Use of oral progestogen in women with threatened miscarriage in the first trimester: a randomized double-blind controlled trial

Running title: Use of oral progestogen in threatened miscarriage

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Abstract

STUDY QUESTION

Will use of oral progestogen in women with threatened miscarriage in the first trimester reduce the miscarriage rate when compared with placebo?

SUMMARY ANSWER

Use of oral progestogen in women with threatened miscarriage in the first trimester did not reduce miscarriage before 20 weeks when compared with placebo.

WHAT IS KNOWN ALREADY

Miscarriage is a common complication of pregnancy and occurs in 15-20% of clinically recognized pregnancies. Use of vaginal progestogens is not effective in reducing miscarriage but there is still no good evidence to support use of oral progestogen for the treatment of threatened miscarriage.

STUDY DESIGN, SIZE, DURATION

This was a randomized double-blind controlled trial. A total of 406 women presenting with threatened miscarriage in the first trimester were recruited from 30 March 2016 to May 2018.

PARTICIPANTS/MATERIALS, SETTING, METHODS

Women attending Early Pregnancy Assessment Clinics (**AUTHOR:** are initial capitals required here? No In the abstract, we normally describe the research centre/clinic rather than specifically name them. Early Pregnancy Assessment clinics are dedicated clinics for pregnancy complications.) because of vaginal bleeding during the first trimester were recruited and randomly assigned to use dydrogesterone 40 mg orally, followed by 10mg orally three times a day or placebo until 12 completed weeks of gestation or 1 week after the bleeding stopped, whichever was later. The primary outcome was the miscarriage rate before 20 weeks of gestation.

MAIN RESULTS AND THE ROLE OF CHANCE

The two groups of women had comparable age, BMI, number of previous miscarriages, gestation and ultrasound findings at presentation. The miscarriage rate before 20 weeks of gestation was similar in both groups, being 12.8% (26/203) in the progestogen group and 14.3% (29/203) in the placebo group (relative risk 0.897, 95% CI 0.548–1.467; p=0.772). The live birth rate was 81.3% in the progestogen group versus 83.3% in the placebo group (p=0.697). No significant differences were found between the two groups in terms of obstetric outcomes and side effects.

LIMITATIONS, REASONS FOR CAUTION

The primary outcome was the miscarriage rate, rather than the live birth rate. Women were recruited from Early Pregnancy Assessment Clinics and those with heavy vaginal bleeding might be admitted into wards directly instead of attending Early Pregnancy Assessment Clinic (**AUTHOR:** your meaning here is a little unclear – are you inferring that some women with heavy bleeding may not have been recruited as they were in a ward? Yes. Please would you clarify this?). The severity of vaginal bleeding was subjectively graded by women themselves. The sample size was not adequate to demonstrate a smaller difference in the miscarriage rate between the progestogen and placebo groups. We did not exclude women with multiple pregnancy, which increased the risk of miscarriage although there was only one set of twin pregnancy in the placebo group.

WIDER IMPLICATIONS OF THE FINDINGS

Use of oral progestogen is not recommended in women with threatened miscarriage in the first trimester.

STUDY FUNDING/COMPETING INTERESTS

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TRIAL REGISTRATION NUMBER

ClinicalTrials.gov with an identifier NCT02128685

TRIAL REGISTRATION DATE: 1 May 2014

DATE OF FIRST PATIENT'S ENROLMENT: 30 March 2016

Keywords: miscarriage, first trimester, vaginal bleeding, oral progestogen, threatened miscarriage, dydrogesterone

AUTHOR: we require a minimum of five and a maximum of ten keywords. Are these acceptable, and please add more if that would be helpful?

Introduction

Miscarriage is a common complication of pregnancy. It occurs in 15–20% of clinically recognized pregnancies (National Guideline 2019) and is associated with significant physical and psychological sequelae (Marcinko et al. 2011; Cheung, Chan, and Ng 2013); In the first trimester, the most common cause of miscarriage is chromosomal abnormalities of fetuses (Stephenson, Awartani, and Robinson 2002), although in some cases the cause cannot be identified.

Progesterone plays a crucial role in the maintenance of pregnancy. It is secreted by the corpus luteum, which provides early pregnancy support until placental production takes over at around 10 weeks of gestation. Low levels of serum progesterone have been linked to impending miscarriage (Osmanağaoğlu et al. 2010). It has been postulated, therefore, that lack of progesterone is a cause of miscarriage rather than a secondary signal of failing pregnancy.

Threatened miscarriage is manifested by vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus remains viable inside the uterine cavity (Cunningham 2001). A Cochrane review which was first published in 2007 and last updated in 2018 (Wahabi et al. 2018) showed that treatment of threatened miscarriage with progestogens compared to placebo or no treatment reduced the risk of miscarriage, with risk ratio (RR) of 0.64 (95% CI 0.47-0.87). The subgroup analysis found that treatment with oral progestogen reduced the miscarriage rate while treatment with vaginal progesterone had little or no effect in reducing the miscarriage rate. Another recent meta-analysis including more randomized controlled trials reached a similar conclusion (Li et al. 2020).

A recent large randomized double-blind placebo-controlled trial (Coomarasamy et al. 2019) confirmed that that administration of vaginal progestogen for first trimester threatened miscarriage did not increase live births compared with placebo. However, use of oral progestogen in women with threatened miscarriage during early pregnancy is still controversial and conclusive evidence in supporting its efficacy is needed due to the poor methodological quality of some of the trials and the small number of women (range 72-191) included in the meta-analyses (Wahabi et al. 2018).

Dydrogesterone, a retro-progesterone with very good oral bioavailability, is structurally and pharmacologically very similar to natural progesterone. It is considered suitable for women with threatened miscarriage as, in contrast to other available synthetic progestogens, it does not have androgenic side effects in the mother (e.g. hirsutism, acne) or estrogenic effects in the fetus (El-Zibdeh and Yousef 2009). It does not inhibit the formation of progesterone in the placenta (Pandian 2009).

This randomized double-blind controlled study aimed to compare the miscarriage rate in women presenting with threatened miscarriage in the first trimester with use of oral progestogen versus placebo. The hypothesis is that use of oral progestogen will reduce the miscarriage rate in women presenting with threatened miscarriage in the first trimester.

Materials and Methods

This randomized double-blind controlled study was conducted in three public hospitals in Hong Kong: Queen Mary Hospital (QMH), Kwong Wah Hospital (KWH) and Pamela Youde Nethersole Eastern Hospital (PYNEH). Ethics approval was obtained from the Institutional Review Board of each hospital (Reference numbers: UW13-292 [QMH]; KW/EX-16-045(97-04) [KWH]; HKEC-2016-056 [PYNEH]). Written informed consent was obtained (**AUTHOR:** is the editing correct for all 406 women who were randomized? Yes) from women at the time of recruitment. The study was registered at ClinicalTrials.gov (registration number: NCT02128685). The protocol of the study was previously published (Chan et al. 2016).

Women presenting with vaginal bleeding during the first trimester in Early Pregnancy Assessment Clinics were approached and recruited if they satisfied the selection criteria. Threatened miscarriage was defined as vaginal bleeding, with or without abdominal pain, in a pregnant woman with pelvic ultrasound confirming an intrauterine gestational sac(s) or fetus(es) with positive fetal heart pulsations (Cunningham 2001).

Inclusion criteria

The inclusion criteria for the study were:

- Age of women from 18 to 40 years at the time of recruitment;
- Between 5 and 12 completed weeks' gestation;

- Presence of intrauterine gestational sac(s) only if a urine pregnancy test was first positive within the past 2 weeks or presence of intrauterine fetus(es) with positive fetal heart pulsations or presence of intrauterine fetus(es) with crown-rump length of less than 7 mm and no fetal pulsation on pelvic scanning; and

- Absence of fever (temperature ≥38.5 °C).

Exclusion criteria

The exclusion criteria for the study were:

- History of recurrent miscarriage defined as three or more consecutive spontaneous miscarriages;

- History of known parental chromosomal abnormalities;

- Heavy vaginal bleeding or severe abdominal pain requiring surgical intervention;

- Absence of cardiac pulsation in a fetal pole with crown-rump length of ≥7 mm on transvaginal scanning;

- Use of hCG or progestogen for threatened miscarriage prior to recruitment or

- Women with current or suspected breast or genital cancers, hepatic disease or tumours.

Women underwent history taking including age, race, last menstrual period, severity of bleeding (mild, moderate and severe, self-reported), presence of abdominal pain, medical history, obstetric and gynaecological history. After physical examination and speculum examination to exclude a local cause of vaginal bleeding and confirm the cervix was closed, transvaginal scanning was performed to assess the presence of an intrauterine sac with or without fetal pole and pulsation. Any abnormal adnexal mass was also noted during scanning. Blood was then taken to measure serum hCG and progesterone levels.

Randomization and intervention

Consecutive women were then randomly assigned into one of the two groups: the progestogen and control groups by computer-generated randomization in a 1:1 ratio in blocks of 10. Each randomization result was put into a sealed opaque envelope. One sequential envelope was opened by the research assistant if a woman agreed to join the study. Both the clinicians and women were blinded from the group assignment. An unblinding procedure was considered if there were adverse drug reactions after treatment, as deemed necessary by the clinician in charge.

Women in the progestogen group received dydrogesterone (Duphaston®, Abbott, Illinois, Chicago, USA) 40 mg orally, followed by 10 mg orally three times a day (in accordance with the prescription instruction), and a placebo with the same external appearance was used in the control group accordingly. Concomitant use of any other hormonal medications or tocolytic agents was not allowed. Women were followed up with weekly pelvic ultrasound and blood tests until 12 weeks of gestation were completed, or 1 week after the bleeding stopped, whichever was later. Drugs were packaged in small bottles at a fixed number of tablets. The number of remaining tablets inside the bottle would be checked during follow-up and compliances would be recorded. Any adverse effects from drugs were also recorded during follow-up.

Treatment was also stopped if the vaginal bleeding became severe and required surgical intervention, or a diagnosis of silent miscarriage was confirmed upon a follow up scan (i.e. the gestational sac or fetal pole failed to grow after 1 week, or there was no cardiac activity in a fetal pole with crown-rump length of ≥7 mm). If the woman had a spontaneous miscarriage, the tissue mass passed or obtained after medical or surgical evacuation was sent for histology

and karyotyping by quantitative fluorescence PCR (QF-PCR) or the array comparative genomic hybridization method. QF-PCR, which was a simple and cheap method, would first be used to exclude common aneuploidy of chromosomes 13, 18, 21 and XY. The array comparative genomic hybridization method was employed in those with negative QF-PCR results to confirm or exclude aneuploidy.

Women received a standard antenatal checkup and follow-up routinely in the antenatal clinic until delivery. Written consent regarding retrieval of pregnancy and delivery data was sought from the women at the time of study entry. The obstetric outcomes were traced.

Statistical analysis

Nominal data were described by frequencies and percentages whereas continuous data were expressed as mean ± SD or median (25^{th}-75^{th} percentile) for normally distributed or skewed data respectively. Chi-square test and Fisher's exact test were used for categorical variables. T-test was used to compare the continuous variables between two groups. The analysis was performed with the intention-to-treat (ITT) and per protocol (PP) analyses. Differences were considered as statistically significant if the p-value was <0.05. All statistical analyses were performed using the IBM SPSS Statistics Version 25(IBM, Armonk, NY, USA).

The primary outcome was miscarriage before 20 weeks of gestation (Zegers-Hochschild et al. 2009). Subgroup analysis for the primary outcome was performed with regard to age of women >=35 years, positive fetal pulsations, drug compliance >80% and abnormal karyotypes in the abortus.

Based on the two previous studies (El-Zibdeh and Yousef 2009; Pandian 2009), with the pooled miscarriage rate in the progestogen group and control group being 27/182 (14.8%) versus 42/155 (27.1%) respectively, a sample size of 171 women per group was needed to demonstrate such a difference with power of 80% and type I error of 0.05. To allow for some drop-out, we aimed to recruit 400 women in total with 200 women in each group.

The secondary outcomes were the live birth rate, gestational weight at delivery, Apgar score, and obstetric complications including antepartum haemorrhage, placenta praevia, pregnancy-induced hypertension, pre-eclampsia, preterm labour, low birthweight at term and congenital abnormality. The definitions of the obstetric complications were as follows:

- Antepartum hemorrhage: any vaginal bleeding during pregnancy from the 24 weeks' gestation to term;
- Placenta previa: placenta inserting partially or wholly in the lower uterine segment, diagnosed by antenatal ultrasound at the second and third trimesters;
- Pregnancy-induced hypertension: development of new-onset hypertension (blood pressure persistently 140/90 mmHg or higher on two occasions at least 4 hours apart) during pregnancy after 20 weeks' gestation, labour or the puerperium in a previously normotensive non-proteinuric woman;
- Pre-eclampsia: development of new-onset hypertension and proteinuria (total protein excretion of >=300 mg per 24 hours, estimated by spot urine protein to creatinine ratio or 24-hour urine collection) during pregnancy after 20 weeks' gestation, labour, or the puerperium in a previously normotensive non-proteinuric woman;
- Preterm labour: any premature spontaneous delivery from 24 to 36 weeks' gestation;

Low birthweight at term: baby born with birthweight less than 2500 g at or after 37 weeks' gestation;

- Intrauterine death: fetal death *in utero* after 24 weeks' gestation.

Results

From 30 March 2016 through May 2018, 1135 women were assessed for eligibility, of which 729 women were excluded and 406 consented to participate (Fig. 1). Two hundred and three women were randomly assigned to the progestogen group and another 203 randomly assigned to the placebo group; 47 of them in total were lost to follow up. Baseline characteristics were similar in the two groups (Table I). The mean (± SD) duration of treatment was 4.9 ± 1.6 weeks in the progestogen group and 4.8 ± 1.6 weeks in the placebo group. The results showed that 70.9% (144 out of 203) and 53.7% (109 out of 203) of women in the progestogen and placebo groups had drug compliance of >80%, respectively.

Primary outcome

The primary outcome is the miscarriage rate before 20 weeks of gestation. There were 21 and 26 women who defaulted all follow-ups in the progestogen and placebo groups, respectively. We included all 406 women in the analysis for the primary outcome as an ITT analysis. The primary outcomes of those who defaulted all follow-ups were traced from the electronic patient record system if available, and those where the primary outcomes were not traceable or ended up in termination of pregnancy were counted as miscarriage in the analysis. The miscarriage rates were 12.8% and 14.3% in the progestogen and placebo groups, respectively (RR 0.897, 95%CI 0.548–1.467; p=0.772) (Table II). Analysis of the primary outcome with PP (n=331) showed similar results.

Of those who had miscarriage, only 10 women could save tissue mass for chromosomal analysis

of which four were found to have chromosomal abnormality, four of them revealed no villus for further testing, and two of them showed normal results.

Subgroup analyses of women aged >=35 years, having positive fetal cardiac pulsations on ultrasound, those with drug compliance of >80% and exclusion of abnormal fetal karyotypes did not show a significant difference in the miscarriage rate between the two groups (Table II).

The primary outcome was not available in nine and eight women in the progestogen group and the placebo group respectively. There are four possible hypothetical outcomes (Supplementary Table SI). A significant difference in the primary outcome between the two groups in favour of the progestogen group was only found when all nine women in the progestogen group did not have miscarriage and all eight women in the placebo group had miscarriage.

Secondary outcomes

There were 334 live births in total, and the live birth rates were similar in both groups (Table III). There was one intrauterine death in the placebo group, which was an intrauterine death of the first twin at 28 weeks of gestation in a twin pregnancy, and the remaining twin was delivered by lower segment Caesarean section at term. There were no significant differences in all secondary outcomes by ITT or PP analysis. (Table III)

Side effects and adverse drug reactions

There were no significant differences between the two groups in the side effects, including nausea and vomiting, headache and dizziness (Table IV). Three cases of adverse drug reactions / drug allergy were noted. One woman in the progestogen group developed a skin rash over her face, trunk and upper limbs after 13 days of medications and her condition resolved after

stopping the medication. Another woman in the placebo group developed an itchy skin rash on limbs after 1 day of medication and the condition resolved after cessation of medication. The third woman in the progestogen group developed an oral ulcer 3 days after commencement of dydrogesterone. She was subsequently managed by the medical team for severe oral ulcers with impression of drug-induced oral mucositis or Herpes simplex virus infection.

Discussion

Our study showed that use of oral progestogen in women with threatened miscarriage in the first trimester did not reduce the miscarriage rate or improve the live birth rate. This was in contrast to the subgroup analysis of the Cochrane meta-analysis (Wahabi et al. 2018), which found that treatment of miscarriage with oral progestogens compared to placebo (Turgal, Aydin, and Ozyuncu 2017) or no treatment (El-Zibdeh and Yousef 2009; Pandian 2009) reduced the risk of miscarriage. The latest meta-analysis (Li et al. 2020), which included the recent large randomized trial (Coomarasamy et al. 2019), also showed the use of oral progestogen reduced risk of miscarriage and increased live birth rate.

In the Cochrane meta-analysis (Wahabi et al. 2018), three studies (El-Zibdeh and Yousef 2009; Pandian 2009; Turgal, Aydin, and Ozyuncu 2017) out of the seven included trials using oral progestogen in threatened miscarriage. However, high risk of bias was noted with a lack of blinding in studies. Small sample sizes [n=146 (El-Zibdeh and Yousef 2009) and n=191 (Pandian 2009)] and relatively higher miscarriage rates in the control group [25.0% (El-Zibdeh and Yousef 2009) and 28.4% (Pandian 2009)] were noted in some of these included trials. The study by Alimohamadi et al (2013) was a randomized double-blind controlled trial of 160 women but there were no clinically significant differences in the miscarriage rate between the

oral progestogen and placebo groups. Other two studies were also small in size [n=83 in (Turgal, Aydin, and Ozyuncu 2017) and n=60 in (Yassaee et al. 2014)] and not double-blinded. There was again no significant difference in the rate of miscarriage between the two groups. Similarly, the latest meta-analysis (Li et al. 2020), including the PRISM trial (Coomarasamy et al. 2019), showed the use of oral progestogen reduced risk of miscarriage (RR 0.58, 95% CI 0.42–0.80; P=0.001) and increased live birth rate (RR 1.17, 95% CI 1.04–1.31; P = 0.008), but not with vaginal progesterone: the conclusion was in contrast to our results. However, the result of the oral progestogen group in the Li et al. (2020) meta-analysis was based on three small randomized trials with poor study methodology.

In the PROMISE trial (Coomarasamy et al. 2015), vaginal progesterone in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with a history of unexplained recurrent miscarriages. In the PRISM trial (Coomarasamy et al. 2019), among women with bleeding in early pregnancy, vaginal progesterone administered during the first trimester also did not result in a significantly higher rate of live births than placebo. These results echo our study findings after oral hormone administration. However, the PROMISE and PRISM trials studied the effect of vaginal micronized progesterone, which has an identical molecular structure to natural progesterone. We differed by investigating the effect of oral synthetic progestogen on women presenting with the first trimester miscarriage. (**AUTHOR:** please would you check and confirm that you have adequately addressed the comment from one reviewer i.e. to provide a valid explanation(s) for why your study differs from the PROMISE and PRISM trials? Thank you. I confirm that this have been adequately addressed here.)

We are aware that for women with three or more previous miscarriages, there was a 15% increase in live birth rate (72% versus 57%; RR, 1.28; 95% CI 1.08–1.51; P = 0.004) with use of vaginal progesterone in the PRISM trial (Coomarasamy et al. 2019). However, this was a secondary analysis of a small subgroup of 183 women and its recommendation on this specific group of women was still uncertain.

One of the strengths of our study was that it was a randomized double-blind controlled trial. Four subgroup analyses were performed and all revealed no significant differences in the miscarriage rate between treatment and placebo groups. Moreover, we included women with early pregnancy of uncertain viability and this enhances the generalizability of the results.

Our study has limitations. The miscarriage rate instead of the live birth rate was chosen as the primary outcome, although we trace the live birth rate and obstetric outcomes. Our sample size was larger than published trials using oral progestogens but not adequate to demonstrate a smaller difference in the miscarriage rate between the progestogen and placebo groups. The primary outcome was not available in nine and eight women in the progestogen group and the placebo group, respectively. We assumed that all these women had a miscarriage. However, a significant difference in the primary outcome between the two groups in favour of the progestogen group was found only when all nine women in the progestogen group did not have miscarriage and all eight women in the placebo group had miscarriage but this is very unlikely. We were unable to save all tissue masses for chromosomal studies after miscarriage. Women were recruited from the Early Pregnancy Assessment clinics which ran in the morning during weekdays and those with heavy bleeding would be admitted into wards through the Department of Accident and Emergency. We did not exclude women with multiple pregnancy, which increased the risk of miscarriage although there was only one set of twin pregnancy in the

placebo group. Women subjectively graded the severity of vaginal bleeding as mild, moderate and severe, rather than using an objective measure e.g. pictorial chart.

The issue of compliance was addressed, as women often miss drugs on some occasions in reality. Nevertheless, 70% of women in the progestogen group had a drug compliance of >80% in our study. The most common reported side effect was nausea and vomiting, occurring in up to one-third of women in both groups with no significant difference between the two groups. This could be due to pregnancy itself rather than side effect of the intervention. There were also no significant differences in the secondary outcomes including obstetric complications. Thus, the use of oral progestogen in the first trimester overall appeared to be safe. Regarding its safety in pregnancy, despite some early suggestions that progestogens may increase the risk of congenital developmental disorders (Goujard and Rumeau-Rouquette 1977; Nora et al. 1978), evidence from subsequent large prospective studies and meta-analyses indicates that any such teratogenic effects are unlikely (Katz et al. 1985; Raman-Wilms et al. 1995; Resseguie et al. 1985). A recent review of maternal use of dydrogesterone during pregnancy also found no evidence for an increased risk of congenital malformations (Queisser-Luft 2009). This study (**AUTHOR:** please clarify which study you are referring to here. Thank you. Queisser-Luft 2009) was not able to detect any long-term complications of dydrogesterone use in pregnancy. Miscarriage has multiple causes. Therefore, giving progesterone or progestogen blindly will not be beneficial and other diagnostic tools are necessary to guide treatment of this common problem.

In conclusion, use of oral progestogen in women with threatened miscarriage in the first trimester did not reduce the risk of miscarriage or improve the live birth rate. Its use is not

recommended in women with threatened miscarriage in the first trimester, although it appears to be safe and would not increase obstetric complications during pregnancy.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

All authors participated in the design of study. DMKC and EHYN drafted the manuscript. All authors read and approved the manuscript. DMKC participated in the coordination of the study. JKYK, SSFY, VCYL and RHWL were responsible for the follow-up of subjects in QMH. SFL and MTL were responsible for the study in KWH, while DYTN was responsible for the study in PYNEH.

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Conflict of interest

The authors declare that they have no competing interests.

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Figure legend (AUTHOR: is this expanded title for Fig. 1 acceptable? Yes, thanks)

Figure 1 CONSORT flowchart for a randomized double-blind controlled trial of oral progestogen versus placebo in women with threatened miscarriage in the first trimester.

Table I Baseline characteristics of women in a randomized double-blind controlled trial of oral progestogen versus placebo in women with threatened miscarriage in the first trimester.

	Progestogen Group (N=203)	Placebo Group (N=203)
Age of women (years)	31.3 ± 4.3	30.8 ± 4.3
Race		
Chinese	197 (97.0%)	197 (97.0%)
Non-Chinese	6 (3.0%)	6 (3.0%)
BMI (kg/m^2)	22.3 ± 3.7	22.2 ± 3.5
Gravida		
1	92 (45.3%)	105 (51.7%)
2	52 (25.6%)	52 (25.6%)
≥3	59 (29.1%)	46 (22.7%)
Parity		
0	119 (58.6%)	143 (70.4%)
1	69 (34.0%)	49 (24.1%)
2	15 (7.4%)	11 (5.4%)
Number of previous miscarriages		
0	174 (85.7%)	174 (85.7%)
1	22 (10.8%)	25 (12.3%)
2	7 (3.4%)	4 (2.0%)
Twin pregnancies	0 (0%)	1 (0.5%)
Gestation at presentation (weeks)	7.1 ±1.7	7.2 ± 1.6
5	38 (18.7%)	35 (17.3%)
6	50 (24.6%)	49 (24.1%)
7	52 (25.6%)	49 (24.1%)
8	32 (15.8%)	40 (19.7%)
9	19 (9.4%)	18 (8.9%)
10-12	12 (5.9%)	12 (5.9%)
Ultrasound findings at presentation		
Intrauterine sac only	28 (13.8%)	31 (15.3%)
Fetal pole	175 (86.2%)	172 (84.7%)
Positive fetal pulsation	175 (86.2%)	172 (84.7%)
Severity of vaginal bleeding before randomization		
Mild	202 (99.5%)	199 (98.0%)
Moderate	1 (0.5%)	4 (2.0%)
Severe	0	0

	Progestogen Group (N=203)	Placebo Group (N=203)
Pre-treatment serum levels		
hCG (IU/L)	95322 (47503-159361)	106892 (59191-166979)
Progesterone (nmol/L)	67.2 (50.3-83.5)	69.7 (56.3-85.0)

Data represented as number (%), mean +/- SD, and median (25-75th centile).

There were no significant differences in baseline characteristics between groups. (**AUTHOR:** correct? Correct but as a RCT, the baseline characteristics should not be compared.)

AUTHOR: please would you state in the table footnotes what statistical test was applied? Thank you. The statistical tests were added in the text.

Table II Primary outcome and subgroup analysis.

Miscarriage before 20 weeks	Progestogen Group	Placebo Group	p-value	**Relative risk (95% CI)**	**Risk difference (95% C.I.)**
Intention-to-treat	26 / 203 12.8%	29 / 203 14.3%	0.772	0.90 (0.55-1.47)	1.5 (-5.18-8.13)
Per protocol analysis	15 /163 9.2%	18 /168 10.7%	0.715	0.86 (0.45-1.65)	1.5 (-4.94-7.96)
Subgroup analysis					
Age of women ≥35 years (N=87)	6 /46 13.0%	7 /41 17.1%	0.756	0.76 (0.28-2.09)	4.0 (-11.1-19.1)
Positive fetal pulsation (N=347)	17 /175 9.7%	21 / 172 12.2%	0.495	0.80 (0.44-1.46)	2.5 (-4.08-9.07)
>80% drug compliance (N=312)	16 /144 11.1%	18 /168 10.7%	1.00	1.04 (0.55-1.96)	-0.4 (-7.34-6.55)
Exclusion of abortus with abnormal karyotypes (N=402)	24 /201 11.9%	27 / 201 13.4%	0.656	0.89 (0.53-1.49)	1.5 (-5.01-8.0)

Table III Analysis of the secondary outcomes.

AUTHOR: please would you edit Table III such that it is presented as one complete table, rather than two i.e. at present it is one table for ITT and one for PP analysis? This is journal style. Thank you.

Intention-to-treat analysis	**Progestogen Group**	**Placebo group**	**p-value**
Live birth (from N=406 women)	165 (81.3%)	169 (83.3%)	0.697
Birthweight (gram) (N=333)	3118 (2876-3330)	3150 (2790-3413)	0.923
Gestation age at delivery (weeks) (N=333)	39.1 (38.2-40.0)	39.1 (38.0-40.0)	0.964
Apgar score (N=300)			
1 min	9.0 (9.0-9.0)	9.0 (8.0-9.0)	0.070
5 min	10.0 (10.0-10.0)	10.0 (9.0-10.0)	0.444
Obstetric complications			
antepartum haemorrhage (N=336)	4 (2.4%)	8 (4.7%)	0.370
placenta previa (N=336)	3 (1.8%)	2 (1.2%)	0.683
gestational hypertension (N=336)	5 (3.0%)	11 (6.5%)	0.200
pre-eclampsia (N=336)	3 (1.8%)	3 (1.8%)	1.000
gestational diabetes (N=336)	20 (12.0%)	25 (14.7%)	0.524
preterm labour (N=336)	11 (6.7%)	13 (7.7%)	0.833
low birthweight at term (N=333)	4 (2.4%)	11 (6.5%)	0.111
intrauterine death (N=406)	0 (0%)	1 (0.5%)*	1.000
congenital abnormality (N=406)	5 (2.5%)	7 (3.4%)	0.771
Per protocol analysis (N=331)	**Progestogen group**	**Placebo group**	**p-value**
Live birth	142 (87.1%)	145 (86.3%)	0.872
Birthweight (gram)	3145 (2855-3337)	3150 (2818-3405)	0.940
Gestation age at delivery (weeks)	39.1 (38.1-40.0)	39.3 (38.3-40.0)	0.773
Apgar score			
1 min	9.0 (9.0-9.0)	9.0 (8.0-9.0)	0.201
5 min	10.0 (10.0-10.0)	10.0 (10.0-10.0)	0.748
Obstetric complications			
antepartum haemorrhage	3 (2.1%)	6 (4.1%)	0.501
placenta previa	3 (2.1%)	2 (1.4%)	0.682
gestational hypertension	4 (2.8%)	8 (5.5%)	0.378
pre-eclampsia	2 (1.4%)	3 (2.1%)	1.000
gestational diabetes	13 (9.2%)	24 (16.4%)	0.078
preterm labour	9 (6.4%)	10 (6.9%)	1.000
low birth weight at term	4 (2.8%)	9 (6.2%)	0.256
intrauterine death	0 (0%)	1 (0.6%)*	1.000
congenital abnormality	5 (3.0%)	7 (4.2%)	0.770

Data are presented as number (%) or median (25-75th centile).

**There was one intrauterine death in the placebo group, which was an intrauterine death of a baby at 28 weeks of gestation in a twin pregnancy, and the remaining twin was delivered by lower segment Caesarean section at term.*

Table IV Side effects in women taking oral progestogen or placebo during the first trimester.

	Progestogen group (N=203)	Placebo group (N=203)	p-value
Nausea and vomiting	49 (24.1%)	48 (23.6%)	1.000
Headache	15 (7.4%)	11 (5.4%)	0.544
Dizziness	9 (4.4%)	11 (5.4%)	0.819
Adverse drug reactions / drug allergy	2 (1.0%)	1 (0.5%)	1.000

Supplementary Table SI The miscarriage rate according to four possible hypothetical outcomes of women whose primary outcome could not be traced.

Miscarriage before 20 weeks	Progestogen Group (n=203)	Placebo Group (n=203)	P value
9 women in the progesterone group and 8 women in the placebo group had miscarriage	26 (12.8%)	29 (14.3%)	0.772
9 women in the progesterone group did not have miscarriage and 8 women in the placebo group had miscarriage	15 (7.4%)	29 (14.3%)	0.037
9 women in the progesterone group had miscarriage and 8 women in the placebo group did not have miscarriage	26 (12.8%)	21 (10.3%)	0.535
9 women in the progesterone group and 8 women in the placebo group did not have miscarriage	15 (7.4%)	21 (10.3%)	0.383

AUTHOR: please would you state here what statistical test was applied? Thank you. The statistical tests were added in the text.