Maturitas 65S (2009) S43–S46

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Dydrogesterone support in threatened miscarriage

Mazen Y. El-Zibdeh*, Lama T. Yousef

Department of Obstetrics and Gynaecology, Islamic Hospital, Amman, Jordan

ARTICLE INFO

Article history:
Received 26 August 2009
Received in revised form
16 November 2009
Accepted 16 November 2009

Keywords:
Bleeding
Dydrogesterone
Pregnancy
Progestogen
Threatened miscarriage

ABSTRACT

Introduction: The aim of this study was to determine whether dydrogesterone helps to preserve pregnancy in women with threatened miscarriage.
Methods: 146 women who presented with mild or moderate vaginal bleeding during the first trimester of pregnancy were randomised to receive oral dydrogesterone (10 mg b.i.d.) ($n = 86$) or no treatment ($n = 60$). Dydrogesterone was continued until 1 week after the bleeding had stopped. All women received standard supportive care.
Results: The incidence of miscarriage was significantly lower in the dydrogesterone group than in the untreated group (17.5% vs. 25%; $p < 0.05$). There were no statistically significant differences between the groups with respect to pregnancy complications or congenital abnormalities.
Conclusion: Dydrogesterone appears to have beneficial effects in women with threatened miscarriage.

1. Introduction

Miscarriage, or the threat of miscarriage, is a traumatic event that can have psychological consequences for the potential parents [1]. Moreover, there is an increased risk of subsequent pregnancy complications, such as pre-term labour or pre-eclampsia, and low birth weight after a threatened miscarriage [2].

The risk of foetal loss is increased in women with a history of miscarriage, stillbirth or congenitally abnormal infants [3]. In women who have had one prior miscarriage, the rate of spontaneous miscarriage in a subsequent pregnancy is about 20%, whilst in women who have had three consecutive losses the rate can be up to 50% [4]. Other factors that contribute to an increased risk include mothers with systemic diseases (such as diabetes or thyroid dysfunction) [5], mothers who have been treated for infertility [6], mothers or fathers with genetic defects [7], and advancing paternal, as well as maternal, age [8,9].

In a normal pregnancy, in which the viability of the embryo has been confirmed and there has been no bleeding during the first trimester, the rate of miscarriage is low (2–4%) [10]. However, approximately 20% of women experience some vaginal bleeding during the first trimester of pregnancy [11]. In these women in whom miscarriage has been threatened, the rate of foetal loss is considerably higher [12–15]. For example, in a study in 182 with threatened miscarriage, the miscarriage rates in women who bled before gestational week 6 and between weeks 7 and 12 were 29% and 8.2%, respectively [12].

A number of options are available to try and preserve pregnancy in cases of threatened miscarriage. These include bed rest, abstention from coitus and a simple wait and watch policy, as well as treatment with progesterone or human chorionic gonadotropin [15–20]. Unfortunately, the bioavailability of oral micronised progesterone is poor and the high doses that are therefore required may result in side-effects such as drowsiness and liver toxicity. Vaginal administration of progesterone is not only inconvenient for women with vaginal bleeding, but the resorption is also unreliable, particularly in those with heavy bleeding [21]. Dydrogesterone is an orally active, highly selective progestogen that is similar to endogenous progesterone, but which has a better bioavailability and hence allows administration of lower doses and avoidance of progestogenic side-effects [22]. In contrast to other available synthetic progestogens, it does not cause androgenic side-effects in the mother (e.g. hirsutism, acne) and has no masculinising effect on the female foetus or feminising effect on the male foetus. The aim of this study was therefore to determine whether treatment with dydrogesterone would help to preserve pregnancy in women with threatened miscarriage.

2. Methods

2.1. Patients

Pregnant women who consecutively presented to the Amman Islamic Hospital clinic between April 1999 and April 2001 with

* Corresponding author. Tel.: +962 6592 4900; fax: +962 6562 5544.
E-mail address: drmazen@go.com.jo (M.Y. El-Zibdeh).

0378-5122/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2009.11.013

Table 1
Baseline characteristics ($n = 146$).

	Dydrogesterone ($n = 86$)	Untreated ($n = 60$)	Student t-test
Age range (n)			
20–24 years	22 (25.6%)	16 (26.7%)	NS
25–29 years	34 (39.5%)	22 (36.7%)	NS
30–34 years	22 (25.6%)	14 (23.3%)	NS
≥35 years	8 (9.3%)	8 (13.3%)	NS
Primigravida	14 (16.3%)	11 (18.3%)	NS
Multiparous	72 (83.7%)	49 (81.7%)	NS
Previous miscarriage in multiparous women	11 (15.3%)	8 (16.3%)	NS

NS: not statistically significant.

mild or moderate vaginal bleeding during the first trimester of pregnancy were included in this randomised, controlled study. The Islamic Hospital is a charitable private hospital and a training centre for postgraduates and residents. Patients attend for antenatal care and are seen by a group of gynaecologists and obstetricians (all the patients included in this study were seen by the authors). The patients seen include referrals from primary and secondary centres for high-risk pregnancies and pregnancy complications. There are approximately 6000 deliveries per year.

All women were scheduled to attend the clinic for their antenatal care and delivery. Exclusion criteria included the presence of a systemic illness or fever, the suspected passage of any foetal or pregnancy materials, and the absence of a normal gestational sac at 5 weeks gestational age, a yolk sac at 5.5–6 weeks gestational age, an embryo at 6–6.5 weeks gestational age or cardiac activity at 7 weeks gestational age. The study was undertaken in accordance with the Jordanian ethical and legal framework operating at the time the study was conducted. All women provided verbal informed consent.

2.2. Assessments

A full medical history and physical examination were carried out at presentation and all women underwent routine antenatal laboratory screening. The amount of blood loss was assessed by the number of pads used: 1–2 pads (mild), 3–4 pads (moderate) or >4 pads plus the presence of blood clots (heavy). An ultrasonographic examination was also performed in order to exclude miscarriage and local causes for the bleeding. A further ultrasound was performed in all patients after 1 week.

2.3. Treatment

The women were randomised to receive oral dydrogesterone (Duphaston®, Solvay Pharmaceuticals; 10 mg b.i.d.) or no treatment. Randomisation was performed according to the day of the week the women presented to the clinic. Patients attending the clinic on Saturday, Monday or Wednesday were allocated to dydrogesterone and those attending on Sunday, Tuesday or Thursday were allocated to the control group. The randomisation was performed by the attending physician, who also gave the treatment to the patients.

Dydrogesterone treatment was started at presentation with bleeding and continued for 1 week after the bleeding had stopped. Treatment was stopped prematurely if the vaginal bleeding became severe, there was passage of pregnancy material, there was an increase in body temperature, the gestational sac failed to grow after 1 week, the foetal pole was absent when the gestational sac was ≥25 cm long or there was no cardiac activity when the crown to rump length was ≥8 cm.

All women received standard supportive care, including iron, folic acid and multivitamin supplements. As much bed rest as possible was recommended, with routine activity to be resumed once the bleeding had stopped. Thereafter, the women were followed routinely in the antenatal clinic.

2.4. Statistical analyses

Pregnancy outcome and complications were compared between the groups using the Student t-test. Statistical significance was defined as $p \leq 0.05$. The assessors who analysed the data were blinded as to which patients were included in which group.

3. Results

A total of 216 women were assessed for eligibility, of whom 70 were excluded due to not meeting the inclusion criteria or refusal to be randomised. Of the 146 women included in the study, 86 were randomised to receive dydrogesterone and 60 to receive no treatment. The age distribution of the women is shown in Table 1. Most women in both groups were multiparous (83.7% in the dydrogesterone group and 81.7% in the untreated group) (Table 1). Of these women, only 15.3% in the dydrogesterone group and 16.3% in the untreated group reported a previous miscarriage. There were no statistically significant differences between the groups with regard to the baseline characteristics.

In the majority of women, dydrogesterone was initiated during the 5th or 6th week of gestation (61%); a further 34.8% started during the 7th or 8th week and 4.6% after the 8th week. Treatment was continued for a mean of 3.2 weeks (range 2–6 weeks). Only three women required hospitalisation due to threatened miscarriage during dydrogesterone treatment, two of whom subsequently aborted. There were no hospitalisations in the untreated group.

Miscarriage was significantly ($p \leq 0.05$) less common in the dydrogesterone group (17.5%; 15/86 women) than in the untreated group (25%; 15/60 women) (Table 2). There were no significant differences between the two groups with respect to the percentage of women experiencing pre-term labour.

There were also no significant differences between the groups with regard to obstetrical complications (Table 3). The congenital abnormalities consisted of one case of neural tube defect in each group, one case of congenital heart disease in the dydrogesterone group and one unspecified type of abnormality in the untreated group.

No adverse effects were reported during treatment with dydrogesterone.

Table 2
Pregnancy outcome ($n = 146$).

	Dydrogesterone ($n = 86$)	Untreated ($n = 60$)
Miscarriage	15 (17.5%)*	15 (25%)
Pre-term labour	6 (7%)	5 (8.3%)
Full-term delivery	65 (75.5%)	40 (66.6%)

* $p \leq 0.05$ vs. untreated.