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ORIGINAL ARTICLE

Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark

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Objective. To compare the efficacy of two different medical treatment regimens: mifepristone 600 mg orally + misoprostol 0.4 mg vaginally (Mf + Ms) or misoprostol 0.4 mg vaginally (Ms) with conventional surgical evacuation (SE) in women with missed abortion.
Materials and methods. Prospective crossover study with alternating regimens every 4 months. The three university clinics of Obstetrics and Gynecology in Gentofte, Herlev and Glostrup of Copenhagen County. During the period October 1999 to October 2000, 176 women with missed abortion accepted to participate in the study.
Results. The proportion of women who needed surgical evacuation after medical treatment, number of women who needed re-evacuation after primary surgical evacuation, duration of vaginal bleeding, treated infections, need of analgesics, and the subjective experiences from the participating women. Fifty-four, 73 and 49 patients were randomized to Mf + Ms, Ms and SE, respectively. Within 1 week, complete expulsion occurred in 40 (74%), 52 (71%), 47 (96%) of the three arms, respectively. Duration of bleeding was 6.9, 7.1 and 2.5 days in the three arms, respectively ($p < 0.01$). Women with an initial plasma chorionic gonadotrophine (p-hCG) between 2000 and 20 000 IU/l and a gestational age less than 75 days had a significantly better response to the medical treatment than those not fulfilling these two criteria. Initial p-progesterone did not correlate with success of medical treatment.
Main outcome measures Proportion of women who needed surgical evacuation after medical treatment, and the number of women who needed re-evacuation after primary surgical evacuation, duration of vaginal bleeding, treated infections, the need of analgesics, and subjective experiences from participating women.
Conclusion. Vaginal misoprostol 0.4–0.6 mg is effective in most patients with missed abortion. Pre-treatment with the antiprogesterone mifepristone does not increase the success rate. The selection of women with missed abortion for medical treatment based on gestational age and initial p-hCG level may increase the success of medical treatment significantly.

Key words: mifepristone, miscarriage, misoprostol, missed abortion

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For decades, the standard treatment for missed abortion has been surgical evacuation. The successful medical treatment of legal abortion up to 9 completed weeks of gestation, suggests that medical treatment of missed abortion could be an alternative. The reported success of medical treatment

of missed abortion has been conflicting (1–5), whereas expectant management of missed abortion with success rates of only 25% has been disappointing (5). The differences in success of medical treatment may be a result of differences in patient selection or differences in medicine type, dose and the method of application, as well as the generally small number of patients included in the studies. The best results have been achieved by vaginal application of the prostaglandin misoprostol in doses of at least 0.4 mg, with success rates up to 88% (3, 6). Giving the antiprogesterone mifepristone as pretreatment has not increased the success rates substantially; 52–92% (1, 2, 4).

The aim of this study was to compare two different medical treatment regimens with surgical evacuation of the uterus in the treatment of missed abortion.

Materials and methods

The missed abortion study spanned the 12 months from October 1999 to October 2000 and was designed as a prospective cross-over study between three gynecologic departments in Gentofte, Herlev and Glostrup, all in Copenhagen County. Copenhagen County has 609 000 citizens, 314 000 are women, and 140 000 of these are of reproductive age. The three participating centers were randomized to alternating treatments every 4 months. The women did not know the result of the randomization until after having given their consent.

The specific entry criteria were: a positive urine human chorionic gonadotrophin (hCG) or plasma (p)-hCG > 30 IU/l and no fresh vaginal bleeding and one of the following four vaginal ultrasound (US) criteria being fulfilled:

1) Foetus with crown rump length (CRL) 6–20 mm with no embryonic cardiac activity, **or**
2) Foetus with CRL < 6 mm, no embryonic cardiac activity and a verified gestational age of at least 6 completed weeks or a rise in p-hCG level of less than 20%/day **or**
3) Anembryonic pregnancy with an empty gestational sac of at least 12 mm and no growth over at least 3 days **or**
4) Anembryonic pregnancy with an empty gestational sac of at least 15 mm and amenorrhea of at least 6 weeks.

A CRL of 20 mm was chosen as the upper limit because it corresponds to the maximum size of CRL in the medical legal termination of pregnancy accepted at the three participating centers.

If the patient fulfilled the entry criteria she was informed about the study, and participating women gave written informed consent.

Patients with fresh bleeding were referred to a spontaneous abortion study, which was on-going at the same centers.

The exclusion criteria were suspicion of ectopic pregnancy, allergy or contraindications for mifepristone or misoprostol, sign of infection, age below 18 years, or women not speaking Danish. Patients who did not want to participate or patients who did not fulfil the entry criteria were offered surgical evacuation.

The three treatment regimens were:

1. Medical treatment (Mf + Ms) with a single dose of mifepristone 600 mg orally on day one. The patient returned to the gynecologic ward on day 3 and was given misoprostol 0.4 mg vaginally. If no vaginal bleeding occurred within 2 h, additional misoprostol 0.2 mg was given. The patient was observed for 4 h in the department.
2. Medical treatment only with misoprostol 0.4 mg vaginally on day 1 (Ms). If no vaginal bleeding occurred within 2 h, additional misoprostol 0.2 mg was given. The women were observed for 4 h in the department.
3. Surgical evacuation in general anesthesia. On day 1, before treatment, p-progesterone (nmol/l) and p-hCG (IU/l) were measured. P-hCG samples were repeated on day 8 and day 14. All patients were offered 100 mg of diclofenac rectally for pain relief at the time of giving misoprostol or immediately after surgical evacuation. Rh-anti-D-immunoglobulin was offered to all Rh-negative women. A US examination was conducted on day 8. If the US was unchanged or the anterior-posterior diameter of the midline echo was > 20 mm, surgical evacuation or (in the case of primary evacuation) re-evacuation was performed.

All patients were asked to return a questionnaire after 14 days. They were asked about the length of bleeding, spotting, need of analgesics, if they had received any antibiotics for pelvic inflammatory disease (PID), and for their own subjective evaluation of the treatment. They were asked, if they would choose the same procedure if they had to go through it again. If they did not want the same procedure, they were asked why not.

The main outcome measures were: need of surgical evacuation after medical treatment, need of re-evacuation after SE, duration of vaginal bleeding, incidence of treated infections, need of analgesics, and the subjective experiences indicated in the returned questionnaires.

Table I. Characteristics of the women at inclusion

		Mifepristone + misoprostol $n=54$	Misoprostol $n=73$	Surgical treatment $n=49$
Age (years)	Mean	32.0	32.1	31.6
	Range	20–46	20–45	18–43
Pregnancy length (days)	Mean	73.2	67.2	76.2
	Range	45–114	38–125	51–127
P-progesterone day 1 (nmol/l)	Mean	40.8	37.1	31.7
	Range	8–240	1–148	1–81
P-hCG day 1 (IU/l)	Mean	21.052	25.011	14.817
	Range	751–196 324	79–184 400	192–75 000

Table II. Result of treatment with mifepristone + misoprostol, misoprostol, and surgical evacuation of missed abortion, respectively

		Mifepristone + misoprostol $n=54$	Misoprostol $n=73$	Surgical treatment $n=49$
Emergency evacuation	n (%)	6 (11.1)*	1 (4.1)[ref.]	–
All evacuations	n (%)	14 (25.9)	21 (28.8)	2 (4.1)
Treated pelvic infection	n (%)	1 (1.9)	3 (1.4)	2 (1.4)
Blood transfusion	n (%)	0	0	0
Analgesic need (days)	Mean	2.5	1.7	1.5
	Range	0–15	0–7	0–10
Duration of bleeding (days)	Mean	6.9**	7.1**	2.6
	Range	0–15	0–16	0–9
Duration of spotting† (days)	Mean	4.7	3.9	4.7
	Range	3–27	1–24	0–17
Recommended by client	n (%)	29/46 (63)	50/65 (77)	38/45 (84)

*$p<0.05$, **$p<0.001$.
†Beyond days of regular bleeding.

The study was approved by the Scientific Ethics Committee of Copenhagen County (KA 99102 s).

Test of significance was calculated by the qui-square test. Length of bleeding was tested also with the nonparametric Wilcoxon test. The level of significance was set at 5%.

Results

During the study period, 365 patients were admitted with missed abortion. Of these, 297 fulfilled the entry criteria, and 176 patients accepted inclusion into the study. Among the 365 patients, the main reasons not to participate in the study were: CRL >20 mm at day 1, $n = 27$; language problems, $n = 19$; or the women did not want to participate, $n = 110$.

The study population is described in Table I. There were no significant differences between the three treatment groups according to age, pregnancy length, and p-hCG or p-progesterone on day 1.

The Mf + Ms treatment was successful (no evacuation) in 40 of 54 (74%) women, and Ms in 52 of 73 (71%) patients. SE was successful (no re-evacuation) in 47 of 49 (96%) clients (Table II).

Additional misoprostol 0.2 mg was given to 13/54 patients (24%) in the Mf + Ms group, and to 43/73 patients (59%) in the Ms group. There was no difference in either group in the proportion given an extra dose of misoprostol between those who succeeded in the treatment and those who underwent evacuation (Table III).

Significantly more patients needed acute evacuation because of heavy bleeding in the Mf + Ms group 6/54 (11%) compared with the Ms group 1/73 (1%) ($p<0.05$). Five of the patients in the Mf + Ms group were evacuated after having received mifepristone only. No patient in the study group needed a blood transfusion. One of the six patients with heavy bleeding had tissue in her cervical ca-

Table III Number of patients given additional misoprostol 0.2 mg

		Mifepristone + misoprostol $n=54$	Misoprostol $n=73$
Secondary evacuation	n (%)	2/14 (14)	13/21 (62)
No secondary evacuation	n (%)	11/40 (28)	30/52 (58)
Total	n (%)	13/54 (24)	43/73 (59)

Table IV. Why the women did not recommend the same treatment again

		Mifepristone + misoprostol $n=46$	Misoprostol $n=66$	Surgical treatment $n=45$
Treatment unsuccessful	n (%)	9 (20)	11 (17)	
Length of bleeding	n (%)	10 (22)	5 (8)	
Length of pain	n (%)	9 (20)	7 (11)	
Medical side-effects	n (%)	6 (13)	3 (5)	
Want to sleep	n (%)	4 (9)	4 (6)	
Want to be awaked	n (%)			2 (4)
Instrumentation unwanted	n (%)			6 (13)
Anesthetic side-effects	n (%)			4 (9)

nal, which was removed by a ring forceps and was why surgical evacuation was not necessary.

One patient (2%) in the Mf + Ms group was treated with antibiotics because of PID compared with three patients (4%) in the Ms group and two (4%) patients in the SE group. One patient developed allergic symptoms (urticaria and itching treated with antihistamines) after the administration of mifepristone.

Distribution of the patients according to the four ultrasound criteria: 72 had CRL 6–20 mm and no heart activity, 27 had a CRL < 6 mm and a gestational age of more than 6 weeks or an insufficient hCG increase, 15 had a gestational sac > 12 mm with no embryo, and 62 had an empty gestational sac > 15 mm. There was no difference in the success rates according to these US criteria.

The overall return rate of the questionnaires was 156/176 or 89% (Table II). The length of bleeding was significantly longer in the two medically treated groups: 6.9 days and 7.1 days vs. 2.6 days in the surgical group ($p < 0.001$). The need of analgesics in the Mf + Ms group was 2.5 days, in the Ms group 1.7 days, and in the SE group was 1.5 days (NS).

The patients who underwent primary SE were concerned about the instrumentation of the uterus, $n = 5$, or about the anesthesia, $n = 3$. In the Mf + Ms group 63% and in the Ms group 76% recommended the treatment. The main reasons for not recommending the medical treatment were (Table IV): unsuccessful treatment: Mf + Ms, $n = 9$, and Ms, $n = 11$; length of bleeding: Mf + Ms, $n = 10$ and Ms, $n = 5$; and pain: Mf + Ms, $n = 9$, and Ms, $n = 7$. There was no difference between the two medical treatment groups.

We did not find any individual prediction for a secondary evacuation according to gestational age, initial p-hCG or in p-progesterone on day one (Fig. 1).

However, combining p-hCG and gestational age revealed a group of women with a low incidence of evacuation (Fig. 1). Of those 41 with a p-hCG of between 2000 and 20 000 and a gestational age less than 75 days, only four (10%) were evacuated compared with an evacuation rate of 35% among the 82 women not fulfilling these criteria ($p < 0.05$).

Discussion

In Table V, we have summarized the results from five previous studies and from this study. It appears that our results are comparable with previous findings. Additional misoprostol 0.2 mg was

Table V. Medical treatment of missed abortion. Results from six studies

Author[ref]	El-Refaey (1)	Lelaidier (2)	Creinin (3)	Nielsen (4)	Zalányi (6)	This study
Year of publication	1992	1993	1997	1997	1998	2001
Nationality	English	French	American	Swedish	Hungarian	Danish
No. of patients	60	44	20	31	25	127
Regimen						
Mifepristone	600 mg orally	600 mg orally	Not given	400 mg orally	Not given	600 mg orally/No*
Misoprostol	600 ug orally	not given	400 ug oral800 ug vg	400 ug orally	400 vaginally	400 ug vaginally
Control	US	US	US	US	US	US, hCG
Control time	4 h, days 10–14	Day 5	Day 1 + 2	Day 6	10 h	Day 8 + 14
Results						
Included	59	23	12/8	31	25	54/73*
Complete abortion	51	17	1/5	16	18	40/52*
Complete anp†	5	–	2/2	–	4	–
Success rate	95%	74%	25%/88%	52%	88%	74%/71%*
Failed	3	6	9/1	15	3	14/21*
Failure rate	5%	26%	75%/12%	48%	12%	26%/29%*
Evacuated if	Gestational sac or no bleeding	Not indicated	Gestational sac	Retained products > 15 mm	Retained products > 15 mm	Retained products > 20 mm

*Only misoprostol 400 ug vaginally.

†anp = after new prostaglandin application.

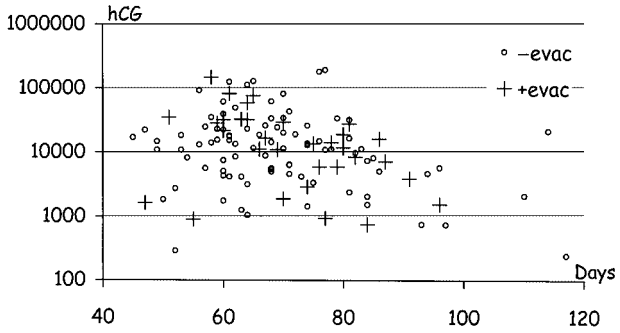

Fig. 1. Plasma-hCG levels and gestational age at inclusion in women who did (+) and did not need (°) evacuation of the uterus.

given to 59% in the Ms group, which could indicate a too low initial dose. Zalányi found an effect of vaginal misoprostol in doses up to 0.6 mg, but no further effect of higher doses (6). El-Refaey received 95% success with a regimen of oral mifepristone 600 mg + oral misoprostol 0.6 mg (1). El-Refaey later demonstrated that vaginal administration of misoprostol is more effective than if given orally (7). Both studies had a high expulsion rate of 88% and 95%, respectively, compared with our rate of 75%. This may have been because of the fact that these two studies defined successful treatment as no visible gestational sac, whereas other investigators (4, 6) defined successful treatment according to a reduction in the anterior-posterior diameter of the midline echo. We defined successful treatment as an anterior-posterior diameter of less than 20 mm on day 8, and we had no patients fulfilling these criteria who were readmitted with retained intrauterine products after discharge. Creinin *et al.* found an expulsion rate of 88% on a regimen of vaginal misoprostol 0.8 mg, but the number of patients ($n = 8$) was low (3).

Oral mifepristone has been used with different success. Lelaidier *et al.* obtained a success rate of 74% with mifepristone 600 mg orally (2), while Nielsen *et al.* reached 52% using mifepristone 400 mg orally combined with misoprostol 0.4 mg orally (4). The dissimilarities of these reports may be the result of the small number of patients included, differences in patient selection, and in the outcome measures used to define success. We did not find any improvement in the expulsion rate by pretreatment with mifepristone. Our hypothesis is that antiprogesterone is not necessary for the medical termination of missed abortion because the function of the placenta is often already abnormal. On the other hand, prostaglandin is required to initiate uterine contractions and expulsion of the conception product. Pre-treatment with antiprogesterone in women with missed abortion may increase the risk of heavy bleeding, as this complication has been reported in our and two previous studies (2, 4).

The reason for the lower efficacy of misoprostol in missed as compared to induced abortion is probably because women who do not experience a spontaneous expulsion of the dead foetus are a select group of women in whom the pregnancy is relatively difficult to expulse as compared to women who begin their abortion process spontaneously.

We found that women with an initial p-hCG between 2000 and 20 000 IU/l and a gestational age of less than 75 days had a significantly better chance of responding to a medical regimen. Jurkovic *et al.* found a positive predictive value with low gestational age (5), and Lelaidier *et al.* found a positive prediction for successful medical treatment in women with low initial p-hCG and p-progesterone and high gestational age (2). The clinical, US inclusion criteria and initial p-progesterone level did not correlate to the success of the medical treatment in our study.

Despite the fact that surgical evacuation of women with missed abortion is effective in more than 95% of cases, there are three reasons for searching for a medical alternative. Many women prefer a less invasive way of terminating their pregnancy in case of missed abortion (and legal medical abortion), and also wish to be awake during the treatment despite the fact that they might experience more pain and longer bleeding compared with women undergoing primary surgical evacuation. Second, even though approximately 25% of medically treated women undergo secondary surgical evacuation, they may still have a lower infection risk as compared to women primarily undergoing surgical evacuation. Third, the waiting time for the operating theatre may (at least in Denmark) sometimes be days, whereas medical treatment may be initiated immediately after diagnosis. Medical treatment in missed abortion as an alternative to evacuation was also recommended in two recent surveys (8, 9).

With the inclusion criteria used in this study, the medical treatment of missed abortion does not seem to increase the risk of missing a diagnosis of ectopic pregnancy or hydatid mola. The approximate 4.5-day longer period of bleeding in medical treatment did not, among the women participating in this study, imply a rejection of the method. It is undoubtedly important that medically treated women are informed to expect a few days more bleeding.

The identified group receiving the highly successful medical treatment (according to gestational age and p-hCG level) need confirmation in other studies. If this finding is confirmed in future studies,

we should probably recommend primary medical treatment for women fulfilling the criteria, and primary surgical evacuation for those who do not.

Conclusion

Vaginally applied misoprostol 0.4–0.6 mg is an alternative treatment in most patients with missed abortion. Pre-treatment with mifepristone does not increase the expulsion rate, but may increase the risk of heavy bleeding. Gestational age and an initial plasma level of hCG or progesterone do not individually predict the success of medical treatment. On the other hand, the combination of a gestational age of less than 75 days and initial plasma levels of hCG between 2000 and 20 000 IU/l may imply higher success of medical treatment than in those women not fulfilling these criteria.

Our tentative recommendation for medical treatment in women with missed abortion is vaginally applied misoprostol 0.4–0.6 mg, if necessary supplemented with a further 0.2 mg in instances of no bleeding 2 h after the primary application.

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