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Once-a-month treatment with a combination of mifepristone and the prostaglandin analogue misoprostol

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In this two centre study, the efficacy of 200 mg mifepristone orally followed 48 h later by 0.4 mg misoprostol orally for menstrual regulation was investigated. The dose of mifepristone was taken the day before the expected day of menstruation. Each volunteer was planned to participate for up to 6 months. A plasma β human chorionic gonadotrophin (HCG) was measured on the day of mifepristone intake. The study was disrupted prematurely due to low efficacy. In 125 treatment cycles the overall pregnancy rate was 17.6% (22 pregnancies) and the rate of continuing pregnancies (failure) was 4.0%. Eight women discontinued the study due to bleeding irregularities which were seen in 15 cycles (12%). These effects on bleeding pattern made the timing of treatment day difficult. Late luteal phase treatment with a combination of mifepristone and misoprostol is not adequately effective for menstrual regulation.

Key words: luteal phase treatment/menstrual regulation/mifepristone/misoprostol

Introduction

The term menstrual regulation was introduced to distinguish late luteal treatment to avoid pregnancy from the term contraception, referring to antifertility treatment between the events of fertilization and nidation.

The possibility of using the antiprogestin mifepristone for menstrual regulation has been evaluated in a number of studies (Ulmann, 1987; Van Santen and Haspels, 1987; Dubois *et al.*, 1988; Lähteenmäki *et al.*, 1988). The overall failure rate per treatment cycle is ~5% and per pregnant cycle 17% (for review, see Swahn *et al.*, 1996). The efficacy rate for menstrual regulation in women with a menstrual delay of 7 days was higher if the antiprogestin was combined with the prostaglandin analogue Cervagem® (Rhône-Poulenc Rorer, Helsingborg, Sweden) 48 h later. Efficacy amongst subjects with elevated β human chorionic gonadotrophin (HCG) was 97.2% and if non-pregnant women were included the overall efficacy was 97.9% (WHO, 1995).

All available data concerning mifepristone treatment in the luteal phase indicate that repeated use on a monthly basis would hamper the bleeding pattern; only treatment in the very early and very late luteal phase will not cause bleeding disturbances (Croxatto *et al.*, 1987; Swahn *et al.*, 1990). Studies made in the luteal phase in which a state of pseudo pregnancy was induced by HCG (Gemzell-Danielsson *et al.*, 1993) indicate that treatment with mifepristone and a prostaglandin analogue just prior to the expected time of menstruation would be well tolerated and not upset the menstrual cycle in a non-pregnant cycle while in the case of pregnancy the combination would be sufficient to induce bleeding and possibly disrupt implantation.

One possible reason why such treatment has not been considered feasible for regular use has been the lack of a suitable oral prostaglandin analogue. A possible one is misoprostol which is effective for the induction of early abortion when used in combination with mifepristone (Aubeny and Baulieu, 1991; Norman *et al.*, 1992; El-Rafaey *et al.*, 1995)

The objectives of the present study were to evaluate the efficacy, safety and to some extent the acceptability of once-a-month administration of a combination of 200 mg mifepristone and 0.4 mg misoprostol for menstrual regulation in the late luteal phase. The effect on bleeding pattern was of special interest.

Materials and methods

Seventy or more healthy volunteers aged <40 years, with proven fertility, sexually active, not using other contraceptive methods than the method to be tested and with regular menstrual periods (24–42 days interval) were planned to be recruited and followed for up to at least 6 months. Two centres participated in the study, Stockholm in Sweden and Shanghai in China. A total of 400 cycles (200 in each centre) was planned. A single oral dose of 200 mg mifepristone was administered on the day before the expected menstruation and followed 48 h later by 0.4 mg misoprostol orally. In cases where bleeding started earlier, the mifepristone dose was taken on the same day. Urinary samples were collected during the period 3 days before and up to 4 days after the presumed ovulation on cycle days 11–18 in a 28 day cycle and frozen for analysis of luteinizing hormone (LH) surge to enable retrospect timing of intercourse and treatment in the cycle. Serum β-HCG was measured immediately before intake of mifepristone. The participating women were asked to keep records of bleeding episodes, side effects and each event of intercourse. If β-HCG was positive before treatment further follow-up visits were arranged. Only women prepared to terminate pregnancies if treatment failed were recruited. The method for termination of pregnancy was left to the discretion of the doctor and the patient.

Recruitment started in November 1994 and ended in April 1996.

Table I. Characteristics of subjects participating in the two centres (mean ± SD)

	Age (years)	Height (cm)	Weight (kg)	Cycle length (days)	Duration of bleeding (days)	Parity	Gravidity
Stockholm	32	172 64	27.6	4.2 ±1.2	1.6	5.0	
	±3.8	±4	±4.8	±0.7	±1.0	±1.2	±2.3
Shanghai	34	161	56.7	28.5	4.8	1.0	2.4
	±3.5	±4.3	±7.4	±2.9	±1.5	±0	±1.1
Total	33.5	164	58.6	28.3	4.7	1.2	3.1
	±3.6	±6.4	±7.6	±2.6	±1.4	±0.6	±1.8

Table II. Number of treatment cycles in the two centres and mean cycle length (±SD)

Treatment cycle	1	2	3	4	5	6
Number of women	32	27	20	16	13	9
Cycle length	29.2 ± 5.1	29.2 ± 4.1	29.2 ± 2.9	31.6 ± 9.1	29.6 ± 3.7	27.4 ± 3.2
Treatment cycle	7	8	9	10		
Number of women	2	2	2	1		
Cycle length	27.3 ± 1.5	26 ± 0	26 ± 1	21		

Assays

In the Chinese centre, analyses of LH in urine was made by enzyme-immunoassay techniques and of serum HCG by radioimmunoassay. In Stockholm immunofluorescence methods with commercial kits from Abbott Diagnostics, Kista, Sweden for IMX equipment were used.

Values for HCG of more than 10 IU/l or 3.1 ng/ml were considered diagnostic for pregnancy.

Statistics

Cycle length was calculated from the first day of the menstrual bleeding to the day before the next bleeding in association with the treatment. In cases of two bleeding episodes after treatment the first one was considered as the menstrual bleeding.

A Pearl Index of 5 was chosen as an acceptable level of efficacy. With a total of 400 cycles the 95% confidence limits would be 0.48 and 9.6. The study was discontinued if the Pearl Index (number of pregnant cycles per 100 woman years) exceeded 9.6. The results were reviewed per 100 treated cycles. Student's *t*-test was used for comparison of cycle lengths.

The study was approved by the Ethics Committee at each centre and by WHO's Secretariat Committee on Research Involving Human Subjects.

Results

Twenty-four women were recruited in Shanghai and eight in Stockholm. Patient characteristics were similar in the two centres except for the number of previous pregnancies which was higher in Stockholm (Table I). The total number of treatment cycles was 125 (84 in Shanghai and 41 in Stockholm). The number of treatment cycles per woman is shown in Table II. Only in Stockholm did the subjects participate for more than six consecutive cycles. The study was interrupted prematurely in accordance with the study protocol by the investigators as the efficacy was found to be too low.

Efficacy

In the 125 treated cycles a pregnancy occurred in 22 cycles, as diagnosed by HCG measurement taken the day before that of expected menses, corresponding to a total pregnancy rate of 17.6%. In five women the pregnancy continued despite treatment corresponding to a failure rate of 4.0% per treatment cycle. In two additional women the treatment resulted in an incomplete abortion with heavy bleeding needing curettage. The failure rate per pregnant cycle was 32% (Table III). One of the continuing pregnancies was seen in Stockholm, the remaining in Shanghai.

Table III. Efficacy rate after treatment with 200 mg mifepristone on the day before expected menstruation followed by 0.4 mg misoprostol 48 h later

	Shanghai	Stockholm	Total
No. of treated cycles	84	41	125
Total no. of pregnancies (positive HCG + continuing + incomplete)	19	3	22
No. of continuing pregnancies/ missed abortions	4/2	1/0	5/2
Total pregnancy rate (%)	22.6[a]	7.3[a]	17.6
95% confidence limits	14.2–33.0	1.5–19.9	
Continuing pregnancy rate per treatment cycle (= failure rate) (%)	8.3	2.4	4.0
Failure rate per pregnant cycle (%)	31	33	32

[a]$P < 0.034$.

In six subjects the mifepristone–misoprostol treatment induced spotting or normal bleeding for up to 7 days in spite of the fact that the pregnancy continued. One patient with continuing pregnancy did not experience any bleeding following treatment. Four of the clinical pregnancies were terminated by medical methods (mifepristone–prostaglandin) and the remaining three by vacuum aspiration.

LH surge

Urine samples for analysis of LH were available in 119 cycles. In 16 cycles the LH surge was not possible to identify. In the cycles with identified LH surge the mean day of treatment occurred on cycle day LH + 12 ± 1.9 (SD) and 14.2 ± 2.5 (SD) in Stockholm and Shanghai respectively.

In Shanghai the participating women reported at least one

act of intercourse in cycle days LH –3 to LH +2 in 69/84 cycles. The corresponding figure for Stockholm was 39/41 cycles.

Effects on bleeding pattern

In the majority of patients the mean length of the cycles was not affected by the treatment (Table II). Eight subjects (one in Stockholm and seven in Shanghai) discontinued the study due to bleeding irregularities which were seen in 15 cycles. In seven cycles two bleeding episodes with a few days interval were seen after treatment. In four cycles the expected menstruation was delayed for up to 1 week. In one cycle treatment did not cause bleeding and only after treatment 1 month later was menstruation induced. In three cycles an irregular bleeding pattern was observed. Two of these cycles were preceded by a positive serum HCG and in these cycles the bleeding episodes were seen on cycle days 9–13 plus 18–24, and on cycle days 20–25 respectively. In the third case a second bleeding was seen on days 17–22. Treatment with RU 486 previous to the cycle with irregular bleeding occurred on day 14.8 ± 3.1 (n = 9; SD) (range LH + 10 to LH + 20) after the LH surge whereas in six cycles the day of treatment in relation to LH surge was impossible to identify. In the 13 remaining women with positive HCG, the subsequent cycle was unaffected with regard to duration and bleeding pattern.

Discussion

In the present study, menstrual regulation with the combination of 200 mg mifepristone 1 day before the expected menstruation, followed 48 h later by 0.4 mg misoprostol, the rate of pregnancy, i.e. failure rate, was 4.0% and per pregnant cycle 32%. Menstrual regulation with mifepristone alone was found to be equally effective in pregnant cycles as termination with mifepristone alone within 10 days after the missed menstrual period (Couzinet *et al.*, 1986; Ulmann, 1987; Swahn *et al.*, 1996). The present results are equivalent to the results with mifepristone alone.

The combination of 600 mg mifepristone and 1 mg Cervagem® for menstrual regulation (WHO, 1995) in women with a menstrual delay of less than 11 days was highly effective. The overall success rate was 97.4% and for pregnant women 97.9%. These results are more favourable than those achieved in our study. The reason for the lower efficacy rate for administration before rather than after the missed menstrual period is not known, but these present results indicate that research on mechanisms of placentation during this early period between implantation and first missed menstrual period is needed. It is noteworthy that four of the continuing pregnancies were later terminated successfully by a medical method using 600 mg mifepristone and 1 mg Cervagem®. The differences in efficacy in the WHO and the present study may be attributed to the dose of mifepristone used, 200 mg in our study and 600 mg in the WHO study, and also to the type of prostaglandin analogue. However, several studies have confirmed the high efficacy of a single dose of 200 mg mifepristone combined with the prostaglandin analogue misoprostol for the termination of pregnancy (Bygdeman, 1995) so this explanation does not seem likely to be the only one.

The overall frequency of pregnancies was lower than expected in both centres, 21.4% in Shanghai and 7.3% in Stockholm. With intercourse in the peri-ovulatory period the probability of pregnancy is 30–50% (WHO, 1983; Wilcox *et al.*, 1995). In Stockholm at least one act of intercourse was reported during the peri-ovulatory period from LH –3 to LH +2 in 39 out of 41 cycles. The corresponding figure in Shanghai was 69 cycles out of 84. The lower sexual activity during the fertile period in Shanghai may explain the low rate of pregnancies in that centre whereas the reason for the low pregnancy rate in Stockholm is unclear. One possible reason for the low number of pregnancies detected might be that timing of the plasma sample of β-HCG in the cycle was not optimal. The fact that the β-HCG test was negative despite a continuing pregnancy detected 19–20 days later might support this hypothesis.

Bleeding disturbances were seen in 15 cycles in the study. The frequency was higher in Shanghai than in Stockholm, where two bleeding episodes were noted in only one cycle. Genetic variations and differences in lean body mass may explain the different effect on bleeding pattern.

It is a well known fact that treatment with mifepristone affects the menstrual cycle. The type of effect is dependent on the timing of drug intake in the cycle. Treatment in the follicular phase inhibits ovulation and folliculogenesis is resumed once treatment is withdrawn and menstruation will be delayed correspondingly. Treatment in the mid-luteal phase may either induce one or two bleeding episodes depending on whether luteolysis occurs or not. In the present study all these predictable effects on the menstrual cycle could be seen. In two cases a positive HCG before treatment seemed to induce bleeding irregularities, although that was not a consistent trait as a positive HCG did not affect the subsequent cycle in 13 cycles.

It has been argued that women would not approve of late luteal contraceptive methods (Rimmer *et al.*, 1992). Our problem with the slow recruitment rate to this study may indicate that women prefer contraceptive methods with other modes of action, but that there would still be a need for alternate methods for a minority of women.

In summary, late luteal phase treatment with 200 mg mifepristone the day before the expected menstruation followed by 0.4 mg misoprostol orally 48 h later every month is not effective enough to be used for menstrual regulation. Also the effect on bleeding pattern makes the timing of treatment impossible in too many cases.

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