios stratified according to the gestational age at birth shown in Figure 4

Outcome	Cervical length (mm)	Gestational age at birth (wk)	HR (95% CI)[a]
Spontaneous births from 24 wk	<30	<32	0.2186 (0.0533–0.8966)
		32–34	1.4162 (0.3118–6.4327)
		All	0.4950 (0.1851–1.3236)
	≥30	<32	1.4006 (0.7344–2.6710)
		32–34	1.8118 (0.9667–3.3955)
		All	1.5768 (1.0065–2.4701)
Spontaneous births from randomization	<30	<32	0.2334 (0.0786–0.6932)
		32–34	1.4162 (0.3118–6.4327)
		All	0.3953 (0.1710–0.9141)
	≥30	<32	0.9890 (0.6204–1.5768)
		32–34	1.8118 (0.9667–3.3955)
		All	1.2169 (0.8396–1.7637)
All births from randomization	<30	<32	0.4466 (0.1878–1.0624)
		32–34	2.6625 (0.6578–10.7769)
		All	0.7424 (0.3706–1.4871)
	≥30	<32	0.9192 (0.6099–1.3854)
		32–34	1.6087 (0.9535–2.7144)
		All	1.1290 (0.8195–1.5554)

CI, confidence interval; *HR*, hazard ratio.

[a] Hazard ratios for mixed-effects Cox regression allowing for chorionicity, parity, method of conception, and hospital.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 8
Nonserious adverse events according to the trial group

Adverse event	Progesterone group (n=596)	Placebo group (n=598)	*P* value
At least one adverse event	200 (34.4)	186 (31.7)	.35
No adverse event	382 (65.6)	401 (68.3)	.35
Vaginal discharge	69 (11.9)	78 (13.3)	.48
Vaginal itching	42 (7.2)	44 (7.5)	.91
Vaginal pain or discomfort	34 (5.8)	34 (5.8)	1.00
Vaginal bleeding	15 (2.6)	7 (1.2)	.09
Headache and or dizziness	43 (7.4)	29 (4.9)	.09
Fatigue	7 (1.2)	6 (1.0)	.79
Depression	5 (0.9)	6 (1.0)	1.00
Insomnia	2 (0.3)	4 (0.7)	.69
Nausea and or vomiting	18 (3.1)	15 (2.6)	.60
Abdominal pain or discomfort	29 (5.0)	31 (5.3)	.89
Diarrhea or constipation	10 (1.7)	12 (2.0)	.83
Joint pain	12 (2.1)	9 (1.5)	.52
Swelling of extremities	4 (0.7)	6 (1.0)	.75
Palpitations	5 (0.9)	2 (0.3)	.29
Itching and or skin rash	11 (1.9)	17 (2.9)	.34
Urinary tract infection	9 (1.5)	8 (1.4)	.81
Other adverse events	14 (2.4)	11 (1.8)	.55

Data are presented as n (%). The percentages of adverse events were calculated after excluding 21 cases of withdrawal of consent and 4 cases with loss to follow-up. Women who withdrew their consent for participation in the study did not allow their data collected before withdrawal to be used in any analysis, and in pregnancies with loss to follow-up, we were unable to know whether they had any adverse events. The group of other adverse events includes 5 cases of gingivitis, 6 cases of nosebleed, 2 cases of varicose veins, 5 cases of hemorrhoids, 2 cases of hypotension, 1 case of hypoglycemia, 1 case of blurred vision, 1 case of numbness of the hands, 1 case of pulmonary embolism, and 1 case with an episode of seizure.

Comparison between groups was done by the Fisher exact test.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL TABLE 9
Pregnancy complications according to the trial group

Pregnancy complications	Progesterone group (n=567)	Placebo group (n=561)	*P* value
Preeclampsia	48 (8.5)	55 (9.8)	.47
Gestational hypertension	17 (3.0)	16 (2.9)	1.00
Gestational diabetes mellitus	55 (9.7)	45 (8.0)	.35
Intrahepatic cholestasis	19 (3.4)	16 (2.9)	.73

Data are presented as n (%). The comparison between groups was performed with the Fisher exact test.

The denominators in the progesterone and placebo groups exclude pregnancies resulting in delivery at <24 weeks' gestation.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

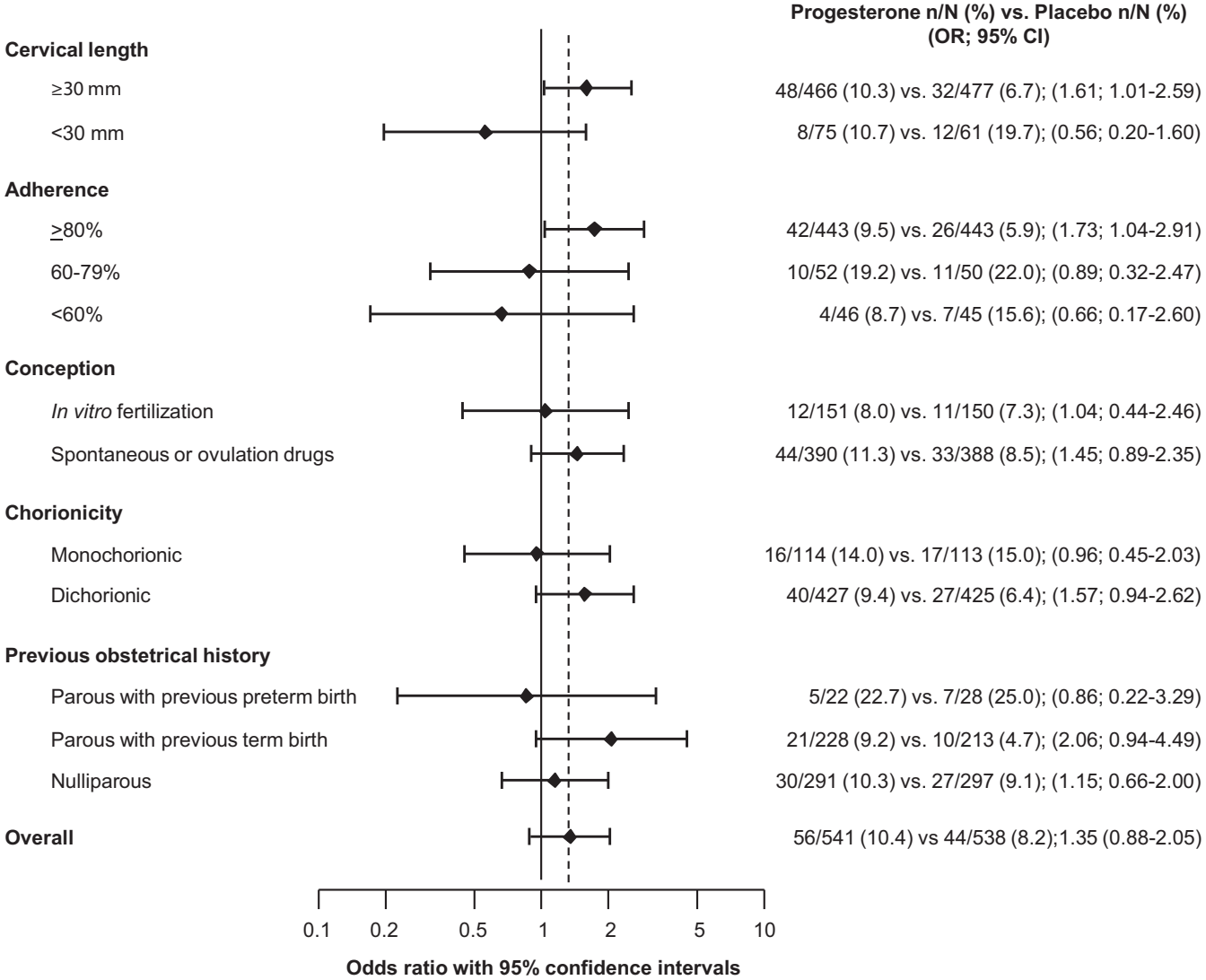
SUPPLEMENTAL TABLE 10
Adherence according to the trial group

Adherence	All (n=1169)	Progesterone group (n=582)	Placebo group (n=587)	*P* value
≥80%	952 (81.4)	474 (81.4)	478 (81.4)	1.00
60%–79.9%	119 (10.2)	60 (10.3)	59 (10.1)	.92
<60%	98 (8.4)	48 (8.2)	50 (8.5)	.92

Data are presented as n (%). Comparison between groups was done by the Fisher exact test.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL FIGURE 1
Subgroup analysis

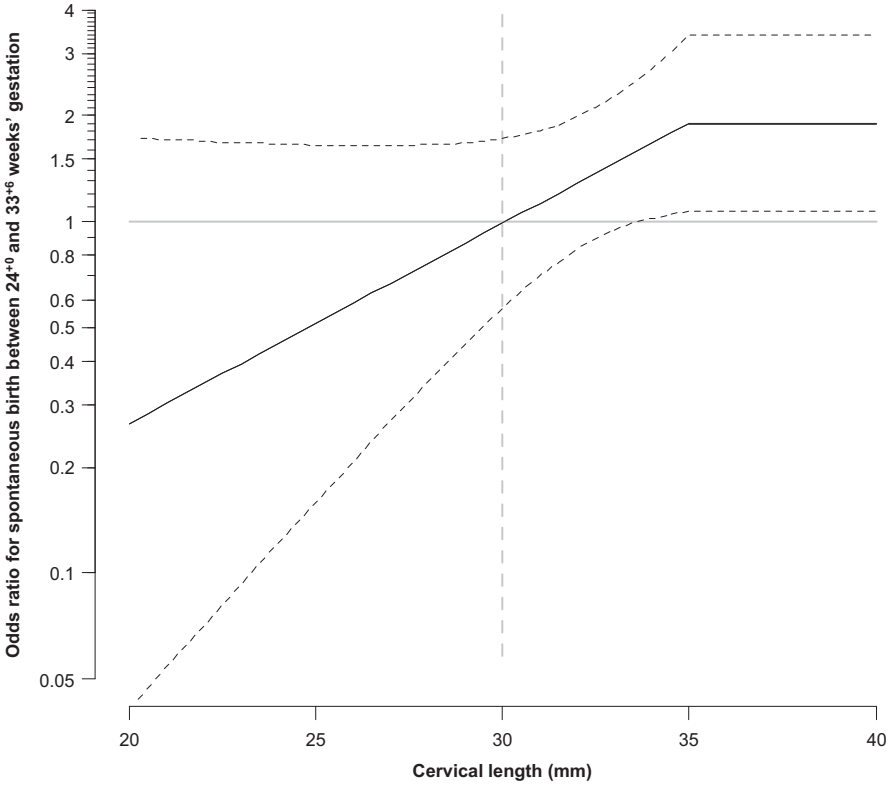


OR in the progesterone group with 95% CIs in different groups according to cervical length, adherence, method of conception, chorionicity, and parity.

CI, confidence interval; *OR*, odds ratio.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.

SUPPLEMENTAL FIGURE 2
Fitted treatment effect according to the interaction model



The full line shows the estimated effect. Broken lines show upper and lower 95% confidence limits.

Rehal et al. Vaginal progesterone in unselected twin pregnancies. Am J Obstet Gynecol 2021.