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A randomised, double blind placebo controlled STudy of Progesterone for the Prevention of Preterm Birth In Twins (STOPPIT), and a meta-analysis of the use of progesterone for preterm birth prevention in twin pregnancy.

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Abstract

Background

Women with twin pregnancy are at high risk for spontaneous preterm delivery. Progesterone appears to be effective in reducing preterm birth in selected high risk singleton pregnancies, albeit with no significant reduction in perinatal mortality and limited evidence of neonatal benefit (1).

Methods.

Five hundred women with twin pregnancy were recruited from UK NHS clinics specialising in the management of twin pregnancy. Women were randomised either to daily vaginal progesterone 90mg (Crinone®) or to placebo, given double blind for ten weeks from 24 weeks gestation. The primary outcome was delivery (or intrauterine death) prior to 34 weeks gestation (ISRCTN 35782581). Additionally we performed a meta-analysis of our own and other published (and unpublished) data to determine the efficacy of progesterone in preventing early (< 34 weeks gestation) preterm birth or intrauterine death in women with twin pregnancy.

Findings

The combined proportion of intrauterine death or delivery prior to 34 weeks of pregnancy was 24.7% (61/247) in the progesterone and 19.4% (48/247) in the placebo group, odds ratio [95% CI] of 1.36 [0.89 to 2.09]. Meta-analysis confirmed that progesterone does not prevent early preterm birth (OR of delivery before 34 weeks of 1.16 [95% CI 0.89 to 1.51]) in women with twin pregnancy.

Interpretation

Progesterone, administered vaginally, fails to prevent preterm birth in women with twin pregnancy. Our data complement those of Rouse (2) who showed that 17 hydroxyprogesterone caproate, administered intramuscularly, failed to prevent preterm birth in twin pregnancy. Different pathophysiological mechanisms may account for the apparent difference in efficacy of progesterone in high risk singleton and twin pregnancy. Progestogens should not be used to prevent preterm birth in twin pregnancy.

Introduction

Multiple births (of which almost all are twins) have been increasing as a percentage of maternities since 1976. In the UK, multiple pregnancies accounted for 1.6% of all births in 2007 (3, 4), with over 98% of these multiple births being twin births (4) Stillbirth and neonatal mortality rates for multiples are 14.9 and 19.8 per 1000 live births respectively: rates 3 – 8 times higher than for singleton pregnancies (5). The economic costs of health care provision in the first five years of life are twice as high per child following twin compared with singleton birth (6). Prematurity continues to be the major cause neonatal death amongst multiple births, with preterm labour potentially the most treatable cause of prematurity amongst multiples (5). In the longer term, the morbidity amongst both singleton and multiple survivors of preterm birth is well documented, leading to poorer health and reduced achievement both in school and in adulthood. Such morbidity is associated with major financial costs to the health service, as well as personal suffering to the individuals and their families.

No effective interventions have been documented to prevent preterm delivery in twin pregnancy. In contrast, the efficacy of progesterone to prevent preterm delivery in high risk singleton pregnancy has been demonstrated in three large randomised trials and supported by subsequent meta-analyses (1, 7-9). The likelihood of preterm birth in women with singleton pregnancy identified at risk of preterm delivery either because of a previous preterm delivery (7, 8) or a short cervix (9) is reduced by antenatal progesterone. Importantly, there is little evidence that this reduction in preterm birth rate is accompanied by neonatal benefit since there is no reduction in perinatal mortality, and neonatal sepsis is the only secondary neonatal outcome whose risk is reduced in babies of women with singleton pregnancy treated with antenatal progesterone (1). Notwithstanding, the effect of progesterone in reducing preterm birth in singleton pregnancies at high risk means that there is great interest in whether progesterone could reduce the risk of preterm delivery in twin pregnancy. The STOPPIT study, reported here, was designed to test the hypothesis that the occurrence of delivery (or intrauterine death) before 34 weeks and 0 days gestation would be lower in women with twin pregnancy randomized to progesterone gel 90mg (daily from 24 – 34 weeks gestation) compared to matching placebo.

Methods

Randomised clinical trial

Participants.

Women were recruited from specialised antenatal clinics caring for women with multiple pregnancy at the following UK NHS hospitals: The Royal Infirmary, Edinburgh; Princess Royal Maternity, Glasgow; Royal Victoria Infirmary, Newcastle; The Queen Mother's Hospital, Glasgow; Ninewells Hospital, Dundee; Aberdeen Maternity Hospital; Forth Park Hospital, Kirkcaldy; University Hospital of Coventry and Warwickshire; The City Hospital, Nottingham and Birmingham Women's Hospital. All women with a twin pregnancy, with gestation and chorionicity established by scan prior to 20 weeks gestation, and attending during the recruitment period were eligible for recruitment. Women were not eligible if their pregnancy was complicated by a recognized structural or chromosomal fetal abnormality at the time of recruitment, ontraindications to progesterone, planned cervical suture, planned elective delivery before 34 weeks gestation or intervention for twin to twin transfusion before 22 weeks gestation.

Interventions

Participants were randomised either to daily progesterone (90mg) (Crinone®) or placebo gel administered vaginally by the participant and starting at 24 weeks + 0 days gestation. Drugs were supplied in a sealed opaque covering. Each cover contained a single use, one piece, white polyethylene applicator with a twist-off top, designed for intravaginal selfinsertion. Each applicator contained 1.45 g of gel and delivered 1.125g of gel, containing either 8% progesterone or excipients (glycerin, light liquid paraffin, hydrogenated palm oil glyceride, carbopol 974P, sorbic acid, polycarbophil, sodium hydroxide and purified water).

Objectives

The aim was to determine whether vaginal progesterone gel, 90mg daily from 24 – 34 weeks gestation, reduces the rate of preterm delivery (or intrauterine death) before 34 weeks in women with twin pregnancy. Specifically, we hypothesised that the proportion of women delivering (or with intrauterine death) before 34 weeks and 0 days gestation following progesterone would be less than with placebo.

Outcomes

The primary outcome was delivery (or intrauterine death) before 34+0 weeks gestation. We used delivery of the first twin to define the time of delivery. If one twin died *in utero* before 34 weeks and the other was born alive after 34 weeks, intrauterine fetal death was defined as occurring before 34 weeks. The gestational age was calculated from the agreed early (before 20 weeks) ultrasound scan. The maternal secondary outcomes were gestation at delivery, mode of delivery (spontaneous vaginal delivery [SVD], vaginal breech, forceps/ventouse, or caesarean section), duration of each stage of labour, and safety outcomes such as prolongation of hospitalisation. Neonatal secondary outcomes include neonatal unit admission and duration of neonatal unit care. We also ascertained maternal satisfaction by questionnaire. Women were followed up from randomisation until birth. Outcomes were recorded from the hospital notes, and entered into a web-based data capture system by a trained clinician, usually a study midwife.

Sample size

The proportion of deliveries before 34 weeks gestation in twin pregnancy is approximately 20% (personal communication, Dr J Chalmers, Information Services Division, NHS Scotland). Our study size of 250 women per group gave 85% power at 5% significance level to show a reduction in the rate of preterm delivery (or intrauterine death) prior to 34 weeks gestation from 20% to 10% in the active treatment group and was based on a conservative estimate of likely effect size derived from previous studies (7, 8).

Randomisation.
We aimed to recruit and randomise women at 22 weeks gestation. Where possible, the project was discussed with women at booking, and again at 22 weeks gestation. All women had at least one week to decide whether to participate. Participants gave written informed consent and the study was granted approval by the West Glasgow Ethics Committee 1 (reference 04/S0703/13). A randomisation schedule using permuted blocks of randomly mixed sizes was used to make up treatment packs (either active or placebo) for each patient, which were held in individual hospital pharmacies until use. On recruitment, the local researcher (usually a midwife) telephoned the Interactive Voice Response randomisation application at the UK CRN registered trials unit (The Centre for Healthcare Randomised Trials [CHaRT], in the Health Services Research Unit, University of Aberdeen), to be given a participant number which corresponded to a specific treatment pack. A minimization algorithm incorporating hospital and chorionicity was used to assign participants to the randomised treatment group.

Masking
All study personnel and participants were blind to treatment assignment for the duration of the study. Only the study statistician and the independent Data Monitoring Committee had access to unblinded data, but none had any contact with study participants.

Statistical methods
Analysis was according to the intention-to-treat principle and followed a pre-specified Statistical Analysis Plan. For the primary outcome the odds ratio of the treatment effect, adjusting for the minimisation covariate (chorionicity), was estimated with a 95% confidence interval, and associated likelihood ratio P-value, using logistic regression. A predefined subgroup analysis of the primary outcome by monochorionicity (Yes/No) was undertaken. Continuous maternal secondary outcomes were analysed using normal linear regression models, adjusting for chorionicity. Treatments effects, 95% confidence intervals and P-values were calculated as described in the statistical analysis plan. Binary categorical secondary outcomes were analysed using logistic regression as per the primary outcome. For data with multiple categories (e.g. mode of delivery) the two randomised groups were compared using a proportional odds model. Fetal outcomes allowed for the clustering within twins. Analyses were as for the maternal outcomes except with the addition of mother as a random effect in the linear and logistic regression models. No missing data were imputed. No adjustment was been made for any multiple comparisons. An independent Data Monitoring Committee met regularly throughout the study. No formal interim analyses were undertaken, and so no adjustment is required for this. All statistical analyses were undertaken in SPSS for Windows, Rel. 17.0.0 (2008, Chicago, SPSS Inc.) and Stata, StataCorp, 2009, Statistical Software: Release 10.1. College Station, TX: Stata Corporation.

Trial registration. The trial was registered on EUDRAct (2004-000780-10) and ISRCTN (35782581).

Meta-analysis
We performed an electronic search of the published medical literature (PubMed and Cochrane Controlled Trials Register) for studies where women with twin pregnancy were randomly allocated to treatment with a progestogen (including progesterone, 17 hydroxyprogesterone caproate) or placebo in the second or third trimester with the intention of preventing preterm birth. We used the search terms “preterm birth” AND [“progesterone” OR “17 hydroxyprogesterone caproate” OR “progestogen”] AND [“pregnancy multiple” OR “pregnancy twin”] AND “randomised controlled trial” AND “human”. All published randomised controlled trials in humans in which progestogens were administered to women with twin pregnancy for the prevention of preterm birth were considered. Those in which progestogens were administered to

women with symptoms of preterm labour, or where data were available in abstract form only were excluded. Two reviewers (JEN and JN) reviewed identified papers for relevance and quality and abstracted the data. Published studies were assessed for quality according to Jadad's quality assessment scale (10).

Our pre-specified primary outcomes were the incidence of delivery (or intrauterine fetal death) before 34 weeks gestation. Where data on our primary outcome of interest was not available in the published report, we successfully contacted the relevant chief investigator to get the required information. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated for the primary outcome.

Role of the funding source.

The funder (Chief Scientist's Office, Scottish Government) and the supplier of active and placebo drugs (Serono) had no role in study design; in the collection, analysis, and interpretation of data, in the writing of the report or and in the decision to submit the paper for publication. The joint study "sponsor" in terms of the EU Clinical Directive was the University of Glasgow / Greater Glasgow Health Board. The sponsor had no role in analysis of data. JEN is the corresponding author and confirms that she had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The flow of participants through the STOPPIT study is shown in Figure 1. Participants attended clinic visits at the time of randomisation (baseline), at intervals during pregnancy and were admitted to the study hospital for delivery and postnatal care. Participants were recruited from December 2004 to April 2008. The baseline demographics and clinical characteristics of the participants are shown in Table 1. Three patients in each of the progesterone and the placebo group were lost to follow up (due to withdrawal of consent or not traceable after moving out of study area); thus data from 494 patients were available for the intention-to-treat analysis of the primary outcome. No patients were considered protocol violators, and none were unblinded prior to ascertainment of all outcomes. Consequently 494 patients remained for the per-protocol analyses.

The proportions of women delivering or with an intrauterine death before 34 weeks in the progesterone and the placebo group were 61/247 [24.7%] and 48/247 [19.4%] respectively (Table 2). The odds ratio (OR) (95% confidence interval [CI]) of preterm delivery (or intrauterine death) before 34 weeks gestation in association with progesterone was 1.36 (95% CI 0.89 to 2.09), P=0.16. Thus, in contrast to our original hypothesis, progesterone did not reduce the incidence of preterm delivery (or intrauterine death) before 34 weeks gestation. Subgroup analysis of the primary outcome by chorionicity showed a significant increase in the rate of preterm delivery (or intrauterine death) before 34 weeks in association with progesterone amongst women with dichorionic pregnancies. However, the P-value for the formal test of interaction between the mono- and dichorionic groups did not reach statistical significance (P=0.056), implying that the response to treatment in the monochorionic and dichorionic group was not formally significantly different. Thus the finding of increased rates of adverse outcomes in the dichorionic group should be interpreted with suitable caution.

Secondary maternal outcomes are shown in Table 3, neonatal outcomes in Table 4, safety issues in Table 5, side effects in Table 6, and maternal satisfaction in Table 7. The only apparent differences between the groups were reduced odds of caesarean [OR 0.53 (95% CI 0.34 to 0.84), P=0.006], operative vaginal delivery [OR 0.42 (95% CI 0.21 to 0.83), P=0.013], and nausea [OR 0.43 (0.20 to 0.94), P=0.035] in the progesterone group. There were no differences in the rate of

adverse events between the two groups, despite a trend towards an increased occurrence of intrauterine death, neonatal death and hospitalisation/prolongation of hospitalisation amongst the progesterone group. Regarding compliance, 136 women in the progesterone group and 151 women in the placebo group returned diaries indicating that they had taken 56/70 (80%) or greater proportion of their medication. The remainder either failed to return their diary or stopped early because of preterm delivery or because they were told to stop, or were incompletely compliant with treatment.

Meta-analysis
Electronic searching of the literature generated 198 results relevant for meta-analysis. Review of the abstracts indicated that only two fulfilled the inclusion criteria. Relevant data could be abstracted from one of these papers (2). Given the discrepancy between the published primary outcome (spontaneous preterm delivery before 34 weeks gestation) and the outcome we planned for the meta-analysis (intrauterine death or any preterm delivery before 34 weeks gestation) we contacted the senior author of the other paper (9) who generously supplied the relevant data. A further paper (11) did not appear on electronic searching, but was brought to the attention of the authors and considered for inclusion. Further reading of this paper showed that the primary outcome (spontaneous preterm delivery prior to 37 completed weeks of gestation) was again different from the one we planned in the meta-analysis, and given the long time interval since publication of this paper in 1980, it was not considered that contacting the author for further information would be helpful. Both trials included in the meta-analysis were rated as of highest quality according to the Jadad score (10). The pooled OR (95% CI) of the effect of progesterone in preterm delivery (or intrauterine death) before 34 weeks gestation was 1.16 (0.89 to 1.51) (Table 8 and Figure 9).

Discussion

We have shown that progesterone did not reduce the composite outcome of risk of delivery or intrauterine death prior to 34 weeks of pregnancy in women with twin pregnancy. Our results are in agreement with the other large published trial in twin pregnancy which used 17 hydroxyprogesterone caproate, 250mg given intramuscularly from 16 – 20 to 35 weeks, and with the most recent meta-analysis on this issue (1). The relative risk of preterm birth (or intrauterine death) prior to 34 weeks in the 655 women available for analysis was 1.1 (0.9 to 1.3) in the active compared with the placebo group (2).. A new meta-analysis of the STOPPIT data reported here, together with data from the other two relevant published studies also supports the findings of this trial, that progesterone does not reduce intrauterine death or preterm delivery (before 34 weeks gestation), with an odds ratio (95% CI) of 1.16 (0.89 to 1.51).

Our study has the following strengths. It was a double-blind placebo-controlled trial with central randomisation, a prespecified sample size which was achieved, a prespecified primary endpoint and analysis plan which was followed and a high rate of follow-up. Loss to follow up for the primary outcome was only 6/500 [1.2%]. We believe that the generalisability of the trial is good. Our exclusion criteria were few, and thus 84% (1249/1483) of women with twin pregnancy were eligible for the study. We are confident therefore that we have ruled out a clinically important reduction in delivery before 34 weeks in this group of patients.

Potential weakness of our study are that the uptake of the study amongst eligible participants was less than we initially anticipated with only 40% (500 / 1249) of eligible women agreeing to participate, and that the study was largely conducted in tertiary referral centres. These issues may have affected the external validity of our trial although this is unlikely. The overall rate of preterm delivery or intrauterine death (before 34 weeks) was 22% (109 / 494), which is similar to another (singleton) study where progesterone was shown to be effective (7).. The dose of vaginal

progesterone was similar to the dose used in one singleton study that demonstrated efficacy (7), although less than that in another (9). The dose we used is at the lower end of demonstrated effective doses, but meta-analyses have not demonstrated a dose response effect (12). We believe therefore that it is unlikely that the dose of progesterone we used was too small.

Our unexpected observation of overall lower rates of both caesarean section and operative vaginal delivery in the progesterone group should be interpreted with caution. There was no effect on any other labour parameters, and no significant effect when prelabour and postlabour caesarean sections were considered separately. The effect on caesarean was not seen in other large studies using progesterone twin pregnancy (relative risk [95% CI] of 1.0 [0.9 to 1.1]) (2) or singleton pregnancy (relative risk [95% CI] 0.94 [0.68 to 1.30]) (8). It is unlikely that progesterone reduced caesarean section by improving fetal wellbeing, in view of the trend towards increased perinatal mortality in STOPPIT (14 deaths versus 10 deaths). Nor is it likely that progesterone improved uterine contractility during labour given that it is known to have a relaxant, rather than a stimulatory effect on the uterus (13). Given that the reduction in caesarean section is one of a number of secondary outcomes in our study, the lack of biological plausibility and lack of confirmation from other studies, we believe that this is most likely to be a chance finding.

The clinical implication of our study is that progestogens should not be given to women with twin pregnancy for prevention of preterm delivery. Although to our knowledge six further clinical trials of the effect of 17 hydroxyprogesterone caproate / progesterone in the prevention of preterm delivery in twin pregnancy are ongoing: two large trials (NCT 00329914 [with a planned sample size of 750]) and ISRCTN40512715 [with a planned sample size of 660]) and four smaller trials (NCT 00343265, NCT 00480402, NCT 00141908 and NCT 00163020, with a combined planned sample size of 957), unless their combined effect size is large with an odds ratio of 0.65 or less, they will not change the overall conclusion of this and the previous(2) study that progesterone is ineffective.

Our results contrast with the randomised trials and meta-analyses of high risk singleton pregnancies where progesterone appears to be effective in reducing preterm birth, although this reduction in preterm birth will only be clinically useful if accompanied by longer term improved offspring health. At present, there is no evidence that this is the case. We and others are specifically addressing this issue in singletons in a randomized trial of progesterone with infant function at 2 – 3 years of age as our primary outcome (OPPTIMUM – www.opptimum.org.uk. ISRCTN 14568373). The biological mechanism by which preterm delivery occurs may be different in twin and singleton pregnancy, and this merits further study. Perhaps stretch plays a more significant role in preterm labour in twin pregnancy and infection / inflammation a role in singletons. We did not recruit women with higher multiple pregnancy (eg triplets), but a recent publication again failed to demonstrate any effect of progesterone in preventing preterm birth in triplet pregnancy (14).

We conclude that progesterone is ineffective in reducing the high risk of preterm birth and intrauterine death in twins and the results of our study show possible (albeit non significant) evidence of harm. Progestogens should not routinely be given for prevention of preterm delivery in uncomplicated twin pregnancy.

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Author's declaration and contributions

JEN and FM conceived the study, JEN, FM, PO, HM, KH, SC, AAC, GM, PD, SS and JN designed the study, JEN, FM, PO, HM, KH, SC, AAC, GM, PD, SS, GT, ST, BM and JGT acquired the data. GMacL and JN analysed the data. JEN drafted the article. All authors interpreted the data, revised the article critically for important intellectual content and approved the final version.

Conflict of interest statements

JEN and ST have received grants from government and charitable organizations for research into understanding the mechanism of term and preterm labour and investigating treatments. JEN has acted as a consultant to a small drug company that was considering developing treatments for preterm labour. In addition, she is named as an inventor on patent applications for two compounds potentially useful in preterm labour prevention. ST has acted as a consultant to the pharmaceutical industry. None of the other authors has any conflicts of interest to declare.

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Table 1: Baseline characteristics

Characteristic	**Level**	**Progesterone N = 250**	**Placebo N = 250**
Demographics and Lifestyle			
Age	Mean(SD)	33 (5)	33 (6)
	Min-Max	18, 44	19, 50
Current Smoking	Yes n(%)	44 (17.6)	31 (12.4)
Current Alcohol	Yes n(%)	179 (71.6)	177 (70.8)
Obstetric History			
Parity	>0 n (%)	119 (47.6)	122 (48.8)
Miscarriage	>0 n (%)	3 (1)	1 (0)
Medical conditions			
Hypertension	Yes n (%)	3 (1)	1 (0)
Insulin dependent diabetes	Yes n (%)	1 (0)	1 (0)
Respiratory disease	Yes n (%)	8 (3)	17 (7)
Cardiac disease	Yes n (%)	2 (1)	1 (0)
Neurological disease	Yes n (%)	0 (0)	1 (0)

Skin condition	Yes n (%)	4 (2)	8 (3)
Thrombophilia	Yes n (%)	2 (1)	2 (1)
Current Pregnancy			
Fetal anomaly scan: Twin 1	Normal n (%)	242 (97)	243 (97)
	Defined abnormality n (%)	3 (1)	1 (0)
	Uncertain abnormality n (%)	0 (0)	0 (0)
	Not done n (%)	5 (2)	6 (2)
Fetal anomaly scan : Twin 2	Normal n (%)	242 (97)	242 (97)
	Defined abnormality n (%)	3 (1)	2 (1)
	Uncertain abnormality n (%)	0 (0)	0 (0)
	Not done n (%)	0 (0)	0 (0)
Amniocentesis : Twin 1	Abnormal	0 (0)	0 (0)
Amniocentesis : Twin 2	Abnormal	0 (0)	0 (0)
CVS	Performed	1 (0)	0 (0)

CVS – chorionic villus sampling

Table 2: Primary Outcome – overall and by subgroup of chorionicity

Outcome	**Progesterone**		**Placebo**		**Progesterone: placebo Odds Ratio (95% CI)**	**p-value**
	N	Event (%)	N	Event (%)		
All pregnancies						
Proportion of women delivering (or with intrauterine death) before 34 weeks n (%)	247	61 (24.7)	247	48 (19.4)	1.36 (0.89, 2.09)	0.16*
Monochorionic pregnancies						
Proportion of women delivering (or with intrauterine death) before 34	46	10 (21.7)	45	14 (31.1)	0.62 (0.24, 1.58)	
Dichorionic pregnancies						
Proportion of women delivering (or with intrauterine death) before 34 weeks n (%)	201	51 (24.5)	202	34 (16.8)	1.73 (1.06, 2.83)	

* refers to p value for proportion in progesterone versus placebo group (from a logistic regression model adjusting for chorionicity)

P-value for Test of Interaction between monochorionic and dichorionic pregnancies: p=0.056

Table 3: Secondary Outcomes: gestational age at birth, duration of labour, and method of delivery

Characteristic	**Progesterone**		**Placebo**		**Mean difference (95% CI)**	**P-value**
	N	**Mean (SD)**	**N**	**Mean (SD)**		
Gestational age birth (weeks)	247	35.4 (3.5)	247	35.7 (3)	-0.3 (-0.9, 0.3)	0.31
Duration Labour Stage 1 mins*	82	327 (284)	63	360 (380)	-33 (-142, 75)	0.55
Duration Labour Stage 2 mins*	82	102 (94)	63	116 (91)	-14 (-45, 17)	0.36
Duration Labour Stage 3 mins*	82	19 (28)	63	16 (29)	3 (-6, 12)	0.53
Duration Labour Overall mins*	82	447 (327)	63	496 (418)	-48 (-171, 74)	0.44
Method of Delivery (hierarchical)	**N**	**Event(%)**	**N**	**Event(%)**	**Odds ratio (95% CI)**	
Not recorded	250	14 (5.6%)	250	21 (8.4%)		
LSCS	250	148 (59.2%)	250	161 (64.4%)	0.53 (0.34, 0.84)	0.006
Forceps or ventouse	250	22 (8.8%)	250	30 (12.0%)	0.42 (0.21, 0.83)	0.013
SVD or vaginal breech	250	66 (26.4%)	250	38 (15.2%)	(referent)	(referent)

LSCS - lower segment caesearean section, SVD – spontaneous vertex delivery,
*vaginal deliveries only

Table 4 : Neonatal Complications: admission to neonatal unit, and duration of neonatal unit stay. These data refer to all twins, both the first and second with the 95% confidence interval and P-values are adjusted for clustering amongst the twin set.

Characteristic	**Progesterone**		**Placebo**		**Progesterone vs. Placebo (95% CI)**	**Pvalue**
	N	**Event (%)**	**N**	**Event (%)**	**Odds Ratio**	
Neonatal unit Admission	494	167 (33.4%)	494	158 (31.6%)	1.08 (0.76, 1.54)	0.647
	N	**Mean (SD)**	**N**	**Mean (SD)**		
Duration of	494	7.5 (19.9)	495	8.7 (23.1)	1.5	0.38

neonatal unit care – all babies (days)					(-1.9, 5.0)	
Duration of neonatal unit care – just babies admitted to neonatal unit (days)	167	26.9 (33.5)	158	23.6 (29.5)	3.3 (-5.3, 11.9)	0.45

Table 5 – Safety Issues. P-value from Fisher's Exact test on subjects.

Type	**Progesterone Subjects (Events)**	**Placebo Subjects (Events)**	**P-value from exact test**
Mother died	0	0	1.00
Intrauterine death	6	4	0.52
Neonatal death	8	6	0.59
Involved or prolonged inpatient maternal hospitalisation	87 (103)	72 (87)	0.16
Involved persistent/significant maternal disability/incapacity	1	0	0.32
Life threatening	1	2	0.56
Chorioamnionitis or intrauterine infection	0	0	1.00
Congenital anomaly / birth defect	0	0	1.00

Table 6 – Tertiary Outcome, Maternal Symptoms. Data shown are any reported symptom at either of the 6 or the 10 week visit, without adjustment for the baseline measure.

Characteristic	N	Event	%	N	Event	%	**Odds Ratio Progesterone versus Placebo (95% CI)**	**P-value**
	Progesterone			Placebo				
Bloating	187	6	3	191	5	3	1.23 (0.37, 4.11)	0.73
Fluid retention	187	20	11	191	22	12	0.92 (0.48, 1.75)	0.80
Breast tenderness	187	14	7	191	12	6	1.20 (0.54, 2.68)	0.64
Excessive	187	2	1	191	2	1	1.02 (0.14,	0.98

weight gain							7.33)	
Nausea	187	10	5	191	22	12	0.43 (0.20, 0.94)	0.035
Headache	187	8	4	191	17	9	0.45 (0.19, 1.09)	0.077
Dizziness	187	8	4	191	9	5	0.90 (0.34, 2.40)	0.84
Difficulty sleeping	187	31	17	191	40	21	0.75 (0.45, 1.26)	0.28
Drowsiness	187	8	4	191	4	2	2.09 (0.62, 7.06)	0.24
Depression	187	6	3	191	5	3	1.23 (0.37, 4.11)	0.73
Itching	187	19	10	191	21	11	0.92 (0.48, 1.77)	0.79
Rash	187	7	4	191	4	2	1.82 (0.52, 6.32)	0.35
Acne	187	4	2	191	2	1	2.07 (0.37, 11.42)	0.41
Excessive hair growth	187	3	2	191	4	2	0.76 (0.17, 3.45)	0.73
Hair loss	187	1	1	191	1	1	1.02 (0.06, 16.45)	0.99
Jaundice (yellow skin)	187		0	191		0		
Allergic reactions	187	1	1	191	1	1	1.02 (0.06, 16.45)	0.99
Vaginal irritation	187	20	11	191	15	8	1.45 (0.70, 2.83)	0.34
Vaginal itching	187	19	10	191	18	9	1.09 (0.55, 2.14)	0.81
Vaginal discharge	187	59	32	191	46	24	1.45 (0.92, 2.29)	0.11
Vaginal discomfort	187	24	13	191	17	9	1.51 (0.78, 2.91)	0.22
Joint pain	187	11	6	191	13	7	0.85 (0.37, 1.96)	0.71
Pubic pain	187	6	3	191	5	3	1.23 (0.37, 4.11)	0.73

Table 7 – Tertiary outcome: Maternal Satisfaction. Data shown are Mean(SD) over 2 visits (6 and 10 weeks), adjusted for the baseline measure**.**

Characteristic		**Progesterone N =153** to **158**	**Placebo N = 159 to 169**	**Odds Ratio Progesterone - Placebo (95% CI)**	**P-value**
How satisfied were you with your study treatment overall?	1=Very satisfied 10=completely dissatisfied	2.8 (2.1)	2.8 (1.9)	0.0(,0.5, 0.4)	0.89

Do you think your study treatment worked?	1=Yes, worked perfectly 10=no, did not work at all	3.8 (2.3)	3.9 (2.5)	-0.1(,0.6, 0.4)	0.73
How easy was your treatment to use overall?	1=very easy 10=very difficult	2.6 (1.9)	2.5 (1.7)	0.2 (-0.2, 0.6)	0.38
How easy was your treatment to insert?	1=very easy 10=very difficult	2.6 (1.9)	2.4 (1.7)	0.2 (-0.2 , 0.6)	0.30
How easy was your treatment to remember to use?	1=very easy 10=very difficult	2.6 (1.7)	2.9 (1.7)	-0.2 (-0.6, 0.2)	0.26
How pleasant was your treatment to use?	1=very pleasant 10=very unpleasant	4.8 (2.0)	4.9 (1.8)	-0.1 (-0.5, 0.3)	0.60
How messy was your treatment to use?	1=very messy 10=not at all messy	5.5 (2.5)	6.1 (2.4)	-0.6 (-1.1, 0.1)	0.026
How uncomfortable was your treatment to use?	1=very uncomfortable 10=very comfortable	6.4 (2.5)	6.5 (2.3)	-.01 (-0.6 , 0.4)	0.65
Were there many side effects of the study treatment overall?	1=a lot of side effects 10=no side effects	8.2 (2.3)	8.4 (1.9)	-0.2 (-0.7, 0.2)	0.32
An alternative would be an intramuscular injection once per week. If this injection were only a bit uncomfortable, which would you prefer?	1=daily vaginal gel 10=weekly injection	4.3 (3.6)	4.2 (3.6)	0.2 (-0.6, 0.9)	0.70
If this injection was quite	1=daily vaginal gel 10=weekly	3.3 (3.0)	3.1 (2.9)	0.2 (-0.4, 0.9)	0.50

uncomfortable, which would you prefer?	injection				
Overall, how satisfied were you with participating in the STOPPIT study?	1=Very satisfied 10=completely dissatisfied	2.5 (2.2)	2.1 (1.6)	0.4 (-0.1, 0.8)	0.093

Table 8 – Meta-analysis of the effect of progesterone in preventing preterm delivery before 34 weeks gestation

Author	Progesterone		Placebo	
	N	Events	N	Events
Fonseca	11	4	13	7
Rouse	325	93	330	89
Norman	247	61	247	48
	Odds ratio (95% CI)			% Weight
Fonseca	0.49 (0.10, 2.53)			3.95
Rouse	1.09 (0.77, 1.53)			61.05
Norman	1.36 (0.89, 2.09)			35.00
M-H pooled OR	1.16 (0.89, 1.51)			100

Figure1: Flow of participants through the STOPPIT study