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Dydrogesterone in threatened miscarriage: A Malaysian experience

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ABSTRACT

Introduction: Threatened miscarriage is a common problem during pregnancy.
Methods: The aim of this prospective, open, randomised study was to determine whether dydrogesterone was more effective than conservative management alone in preventing miscarriage in women with vaginal bleeding up to week 16 of pregnancy. Women were excluded if they had a history of recurrent miscarriage. A total of 191 women were randomised to dydrogesterone (40 mg stat followed by 10 mg twice daily) or conservative management (control group). The treatment was considered successful if the pregnancy continued beyond 20 weeks of gestation.
Results: The success rate in the dydrogesterone group was statistically significantly higher than that in the control group (87.5% vs. 71.6%; $p < 0.05$). Miscarriage occurred in 12.5% of women in the dydrogesterone group compared with 28.4% in the control group ($p < 0.05$). There were no differences between the groups with regard to the incidence of Caesarean section, placenta praevia, antepartum haemorrhage, preterm labour (weeks 28–36), pregnancy-induced hypertension or low birth weight (<2500 g) babies. There were no intrauterine deaths or congenital abnormalities in either group.
Conclusion: Compared with conservative management, dydrogesterone had beneficial effects on maintaining pregnancy in women with threatened miscarriage.

1. Introduction

Threatened miscarriage, which is characterised by bleeding with or without pain when the cervical os is closed, is a common complication of pregnancy that causes considerable anxiety and stress. Approximately 20% of pregnant women will experience threatened miscarriage and about half of these will eventually suffer an actual miscarriage [1–4].

Progesterone plays a crucial role in the maintenance of pregnancy. As well as inducing secretory changes in the endometrium during the luteal phase that promote implantation and support early pregnancy [5,6], it modulates the maternal immune response to prevent foetal rejection [7] and relaxes the uterine smooth musculature [8]. Despite this physiological evidence, which has led to progestogens being used in the management of threatened miscarriage for many years, there is little data available from well designed and well controlled clinical trials to support their routine use in this indication [9].

Dydrogesterone is a retro-progesterone; it is structurally and pharmacologically very similar to natural progesterone but has good oral bioavailability. It is especially suitable for women with threatened miscarriage as it does not have androgenic or oestrogenic effects on the foetus, it does not alter the normal secretory transformation of the endometrium, and does not inhibit the formation of progesterone in the placenta [10]. A number of recent studies have suggested that dydrogesterone can reduce pregnancy loss in women with threatened miscarriage [11–14]. The aim of the current study was therefore to determine whether dydrogesterone is more effective than conservative management in enabling pregnancy to continue beyond week 20 in women with threatened miscarriage.

2. Methods

This prospective, open, randomised study was conducted over a period of three years, from the 1st January 2003 to the 31st December 2005, in the Department of Obstetrics and Gynaecology, Seberang Jaya Hospital, Malaysia. This is a general state-run hospital, with approximately 7500 deliveries per year in the Obstetrics and Gynaecology Department. All women presenting with vaginal bleeding up to 16 weeks of pregnancy were assessed for inclusion. Prior to inclusion, the women underwent a general and pelvic examination, a pelvic ultrasound, and full blood count, prothrombin time and activated partial thromboplastin time were measured.

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Table 1
Baseline characteristics: *n* (%).

	Dydrogesterone ($n=96$)	Control ($n=95$)
Age (years)		
<20	19 (20%)	17 (18%)
21–29	48 (50%)	55 (58%)
≥30	29 (30%)	23 (24%)
Gravida (*n*)		
1	39 (40%)	31 (32%)
2–4	45 (47%)	49 (52%)
≥5	12 (13%)	15 (16%)
Race		
Malay	65 (68%)	63 (66%)
Chinese	13 (14%)	11 (12%)
Indian	16 (15%)	20 (21%)
Other	2 (2%)	1 (1%)
Gestation (weeks)		
<8	47 (48%)	41 (43%)
9–11	32 (33%)	37 (39%)
12–14	11 (11%)	13 (14%)
≥15	6 (8%)	4 (4%)

In order to be included in the study, the women were required to have no systemic illness or fever, no loss of conception tissue, normal gestational sac morphology at 5 weeks gestation, and the presence of a yolk sac and foetal cardiac activity at 6 weeks gestation or later. Women were excluded if they had a history of recurrent miscarriage (≥3 previous miscarriages), heavy vaginal bleeding (>2 pads soaked), cervical polyps, or if ultrasound showed an empty gestation sac of more than 26 mm or multiple gestation sacs. Because the prognosis is relatively good in such women, management with conservative measures like bed rest is often employed as standard care. The study was undertaken in accordance with the Malaysian ethical and legal framework operating at the time the study was conducted. All women provided their verbal informed consent.

The women were randomised to receive treatment with dydrogesterone (40 mg stat followed by 10 mg twice daily) or conservative management with bed rest only (control group). Randomisation was achieved by asking the patients to select a sealed envelope containing one of the treatment options. Treatment continued until 16 weeks of gestation and the women were followed up until the end of pregnancy. Women using dydrogesterone were not specifically recommended bed rest. The treatment was considered successful if the pregnancy continued beyond 20 weeks of gestation.

Power calculations were performed to determine the number of women to be included in each group. Analysis of the data was conducted under blind conditions. Data were analysed using the Pearson Chi-square test. The test was considered significant if the *p*-value was <0.05.

Table 2
Success rate (continuation of pregnancy beyond 20 weeks) with dydrogesterone treatment or conservative management.

	Success		Total
	Yes	No	
Dydrogesterone	84 (87.5%)	12 (12.5%)	96
Control	68 (71.6%)	27 (28.4%)	95
Total	152 (79.6%)	39 (20.4%)	191

Pearson Chi-square value: 7.837; likelihood ratio: 8.350.

3. Results

Data obtained over three years showed that approximately 1 in every 12 admissions was for threatened miscarriage: 218/2867 (7.6%) in 2002, 231/2872 (8.1%) in 2003 and 242/2897 (8.3%) in 2004. A total of 391 women were assessed for eligibility, of whom 200 did not meet the inclusion criteria. All 191 women who were included were followed up to the conclusion of the study. There were no statistically significant differences in the baseline characteristics between the dydrogesterone and control groups (Table 1). The majority of women were less than 30 years old, had undergone less than five pregnancies and presented before the 12th week of pregnancy. There were also no significant differences between the groups regarding pelvic examination, haematocrit values, white blood cell count and coagulation parameters. All pregnancies in both groups were the result of spontaneous conception and none of the women had received fertility treatment.

In all cases, treatment was started within 24 h of the onset of symptoms and within 2 h of an ultrasound being performed.

Dydrogesterone was more effective than conservative management in preventing miscarriage. The success rate in the dydrogesterone group was statistically significantly higher than that in the control group (87.5% vs. 71.6%; $p<0.05$) (Table 2). Miscarriage occurred in 12.5% of women in the dydrogesterone group compared with 28.4% in the control group ($p<0.05$; odds ratio: 0.36; 95% confidence interval 0.172–0.756) (Table 2). All 39 women with miscarriage required evacuation. The miscarriages all occurred during the treatment phase (i.e. up to 16 weeks gestation). Miscarriage was confirmed by ultrasound and a subsequent histopathology report.

Table 3 summarises the progression and outcome of the pregnancies in the two groups. At a follow-up ultrasound performed after 28 weeks of gestation, three women in the dydrogesterone group and four in the control group were found to have placenta praevia, all of whom underwent Caesarean section. There were also no differences between the two groups with regard to the incidence of indeterminate antepartum haemorrhage, preterm labour (weeks 28–36) and pregnancy-induced hypertension or the percentage of women who underwent Caesarean section. There were no intrauterine deaths or congenital abnormalities in either group.

Table 3
Progression and outcome of pregnancies.

	Dydrogesterone ($n=96$)	Control ($n=95$)	*p*-Value
Miscarriage (<20 weeks)	12 (12.5%)	27 (28.4%)	<0.05
Successful delivery	84 (87.5%)	68 (71.6%)	<0.05
Caesarean section	13 (13.5%) (10 emergency and 3 elective)	12 (12.6%) (8 emergency and 4 elective)	NS
Placenta praevia (>28 weeks)	3 (3.1%)	4 (4.2%)	NS
Preterm labour (28–36 weeks)	6 (6.3%)	4 (4.2%)	NS
Antepartum haemorrhage	4 (4.2%)	6 (6.3%)	NS
Pregnancy-induced hypertension	12 (12.5%)	14 (14.7%)	NS
Intrauterine death/congenital abnormality	0	0	NS
Low birth weight (<2500 g)	3 (3.1%)	2 (2.1%)	NS

NS: not statistically significant.