Ultrasound Obstet Gynecol 2011; **38**: 272–280
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.9093

Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone

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KEYWORDS: placebo-controlled; preterm delivery; progesterone; randomized trial; twin pregnancies

ABSTRACT

Objective *Studies on high-risk singleton gestations have shown a preventive effect of progesterone treatment on preterm delivery. This study was conducted to investigate the preventive effect of vaginal micronized progesterone in a large population of twin gestations.*

Methods *This was a double-blind, placebo-controlled randomized trial performed in 17 centers in Denmark and Austria. Women with twin gestations were randomized to daily treatment with progesterone pessaries or apparently identical placebo pessaries, starting from 20–24 weeks until 34 weeks' gestation. Primary outcome was incidence of delivery before 34 weeks' gestation. Secondary outcomes were maternal and neonatal complications and long-term infant follow-up, by Ages and Stages Questionnaire (ASQ), 6 months and 18 months after the expected date of delivery. We also updated a published meta-analysis to include our data and those of another recently published twin trial.*

Results *A total of 677 women were randomized to the two treatments. Two women in the placebo group were lost to follow-up. Baseline characteristics for the groups were similar. Incidence of delivery before 34 weeks was 15.3% in the progesterone group vs 18.5% in the placebo group (odds ratio, 0.8 (95% CI, 0.5–1.2)). Risks of maternal and neonatal complications were comparable for the two groups. Mean ASQ scores at 6 months and 18 months were not significantly different between the two groups (215 for infants in the progesterone group and 218 for infants in the placebo group at 6 months (*$P = 0.45$*) and 193 and 194, respectively, at 18 months (*$P = 0.89$*)). The meta-analysis gave a pooled odds ratio of 1.06 (95% CI, 0.86–1.31).*

Conclusion *Progesterone treatment did not prevent preterm delivery in twin gestations. There were no harmful effects to fetuses and infants of maternal progesterone treatment. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Very preterm delivery is an obstetric complication associated with high perinatal morbidity and mortality, and survival of the preterm infant is related directly to gestational age at delivery. Survival increases from less than 50% before 24 weeks to more than 95% by 33 weeks' gestation and there is a corresponding inverse relationship between the risk of severe disability in survivors and gestational age at delivery[1,2]. Complications from preterm birth, are not limited to the neonatal period, such as in retinopathy of prematurity, intraventricular hemorrhage, necrotizing enterocolitis, respiratory disorder and sepsis; they can also constitute sequelae such as abnormal neurophysiological development in early childhood and underachievement at school[3–5].

In Austria and Denmark, multiple gestations account for approximately 2% of all pregnancies, but constitute at least 10% of cases of preterm delivery and more than half of admissions to neonatal intensive care units (NICUs). More than 25% of infants liveborn before 28 weeks' gestation are twins[6,7]. Efforts to treat or prevent preterm delivery in twin gestations, with bed rest, antibiotics, tocolytics and cerclage, have not been effective[8–10]. In contrast, it is now well-established that progesterone treatment is effective in reducing preterm birth rates in women with singleton pregnancies and previous preterm birth, and potentially also in women with a short

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Accepted: 27 June 2011

cervix[11–18]. As mechanisms for initiation of preterm labor or preterm shortening of the cervix may be different in twin compared with singleton pregnancies, results from singleton studies cannot be extrapolated to twin gestations. Hence, several studies on the preventive effect of progesterone on preterm birth in multiple gestations were planned following the publication of two large singleton trials in 2003[19,20].

The PREDICT study was conducted in order to test the hypothesis that in twin gestations, treatment with progesterone pessaries, compared with placebo treatment, would reduce the rate of delivery before 34 weeks' gestation.

METHODS

Participants

Women were recruited to this double-blind, placebo-controlled, randomized clinical trial, between 1 June 2006 and 31 October 2008, from 13 hospitals in Denmark and four hospitals in Austria. Women with a live, diamniotic twin pregnancy and chorionicity assessed by ultrasound before 16 weeks' gestation were eligible for recruitment. Exclusion criteria were: (1) age < 18 years; (2) known allergy to progesterone or peanuts (as the active treatment contained peanut oil); (3) history of hormone-associated thromboembolic disorders; (4) rupture of membranes; (5) treatment for or signs of twin-to-twin transfusion syndrome (TTTS); (6) intentional fetal reduction; (7) known major structural or chromosomal fetal abnormality; (8) known or suspected malignancy in genitals or breasts; (9) known liver disease; (10) women with higher-order multiple pregnancies; (11) women who did not speak and understand Danish or German, as appropriate. All participants gave written informed consent before enrolment. The Danish Data Protection Agency, the Danish and Austrian Medicines Agencies, the Danish Scientific Ethical Committee and the Ethical Committee of the Medical University of Vienna approved the study.

Intervention and randomization

Participants were assigned randomly to receive either vaginal progesterone pessaries (200 mg; Utrogestan, Besins Healthcare, Brussels, Belgium) or vaginal placebo pessaries (Besins Healthcare). Each participant was supplied with pessaries in five blister packs of 21 pessaries each (105 pessaries in total) in one sealed box. Utrogestan pessaries contained micronized progesterone, peanut oil, soy lecithin, gelatine, glycerol and titanium dioxide (E171) in soft capsules. The placebo pessaries contained safflower oil, gelatine, glycerol and titanium dioxide (E171) in identical soft capsules.

The Perinatal Epidemiology Research Unit, Skejby Hospital, Århus, Denmark created a randomization sequence with a 1 : 1 ratio. The boxes of progesterone and placebo were packed and labeled by Bilcare (Waller House, Wales, UK) according to this randomization sequence and shipped to Copenhagen University Hospital, from where the study medication was distributed to the participating departments. The randomization sequence consisted of batches of 18 boxes with permuted blocks of randomly mixed sizes (two, four or six). We stratified by center and chorionicity using an interactive voice-response randomization system at the above-mentioned Perinatal Epidemiology Research Unit. Each local researcher telephoned the randomization system, entered the participant's social security number and chorionicity, and was given a randomization number that corresponded to a specific treatment box from a given batch.

All participants and study personnel were blinded to treatment assignment for the duration of the trial, and the randomization code was not broken before all data had been collected, including the infant follow-up at 18 months of age. Only the statistician and the independent Data Monitoring and Safety Committee had access to unblinded data during the study period. None of these people had any contact with participants in the study.

Procedures

Women were randomized between 18 and 24 weeks' gestation. In order to give the women at least 1 week to decide whether to participate, they were informed about the project twice: at the nuchal translucency scan at 11–14 weeks and again at the anomaly scan at 19–21 weeks' gestation, or at the anomaly scan and again at the cervical scan at 23 weeks' gestation. Gestational age was based on crown–rump length of the largest twin at the time of the nuchal translucency scan. All women had an anomaly scan before inclusion. We aimed to perform a cervical scan before inclusion in approximately two thirds of the participants in order to perform subgroup analysis on women with a short cervix.

Treatment started between 20 + 0 weeks and 23 + 6 weeks' gestation and was self-administered daily by the participants. Treatment was planned to continue until 33 + 6 weeks' gestation or until occurrence of either rupture of membranes or delivery. Additional indications for treatment cessation were: (1) symptomatic placenta previa; (2) TTTS; (3) suspected thromboembolic disorder; (4) severe liver disease. Participants were interviewed by telephone at 25, 30, 34 and 36 weeks' gestation in order to assess side effects and compliance.

Women who presented with preterm labor were treated with admission, corticosteroids, tocolytics and antibiotics at the treating physician's discretion and according to the guidelines of the individual department.

After delivery, information on onset of labor, mode of delivery, infant birth weight, delivery complications and postpartum complications were retrieved from patient files. Information on neonatal complications was collected from discharge letters for all infants who had been admitted to a NICU.

Physical and neurological development of the children was assessed 6 and 18 months after the estimated date

of delivery via Ages and Stages Questionnaire (ASQ)[21,22]. The ASQ is a parent-administered structured questionnaire that includes questions on five domains of child development: gross motor, fine motor, communication, problem solving and personal-social, and has been validated against the Bayley Scales of Infant Development[23]. Scores for all five domains were summed to give a total score for each infant. We used the 24-months ASQ at 18 months to allow for response time and to facilitate distinction between low and high scores. A cut-off of 115 points (based on mean score minus 2 SD for the first 40 questionnaires received) was chosen to define a low score.

Outcomes and statistics

The primary outcome was incidence of delivery before 34 + 0 weeks' gestation. Prespecified secondary outcomes were: (1) delivery before 22, 28 and 32 weeks' gestation; (2) number of liveborn infants; (3) treatment with tocolytics and corticosteroids; (4) birth weight; (5) selected neonatal complications; (6) neurophysiological development 6 and 18 months after the estimated date of delivery.

A secondary aim of the trial was to investigate a possible relationship between cervical length and progesterone treatment in the subgroup that had a cervical-length measurement before starting treatment. A cervical scan was performed before treatment in only approximately 65% of participants, and these data are therefore not included in the present paper. However, these data are presented in a separate subanalysis[24].

The estimated sample size of 650 participants was based on a 50% reduction in a previously reported incidence of 13% for spontaneous delivery before 34 weeks' gestation in a large Danish twin population[25], a power of 80%, and a significance level of 5%.

All analyses were performed according to the intention-to-treat principle. Binary outcomes were analyzed by logistic regression models and continuous outcomes by linear regression models. For infant outcomes, the correlation within pairs of twins was accounted for by considering robust estimates of variance based on the method of generalized estimating equations (GEE)[26]. GEE models for mean ASQ scores were adjusted for time between estimated date of delivery and the date on which the questionnaire was completed by the parents. Results are presented as odds ratios (OR) with corresponding 95% CIs. Statistical analyses were performed in cooperation with an external statistician.

Women who declined to be randomized (decliners) were invited to fill out the trial's background questionnaire in order to compare baseline characteristics for participants and decliners. The Danish Data Protection Agency permitted us to collect data on women who were informed about but not included in the trial from the Danish National Birth Register. Data on Austrian decliners was collected from local obstetric databases. Decliners were invited to sign a consent form allowing for reviews of patient files in case additional information was needed. Data on non-participants were analyzed anonymously.

RESULTS

During the study period 2256 women with twin pregnancies had a nuchal translucency scan at one of the 17 participating departments (Figure 1), and approximately 67% ($n = 1507$) of them were assessed for eligibility. Of the 1288 who were informed, 677 (52.6%) women were randomized. We stopped informing women about the trial when the sample size of 650 had been achieved (22 September 2008). Women already informed about the trial were, however, allowed to enter the trial until 31 October 2008. Outcome measures were available for 675 women, as one woman was lost to follow-up and another withdrew her consent; both women were from the placebo group. Baseline characteristics were comparable for the groups (Table 1). There were slightly more monochorionic gestations in the placebo group (16.6% vs. 12.9%) but the difference was not statistically significant ($P = 0.19$). Six women underwent cerclage placement before inclusion, two from the progesterone group (2/334) and four from the placebo group (4/343).

Amongst the 611 women who were informed about the trial but did not participate, 403 filled out the background questionnaire. A total of 85 women did not respond regarding participation in the trial. Decliners and participants were comparable with respect to baseline characteristics (Table 1).

The mean (SD) gestational age at delivery was 252 (19.6) days in the progesterone group vs 251 (19.1) days in the placebo group ($P = 0.43$). The rate of the primary outcome of delivery before 34 weeks' gestation was 15.3% in the progesterone group and 18.5% in the placebo group (OR, 0.8 (95% CI, 0.5–1.2)). Figure 2 shows a Kaplan–Meier plot comparing the proportion of women remaining pregnant between randomization and delivery in the two treatment groups. The estimated distributions were similar ($P = 0.65$). Categorical maternal outcomes as well as pregnancy outcomes are shown in Table 2. There were no statistically significant differences between the two groups, except for risk of emergency Cesarean section, which was reduced in the progesterone group (OR, 0.7 (95% CI, 0.5–0.9). The number of days of maternal hospitalization was comparable between the two groups: median, 9 (interquartile range, 2–82) days for the progesterone group and median, 9 (interquartile range, 1–92) days in the placebo group ($P = 0.42$). In 17 pregnancies, a fetus or infant died. These included nine pregnancies (13 fetuses/infants) in the progesterone group and eight pregnancies (12 fetuses/infants) in the placebo group (OR, 1.1 (95% CI, 0.4–2.9)). One woman from the progesterone group and one woman from the placebo group received cerclage as cointervention after inclusion.

The mean birth weight was comparable for the two groups: 2468 g in the progesterone group versus 2418 g in the placebo group ($P = 0.41$). Table 3 shows that neonatal outcomes did not differ between the two groups. Six infants in the progesterone group were born with malformations of the extremities, whereas there were

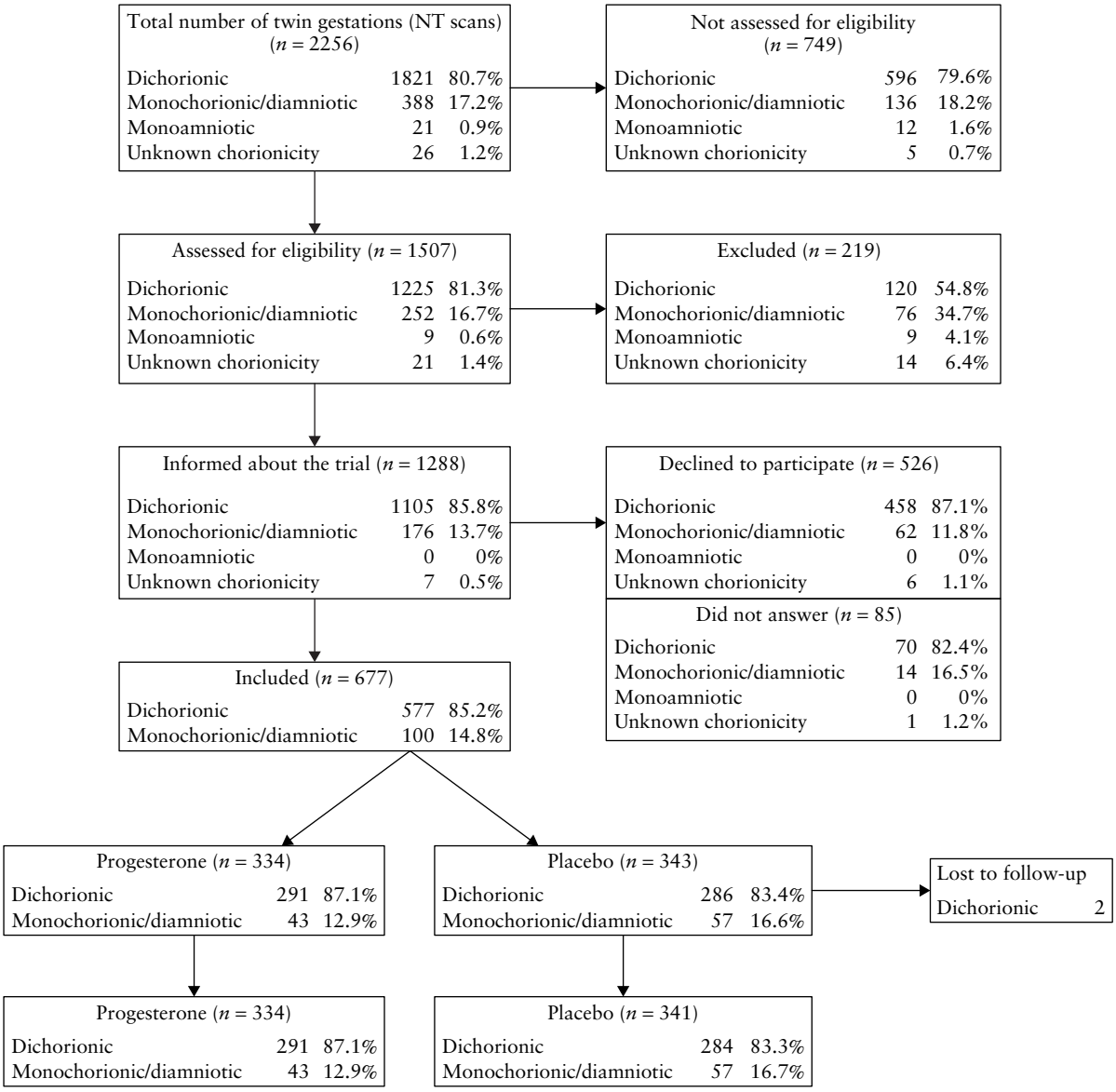

Figure 1 Flowchart of the trial.

none in the placebo group. The affected cases constituted: four infants with pes equinovarus, of which two were diagnosed by ultrasound before randomization; one infant with malformation of three fingers on one hand; one infant with bilateral contractures of hands. In the latter case, valproate embryopathy was suspected.

We received ASQs from 1050 (79.2%) of the liveborn children at 6 months of age; 78.8% from the progesterone group versus 79.7% from the placebo group. The mean ASQ score was 215 (SD, 37.5) in the progesterone group and 218 (SD, 36.7) in the placebo group ($P = 0.45$). A total of 991 (74.8%) children had an 18-month ASQ assessment, again with similar response rates in the two groups (76.8% vs 72.8%). The mean ASQ scores at 18 months were 193 (SD, 42.6) and 194 (SD, 40.6), respectively ($P = 0.89$). The proportion of infants with an 18-month ASQ score below the selected cut-off of 115 was 3.8% in the progesterone group vs 3.7% in the placebo group.

Table 4 shows side effects and compliance according to treatment. There were no significant differences in reported side effects. The mean number of pessaries returned after treatment was similar between the two groups. Nine women in the progesterone group and four women in the placebo group never started treatment because they changed their minds with respect to participation ($n = 8$), they miscarried or a fetus died *in utero* ($n = 2$) or they were withdrawn from the study ($n = 3$, one due to signs of TTTS, another due to Factor V Leiden homozygosity and the third because chorionicity had not been assessed before 16 weeks' gestation). These women all returned the boxes with pessaries unopened.

The slightly larger proportion of monochorionicity in the placebo group can be explained in part by the fact that the randomization sequence allocated placebo treatment to the first monochorionic gestation randomized at each center. Combined with a low number of monochorionic inclusions in six centers, this allocation

Table 1 Baseline characteristics for women with twin pregnancies who were eligible to participate in the trial

Characteristic	*Progesterone group (n = 334)*	*Placebo group (n = 343)*	*Decliners who filled out background questionnaire (n = 403)*
Maternal age (years)	32.0 ± 4.5	31.9 ± 4.4	31.9 ± 4.3
Nulliparous	169/333 (50.8)	193/343 (56.3)	222/399 (55.6)
Previous delivery before 34 weeks	5/333 (1.5)	10/343 (2.9)	5/399 (1.3)
Previous delivery between 34 and 37 weeks	17/333 (5.1)	11/343 (3.2)	10/399 (2.5)
Previous miscarriage after 12 weeks	8/333 (2.4)	11/343 (3.2)	19/399 (4.8)
Previous miscarriage before 12 weeks	77/333 (23.1)	76/343 (22.2)	77/399 (19.3)
Body mass index (kg/m^2)	22.6 (20.6–26.0)	22.7 (20.6–25.7)	22.7 (20.8–25.7)
Completed ≥ 12 years in school*	231/328 (70.4)	266/339 (78.5)	294/398 (73.9)
Marital status			
Married	199/333 (59.8)	205/342 (59.9)	232/403 (57.6)
Unmarried but cohabiting	127/333 (38.1)	133/342 (38.9)	149/403 (37.0)
Living alone	7/333 (2.1)	4/342 (1.2)	22/403 (5.5)
Fertility treatment	156/334 (46.7)	163/343 (47.5)	198/402 (49.3)
Previous progesterone treatment in current pregnancy†	106/333 (31.8)	120/342 (35.1)	130/402 (32.3)
Do not remember	2/333 (0.6)	4/342 (1.2)	25/402 (6.2)
Smoking before pregnancy	88/333 (26.4)	88/342 (25.7)	91/403 (22.6)
Smoking during pregnancy	36/333 (10.8)	33/342 (9.6)	39/403 (9.7)
Monochorionic	43/334 (12.9)	57/343 (16.6)	48/432 (11.1)
Medical disorders before pregnancy	77/333 (23.1)	72/342 (21.1)	67/383 (17.5)
Gestational age at randomization (days)	146.0 (139–157)	146.5 (139–158)	154.0 (138–164)‡

Data presented as *n* (%), mean ± SD or median (interquartile range). Two women, who were included but never started project treatment, did not return the background questionnaire. *Missing cases are women that did not provide details on educational level. †In relation to fertility treatment or to prevent spontaneous miscarriage. ‡Gestational age at response to participation.

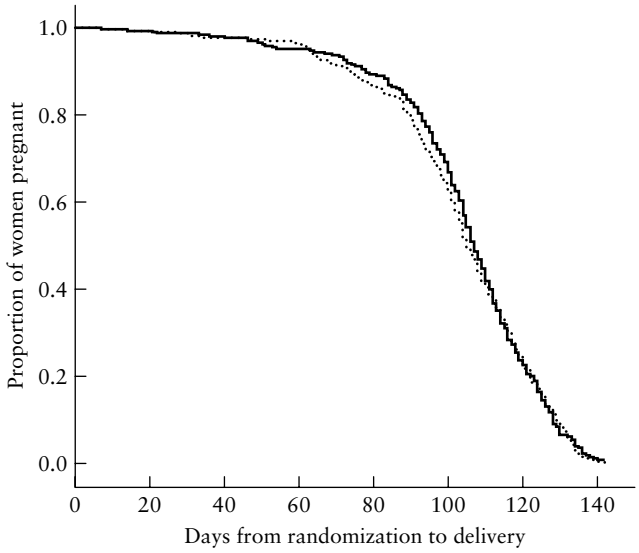

Figure 2 Proportions of women remaining pregnant from randomization to delivery in the two treatment groups (progesterone group (———) and placebo group (· · · · · ·)) were similar (log rank test, $P = 0.65$).

sequence yielded an excess placebo allocation of nine. In addition, one center unfortunately misclassified three gestations at randomization; two cases were randomized as monochorionic but review of patient files showed that they were actually dichorionic, and one case was randomized as dichorionic but was in fact monochorionic.

We performed subgroup analyses according to chorionicity on selected outcomes (these analyses were not prespecified). For dichorionic gestations, the mean gestational age at delivery or intrauterine death was 252 (SD, 20.8) days for the progesterone group vs 252 (SD, 19.8) days for the placebo group ($P = 0.74$), and the mean birth weight was similar in the two groups: 2475 (SD, 588) g and 2455 (SD, 547) g ($P = 0.83$). The mean gestational age at delivery or intrauterine death was 252 (SD, 14.1) days in the progesterone group vs 245 (SD, 22.0) days in the placebo group for monochorionic gestations ($P = 0.08$), and the rate of spontaneous delivery or intrauterine death before 34 weeks' gestation was 9.3% vs 15.8%, respectively ($P = 0.39$). The mean birth weight was 2420 (SD, 472) g compared with 2243 (SD, 589) g ($P = 0.10$). The proportion of infants with birth weight < 1500 g was 1.2% (1/84) in the progesterone group vs 13.2% (15/114) in the placebo group (OR, 0.1 (95% CI, 0.0–0.6)). Four infants died during delivery or within the first week of delivery amongst the monochorionic gestations. All four were from the placebo group, as were the six infants who had a 5-min Apgar score < 7. There were no statistically significant differences in other selected complications.

For decliners, the mean gestational age at delivery or intrauterine death was 248 (SD, 21.5) days for monochorionic gestations and the mean birth weight was 2367 (SD, 598) g. The corresponding figures were 253 (SD, 19.6) days and 2488 (SD, 529) g for dichorionic gestations. The rate of intrauterine death was 0.5% (3/611 pregnancies) and infant death (including stillbirth) was observed in 2.3% (28/1219) of infants. There were five cases of infants with foot malformations (5/601 pregnancies, 5/1202 infants) amongst women who were informed but not included. Information on malformations

Table 2 Maternal and twin pregnancy outcomes according to treatment group: progesterone ($n = 334$) or placebo ($n = 341$)

Outcome	*Progesterone group* (n *(%)*)	*Placebo group* (n *(%)*)	*Odds ratio (95% CI)*
Gestational age at delivery			
< 22 weeks	1/334 (0.3)	1/341 (0.3)	1.0 (0.1–16.4)
< 28 weeks	9/334 (2.7)	7/341 (2.1)	1.3 (0.5–3.6)
< 32 weeks	24/334 (7.2)	31/341 (9.1)	0.8 (0.4–1.3)
< 34 weeks	51/334 (15.3)	63/341 (18.5)	0.8 (0.5–1.2)
< 34 weeks, spontaneous delivery	42/334 (12.6)	53/341 (15.5)	0.8 (0.5–1.2)
< 34 weeks, induced delivery	9/334 (2.7)	10/341 (2.9)	1.0 (0.4–2.3)
< 37 weeks	158/334 (47.3)	179/341 (52.5)	0.8 (0.6–1.1)
Delivery by Cesarean section	207/332 (62.3)	232/338 (68.6)	0.8 (0.5–1.0)
Emergency Cesarean section	109/332 (32.8)	141/338 (41.7)	0.7 (0.5–0.9)
Planned Cesarean section	98/332 (29.5)	91/338 (26.9)	1.1 (0.8–1.6)
Number of pregnancies with 2, 1 or 0 liveborn infants			
2	330/334 (98.8)	336/341 (98.5)	1.2 (0.3–4.6)
1	3/334 (0.9)	3/341 (0.9)	1.0 (0.2–5.1)
0	1/334 (0.3)	2/341 (0.6)	0.5 (0.0–5.6)
Miscarriage	1/334 (0.3)	1/341 (0.3)	1.0 (0.1–16.4)
Intrauterine death*	2/334 (0.6)	2/341 (0.6)	1.0 (0.1–7.3)
Infant death during delivery			
One infant	1/334 (0.3)	1/341 (0.3)	1.0 (0.1–16.4)
Both infants	0/334 (–)	1/341 (0.3)	NA
Corticosteroid treatment for fetal lung maturation	76/334 (22.8)	97/341 (28.4)	0.7 (0.5–1.0)
Tocolytic therapy	41/333 (12.3)	60/341 (17.6)	0.7 (0.4–1.0)
Maternal adverse outcome			
Gestational diabetes	16/332 (4.8)	12/341 (3.5)	1.4 (0.6–3.0)
Increased liver enzymes	11/332 (3.3)	25/341 (7.3)	0.4 (0.2–0.9)
Pre-eclampsia	27/332 (8.1)	30/341 (8.8)	0.9 (0.5–1.5)
Thromboembolic event	0/332 (0)	1/341 (0.3)	NA

*All cases of intrauterine death involved death of one twin only. NA, not applicable.

was missing in the Danish National Birth Register for 10 women who were informed but did not participate.

Other studies have reported intrauterine death or delivery before 34 weeks as the primary outcome[27,28]. In our population, only one pregnancy with intrauterine death resulted in delivery after 34 weeks' gestation, whereas the other three cases delivered before 34 weeks. The rate of intrauterine death or delivery before 34 weeks in our population was therefore 51/334 (15.3%) in the progesterone group vs 64/341 (18.8%) in the placebo group (OR, 0.8 (95% CI, 0.5–1.2)). Figure 3 shows an updated version of the meta-analysis that was published in the Lancet in 2009[27], including our data as well as data from a recently published trial[29]. Inclusion of the newest data changed the pooled OR from 1.16 (95% CI, 0.89–1.51) to 1.06 (95% CI, 0.86–1.31).

DISCUSSION

This study is one of the largest trials to investigate the effect of progesterone treatment on prevention of preterm delivery in twin gestations. In accordance with previous trials[27–31], we found that treatment with progesterone does not prevent preterm delivery. We are the first to provide a long-term follow-up on the twins, as we assessed infants from the study both 6 and 18 months after the estimated date of delivery via the ASQ. There was no difference between ASQ scores in the two groups, and our results therefore indicate that progesterone treatment is neither beneficial nor harmful to the infants. Whereas results from previous studies, including a recent meta-analysis[27], have shown an increased but not statistically significant risk of preterm delivery in progesterone-treated women, our results did not indicate that progesterone treatment in twin gestations is harmful. In contrast, most ORs were < 1 although not significant. Inclusion of our study in the meta-analysis therefore changed the overall relative risk towards but not below 1, i.e. no effect of progesterone treatment. The rate of intrauterine death, stillbirth and infant death did not differ between the two treatment groups and was comparable to rates in women who were eligible but did not participate. All infants in the trial who were born with foot malformations were found amongst the progesterone-treated mothers. However, two of these cases were diagnosed before inclusion and the rate was comparable to the rate amongst eligible women who did not participate. In accordance with Norman *et al.*[27], we found a preventive effect of progesterone on the risk of emergency Cesarean section, with an OR of 0.7 (95% CI, 0.5–0.9). A biological explanation for the possible association between vaginal progesterone treatment and a reduced risk of Cesarean section should be investigated.

The results from our trial can be generalized to most women with twin gestations in Denmark and Austria as women were included from 13 of the largest hospitals in Denmark, where 70% of Danish twins are delivered,

Table 3 Neonatal outcome in twin pregnancies according to treatment group: progesterone ($n = 664$) or placebo ($n = 678$)

Outcome	*Progesterone group* (n *or* n *(%))*	*Placebo group* (n *or* n *(%))*	*Odds ratio (95% CI)*
Birth weight			
< 2500 g	306/659 (46.4)	357/677 (52.9)	0.8 (0.6–1.0)
< 1500 g	36/659 (5.5)	48/677 (7.1)	0.8 (0.4–1.4)
Apgar score < 7 at 5 min	10/648 (1.5)	14/669 (2.1)	0.7 (0.3–1.7)
Infant death	9/664 (1.4)	8/678 (1.2)	1.2 (0.3–4.0)
Death during delivery	1	3	
Neonatal death (within 28 days after delivery)	7	2	
Death after 28 days, but in relation to NICU admittance	0	2	
Sudden infant death	1*	1†	
Congenital or chromosomal anomalies	25/663 (3.8)	27/677 (4.0)	1.0 (0.5–1.7)
Abdomen	1	0	
CNS	2	1	
Extremities	6	0	
Heart	9	15	
Chromosome/syndrome	2‡	5§	
Thorax	1	1	
Urogenital	6	8	
Perinatal complication			
Hypoglycemia	30/659 (4.6)	48/674 (7.1)	0.6 (0.4–1.1)
Intraventricular hemorrhage	10/659 (1.5)	6/674 (0.9)	1.7 (0.5–5.6)
Jaundice	106/659 (16.1)	116/674 (17.2)	0.9 (0.6–1.3)
Necrotizing enterocolitis	1/659 (0.2)	2/674 (0.3)	0.5 (0.0–5.6)
Patent ductus arteriosus	12/659 (1.8)	19/674 (2.8)	0.6 (0.3–1.5)
Respiratory distress syndrome	73/659 (11.1)	69/674 (10.2)	1.1 (0.7–1.7)
Retinopathy of prematurity	4/659 (0.6)	4/674 (0.6)	1.0 (0.2–4.8)
Septicemia	20/659 (3.0)	18/674 (2.7)	1.1 (0.5–2.4)
Admission to NICU	307/664 (46.2)	354/678 (52.2)	0.8 (0.6–1.1)
CPAP treatment of at least 24 h	105/659 (15.9)	121/674 (18.0)	0.9 (0.6–1.3)
Respirator treatment	12/659 (1.8)	12/674 (1.8)	1.0 (0.4–2.6)

*At 4 months. †At 6 months. ‡One trisomy 21 and one Kartagener syndrome. §One trisomy 21, two siblings with idiopathic thrombocytopenia and two siblings with adrenogenital syndrome. CNS, central nervous system; CPAP, continuous positive airway pressure; NICU, neonatal intensive care unit.

Table 4 Side effects and compliance in twin pregnancies according to treatment group: progesterone ($n = 334$) or placebo ($n = 341$)

	Progesterone group	*Placebo group*
*Side effects**		
Central nervous system	32 (9.6)	39 (11.4)
Headache	13 (3.9)	17 (5.0)
Skin	11 (3.3)	10 (2.9)
Gastrointestinal	13 (3.9)	21 (6.2)
Reproductive system and breasts	194 (58.1)	213 (62.5)
Vaginal discharge	150 (44.9)	168 (49.3)
Vaginal itching	14 (4.2)	17 (5.0)
Miscellaneous	13 (3.9)	16 (4.7)
Compliance†		
Compliant	276 (82.6)	283 (83.0)
Not compliant because of:		
Side effect	23 (6.9)	25 (7.3)
Intrauterine death	2 (0.6)	1 (0.3)
Admission to hospital	6 (1.8)	7 (2.1)
Other reasons/unknown	18 (5.4)	21 (6.2)
Never started treatment (returned sealed box)	9 (2.7)	4 (1.2)
Number of pessaries used per woman (mean ± SD)	79.5 ± 24.9	78.9 ± 24.1

Data presented as *n* (%) unless stated. *Grouped according to organ system. †Compliance defined as continuing treatment until 34 weeks, preterm rupture of membranes or delivery.

and from four large centers in Austria, where approximately 50% of Austrian twins are delivered. We compared women who participated with women who were eligible but declined to participate and did not find any differences in baseline characteristics for these women. The overall rate of spontaneous delivery before 34 weeks' gestation of 14.1% corresponds to a previously estimated rate of spontaneous preterm delivery in a Danish population with approximately 15% monochorionic gestations[25]. It is noteworthy that nearly 30% of women with monochorionic gestations who were assessed for eligibility were excluded, mainly due to signs or diagnosis of TTTS. The population of monochorionic gestations in this trial therefore represents monochorionic pregnancies in which outcome is expected to be better than that in an unselected population. Approximately 10% of dichorionic gestations were excluded, mainly because the women did not speak Danish/German, they were planning to move, there were fetal malformations or intentional fetal reduction was performed.

As the proportion of monochorionic gestations was slightly higher in the placebo group, we performed subgroup analyses on dichorionic and monochorionic gestations separately. Surprisingly, the results from these subgroup analyses suggest that there may be an effect of progesterone treatment in monochorionic gestations,

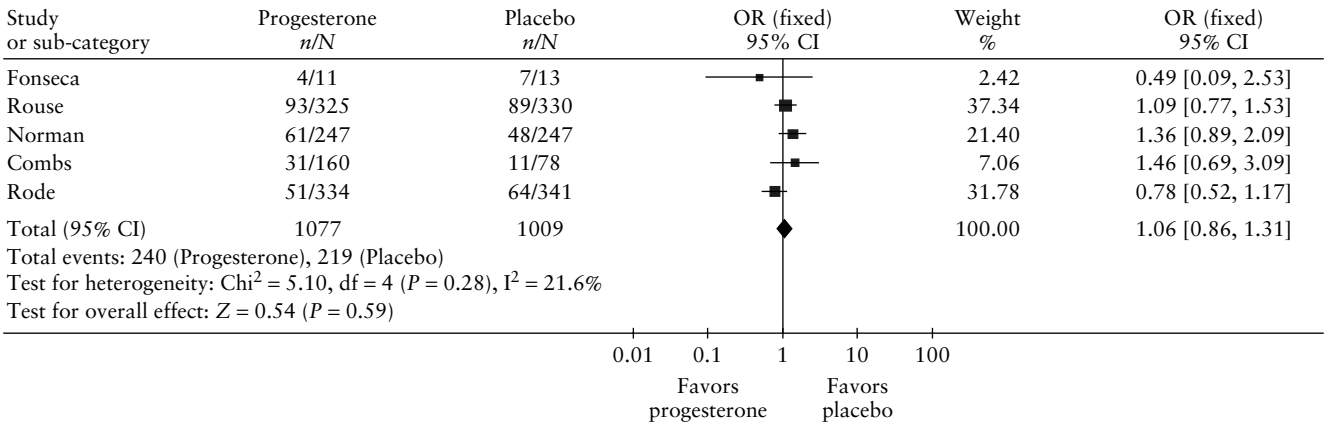

Figure 3 Meta-analysis of the preventive effect of progesterone on delivery before 34 weeks' gestation in twin pregnancies. OR, odds ratio.

although the study was underpowered for the primary outcome. These analyses were, however, not prespecified and results should be interpreted with caution. As the monochorionic population in this trial represents a selected group of pregnancies, the rate of spontaneous very preterm delivery was low (approximately 12% overall). In addition, the mean gestational age at delivery or intrauterine death for women with monochorionic gestations who were found eligible but did not participate was higher than that for the placebo group but lower than that for the progesterone group. The mean gestational age at delivery or intrauterine death was similar in the progesterone group, placebo group and non-participants with dichorionic gestations. We do not believe that there is a biologically plausible explanation as to why an effect should be noticed in monochorionic gestations but not in dichorionic gestations. Norman *et al.*[27] found a non-significant OR < 1 in monochorionic gestations, but an inverse but non-significant relation was found in dichorionic gestations (OR 1.7). Rouse *et al.*[28] did not perform subgroup analyses according to chorionicity. A comparison of the effect of progesterone treatment in monochorionic and dichorionic gestations would require another study set-up or a meta-analysis.

We chose to use micronized natural progesterone in pessary form as a consequence of the positive results from the da Fonseca trial in 2003[19], in which a dosage of 100 mg was used in singleton gestations. We doubled the dose to 200 mg because our trial involved twin gestations, which would be expected to have higher endogenic progesterone production. In 2007, Fonseca *et al.* showed a positive effect on the risk of preterm delivery in women with a short cervix using the same pessaries with a dose of 200 mg[18]. The previously published trials including twin gestations have used micronized natural progesterone as gel[27] and 17-alpha-hydroxyprogesterone caproate[28–30].

The effect of the most common progesterone treatment modalities, therefore, has now been investigated and no study has found a significant effect of prevention of preterm delivery in twin gestations. It is noteworthy that in singleton gestations, a preventive effect of progesterone has been observed in high-risk women only, i.e. women with previous preterm delivery or short cervix at 23 weeks' gestation. It remains to be investigated if there is an effect of progesterone treatment on the risk of preterm delivery in twin gestations with a short cervix.

ACKNOWLEDGMENTS

The trial was registered on EudraCT (2006-000503-41) and in ClinicalTrials.gov (NCT00329914).

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Funding

Funding was provided by The Danish Medical Research Council, The Fetal Medicine Foundation, The Copenhagen University Hospital's Research Fund, The Aase and Ejnar Danielsens Fund, The Augustinus Fund, The Ivan Nielsen Fund, The Doctor Sofus Carl Emil Friis and wife Olga Doris Friis' Fund, The Simon Fougner Hartmanns Family Fund, The Danish Medical Society in Copenhagen and The A.P. Moeller Foundation.

Conflicts of interest

None of the authors states any conflicts of interest.

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