

A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity

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Accepted 5 May 2014. Published Online 27 August 2014.

Objective To determine whether 17 alpha-hydroxyprogesterone caproate (17OHPC) prolongs gestation beyond 37 weeks of gestation (primary outcome) and reduces neonatal morbidity (secondary outcome) in twin pregnancy.

Design Randomised controlled double-blind clinical trial.

Setting Tertiary-care university medical centre.

Population Unselected women with twin pregnancies.

Methods Participants received weekly injections of 250 mg 17OHPC ($n = 194$) or placebo ($n = 94$), from 16–20 to 36 weeks of gestation. Randomisation was performed using the permuted-block randomisation method. Data were analysed on an intention-to-treat basis.

Main outcome measure Preterm birth (PTB) rate before 37 weeks of gestation.

Results There were no significant differences in the average gestational age at delivery, or in the rates of PTB before 37, 32, and 28 weeks of gestation, between the two groups. The

proportion of very-low-birthweight neonates (<1500 g) was significantly lower in the 17OHPC group (7.6%) compared with placebo (14.3%) (relative risk, RR 0.5; 95% confidence interval, 95% CI 0.3–0.9; $P = 0.01$). Progesterone-treated neonates had a significantly lower composite neonatal morbidity (19.1%) compared with placebo (30.9%) (odds ratio, OR 0.53; 95% CI 0.31–0.90; $P = 0.02$), with significantly lower odds for respiratory distress syndrome (14.4 versus 23.4%; OR 0.55; 95% CI 0.31–0.98; $P = 0.04$), retinopathy of prematurity (1.1 versus 4.6%; OR 0.21; 95% CI 0.05–0.96; $P = 0.04$), and culture-confirmed sepsis (3.4 versus 12.8%; OR 0.24; 95% CI 0.10–0.57; $P = 0.00$).

Conclusions Intramuscular 17OHPC therapy did not reduce PTB before 37 weeks of gestation in unselected twin pregnancies. Nonetheless, 17OHPC significantly reduced neonatal morbidity parameters and increased birthweight.

Keywords 17-Alpha-hydroxyprogesterone caproate, preterm birth, prevention, progesterone, twin gestation.

Awwad J, Usta IM, Ghazeeri G, Yacoub N, Succar J, Hayek S, Saasouh W, Nassar AH. A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity. BJOG 2015;122:71–79.

Introduction

Preterm birth (PTB), a leading cause of perinatal mortality and morbidity, affects about 60% of twin gestations.^{1–3} With the rise in the incidence of multiple gestations as a result of the widespread use of assisted reproductive technologies, the burden of prematurity has become increasingly disproportionate and substantial. Compared with singletons, twins are born earlier, weigh less, and are more

likely to die in the first year of life, accounting for 70% of neonatal deaths.⁴

Enthusiasm for exploring the potential benefits of progesterone for the reduction of PTB in pregnancy is derived from the proposed role of progesterone in the control of parturition in primates.⁵ Progesterone has been found to promote uterine quiescence, prevent cervical ripening, and modulate the production of cytokine by amnion epithelial cells.⁶ Research has demonstrated that antenatal

progesterone are successful in preventing PTB in singleton pregnancies;^{7–9} namely, in those at risk of preterm labour (PTL) as a result of a short cervix,^{8,10} or because of a previous history of PTB.^{7,11} Little evidence is available to suggest that this effect may also be associated with reduced perinatal morbidity and mortality, however. Moreover, this proposed strategy has not proven successful in the preventive management of PTL in unselected twin pregnancies.^{12–14}

Our working hypothesis was that prophylactic 17-alpha-hydroxyprogesterone caproate (17OHP) therapy might reduce births prior to 37 weeks of gestation in twin pregnancies. We designed this randomised controlled double-blind trial (RCT) to evaluate the efficacy of weekly 250-mg injections of 17OHP, compared with placebo, for preventing PTB in unselected twin pregnancies.

Methods

Trial design

This was a single-centre, controlled, double-blind trial with randomisation into two parallel groups, with a treatment to placebo allocation ratio of 2:1. The study protocol was approved by the American University of Beirut (AUBMC) Institutional Review Board. Once identified, eligible women were approached by research assistants during routine antenatal visits, who explained the objectives, methods, and potential side effects of the intervention. Signed informed consent was obtained from all participants. The trial was registered at ClinicalTrials.gov (NCT00141908).

Inclusion and exclusion criteria

Inclusion criteria were: twin pregnancy diagnosed by ultrasound and maternal age ≥ 18 years. Exclusion criteria consisted of the following: ultrasonographically diagnosed fetal anomalies; elective cervical cerclage prior to 14 weeks of gestation; hypertension; diabetes mellitus; asthma; history of deep vein thrombosis; history of hepatic disease or abnormal liver enzymes; pre-existing renal disease or abnormal kidney function; and seizure disorders.

Primary and secondary outcomes

The primary clinical outcome measure was defined as the PTB rate prior to 37 weeks of gestation. Secondary clinical outcome measures included early preterm birth (prior to 32 and 28 weeks of gestation), low birthweight (LBW; < 2500 g), very low birthweight (VLBW; < 1500 g), extremely low birthweight (ELBW; < 1000 g), neonatal morbidity, perinatal mortality, and maternal morbidity. Neonatal morbidity was defined as any of the following neonatal complications: respiratory distress syndrome; pneumonia; culture-confirmed sepsis; intraventricular haemorrhage (grades III and IV), necrotising enterocolitis; periventricular

leukomalacia; retinopathy of prematurity; patent ductus arteriosus; seizures; and/or bronchopulmonary dysplasia. Perinatal death was calculated as the sum of stillbirths (intrauterine fetal death after 24 weeks of gestation) and neonatal deaths (within the first 28 days of life). Maternal morbidity included any of the following maternal complications occurring during the course of pregnancy: gestational diabetes; hypertensive disorders; and preterm premature rupture of membranes. Safety outcome measures were local side effects (injection site soreness, bruising, itching, and pruritus) and systemic adverse effects.

Randomisation

Women were individually randomised to one of the parallel groups using the permuted-block randomisation method. The randomisation envelopes were prepared by means of random number tables in the pharmacy department. Immediately following recruitment, the research assistant opened the next numbered opaque envelope to assign the consenting patient to receive either 17OHP or placebo. Treating doctors, investigators, ancillary personnel, and participants were all blinded to treatment assignment for the duration of the trial. Randomisation was not stratified by chorionicity, although the latter was ascertained at the delivery by inspection.

Participants

Eligible women were recruited at 12–20 weeks of gestation. Randomisation was performed on the day of recruitment, but the allocated treatment was started between 16 and 20 weeks of gestation following the fetal morphology scan. Recruitment started on 1 September 2006 and ended on 31 December 2011. Women were followed-up until delivery and neonates were followed-up until discharge from hospital.

Interventions

Women received weekly intramuscular injections of the allocated treatment from 16–20 until 36 weeks of gestation. Treatment consisted of 250 mg of active 17OHP (Proluton Depot[®]; Schering AG, Berlin, Germany); the placebo was castor oil provided by the hospital pharmacy. Both compounds had the same external appearance. Participants were offered to receive the allocated treatment from a study nurse either in hospital or at home.

Follow-up visits were performed at 24, 28, 32, 34 and 36 weeks of gestation, unless otherwise required. Participants were managed according to routine clinical protocol. Medications were dispensed during each clinic visit by the hospital pharmacy on an exchange basis, whereby participants received injection refills after they returned empty vials. Treatment compliance was closely monitored and patients were called on a weekly basis by a

research assistant to remind them to take the injection. Non-compliance was recorded when more than 10 days had elapsed from the last injection date. Interruption of treatment assignment was considered in the event of one of the following complications: vaginal bleeding; cholestasis of pregnancy; premature rupture of membranes; or drug side effects. The use of other progestogens was considered a violation to the study protocol.

Sample size estimation

On the basis of data from a previous study by our group,¹⁵ we estimated that about 54% of twin gestations in the placebo group would deliver before 37 completed weeks of gestation. A total sample size of 290 women (193 in the 17OHPC group and 97 in the placebo group) was therefore estimated to be appropriate to detect a 33% reduction in the rate of preterm delivery prior to 37 weeks of gestation, under the assumptions of a type-I error (two-sided) of 5% and a power of 80%. A treatment to placebo allocation ratio of 2:1 was chosen because of the promising results of the protective effect of progestogens in high-risk singleton pregnancies upon the initiation of the study. It was felt that patients assigned to the placebo group would receive painful injections on a weekly basis with no possibility of direct benefit.

Statistical analyses

Statistical analysis was performed using SPSS 20 (SPSS Inc., IBM, Armonk, NY, USA), adjusting for clustering and using the intention-to-treat model. To account for missing data as a result of patient drop-out, imputation of the mean of the other group was performed for numeric outcomes and worst-case analysis for non-parametric outcomes.

Baseline characteristics were presented as means (standard deviations) and frequencies, and were analysed across treatment groups using an unpaired Student's *t*-test for continuous variables, after confirming the normality and homogeneity of variances, Fisher's exact test for dichotomous variables, and the chi-square test for categorical variables. The primary outcome, PTB rate prior to 37 weeks of gestation, was presented as frequency, measured at the woman-level and compared across treatment groups using Fisher's exact test. A relative risk was also estimated using the placebo group as a reference. The secondary neonatal outcomes, LBW, VLBW, neonatal morbidity, and perinatal mortality were presented as frequencies, taking the neonate as the unit of analysis. Birthweight was presented as mean (standard deviation), and was measured at the neonate level. To account for dependence between outcomes of neonates within the same pregnancy, the generalised estimating equation (GEE) approach was used to adjust for clustering, using an unstructured working correlation matrix, robust (empirical) variance estimator, and kernel

log quasi-likelihood function under the Independence Model Criterion (QIC). The logit link function was used for secondary neonatal outcomes with binary response variables. The identity link function was used for birthweight. Maternal morbidity outcomes were presented as frequencies, measured at the woman level, and compared across allocation groups using Fisher's exact test.

Gestational age at birth was measured at the woman level and compared using the Wilcoxon rank sum test for non-normally distributed continuous variables. A Kaplan–Meier survival analysis was performed using the Gehan–Wilcoxon test to evaluate the proportion of undelivered women in each allocation treatment group. No adjustment to the type-I error rate was performed for any secondary outcomes. *P* < 0.05 was considered statistically significant.

Results

Of the 344 women with twin pregnancy initially screened, 323 were found eligible to participate (93.9%) and 293 were randomised after giving informed consent (85.2%); 275 were found to be fully compliant with the treatment protocol (91.7%; Figure 1, 93.4% in the 17OHPC group compared with 94.8% in the placebo group). The baseline demographic and clinical characteristics of participants in both treatment allocation groups were comparable (Table 1). All participants were white and none used alcohol or illicit drugs. No cases of twin-to-twin transfusion syndrome were encountered.

Local side effects were reported in ten (5.1%) participants in the 17OHPC group and in seven (7.4%) participants in

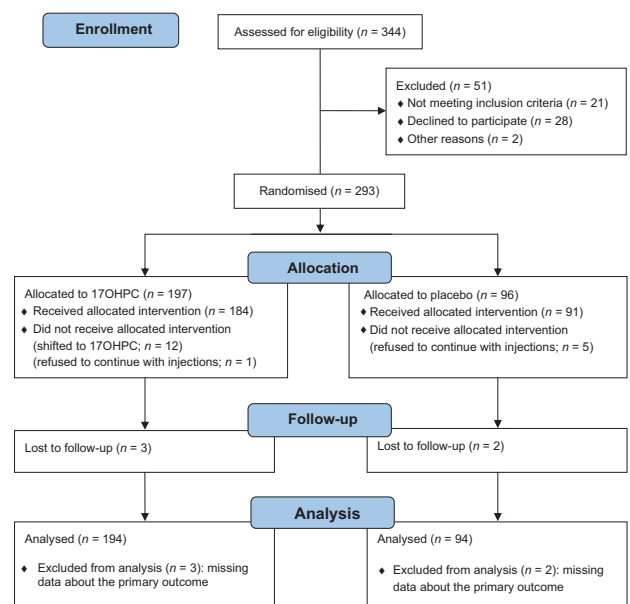


Figure 1. Women recruits at each stage of the trial.

Table 1. Baseline demographic and clinical characteristics of participants with twin pregnancy randomised to receive 17-hydroxyprogesterone caproate (17OHPC) or placebo

	17OHPC (n = 194)	Placebo (n = 94)
Maternal age, years (SD)	30.5 (5.6)	30.7 (5.0)
Gestational age at randomisation, weeks (SD)	19.0 (2.1)	19.2 (1.7)
Pre-pregnancy body mass index, kg/m² (SD)	23.8 (5.2)	23.9 (4.6)
Nulliparity, n (%)	126 (64.9)	68 (72.3)
Previous preterm birth, n (%)	8 (4.1)	4 (4.3)
Method of conception, n (%)		
Spontaneous	50 (25.9)	19 (20.2)
Ovulation induction	24 (12.4)	7 (7.4)
IVF/ICSI*	119 (61.6)	68 (72.4)
Monochorionicity, n (%)	32 (16.6)	16 (17.2)
Bleeding during first trimester, n (%)	39 (20.1)	21 (22.3)
Amniocentesis, n (%)	9 (4.6)	3 (3.2)
Smoking during pregnancy, n (%)	2 (1.0)	1 (1.1)

*IVF/ICSI, *in vitro* fertilisation/intracytoplasmic injection.
Comparison between groups: $P = \text{NS}$.

the placebo group. The differences were not statistically significant. There were no withdrawals as a result of medication intolerance, and there were no severe adverse effects in any of the participating groups.

The incidence of pregnancy-related complications (gestational diabetes, hypertensive disorders, preterm prolonged rupture of membranes, and chorioamnionitis) was similar in both groups (Table 2). No cases of chorioamnionitis were observed. The proportion of women receiving tocolytic therapy and corticosteroid injections for fetal lung maturation was similar in both groups. The rate of caesarean delivery was also comparable.

Table 2. Maternal outcomes and pregnancy-related complications according to treatment allocation groups

	17OHPC	Placebo	OR (95% CI)	P
Antenatal interventions, cases/n (%)				
Tocolytic therapy	67/194 (34.5)	33/94 (35.1)	1.0 (0.6–1.6)	0.92
Corticosteroids for fetal lung maturation	81/194 (41.8)	43/93 (46.2)	0.8 (0.5–1.4)	0.47
Caesarean delivery	161/194 (83.0)	81/94 (86.2)	0.8 (0.4–1.6)	0.49
Maternal complications, cases/n (%)				
Composite maternal morbidity*	29/194 (14.9)	14/93 (15.1)	1.0 (0.5–2.0)	0.98
Gestational diabetes	13/194 (6.7)	7/94 (7.4)	1.0 (0.3–2.3)	0.51
Hypertensive disorders	16/194 (8.2)	7/94 (7.4)	1.1 (0.4–2.8)	0.51
Preterm premature rupture of membranes	6/131 (4.6)	2/56 (3.6)	1.3 (0.2–6.6)	0.55

*Composite maternal morbidity was defined as any of the following occurring maternal complications: gestational diabetes, hypertensive disorders, and/or preterm premature rupture of membranes.

There was no significant difference in the mean gestational age at delivery between the two groups: 35.1 weeks in the 17OHPC group and 34.6 weeks in the placebo group ($P = \text{NS}$; Table 3). There were no significant differences between groups in the rates of PTB before 37, 32, and 28 weeks of gestation; there was nonetheless a trend towards a lower rate of deliveries before 32 weeks of gestation in the 17OHPC group (9.3%) compared with placebo (16.0%) (relative risk, RR 0.5; 95% confidence interval, 95% CI 0.3–1.1; $P = 0.09$). Kaplan–Meier survival analysis of the proportion of undelivered pregnancies throughout weeks of gestation using the Gehan–Wilcoxon test showed no significant differences between the two groups ($P = 0.62$; Figure 2).

The mean birthweight was found to be significantly larger in the 17OHPC group (2280 g) compared with placebo (2142 g) ($P = 0.01$; Table 3). The proportion of VLBW neonates was significantly lower in the 17OHPC group (7.6%) compared with the placebo group (14.3%) (RR 0.5; 95% CI 0.3–0.9; $P = 0.01$).

Progesterone-treated neonates had a significantly lower composite neonatal morbidity (19.1%) compared with placebo (30.9%) (odds ratio, OR 0.53; 95% CI 0.31–0.90; $P = 0.02$; Table 4). Progesterone treatment was associated with significantly lower odds for respiratory distress syndrome (14.4 versus 23.4%; OR 0.55; 95% CI 0.31–0.98; $P = 0.04$), retinopathy of prematurity (1.1 versus 4.6%; OR 0.21; 95% CI 0.05–0.96; $P = 0.04$), and culture-confirmed sepsis (3.4 versus 12.8%; OR 0.24; 95% CI 0.10–0.57; $P = 0.00$). The proportion of 5-minute Apgar scores below 7 was comparable between the groups. No between-group differences were found for duration of stay in the neonatal intensive care unit and the proportion of neonates requiring assisted ventilation. There were 17 perinatal deaths in the progesterone group (4.4%) and 15 perinatal deaths in the placebo group (8.0%) (OR 0.53; 95% CI 0.21–1.33; $P = 0.18$).

Table 3. Gestational age and birthweight at delivery according to treatment allocation groups

	17OHP	Placebo	RR (95% CI)	P
Gestational age at birth	35.1 (3.1)	34.6 (3.8)	–	0.21
Preterm birth categories, cases/n (%)				
<37 weeks of gestation	119/194 (61.3)	58/94 (61.7)	1.0 (0.6–1.6)	0.95
<32 weeks of gestation	18/194 (9.3)	15/94 (16.0)	0.5 (0.3–1.1)	0.09
<28 weeks of gestation	8/194 (4.1)	8/94 (8.5)	0.5 (0.2–1.3)	0.13
Birthweight, g (SD)	2280 (560)	2142 (594)	–	0.01
Birthweight categories, cases/n (%)				
<2500 g	241/383 (62.9)	127/182 (69.8)	0.7 (0.5–1.1)	0.11
<1500 g	29/383 (7.6)	26/182 (14.3)	0.5 (0.3–0.9)	0.01
<1000 g	10/383 (2.6)	5/182 (2.7)	0.9 (0.3–2.8)	0.92

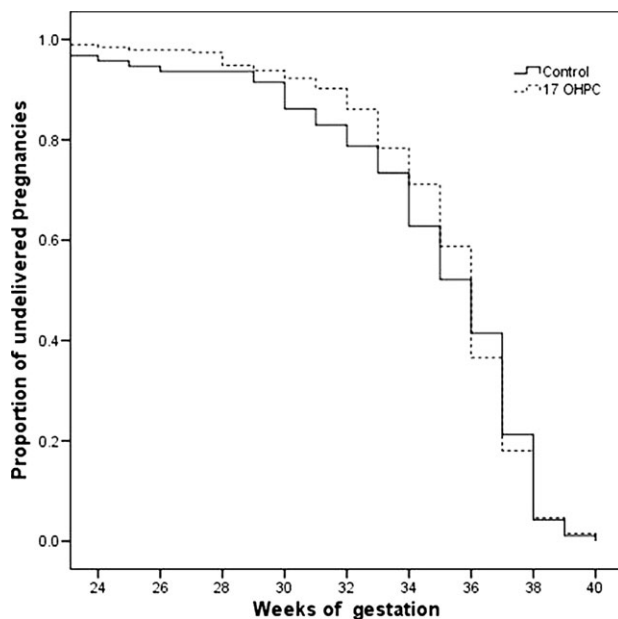


Figure 2. Kaplan–Meier survival analysis of women in each allocation group remaining pregnant at each gestational age ($P = 0.62$).

In order to account for missing values as a result of patient drop-out, the following strategies were used to avoid violating the intention-to-treat principle. Imputation of the mean of the other group method did not alter the significant difference in birthweight in favour of the proposed intervention (2278 ± 556 g versus 2141 ± 587 g; $P = 0.01$). Worst-case analyses were also performed for binary outcome variables by imputing all ‘bad outcomes’ in the progestogen group and all ‘good outcomes’ in the placebo group. While strengthening the significance of the decrease in composite neonatal morbidity (OR 0.57; 95% CI 0.33–0.96; $P = 0.04$) and culture-confirmed sepsis (OR 0.32; 95% CI 0.14–0.72; $P = 0.01$) in the progestogen intervention group, this imputation method failed to

support the significant improvements previously demonstrated for the following outcomes: retinopathy of prematurity (OR 0.69; 95% CI 0.21–2.24; $P = 0.54$); respiratory distress syndrome (OR 0.63; 95% CI 0.36–1.11; $P = 0.11$); and VLBW (RR 0.52; 95% CI 0.26–1.05; $P = 0.06$).

Subgroup analysis of the primary outcome by chorionicity suggested no significant differences in the rate of PTB before 37 weeks of gestation for dichorionic twins treated with progestogens (62%) and placebo (62%) ($P = \text{NS}$). Insignificant differences were also found for monochorionic twins (56 versus 59%; $P = \text{NS}$). Similarly, subgroup analysis of VLBW and composite neonatal morbidity showed no significant between-group differences for dichorionic and monochorionic twins.

Discussion

Main findings

Our study demonstrated that 17OHP does not prolong gestation in unselected twin pregnancies. Survival analysis confirmed the lack of a significant difference in expectancy-to-delivery rates between treatment allocation groups. The use of 17OHP was associated with larger twins, and a significantly lower composite neonatal morbidity rate: namely decreased odds for culture-confirmed sepsis, and possibly for respiratory distress syndrome and retinopathy of prematurity. Subgroup analysis by chorionicity revealed no significant differences in PTB rates, low birthweights, and composite neonatal morbidity for dichorionic and monochorionic twins in both groups.

Strengths and limitations

The strengths of this study are the prospective and randomised placebo-controlled double-blind design and the high patient eligibility (93.9%), consent (85.2%), and compliance rates (91.7%). One possible limitation may be the choice of 17OHP dose. Extrapolation from the 250-mg

Table 4. Neonatal outcome according to treatment allocation, taking the neonate as the unit of analysis

	17OHP	Placebo	OR (95% CI)	P
Morbidity, cases/n (%)				
Composite neonatal morbidity*	74/388 (19.1)	58/188 (30.9)	0.53 (0.31–0.90)	0.02
Apgar score at 5 minute <7	15/388 (3.9)	12/188 (6.4)	0.59 (0.22–1.56)	0.29
Patent ductus arteriosus	3/375 (0.8)	5/180 (2.7)	0.29 (0.06–1.5)	0.14
Pneumonia	4/377 (1.1)	6/186 (3.2)	0.32 (0.05–1.58)	0.16
Seizures	2/374 (0.5)	6/186 (3.2)	0.16 (0.02–1.49)	0.11
Retinopathy of prematurity	4/379 (1.1)	9/186 (4.6)	0.21 (0.05–0.96)	0.04
Respiratory distress syndrome	55/381 (14.4)	44/188 (23.4)	0.55 (0.31–0.98)	0.04
Sepsis (culture-confirmed)	13/384 (3.4)	24/188 (12.8)	0.24 (0.10–0.57)	0.00
Necrotising enterocolitis	4/386 (1.0)	6/188 (3.2)	0.32 (0.06–1.57)	0.16
Bronchopulmonary dysplasia	6/385 (1.6)	9/188 (4.8)	0.31 (0.08–1.23)	0.10
Intraventricular haemorrhage, grade III–IV	7/381 (1.8)	6/188 (3.2)	0.57 (0.15–2.17)	0.41
Periventricular leukomalacia	0/382	0/188	–	–
Assisted ventilation	36/374 (9.6)	28/184 (15.2)	0.59 (0.29–1.18)	0.14
Congenital malformations	8/383 (2.1)	7/186 (3.8)	0.53 (0.17–1.66)	0.27
Mortality, cases/n (%)				
Perinatal death	17/388 (4.4)	15/188 (8.0)	0.53 (0.21–1.33)	0.18
Stillbirth	12/388 (3.1)	10/188 (5.3)	0.61 (0.21–1.83)	0.38
Neonatal death	5/388 (1.3)	5/188 (2.7)	0.48 (0.10–2.32)	0.36
Hospital stay (days), mean (SD)				
	9 (17)	13 (17)	–	0.15

Composite neonatal morbidity included any of the following: respiratory distress syndrome, pneumonia, culture-confirmed sepsis, intraventricular hemorrhage (grade III–IV), necrotizing enterocolitis, periventricular leukomalacia, retinopathy of prematurity, patent ductus arteriosus, seizures, and/or broncho-pulmonary dysplasia.

weekly dose that showed favourable effects in singletons,¹¹ without taking account of the particular haemodynamic changes that occur in multiple gestations, may prove inappropriate. One may postulate that dose adjustment of the progestogen could contribute differently to the primary outcome effect. Recently, however, fetal number was not found to significantly affect 17OHP concentrations.¹⁶ In fact, 1000-mg weekly 17OHP treatments in twin gestations was associated with a paradoxical increase in PTB rates <32 weeks of gestation.¹⁷ Caritis et al.¹⁸ showed a negative correlation between 17OHP plasma concentrations and twin gestational age at delivery (hazard ratio, HR 1.14; $P = 0.001$; $r^2 = 0.49$). On the other hand, increasing the daily dose of vaginal progesterone from 200 to 400 mg did not cause negative effects on PTB rates in dichorionic diamniotic twins.¹⁹

Other limitations are the lack of baseline assessment data on cervical length and/or biomarkers of PTB, and that its design did not stratify twin pregnancies into risk levels for PTB, which may have led to a general dilution effect on the final outcome measures.

Interpretation

Similar to our study, several RCTs that evaluated antenatal progestogens in twin pregnancies could not demonstrate any reduction in PTB rates.^{12–14,20,21} The STOPPIT trial

even showed a higher incidence of PTB <34 weeks of gestation in twins treated with vaginal progesterone (OR 1.36; 95% CI 0.89–2.09).²² In contrast, a higher incidence was found for the same outcome in the placebo group in another RCT (OR 3.48; 95% CI 1.16–10.46).²³ Combs et al.¹⁴ demonstrated a significant difference in latency-to-delivery rates by Kaplan–Meier survival analysis; however, the 3-day gain favouring 17OHP was deemed to be of little clinical significance.

The efficacy of progestogen therapy has been well documented in selected high-risk singleton pregnancies.^{7–11} It remains unclear as to why progestogens express this differential effect on PTB prevention. Aside from the protean nature of the PTL process, it is possible that the mechanisms underlying labour in twins are different from those in singletons.²⁴ In singleton pregnancies, an inverse relationship was found between cervical length and a progesterone-lowering effect on PTB rates.²⁵ Singleton pregnancies with short cervixes are therefore more likely to benefit from progestogen therapy.^{7–10} This has not been supported in twin gestations, despite the proven powerful predictor of a short cervix for PTB in twins.²⁶ Although several RCTs failed to demonstrate any beneficial effects of 17OHP on PTB rates in twin pregnancies with short cervixes,^{14,20,27} a more recent study demonstrated a significantly increased rate of PTB <32 weeks of gestation

in the progestogen group.¹⁷ It may be presumed that in twins, unlike singletons, cervical ripening may not be a primary player in the pathogenesis of PTB.

It has also been proposed that the placental to myometrial surface area ratio, which is decreased in multiple gestations, could reflect the capability to delay labour.²⁸ The lack of uterine responsiveness to progestogens in twin pregnancies, despite higher progesterone production, may indicate different pathways of parturition control than those operating in singleton pregnancies, with excessive uterine distention being a plausible mechanism. The finding that progesterone failed to inhibit stretch-induced mitogen-activated protein kinase (MAPK) gene expression in human myometrial cells sheds further doubts about the promise of a valuable role in the prevention of PTB in multiple gestations.²⁹

Whereas most studies found no birthweight differences in multiple gestations receiving progestogen therapy, compared with placebo,^{13,30} distinctive findings of two RCTs indicate that 17OHPC could even be associated with a significant increase in VLBW (RR 2.0; 95% CI 1.0–3.9) and LBW (RR 1.9; 95% CI 1.2–3.1) neonates.^{12,14} Senat et al.¹⁷ also reported a significant reduction of birthweights in association with 17OHPC.

A unique pattern of outcome response to progestogens has been suggested to occur as a function of chorionicity; however, this was not demonstrated in our study. Subgroup analysis of the primary outcome in the STOPPIT trial showed a non-significant trend towards decreased PTB rates <34 weeks of gestation with vaginal progesterone in monochorionic twins (OR 0.62; 95% CI 0.24–1.58), contrasted with increased rates in dichorionic twins (OR 1.73; 95% CI 1.06–2.83).²² Although underpowered, a subgroup analysis of the PREDICT trial also showed a higher mean gestational age at delivery (252 ± 14.1 versus 245 ± 22.0 days; $P = 0.08$) and a lower proportion of VLBW neonates (1.2 versus 13.2%; OR 0.1; 95% CI 0.0–0.6) in the progesterone group in monochorionic twins.²¹

In singletons, little data exist to support significant improvement in neonatal outcomes with antenatal progestogens.^{7–10} One RCT reported reduced neonatal sepsis in singleton pregnancies with short cervixes (RR 0.28; 95% CI 0.08–0.97).³¹ Another RCT showed a reduction in the rates of intraventricular haemorrhage.¹¹ These concur with results derived from a subgroup analysis of an individual patient meta-analysis, in which vaginal progesterone decreased neonatal morbidity and mortality in twin pregnancies with short cervixes (RR 0.52; 95% CI 0.29–0.93).¹⁰ In both the AMPHIA and the Combs et al. trials, 17OHPC did not improve individual component morbidities or the composite neonatal morbidity measure, compared with placebo (RR 1.34; 95% CI 0.95–1.89;²⁰ OR 1.2; 95% CI 0.6–2.5¹⁴). In our study, however, a significant trend favouring an overall beneficial effect of 17OHPC is clearly

apparent across various primary and secondary outcome measures: decreased rate of PTB <32 weeks of gestation, reduced rate of VLBW, increased mean birthweight, lower composite neonatal morbidity rate, and less respiratory distress syndrome, retinopathy of prematurity, and culture-confirmed sepsis. These findings clearly stand out when compared with results from most other published RCTs on the subject.

Differences in racial and genetic characteristics of the study population could account for the wide discrepancy in response patterns. Recently, evidence in favour of a relationship between clinical response to 17OHPC and progesterone receptor (PR) polymorphisms has been demonstrated.³² Specific single-nucleotide polymorphisms have been linked to increased PTB risk during 17OHPC treatment.³² Particular haplotypes have been associated with a 13- to 16-fold increased risk of PTB <32 weeks of gestation when white and Hispanic women were treated with 17OHPC.³² PR genotypic heterogeneity and variable pattern of PR signaling could then explain racial disparity in PTL risk,^{33,34} and also predict the response effect to 17OHPC therapy.³⁵ The spontaneous recurrent PTB rate <34 weeks of gestation was found to be higher following 17OHPC treatment in African American women, compared with white women (OR 2.1; 95% CI 1.7–2.4).³⁵

Conclusion

Despite all controversies on the role of progestogens in the preventive management of preterm birth in twin pregnancies, our findings confirm the growing body of evidence indicating that 17OHPC therapy is not effective in prolonging the gestation of unselected twin pregnancies. We nonetheless have shown a significant reduction in composite neonatal morbidity and increased birthweight when 17OHPC was started at 16–20 weeks of gestation.

Disclosure of interests

None of the authors of this article have any conflicts of interest to report.

Contribution to authorship

JA provided guidance regarding the study question, performed the statistical analyses, and was involved in the write-up and editing of the article. IMU conducted the statistical analyses and helped with editing the article. GG organised the acquisition of the data, provided expert guidance on the article, and helped with editing the article. NY helped in data collection and data entry, and was involved in drafting the article. JS, SH, and WS contributed to the gathering of data and data entry, and called women to remind them of their weekly injections. AHN conceived the idea, developed the study objectives, was the principle

investigator, and led the preparation of the article, including data analysis, writing, and editing. All authors reviewed and approved the final version of the article.

Details of ethics approval

This study was approved by the Institutional Review Board at the American University of Beirut on 14 October 2005. The trial was registered at ClinicalTrials.gov: NCT00141908.

Funding

This study was funded by a grant from the Medical Practice Plan at the American University of Beirut, Beirut, Lebanon (principal investigator: Anwar H. Nassar, MD). The funding agency did not play any role in any aspect of the study.

Acknowledgements

We are very grateful to all of the women who participated in the study. We would like to thank the pharmacy department and particularly Dr Ulfat Usta Shanouha, the pharmacy director, for their voluntary work in dispensing the medications to patients. We also extend special thanks to all the nursing team for their help in giving injections to patients who elected to receive the treatment medication in the hospital. ■

References

- Büscher U, Horstkamp B, Wessel J, Chen FCK, Dudenhausen JW. Frequency and significance of preterm delivery in twin pregnancies. *Int J Gynaecol Obstet* 2000;69:1–7.
- de la Torre L, Istwan NB, Desch C, Rhea DJ, Roca L, Stanziano GJ, et al. Management of recurrent preterm labor in twin gestations with nifedipine tocolysis. *Am J Perinatol* 2008;25:555–60.
- Stock S, Norman J. Preterm and term labour in multiple pregnancies. *Semin Fetal Neonatal Med* 2010;15:336–41.
- Centers for Disease Control and Prevention (CDC). Racial/ethnic disparities in neonatal mortality – United States. *MMWR Morb Mortal Wkly Rep* 2004;53:655–8.
- Astle S, Slater DM, Thornton S. The involvement of progesterone in the onset of human labour. *Eur J Obstet Gynecol Reprod Biol* 2003;108:177–81.
- Loudon JA, Elliott CL, Hills F, Bennett PR. Progesterone represses interleukin-8 and cyclo-oxygenase-2 in human lower segment fibroblast cells and amnion epithelial cells. *Biol Reprod* 2003;69:331–7.
- Da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2003;188:419–24.
- 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.
- Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, 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.
- Romero R, Nicolaides K, Conde-Agudo A, Tabor A, O'Brien JM, Cetingoz E, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol* 2012;206:124.e1–19.
- Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348:2379–85.
- Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. *N Engl J Med* 2007;357:454–61.
- Briery CM, Veillon EW, Klausner CK, Martin RW, Chauhan SP, Magann EF, et al. Progesterone does not prevent preterm births in women with twins. *South Med J* 2009;102:900–4.
- Combs CA, Garite T, Maurel K, Das A, Porto M; Obstetrix Collaborative Research Network. 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial. *Am J Obstet Gynecol* 2011;204:221.e1–8.
- Nassar AH, Usta IM, Rechdan JB, Harb TS, Adra AM, Abu-Musa AA. Pregnancy outcome in spontaneous twins versus twins who were conceived through in vitro fertilization. *Am J Obstet Gynecol* 2003;189:513–18.
- Caritis SN, Sharma S, Venkataraman R, Rouse DJ, Peaceman AM, Sciscione A, et al. Pharmacokinetics of 17-hydroxyprogesterone caproate in multifetal gestation. *Am J Obstet Gynecol* 2011;205:40.e1–8.
- Senat M, Porcher R, Winer N, Vayssière C, Deruelle P, Capelle M, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. *Am J Obstet Gynecol* 2013;208:194.e1–8.
- Caritis SN, Simhan HN, Zhao Y, Rouse DJ, Peaceman AM, Sciscione A, et al. Relationship between 17-hydroxyprogesterone caproate concentrations and gestational age at delivery in twin gestation. *Am J Obstet Gynecol* 2012;207:396.e1–8.
- Serra V, Perales A, Meseguer J, Parrilla JJ, Lara C, Bellver 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.
- Lim AC, Schuit E, Bloemenkamp K, Bernardus RE, Duvekot JJ, Erwich JJ, et al. 17 α -hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlled trial. *Obstet Gynecol* 2011;118:513–20.
- Rode L, Klein K, Nicolaides KH, Krampfl-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.
- Norman JE, Mackenzie F, Owen P, Mactier H, Hanretty K, Cooper S, 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.
- Cetingoz E, Cam C, Sakalli M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo controlled trial. *Arch Gynecol Obstet* 2011;283:423–9.
- Klein K, Rode L, Nicolaides KH, Krampfl-Bettelheim E, Tabor A; PREDICT Group. Vaginal micronized progesterone and risk of

- preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis. *Ultrasound Obstet Gynecol* 2011;38:281–7.
- 25 DeFranco EA, O'Brien JM, Adair CD, Lewis DF, Hall DR, Fusey S, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2007;30:697–705.
 - 26 Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2010;203:128.e1–12.
 - 27 Durnwald CP, Momirova V, Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, et al. Second trimester cervical length and risk of preterm birth in women with twin gestations treated with 17- α hydroxyprogesterone caproate. *J Matern Fetal Neonatal Med* 2010;23:1360–4.
 - 28 Steinman G. Difficulties in controlling and preventing preterm labor in multiple gestations: a clinical perspective. *J Reprod Med* 2010;55:143–6.
 - 29 Lei K, Chen L, Cryar BJ, Hua R, Sooranna SR, Brosens JJ, et al. Uterine stretch and progesterone action. *J Clin Endocrinol Metab* 2011;96:E1013–24.
 - 30 Combs CA, Garite T, Maurel K, Das A, Porto M; Obstetrix Collaborative Research Network. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. *Am J Obstet Gynecol* 2010;203:248.e1–9.
 - 31 Dodd JM, Flenady VJ, Cincotta R, Crowther CA. Progesterone for the prevention of preterm birth: a systematic review. *Obstet Gynecol* 2008;112:127–34.
 - 32 Manuck TA, Lai Y, Meis PJ, Dombrowski MP, Sibai B, Spong CY, et al. Progesterone receptor polymorphisms and clinical response to 17-alpha-hydroxyprogesterone caproate. *Am J Obstet Gynecol* 2011;205:135.e1–9.
 - 33 Ananth CV, Misra DP, Demissie K, Smulian JC. Rates of preterm delivery among black women and white women in the United States over two decades: an age-period-cohort analysis. *Am J Epidemiol* 2001;154:657–65.
 - 34 Aveyard P, Cheng KK, Manaseki S, Gardosi J. The risk of preterm delivery in women from different ethnic groups. *BJOG* 2002;109:894–9.
 - 35 Timofeev J, Singh J, Istwan N, Rhea D, Driggers RW. Spontaneous preterm birth in African-American and Caucasian women receiving 17 α -hydroxyprogesterone caproate. *Am J Perinatol* 2014;31: 55–60.



'Your English is better than my Dutch'

BEN MOL, PROFESSOR OF OBSTETRICS AND GYNAECOLOGY, AUSTRALIA

I asked the current *BJOG* Editor-in-Chief, Khalid Khan, why he had followed and then unfollowed me on Twitter. He replied: 'Half of your Tweets I don't understand, since they are in Dutch'.

In the mid 90s I was a PhD student at the Academic Medical Centre in Amsterdam. At that time we submitted three paper copies of manuscripts in large A4 envelopes. From the format of the journal's return envelope you could guess the outcome: a small envelope was a letter of rejection with reviewers' comments; a large envelope was a positive reply. The *Green Journal* (Obstetrics and Gynecology) had a green envelope, *Fertility and Sterility* had a red envelope, and *BJOG* had blue. Although not a formal acceptance, you knew that when the editor had edited your manuscript with his pen, you were safe.

My first *BJOG* submission was in 1996. I had performed an economic analysis comparing salpingostomy with salpingectomy for ectopic pregnancy (*BJOG* 1997;104:834–9). The *BJOG* response was a big envelope – hurrah! John Grant, the Editor-in-Chief, had edited the manuscript. After some encouraging initial statements in the accompanying letter, John announced, 'Since I do not speak a word of Dutch, I admire your capacity to write English. However, ...' He had completely rewritten my paper. The red of his pen was the dominant colour on the white paper manuscript with black print that I had submitted. Since then, I have continued to submit my work to *BJOG*, resulting in over 60 publications, each time with fewer and fewer comments on the language (probably indicative of the proficiency in English of the PhD students that I work with). We are

making progress! When I promised Khalid to Tweet in English only, he followed me again with his first Tweet to me stating 'Your English is better than my Dutch'. It reminded me of my first *BJOG* paper nearly 20 years ago. Chief Editors may change, but some things don't change. The unaltered fact is that the *BJOG* Editor-in-Chief cannot value Dutch poetry, even when he is skating with his son.

Disclosure of interests

My institute has been paid for lectures and consultancy for pharmaceutical companies.

Supporting Information

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

Appendix S1. Schaatsenrijder, by Gerrit Achterberg (1944).

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