Vaginal Progesterone to Prevent Preterm Delivery in Unselected Women with Twin Pregnancy: a Randomised, Placebo-controlled, Double-blind Trial

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Objective: To evaluate the efficacy of vaginal progesterone in preventing preterm birth before 34 weeks in unselected twin pregnancies.
Methods: Women with a twin pregnancy were randomised in a one-to-one ratio to receive either 100 mg daily vaginal progesterone or placebo from 24 to 34 weeks of gestation. Low vaginal swab, serum human chorionic gonadotrophin, progesterone, C-reactive protein, and 75 g oral glucose tolerance test were examined at recruitment and at 30 to 32 weeks of gestation. The primary outcome was the rate of preterm delivery before 34 weeks.
Results: Of 165 women recruited, 23 were excluded and 142 were included for analysis, of whom 71 received vaginal progesterone and 71 received placebo. Basic demographics of the two groups were similar. The treatment and placebo groups were comparable in terms of maternal, obstetric, and neonatal outcomes, including the preterm delivery rate before 34 weeks (31% vs. 20%, p=0.123) and gestational age at delivery (35.3±2.6 weeks vs. 35.7±2.1 weeks, p=0.614).
Conclusion: In unselected women with twin pregnancy, vaginal progesterone did not prevent preterm delivery.

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Keywords: Pregnancy, twin; Premature birth; Progesterone

Introduction

Preterm birth, defined as delivery before 37 gestational weeks, accounts for 75% of perinatal deaths and >50% of long-term neurological disabilities[1,2]. Preterm neonates are at increased risk of respiratory distress syndrome, chronic lung disease, retinopathy of prematurity, necrotising enterocolitis, intraventricular haemorrhage, cerebral palsy, motor and sensory impairment, learning difficulties, and chronic disease[3]. Complications from preterm birth are the leading cause of death for children under 5 years of age[4]. In the United States, the societal cost of preterm birth is estimated to be US$26 billion annually[5].

Twin pregnancy is associated with a higher risk of preterm labour compared with singleton pregnancy; the rate of preterm delivery has been reported as 59.1% and 7.8%, respectively[6]. In 2015, twin pregnancy accounted for 20.5% of preterm deliveries in the United States[6]. Strategies to prevent preterm birth in twin pregnancy include bed rest with and without hospitalisation[7], beta agonist therapy[8], cervical cerclage[9], cervical pessary[10], and progesterone[11-14]. Nonetheless, in unselected twin pregnancy, evidence to support the beneficial effect of these treatments is lacking. This study aimed to evaluate the efficacy of vaginal progesterone in preventing preterm birth before 34 weeks in unselected twin pregnancy.

Methods

This randomised, double-blind, placebo-controlled study was approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (HKUCTR-2231). Written informed consent was obtained from each participant. Women aged >18 years with a twin pregnancy confirmed by ultrasonography at Queen Mary Hospital from May 2005 to December 2008 were invited to participate. Women were excluded if they were registered after 24 weeks, had contraindication to progesterone such as a history of vascular or thrombolic diseases, had allergy to progesterone

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or combined oral contraceptive pills, or planned to deliver outside our hospital.

Sample size calculation was based on our hospital's incidence of preterm delivery in twin pregnancies before 34 weeks (29.3%); 88 women in each group were required to show a three-fold risk reduction with a power of 80%, type I error of 5%, and 10% attrition rate.

Both women and clinicians were blinded to the group assigned; randomisation was done by the pharmacy in a one-to-one ratio. Women were instructed to self-administer daily a 100-mg natural progesterone pessary (Utrogestan, Besins Healthcare, UK) or placebo from 24 to 34 weeks. Low vaginal swab and tests for serum human chorionic gonadotrophin, progesterone, C-reactive protein, and 75 g oral glucose tolerance were performed at baseline and at 30 to 32 weeks of gestation. One-hour tocogram monitoring[15] was performed; a positive result was defined as ≥4 contractions in an hour before 30 weeks, and ≥6 contractions in an hour after 30 weeks. Women were given a contact number to report any adverse events. Women were followed up every 4 weeks before 30 weeks and thereafter 2 weeks until delivery. The timing and the mode of delivery were based on the obstetric condition and the preference of the woman.

The primary outcome was the rate of preterm delivery before 34 weeks. The Student's *t* test or Wilcoxon Rank Sum test was used to compare quantitative variables, whereas the Chi squared test or Fisher's exact test were used to compare qualitative variables. A p value of <0.05 was considered statistically significant.

Results

Of 165 women recruited, 23 were excluded and 142 were included for analysis, of whom 71 received vaginal progesterone and 71 received placebo (Figure). Basic demographics of the two groups were similar (Table 1). No women had a history of preterm delivery; 83.1% of pregnancies were conceived by assisted reproductive techniques; and >90% of women had a dichorionic diamniotic twin pregnancy.

The treatment and placebo groups were comparable in terms of maternal, obstetric, and neonatal outcomes, including the preterm delivery rate before 34 weeks (31% vs. 20%, p=0.123) and gestational age at delivery (35.3±2.6 weeks vs. 35.7±2.1 weeks, p=0.614), except that serum progesterone level at 30 weeks was higher in the treatment group (814.8±278.5 nmol/l vs. 751.6±218.9 nmol/l, p=0.032) [Table 2].

49 women required oral nifedipine for threatened preterm labour. Of them, 41 (83.7%) had excess uterine activity and required hospitalisation. Three patients required terbutaline for tocolysis.

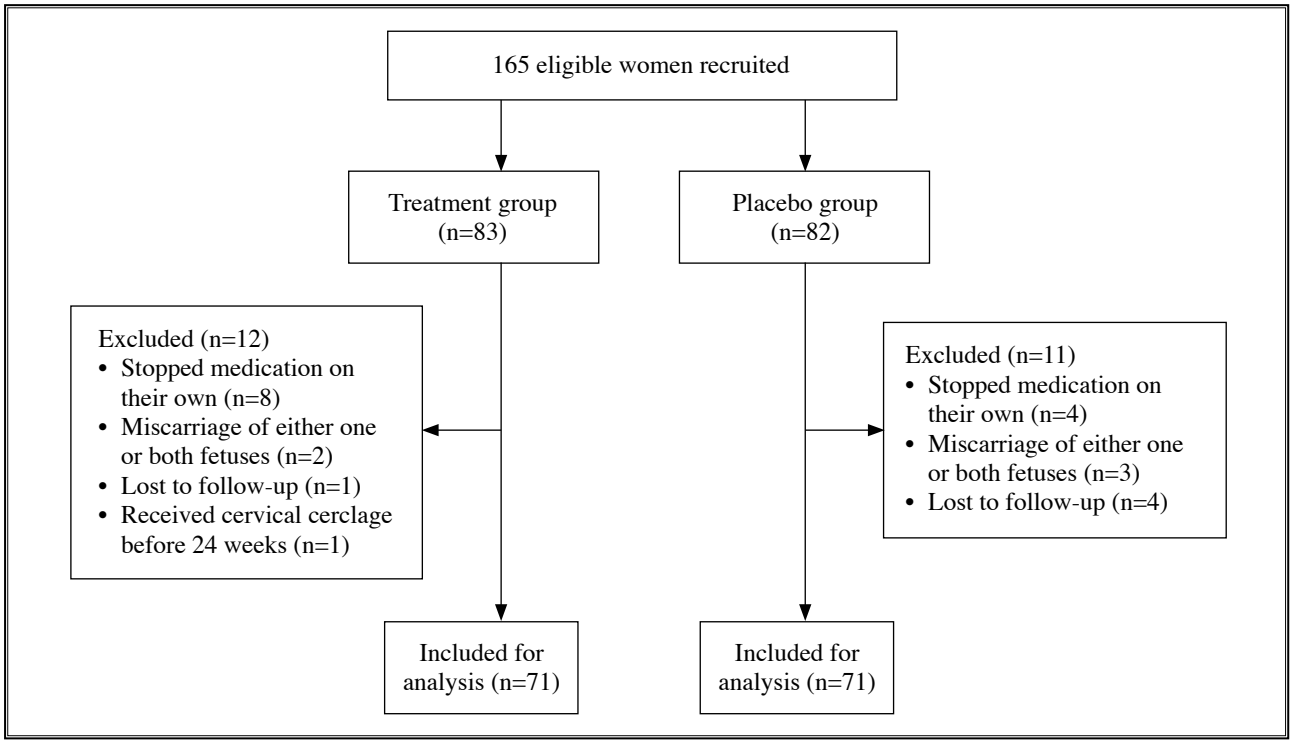

Figure. Flowchart of participant recruitment

Table 1. Basic demographics of unselected women with twin pregnancy

Variable	Placebo (n=71)*	Treatment (n=71)*	p Value
Age, y	34.1±3.02	34.6±3.39	0.393
Gravida	1.6±0.77	1.6±0.90	0.801
No. of termination of pregnancy	0.18±0.5	0.18±0.48	0.841
No. of miscarriage	0.20±0.40	0.21±0.56	0.598
Parity	0.17±0.41	0.13±0.34	0.609
History of preterm delivery	0	0	-
Educational level			0.300
Primary	5 (7)	2 (2.8)	
Secondary	43 (60.6)	39 (54.9)	
Tertiary	23 (32.4)	30 (42.3)	
Race			0.172
Chinese	67 (94.4)	70 (98.6)	
Asian, non-Chinese	4 (5.6)	1 (1.4)	
Occupation			0.402
Housewife	36 (50.7)	28 (39.4)	
Clerical	30 (42.3)	37 (52.1)	
Professional	5 (7)	6 (8.5)	
Medical history			0.220
Good past health	46 (64.8)	48 (67.6)	
Thyroid disease	9 (12.7)	5 (7.0)	
Polycystic ovaries	3 (4.2)	0 (0)	
History of tuberculosis	0 (0)	2 (2.8)	
Ovarian cyst	4 (5.6)	7 (9.9)	
Others	9 (12.7)	9 (12.7)	
Type of conception			0.370
Natural	10 (14.1)	14 (19.7)	
Ovulation induction	0 (0)	1 (1.4)	
Intrauterine insemination	2 (2.8)	6 (8.5)	
In vitro fertilisation	59 (83.1)	50 (70.4)	
Chorionicity			0.771
Dichorionic diamniotic	65 (91.6)	64 (90.1)	
Monchorionic diamniotic	6 (8.4)	7 (9.9)	
Antenatal complication	(n=69)	(n=71)	0.577
None	36 (52.2)	42 (59.2)	
Gestational diabetes	25 (36.2)	20 (28.2)	
Gestational hypertension	1 (1.5)	0 (0)	
Antepartum haemorrhage	2 (2.9)	2 (2.8)	
Pre-eclampsia	4 (5.7)	7 (9.9)	
Polyhydramnios	1 (1.5)	0 (0)	
Low vaginal swab at baseline	(n=70)	(n=71)	0.488
Commensal	53 (75.7)	51 (71.8)	
Streptococci B	6 (8.6)	9 (12.7)	
Gardnerella vaginalis	4 (5.7)	4 (5.6)	
Candida species	6 (8.6)	3 (4.2)	
Torulopsis glabrata	1 (1.4)	4 (5.6)	
Diphtheroid bacilli	1 (1.4)	0 (0)	
Human chorionic gonadotropin level at baseline, IU/L	67337±65588	71016±54400	0.469
Progesterone level at baseline, nmol/L	377.8±105.5	383.4±98.8	0.648
C-reactive protein level at baseline, mg/dL	0.52±0.57	0.47±0.25	0.863
Fasting glucose level at baseline, mmol/L	4.25±0.48	4.17±0.31	0.613
75 g oral glucose tolerance test 2-hour glucose level at baseline, mmol/L	6.44±1.58	6.46±1.62	0.913

* Data are presented as mean±standard deviation or No. (%) of subjects

Table 2. Maternal, obstetric and fetal outcomes

Variable	Placebo (n=71)*	Treatment (n=71)*	p Value
Delivery			
Before 28 weeks	1 (1.4)	2 (2.8)	0.560
Before 30 weeks	3 (4.2)	4 (5.6)	0.698
Before 32 weeks	6 (8.5)	11 (15.5)	0.196
Before 34 weeks	14 (20.0)	22 (31.0)	0.123
Gestation at delivery, w	35.69±2.06	35.30±2.62	0.614
Use of oral nifedipine	25 (35.2)	24 (33.8)	0.860
Uterine activity (No. of contractions in 10 minutes)			
At 24 weeks	0.06±0.25	1.1±4.33	0.062
At 26 weeks	0.54±1.33	1.15±2.60	0.159
At 28 weeks	1.23±2.92	1.16±2.12	0.512
At 30 weeks	1.13±2.62	1.24±1.87	0.206
At 31 weeks	0.83±2.00	1.67±2.76	0.079
At 32 weeks	1.97±3.79	1.87±2.88	0.861
At 33 weeks	2.00±4.30	1.91±3.21	0.438
At 34 weeks	2.02±3.46	2.47±4.66	0.962
Low vaginal swab at 30 weeks	(n=70)	(n=69)	0.296
Commensal	57 (81.4)	47 (68.1)	
Streptococci B	2 (2.9)	9 (13.0)	
Gardnerella vaginalis	3 (4.3)	6 (8.7)	
Candida species	4 (5.7)	2 (2.9)	
Proteus species	1 (1.4)	1 (1.5)	
Lactobacillus	1 (1.4)	1 (1.5)	
Torulopsis glabrate	2 (2.9)	3 (4.3)	
Human chorionic gonadotropin level at 30 weeks, IU/l	70876±63872	67401±38654	0.705
Progesterone level at 30 weeks, nmol/l	751.6±278.5	814.8±218.9	0.032
C-reactive protein level at 30 weeks, mg/dl	0.47±0.28	0.43±0.19	0.667
Fasting glucose level at 30 weeks, mmol/l	4.20±0.39	4.20±0.38	0.935
75 g oral glucose tolerance test 2-hour glucose level at 30 weeks, mmol/l	6.91±1.33	6.49±1.11	0.098
Placental histology			0.747
Normal	64 (90.1)	64 (90.1)	
Chorioamnionitis	3 (4.2)	2 (2.8)	
Placental or focal infarct	0 (0)	2 (2.8)	
Acute chorionitis and funistis	1 (1.4)	1 (1.4)	
Not applicable	3 (4.2)	2 (2.8)	
Mode of delivery of twin 1			0.187
Normal spontaneous delivery	5 (7.0)	5 (7.0)	
Vacuum extraction	3 (4.2)	0 (0)	
Low forceps	1 (1.3)	4 (5.6)	
Caesarean section	62 (87.3)	62 (87.3)	
Mode of delivery of twin 2			0.307
Normal spontaneous delivery	3 (4.2)	4 (5.6)	
Vacuum extraction	4 (5.6)	0 (0)	
Low forceps	1 (1.4)	2 (2.8)	
Assisted breech delivery	1 (1.4)	2 (2.8)	
Caesarean section	62 (87.3)	63 (88.7)	
Birth weight of twin 1, g	2367.8±466.4	2235.4±509.6	0.098
Birth weight of twin 2, g	2340.4±480.8	2239.1±518.1	0.264
Apgar score at 1 minute of twin 1	8.63±1.23	8.38±1.39	0.221
Apgar score at 1 minute of twin 2	8.62±1.29	8.41±1.25	0.204
Apgar score at 5 minutes of twin 1	9.77±0.51	9.65±0.74	0.495
Apgar score at 5 minutes of twin 2	9.82±0.54	9.66±0.66	0.055

* Data are presented as mean±standard deviation or No. (%) of subjects

Discussion

In unselected women with twin pregnancy, the use of 100 mg vaginal progesterone from 24 to 34 weeks did not reduce the risk of preterm delivery and had no significant impact on other obstetric or neonatal outcomes. Nonetheless, vaginal progesterone has been reported to be effective in reducing the rate of preterm delivery in women with a singleton pregnancy and asymptomatic short cervix at second trimester[16]. It was assumed that vaginal progesterone could have the same effect on twin pregnancy, which itself is a major risk factor for preterm delivery.

The anti-inflammatory effect of progesterone can maintain uterine quiescence[17]. In our study, women with vaginal progesterone had a higher serum progesterone level but similar uterine activity. One reason could be inadequate serum progesterone level to suppress uterine activity and subsequent preterm delivery. In four double-blind, randomised, controlled trials of various natural progesterone regimens to prevent preterm birth before 34 weeks, none reported a reduced preterm delivery rate in unselected women with twin pregnancy, regardless of the progesterone preparation, dosage, time of initiation, or duration of treatment[11-14]. In a systematic review of 13 trials involving 3768 women, neither vaginal progesterone nor 17-hydroxyprogesterone caproate had any beneficial effect in preventing preterm delivery or adverse perinatal outcomes[18]. Uterine overdistension may be the cause of preterm delivery in multiple pregnancy and therefore mere progesterone supplementation will not work.

There were limitations to our study. We originally aimed to recruit 176 subjects. The estimated three-fold risk reduction in preterm delivery by vaginal progesterone was based on a Brazilian study that reported vaginal progesterone could reduce 85% the risk of preterm delivery before 34 weeks in singleton pregnancy[15]. Twin pregnancy conceived with assisted reproductive technique has been reported to be at higher risk of preterm delivery before 34 weeks[19], with the risk reported as high as 36.1%[20]. In our study, over 80% of twin pregnancies were the result of an assisted reproductive technique, and the preterm delivery rate before 34 weeks was higher than that reported in other studies (25.4% vs. 12.4%-20.2%)[12-14]. Owing to the slower than expected recruitment rate, an unplanned interim analysis was performed after recruiting 165 women. Further recruitment was stopped because it was unlikely to obtain significant results. In addition, cervical length was not measured at 24 weeks as this was not our routine practice. Women with a shortened cervix at mid trimester have been reported to benefit from progesterone treatment[21]. A meta-analysis reported that a cervical length of ≤25 mm at 20-24 weeks is predictive of preterm birth before 28 weeks in asymptomatic twin pregnancy[22]. Another meta-analysis reported that in women with a shortened cervix and twin pregnancy, compared with placebo, vaginal progesterone significantly reduced the risk of preterm delivery before 33 weeks, neonatal mortality, birth weight of <1500 g, respiratory distress syndrome, and need for mechanical ventilation[21]. The underlying mechanism of progesterone in women with a shortened cervix remains poorly understood. In addition, we did not assess the compliance of women, which was important in a drug trial. Nonetheless, the observed higher progesterone level in the treatment group supported their compliance. Subjects' compliance has been reported to have no significant impact on preterm delivery rate[11-14]. Moreover, one third of our patients were given oral nifedipine for uterine activities based on tocogram monitoring. The frequent tocogram monitoring might have given a false positive alarm to both patients and obstetricians. As 80% of pregnancies were conceived by an assisted reproductive technique, the obstetricians might be more prone to prescribe oral nifedipine. The use of nifedipine might have reduced the overall preterm delivery rate in both groups. Finally, the study was carried out >10 years ago. Nonetheless, it was a double-blind, randomised controlled study of unselected twin pregnancy in the Chinese population. The mean gestational age at delivery (35-36 weeks) was comparable with other studies. We analysed the change in serum hormone level and vaginal microorganisms before and after vaginal progesterone. This has not been addressed in previous studies.

Conclusion

In unselected women with twin pregnancy, vaginal progesterone did not prevent preterm delivery.

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Declaration

All authors have no conflicts of interest to disclose.

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