Ultrasound Obstet Gynecol 2011; **38**: 281–287
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.9092

Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis

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KEYWORDS: high-risk twin pregnancies; preterm delivery; vaginal progesterone

ABSTRACT

Objectives *Progesterone treatment reduces the risk of preterm delivery in high-risk singleton pregnancies. Our aim was to evaluate the preventive effect of vaginal progesterone in high-risk twins.*

Methods *This was a subanalysis of a Danish-Austrian, double-blind, placebo-controlled, randomized trial (PREDICT study), in which women with twin pregnancies were randomized to daily treatment with progesterone or placebo pessaries from 20–24 weeks until 34 weeks' gestation. This subpopulation consisted of high-risk pregnancies, defined by the finding of cervical length $\leq 10^{th}$ centile at 20–24 weeks' gestation or history of either spontaneous delivery before 34 weeks or miscarriage after 12 weeks. Primary outcome was delivery before 34 weeks. Secondary outcomes were complications for infants including long-term follow-up by Ages and Stages Questionnaire (ASQ) at 6 and 18 months of age.*

Results *In 72 (10.6%) of the 677 women participating in the PREDICT study, the pregnancy was considered to be high-risk, including 47 with cervical length $\leq 10^{th}$ centile, 28 with a history of preterm delivery or late miscarriage and three fulfilling both criteria. Baseline characteristics for progesterone and placebo groups were similar. Mean gestational age at delivery did not differ significantly between the two groups either in patients with a short cervix (34.3 ± 4.1 vs 34.5 ± 3.0 weeks, $P = 0.87$) or in those with a history of preterm delivery or late miscarriage (34.6 ± 4.2 vs 35.2 ± 2.7 weeks, $P = 0.62$). Similarly, there were no significant differences between the treatment groups in maternal or neonatal complications and mean ASQ score at 6 and 18 months of age.*

Conclusion *In high-risk twin pregnancies, progesterone treatment does not significantly improve outcome.* *Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Preterm delivery is the leading cause of perinatal mortality and morbidity in industrialized countries, accounting for 28% of neonatal mortality worldwide[1]. Mortality and morbidity are inversely related to gestational age at delivery, and the most severe consequences occur when delivery is preterm, before 34 weeks of gestation[2,3]. The risk of spontaneous preterm delivery in both singleton and twin pregnancies is inversely correlated with cervical length: the shorter the cervix the higher the risk of preterm delivery[4,5]. Another important predictor of spontaneous preterm delivery in both singleton and twin gestations is obstetric history, in particular previous spontaneous preterm delivery and late miscarriage[6,7].

In singleton pregnancies, prophylactic progesterone treatment during the second and third trimesters has been shown to reduce the rate of preterm delivery both in those with a history of previous spontaneous preterm delivery[8–11] and in asymptomatic women found by ultrasound examination to have a short cervical length at 20–24 weeks' gestation[12–14]. In contrast, recent trials have not shown any significant effect of progesterone on the rate of preterm delivery in unselected twin

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Accepted: 27 June 2011

pregnancies[15–18]. There is only one published study investigating the effect of progesterone in twin pregnancies with a short cervix[19], and there have been none examining the effect of prophylactic use of progesterone in twin pregnancies with a previous preterm delivery or late miscarriage.

Our aim was to evaluate the effect of vaginal micronized progesterone on the rate of delivery before 34 weeks' gestation in twin pregnancies with a short cervix at 20–24 weeks' gestation in the current pregnancy and those with a history of preterm delivery or late miscarriage in a previous pregnancy.

METHODS

This study analyzed a subgroup of women who participated in a double-blind, placebo-controlled randomized clinical trial comparing the effect of vaginal micronized progesterone and placebo on the rate of preterm delivery in twin pregnancies, which is reported in the accompanying article in this issue of the Journal (the PREDICT study)[18]. This subpopulation consisted of high-risk pregnancies defined by the measurement of cervical length $\leq 10^{th}$ centile at 20–24 weeks' gestation in the current pregnancy or history of either spontaneous delivery before 34 weeks or miscarriage after 12 weeks.

This secondary analysis of the trial was planned before enrolment of participants started, and this was indicated at trial registration. Details of the randomized clinical trial, such as study period, inclusion and exclusion criteria, details on randomization and progesterone and placebo treatment, as well as the definition of primary and secondary outcomes, are provided in the accompanying report of the randomized clinical trial[18].

In the PREDICT study all participants were asked for details of history of preterm delivery or miscarriage after 12 weeks and, when in doubt, patient records were checked for previous preterm delivery and late miscarriage with participants' consent. All participants were offered a cervical scan before inclusion in the PREDICT study and this was performed in 448 (66.2%) of the 677 women, including 222 in the progesterone group and 226 in the placebo group. Cervical length measurement was performed by trained operators. The patients were examined in the supine position, with flexed hips and knees, after they had emptied their bladder. The ultrasound probe was placed within the introitus vaginae and moved forward to the anterior fornix of the vagina, avoiding pressure on the cervix during measurement. Cervical length was measured and recorded when the internal and external ora were clearly visible and the whole length of the cervical canal, with an echogenic endocervical mucosa, was obtained. We chose the 10^{th} centile, corresponding to 30 mm, as the cut-off for short cervix.

The primary end point of the study was the incidence of delivery before 34 weeks of gestation. Secondary outcomes were selected maternal and infant complications.

Statistical analysis

Parametric continuous variables were summarized as means (± SD), non-parametric continuous variables as medians (interquartile range (IQR)) and categorical data as percentages. The Kolmogorov–Smirnov test was used to identify non-parametric variables. Categorical variables were analyzed using chi-square or Fisher's exact test and continuous variables were compared using unpaired *t*-test, Kruskal–Wallis and Mann–Whitney *U*-tests. Binary outcomes were analyzed by logistic regression models.

RESULTS

In 72 (10.6%) of the 677 women participating in the PREDICT study, the pregnancy was considered to be high-risk: 47 women had cervical length ≤ 30 mm (17 in the progesterone and 30 in the placebo group) and 28 women had a history of spontaneous preterm delivery before 34 weeks' gestation or miscarriage after 12 weeks (10 in the progesterone and 18 in the placebo group); three of these women had both cervical length ≤ 30 mm and a history of spontaneous preterm delivery or late miscarriage (two in the progesterone and one in the placebo group).

Baseline characteristics for the high-risk and non-high-risk groups of the PREDICT study are compared in Table 1. Compared with the non-high-risk group, the high-risk group delivered significantly more frequently before 32 weeks and 34 weeks' gestation (20.8% vs 5%, $P < 0.001$ at 32 weeks and 33.3% vs 11.9%, $P < 0.001$ at 34 weeks) but the proportions delivering before 28 weeks were not significantly different (4.2% vs 2.2%, $P = 0.24$).

Characteristics of the high-risk patients treated with progesterone and placebo are compared in Table 2. The progesterone group did not differ significantly from the placebo group in any of the baseline characteristics, either in patients with a short cervix or in those with a history of preterm delivery or late miscarriage.

The median gestational age at cervical scan was 21.9 (IQR, 20.6–22.9) weeks. There was no significant difference in the median time interval between randomization and delivery between the progesterone and placebo groups in either the patients with a short cervix (14.1 (IQR, 10.8–15.0) weeks vs 13.3 (IQR, 10.8–15.4) weeks, $P = 0.86$) or in those with a history of preterm delivery or late miscarriage (13.6 (IQR, 8.9–17.5) weeks vs 14.8 (IQR, 10.6–16.8) weeks, $P = 0.67$). Similarly, there was no significant difference in the mean gestational age at delivery between the progesterone and placebo groups in either the patients with a short cervix (34.3 (SD, 4.1) weeks vs 34.5 (SD, 3.0) weeks, $P = 0.87$) or in those with a history of preterm delivery or late miscarriage (34.6 (SD, 4.2) weeks vs 35.2 (SD, 2.7) weeks, $P = 0.62$). From the time of randomization, the estimated distributions of time to delivery before 34 weeks of gestation did not differ significantly between the progesterone and placebo groups in either the patients with a short cervix ($P = 0.46$,

Table 1 Comparison of baseline characteristics in high-risk and non-high-risk twin pregnancies participating in the PREDICT study[18]

Characteristic	*High-risk** (n = 72)	*Non-high-risk* (n = 605)	P
Maternal age (years)	32.1 ± 4.6	31.9 ± 4.4	0.72
Nulliparous	34 (47.2)	328 (54.2)	0.49
Body mass index (kg/m^2)	22.3 (20.0–28.0)	22.6 (20.6–25.8)	0.71
Fertility treatment	34 (47.2)	285 (47.1)	0.89
Previous progesterone in current pregnancy†	25 (34.7)	200 (33.1)	0.64
Smoking before pregnancy	25 (34.7)	150 (24.8)	0.14
Smoking during pregnancy	12 (16.7)	56 (9.3)	0.14
Monochorionic pregnancy	9 (12.5)	91 (15.0)	0.57
Medical disorders before pregnancy	17 (23.6)	131 (21.7)	0.18

Data are given as mean ± SD, *n* (%) or median (interquartile range). *Twin gestations with cervical length ≤ 30 mm, with previous preterm delivery < 34 weeks or with previous miscarriage after 12 weeks. †In relation to fertility treatment or to prevent spontaneous miscarriage.

Table 2 Baseline characteristics according to treatment for the high-risk group ($n = 72$), divided into women with twin pregnancy and cervical length ≤ 30 mm and women with previous preterm delivery before 34 weeks or previous miscarriage after 12 weeks

	Cervical length ≤ 30 mm			*History of spontaneous preterm delivery or late miscarriage*		
Characteristic	*Progesterone group* (n = 17)	*Placebo group* (n = 30)	P	*Progesterone group* (n = 10)	*Placebo group* (n = 18)	P
Maternal age (years)	30.8 ± 4.7	31.8 ± 4.3	0.44	33.6 ± 4.1	33.3 ± 5.2	0.85
Nulliparous	9 (52.9)	17 (56.7)	0.81	3 (30.0)	6 (33.3)	0.99
Previous miscarriage > 12 weeks	0	1 (3.3)	0.99	8 (80.0)	11 (61.1)	0.31
Previous delivery < 34 weeks	1 (5.9)	1 (3.3)	0.99	2 (20.0)	7 (38.9)	0.42
Previous delivery 34–37 weeks	2 (11.8)	0	0.13	1 (10.0)	3 (16.7)	0.99
Body mass index (kg/m^2)	21.7 (19.5–30.2)	21.3 (19.1–24.7)	0.32	22.9 (20.6–28.9)	25.4 (21.4–32.4)	0.52
Fertility treatment	10 (58.8)	17 (56.7)	0.89	2 (20.0)	6 (33.3)	0.67
Previous progesterone in current pregnancy*	5 (29.4)	13 (43.3)	0.36	3 (30.0)	5 (27.8)	0.99
Smoking before pregnancy	5 (29.4)	9 (30.0)	0.97	4 (40.0)	9 (50.0)	0.71
Smoking during pregnancy	4 (23.5)	1 (3.3)	0.08	3 (30.0)	5 (27.8)	0.99
Monochorionic pregnancy	1 (5.9)	4 (13.3)	0.64	1 (10.0)	3 (16.7)	0.99
Medical disorders before pregnancy	4 (23.5)	8 (26.7)	0.52	0	5 (27.8)	0.13

Numbers are presented as mean ± SD, *n* (%) or median (interquartile range). Three women had both cervical length ≤ 30 mm and history of spontaneous preterm delivery or late miscarriage. *In relation to fertility treatment or to prevent spontaneous miscarriage.

Figure 1) or in those with a history of preterm delivery or late miscarriage ($P = 0.52$, Figure 2).

There were no significant differences in maternal and infant outcomes between the progesterone and placebo groups in either the patients with a short cervix (Table 3) or in those with a history of preterm delivery or late miscarriage (Table 4).

Follow-up of the children was assessed by Ages and Stages Questionnaires (ASQ) at 6 and 18 months of age[20], as described in our accompanying article (the PREDICT study)[18]. From the 72 high-risk pregnancies, we received Ages and Stages Questionnaires (ASQ) for 112 (77.8%) children at 6 months of age and for 102 (70.8%) children at 18 months of age. The mean total ASQ score at 6 and 18 months was 231.1 (SD, 30.4) and 208.5 (SD, 39.4), respectively. The mean total ASQ score at 6 and 18 months did not differ significantly between the progesterone and the placebo groups, either in the cases with a short cervix ($P = 0.55$ and $P = 0.64$, respectively) or in those with a history of preterm delivery or late miscarriage ($P = 0.62$ and $P = 0.83$, respectively).

We performed a meta-analysis of the preventive effect of progesterone on the risk of delivery before 34–35 weeks' gestation in twin pregnancies with a short cervix at mid-trimester, including two published studies and our data (Figure 3)[12,19]. We found there to be no significant effect of progesterone (pooled odds ratio (OR), 1.07 (95% CI, 0.52–2.19).

DISCUSSION

This is the largest trial evaluating the effect of prophylactic progesterone treatment on preterm delivery in high-risk twin gestations. We found that treatment with vaginal progesterone did not have a significant effect on the rate of preterm delivery in either women with cervical length ≤ 10th centile or those with a history of previous preterm delivery or late miscarriage.

In our high-risk group of patients, compared with the non-high-risk group of participants in the PREDICT study, the rate of preterm delivery before 32 and 34 weeks'

gestation was significantly higher. This is not surprising, since there is a well-described inverse association between cervical length and rate of preterm delivery[5,21,22].

Our findings in twin pregnancies with a short cervix are compatible with the results of two previous studies[12,19]. Da Fonseca *et al.*[12] examined 24 twin pregnancies

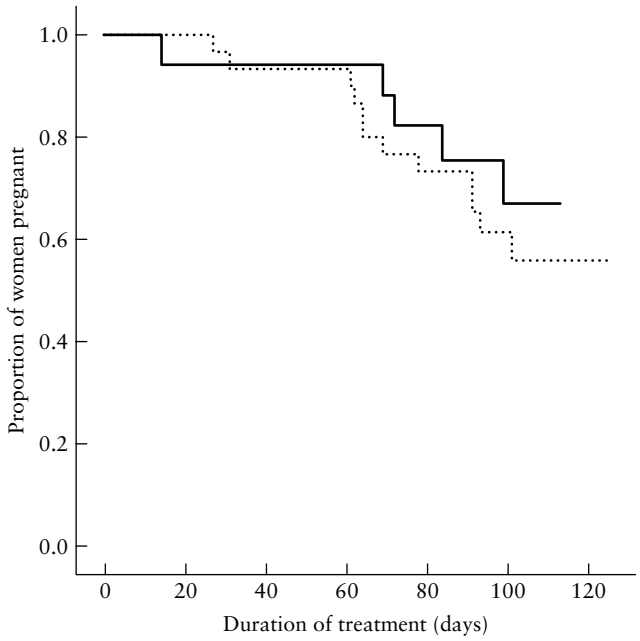

Figure 1 Proportion of women with cervical length ≤ 30 mm remaining pregnant from time of recruitment until 34 weeks of gestation (———, progesterone group; ·····, placebo group).

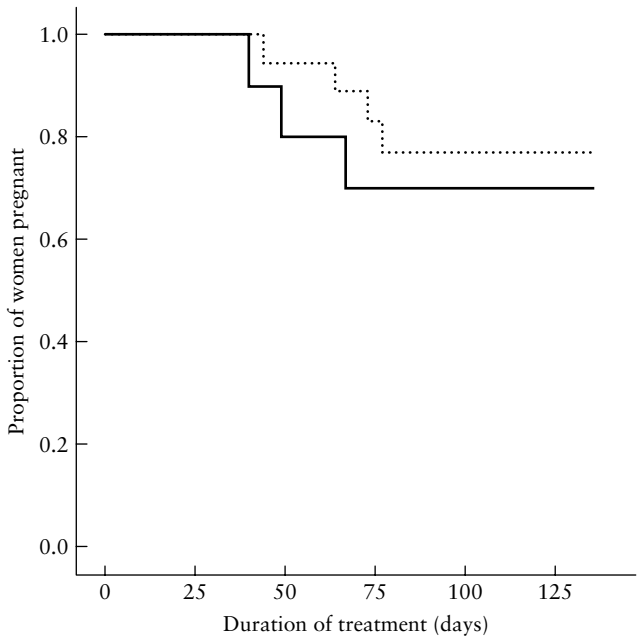

Figure 2 Proportion of women with previous preterm delivery before 34 weeks or previous miscarriage after 12 weeks remaining pregnant from time of recruitment until 34 weeks of gestation (———, progesterone group; ·····, placebo group).

Table 3 Maternal and infant outcomes according to treatment with progesterone ($n = 17$) or placebo ($n = 30$) in women with twin pregnancy and cervical length ≤ 30 mm

Outcome	*Progesterone group* (n *(%)*)	*Placebo group* (n *(%)*)	*Odds ratio (95% CI)*	P†
Gestational age at delivery				
< 32 weeks	4 (23.5)	5 (16.7)	1.54 (0.35–6.73)	0.57
< 34 weeks	5 (29.4)	12 (40.0)	0.63 (0.18–2.23)	0.47
Two live births	17 (100.0)	30 (100.0)	—	—
Corticosteroid treatment for fetal lung maturation	10 (58.8)	19 (63.3)	0.83 (0.24–2.80)	0.76
Tocolytic therapy	7 (41.2)	11 (36.7)	1.21 (0.36–4.09)	0.76
Maternal adverse outcome				
Gestational diabetes	1 (5.9)	0	—	0.36
Pre-eclampsia	0	2 (6.7)	—	0.53
Birth weight*				
< 2500 g	12 (70.6)	25 (83.3)	0.48 (0.12–1.98)	0.31
< 1500 g	4 (23.5)	6 (20.0)	1.23 (0.29–5.16)	0.78
Apgar score < 7 at 5 min*	2 (11.8)	1 (3.3)	3.73 (0.31–44.62)	0.30
Perinatal death*	1 (5.9)	0	—	0.36
Admission to NICU*	10 (58.8)	18 (60.0)	0.95 (0.28–3.20)	0.94
CPAP treatment for at least 24 h*	4 (23.5)	11 (36.7)	0.53 (0.14–2.04)	0.36
Perinatal complication*				
Hypoglycemia	2 (11.8)	2 (6.7)	1.87 (0.24–14.61)	0.55
Intraventricular hemorrhage	1 (5.9)	1 (3.3)	1.81 (0.11–30.98)	0.68
Jaundice	6 (35.3)	10 (33.3)	1.09 (0.31–3.81)	0.89
Necrotizing enterocolitis	0	0	—	—
Patent ductus arteriosus	2 (11.8)	3 (10.0)	1.2 (0.18–8.00)	0.85
Respiratory distress syndrome	5 (29.4)	8 (26.7)	1.15 (0.31–4.29)	0.84
Retinopathy of prematurity	1 (5.9)	0	—	0.36
Septicemia	2 (11.8)	1 (3.3)	3.87 (0.32–46.18)	0.29

*At least one infant of the pregnancy. †By logistic regression analysis or Fisher's exact test. CPAP, continuous positive airway pressure; NICU, neonatal intensive care unit.

Table 4 Maternal and infant outcomes according to treatment with progesterone ($n = 10$) or placebo ($n = 18$) in women with a history of spontaneous preterm delivery before 34 weeks or miscarriage after 12 weeks

Outcome	*Progesterone group* (n (%))	*Placebo group* (n (%))	*Odds ratio* (95% CI)	P†
Gestational age at delivery				
< 32 weeks	3 (30.0)	3 (16.7)	2.14 (0.34–13.42)	0.42
< 34 weeks	3 (30.0)	4 (22.2)	1.50 (0.26–8.64)	0.65
Two live births	10 (100.0)	18 (100.0)	—	—
Corticosteroid treatment for fetal lung maturation	5 (50.0)	6 (33.3)	2.00 (0.41–9.71)	0.39
Tocolytic therapy	3 (30.0)	6 (33.3)	0.86 (0.16–4.55)	0.86
Maternal adverse outcome				
Gestational diabetes	2 (20.0)	2 (11.1)	2.00 (0.24–16.93)	0.53
Pre-eclampsia	0	1 (5.6)	—	0.99
Birth weight*				
< 2500 g	8 (80.0)	13 (72.2)	1.54 (0.24–9.90)	0.65
< 1500 g	3 (30.0)	3 (16.7)	2.14 (0.34–13.42)	0.42
Apgar score < 7 at 5 min*	2 (20.0)	0	—	0.12
Perinatal death*	0	0	—	—
Admission to NICU*	5 (50.0)	11 (61.1)	0.64 (0.13–3.023)	0.57
CPAP treatment at least 24 h*	3 (30.0)	5 (27.8)	1.11 (0.20–6.11)	0.90
Perinatal complication*				
Hypoglycemia	0	1 (5.6)	—	0.99
Intraventricular hemorrhage	1 (10.0)	0	—	0.38
Jaundice	4 (40.0)	5 (27.8)	1.73 (0.34–8.87)	0.51
Necrotizing enterocolitis	0	0	—	—
Patent ductus arteriosus	1 (10.0)	1 (5.6)	1.89 (0.11–33.89)	0.67
Respiratory distress syndrome	2 (20.0)	5 (27.8)	0.65 (0.10–4.18)	0.65
Retinopathy of prematurity	0	1 (5.6)	—	0.99
Septicemia	2 (20.0)	1 (5.6)	4.25 (0.33–54.07)	0.27

*At least one infant of the pregnancy. †By logistic regression analysis or Fisher's exact test. CPAP, continuous positive airway pressure; NICU, neonatal intensive care unit.

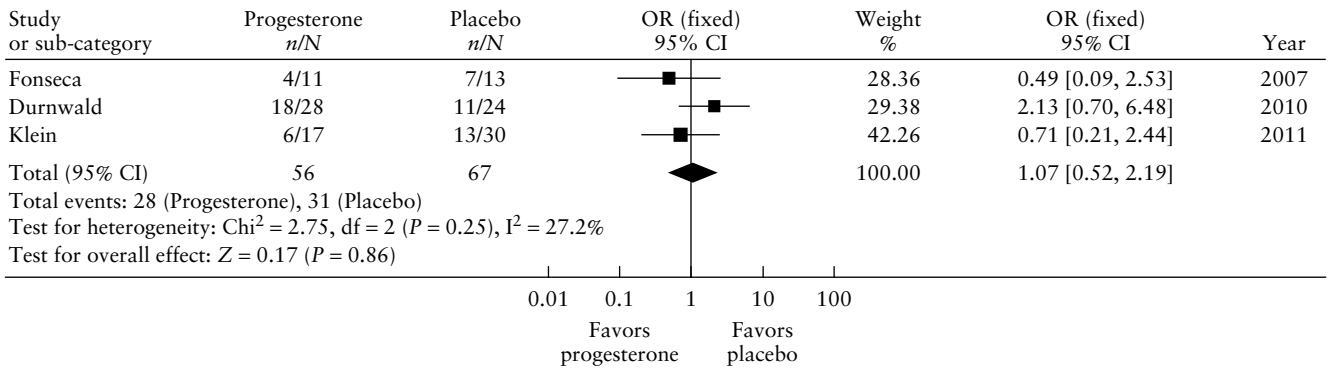

Figure 3 Meta-analysis of the preventive effect of progesterone on delivery before 34/35 weeks' gestation in twin pregnancies with a short cervix at mid-trimester. OR, odds ratio.

with cervical length ≤ 15 mm at 20–24 weeks' gestation and reported that prophylactic treatment with vaginal progesterone was associated with a non-significant reduction in the rate of preterm delivery before 34 weeks (relative risk, 0.7 (95% CI, 0.25–1.8)). Durnwald *et al.*[19] examined 52 twin pregnancies with cervical length ≤ 25th centile (36 mm) at 16–20 weeks' gestation and reported that treatment with 17 alpha-hydroxyprogesterone caproate, compared with placebo, was not associated with a significant reduction in the rate of spontaneous delivery before 35 weeks (64% vs 46%, $P = 0.18$). In our study, in women with a short cervix, the rate of preterm delivery before 34 weeks was lower in the progesterone than in the placebo group (29.4% vs 40.0%). Including the results of the two previous studies and our results in a meta-analysis, with a total of 123 twin pregnancies with a short cervix, no significant effect of progesterone on the risk of preterm delivery was shown (pooled OR, 1.07 (95% CI, 0.52–2.19). However, to demonstrate such a difference to be statistically significant,

it would be necessary to randomize more than 600 twin pregnancies with a short cervix and therefore screen more than 6000 twin pregnancies. It is unlikely that such a study would be performed.

This study is the first to investigate the effect of progesterone on the long-term follow-up of infants from high-risk twin pregnancies. We used the ASQ at 6 and 18 months after the estimated date of delivery because this evaluation tool has a high sensitivity and specificity to detect children with developmental delays[23]. There was no significant difference in total ASQ scores at 6 and 18 months between the progesterone and the placebo groups, in either those with a short cervix or in those with a history of preterm delivery or late miscarriage.

In high-risk singleton pregnancies with a short cervix or a history of preterm delivery, prophylactic progesterone treatment during the second and third trimesters of pregnancy has been shown to reduce the rate of preterm delivery and to improve neonatal outcome[8–14]. The absence of a significant effect of progesterone treatment on the rate of preterm delivery in either unselected[15–17] or high-risk[19] twin pregnancies suggests that the mechanisms underlying spontaneous preterm delivery in twins are different from those in singletons. Although not fully elucidated, it is now well established that hormones such as progesterone, estrogen, cortisol, corticotropin-releasing hormone and oxytocin are essential for maintenance of uterine quiescence as well as for initiation of a cascade of events leading to labor, cervical ripening and hence parturition at term. Premature activation of these events, by such mechanisms as maternal or fetal stress or by inflammation, may be the main reason for preterm labor and preterm cervical ripening in singleton gestations[24,25]. In twin pregnancies, rapid uterine distension may be an underlying trigger for the cascade of events leading to preterm delivery. It is therefore biologically plausible that progesterone treatment may be effective in singleton pregnancies, whereas it has no effect in twin and in higher-order multiple pregnancies, irrespective of risk factors for preterm delivery such as short cervix or history of preterm delivery.

In conclusion, prophylactic use of progesterone in high-risk twin pregnancies does not have a significant effect on the rate of preterm delivery, perinatal outcome or long-term development of the infants and consequently there is no justification for such treatment.

ACKNOWLEDGMENTS

The PREDICT Group

Helle Larsen, Ålborg Hospital, Denmark; Anni Holmskov, Viborg Hospital, Denmark; Kirsten Riis Andreasen, Hvidovre Hospital, Denmark; Niels Uldbjerg, Aarhus University Hospital Skejby, Denmark; Jan Ramb, Sønderborg Hospital, Denmark; Birgit BøDenmarker, Hillerød Hospital, Denmark; Lillian Skibsted, University Hospital Roskilde, Denmark and University of Copenhagen, Denmark; Lene Sperling, Herlev Hospital, Denmark; Stefan Hinterberger, General Hospital of Klagenfurt, Austria; Lone Krebs, Holbæk Hospital, Denmark; Helle Zingenberg, Glostrup Hospital, Denmark; Eva-Christine Weiss, Medical University of Graz, Austria; Isolde Strobl, Medical University of Innsbruck, Austria; Lone Laursen, Odense University Hospital, Denmark; Jeanette Tranberg Christensen, Gentofte Hospital, Denmark; Ida Vogel, Aarhus University Hospital Skejby, Denmark; Bo Mølholm Hansen, Copenhagen University Hospital, Rigshospitalet, Denmark; Ane Lando, Copenhagen University hospital, Rigshospitalet, Denmark.

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