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Management of miscarriage: a randomized controlled trial of expectant management versus surgical evacuation

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BACKGROUND: In many countries, surgical uterine evacuation is the standard treatment for women with a miscarriage, but expectant management has been advocated as an alternative. The choice between the two options cannot be based on published evidence alone, because randomized clinical trials are scarce while generalizability of findings to patients with a strong preference for either management options is unclear. METHODS: In a randomized controlled trial, the complications and efficacy of either expectant or surgical management for miscarriages were compared, and the results in patients who refused randomization and were managed according to their own preference were studied. In total, 122 patients were randomized and 305 were managed according to their choice. RESULTS: No differences were found in the number of emergency curettages and complications between expectant and surgical management. Efficacy at 6 weeks was 30/64 (47%) in women allocated to expectant management, and 55/58 (95%) in women allocated to surgical evacuation. After 7 days, 37% of expectantly managed women had a spontaneous complete miscarriage. After 6 weeks, intention-to-treat analysis including cross-overs showed similar effectiveness (92% versus 100%). Results in the preference groups were comparable with those in the randomized groups. CONCLUSION: In our experience a waiting period of 7 days after diagnosis may prevent 37% of surgical procedures.

Keywords: choice behaviour/curettage/randomized controlled trial/spontaneous abortion/treatment outcome

Introduction

In many countries, surgical uterine evacuation is the standard treatment for women with a miscarriage. Expectant management has been advocated as an alternative in several observational studies in a primary care setting (Ambulatory Sentinel Practice Network, 1988; Wiebe and Janssen, 1998). Just one randomized clinical trial has compared both management options in a hospital setting, and this suggested the outcomes to be similar (Nielsen and Hahlin, 1995). However, the duration of expectant management in this study was restricted to only 3 days. From a clinical and health policy point of view, this information should be regarded as important, yet currently insufficient on which to base guidelines and individual decisions. A longer period of expectant management and more information on the preference of patients are necessary. Patients' preferences might even play a decisive role if no substantial differences exist in the effectiveness, costs and availability of both treatment modalities.

A randomized controlled trial was conducted to compare expectant management with surgical evacuation. Eligible women who refused randomization because of a strong preference for either surgery or expectant management were managed according to their choice, and evaluated similarly to randomized patients. By using this particular study design, the aim was to enhance the generalizability of the study findings.

Materials and methods

Protocol

The study was conducted between April 1998 and September 2000 in two Amsterdam hospitals: the Academic Medical Center and the Onze Lieve Vrouwe Gasthuis. General practitioners working in the health district covered by these two hospitals were asked to refer women with first-trimester vaginal bleeding for an ultrasound assessment. In addition, all women attending the emergency departments or the outpatient clinics of both hospitals because of first-trimester vaginal bleeding were also asked to participate.

Patients with an established diagnosis of early fetal demise or incomplete miscarriage at a gestational age of <16 completed weeks were included in the study. Transvaginal sonographic criteria for early

fetal demise were: a mean gestational sac diameter >15 mm without a measurable embryonic pole; an embryo without cardiac activity; or a gestational sac diameter <15 mm, not showing any growth after a 7-day interval (Coulam *et al.*, 1997; Deaton *et al.*, 1997). An incomplete miscarriage was diagnosed in case of ultrasound evidence of retained products of conception (RPOC) >15 mm anteroposterior (AP) diameter. All transvaginal scans were performed by trained physicians using a transvaginal 6.5 MHz sonographic probe (Hitachi Corporation, Tokyo, Japan).

Exclusion criteria for enrolment in the study were: age under 18 years; inability to understand the Dutch or English informed consent form; and/or severe bleeding, pain or fever necessitating immediate surgical evacuation.

The study was approved by the medical ethics committees of both hospitals.

Assignment

After written informed consent had been obtained, patients were allocated randomly by the attending physician to either expectant management or surgical evacuation (randomized groups) using central electronic randomization. Randomization was stratified for referral setting (directly by general practitioners versus outpatient clinics) and for gestational age (4–8, 8–12 and 12–16 weeks of amenorrhoea). Eligible women who expressed a strong preference for one of the treatment options and refused informed consent for randomization, were invited to participate in the observational study and received the treatment of their choice (preference groups). These women were asked to consent to the same follow-up procedures as applied in randomized patients.

Interventions and follow-up

Surgical uterine evacuation using suction curettage was performed within a week after inclusion in the study under local or general anaesthesia in daytime surgery. Planning of surgery depended on the availability of theatre facilities only and was independent of group assignment (randomized or preference). Local anaesthesia was attained by paracervical injection of mepivacaine, after premedication with intravenous atropine. Occasionally, this was combined with midazolam for sedation. General anaesthesia was used whenever cardiopulmonary monitoring was required, or when requested by the patient. General anaesthesia was achieved by i.v. administration of propofol. The cervical canal was dilated to a maximum of Hegar 12. Vacuum aspiration was carried out using 8, 10 or 12 mm curettes (Rocket of London Ltd, UK). Rhesus-negative patients received 375 IU anti-D immunoglobulin. Patients left the hospital after 2–4 h of postoperative observation. Expectant management involved bi-weekly scheduled visits to the outpatient clinic. Further management in this group depended on clinical developments. Women who became impatient while being managed expectantly, and requested surgical evacuation, were scheduled to undergo curettage within a week.

All women (randomized and preference groups) were assessed clinically and sonographically during the bi-weekly appointments until a complete evacuation of the uterus was established either by surgical evacuation or through spontaneous loss. Women had access to a telephone consultation at all times, and emergency admission could be arranged, if necessary.

To identify long-term complications, active follow-up was continued for a period of up to 3 months.

Data collection

During the first visit the attending physician collected baseline data on clinical signs and symptoms, obstetric history and gestational age. Additional information on symptoms and sociodemographic data was collected by means of a structured questionnaire (two languages, Dutch and English, both available on request).

All patients were asked to report (using a standardized diary) the amount of bleeding, the degree of abdominal pain and the ability to work. Bleeding was registered daily on a validated pictorial blood loss assessment chart; pain was scored on a visual analogue scale (Higham *et al*., 1990).

During the bi-weekly visits, diaries were taken in, and patients received instructions about the diary for the next interval.

Outcome measures

The following hierarchy was applied in comparing the outcomes of both strategies: complications, efficacy and duration of vaginal bleeding and pain.

Complications: excessive bleeding (>500 ml), ascending genital tract infection, cervical tear and uterine perforation were considered as short-term complications. Intrauterine synechiae (Asherman's syndrome) demonstrated during hysteroscopy was considered a long-term complication. Whenever this complication was suspected on clinical grounds, i.e. in case of hypomenorrhoea, dysmenorrhoea or amenorrhoea, a hysteroscopy was performed (Westendorp *et al*., 1998).

Efficacy: expectant management was considered to be successful if a spontaneous loss had occurred within 6 weeks. Surgical evacuation was successful if the curettage was performed without the need for repeat curettage within 6 weeks. Additional analysis compared uterine evacuation rates after 6 weeks including cross-overs (intention to treat).

Duration of clinical symptoms: this was based on patients' self-reported symptoms as recorded in their diary. Emergency curettage was defined as the need to perform an unscheduled curettage for severe vaginal bleeding or pain.

Sample size: assuming no substantial differences between the two treatments in the randomized trial in terms of safety and complications, the aim was to demonstrate a 20% difference in efficacy (65% for expectant management and 85% for curettage). In order to reach a power of 0.80, a total of 162 patients was needed to be randomized.

Statistical analysis

Complication rate and duration of clinical symptoms were analysed according to the intention-to-treat principle. Outcome measures were analysed using descriptive statistics, with the application of the *t*-test, χ^2 and Wilcoxon–Mann–Whitney tests as appropriate. For the analysis of time until evacuation and time until bleeding or pain stopped, conventional survival analysis methods were applied and appropriate comparative tests (log-rank test) used. Medians were 50% cumulative probabilities as estimated with Kaplan–Meier analysis, unless stated otherwise.

All statistical analyses were repeated for the preference groups with application of comparative statistical tests for descriptive purposes only. The Statistical Package of the Social Sciences (SPSS, version 9.0) was used for all analyses.

Results

Participant flow and follow-up

Among 1101 women referred for an early pregnancy assessment, 652 were excluded because of their diagnosis (viable pregnancy, complete miscarriage, other reasons) and 449 were eligible for the study (Figure 1). Twenty-two women were excluded because of severe bleeding or pain necessitating immediate curettage. Of the 427 remaining women, 122

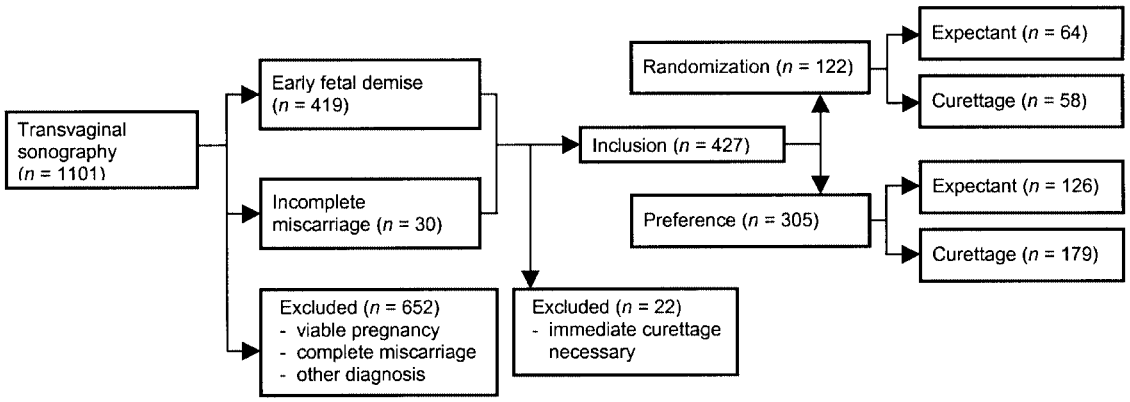

Figure 1. Trial profile.

Table I. Patient characteristics at inclusion according to treatment allocation and preference[a]

Characteristic	Randomized group		Preference group	
	Expectant (n = 64)	Curettage (n = 58)	Expectant (n = 126)	Curettage (n = 179)
Mean age (years)	32.1	33.4	32.5	32.2
Parity				
0	32 (50.0)	22 (37.9)	57 (45.2)	87 (48.6)
1	21 (32.8)	22 (37.9)	37 (29.4)	53 (29.7)
>1	11 (17.3)	14 (24.1)	32 (25.5)	39 (21.8)
Previous experience				
No previous miscarriage or curettage	37 (57.8)	33 (56.9)	72 (57.1)	96(53.6)
Prior curettage	17 (26.6)	18 (31.0)	34 (27.0)	56 (31.3)
Prior spontaneous miscarriage	7 (10.9)	5 (8.6)	11 (8.7)	9 (5.0)
Prior curettage and spontaneous miscarriage	3 (4.7)	2 (3.4)	5 (4.0)	14 (7.8)
Unknown	–	–	4 (3.2)	4 (2.2)
Gestational age				
<8 weeks	9 (14.1)	8 (13.8)	9 (7.1)	18 (10.1)
8–12 weeks	36 (56.3)	29 (50.0)	65 (51.6)	93 (52.0)
12–16 weeks	15 (23.4)	18 (31.0)	40 (31.7)	50 (27.9)
Uncertain	4 (6.3)	3 (5.2)	12 (9.5)	18 (10.1)
Intact gestational sac	60 (93.8)	54 (93.1)	113 (89.7)	170 (95.0)
Incomplete miscarriage	4 (6.2)	4 (6.9)	13 (10.3)	9 (5.0)
Vaginal bleeding present	48 (75.0)	45 (77.6)	93 (73.8)	131 (73.2)
Bleeding until inclusion (days)[a]	3 (0–9)	2.5 (1–6)	2 (0–6)	2 (0–7)
Pain until inclusion (days)[a]	0 (0–2)	0.5 (0–3)	0 (0–1)	0 (0–2)
Native country				
Western Europe and USA	39 (60.9)	29 (50.0)	63 (50.0)	93 (52.0)
African country	3 (4.7)	8 (13.8)	9 (7.1)	10 (5.6)
Surinam and Antilles	11 (17.2)	12 (20.7)	23 (18.3)	31 (17.3)
Other and unknown	11 (17.2)	9 (15.5)	31 (24.6)	45 (25.1)

Values in parentheses are percentages.
[a]Values are true median, with 25–75 percentiles in parentheses.

accepted randomization while 305 expressed their own treatment preference and gave consent for data collection and follow-up.

Data analysis

Randomized groups

No significant differences in patient characteristics were present between the two randomized groups (Table I). Neither was any difference in prior experience with one of the management options observed. According to intention-to-treat analysis, the complication rate in randomized patients was low and did not differ significantly between the two management strategies (6.3 versus 3.4%) (Table II).

In the group allocated to expectant management, 30 out of 64 women (47%) actually had a spontaneous loss within 6 weeks, while another two women experienced a complete loss even later. The other 32 (50%) underwent surgical evacuation: 25 (39%) on their own request and seven (11%) as an emergency procedure because of intolerable bleeding or pain. The median time to reach complete evacuation of uterine

Table II. Outcome measures according to treatment allocation and preference

Outcome	Randomized group			Preference group	
	Expectant (n = 64)	Curettage (n = 58)	P[a]	Expectant (n = 126)[b]	Curettage (n = 179)[b]
Successful treatment at 6 weeks	30 (46.9)	55 (95)	<0.001	53 (42.1)	160 (89.4)
Second curettage	2 (3.1)	3 (5.2)	NS	2 (1.6)	12 (6.7)
Emergency curettage	7 (10.9)	6 (10.3)	NS	19 (15.1)	18 (10.1)
Complications					
Bleeding, transfusion needed	1 (1.6)	–	NS	3 (2.4)	–
Haemorrhage (>500 ml)	2 (3.1)	1 (1.7)	NS	5 (4.0)	7 (3.9)
Cervical tear	1 (1.6)	–	NS	–	–
Uterine perforation	–	–		–	1 (0.6)
Infection	–	–		–	2 (1.1)
Asherman's syndrome	–	1 (1.7)	NS	–	1 (0.6)
Total	4 (6.3)	2 (3.4)	NS	8 (6.4)	11 (6.2)
Time until evacuation[c]	7 (3–16)	5 (2–7)	<0.001	10 (4–18)	5 (2–8)
Time to stop bleeding[c]	17 (10–26)	13 (9–17)	0.04	22 (15–35)	15 (9–25)
Time to stop pain[c]	14 (7–24)	11 (6–26)	NS	17 (7–24)	11 (6–21)

Values in parentheses are percentages.
[a]Randomized groups.
[b]Women lost to follow-up were treated as failures (12 in the expectant group, seven in the curettage group).
[c]Median time after inclusion defined as the 50% probability of evacuation, cessation of bleeding or pain following Kaplan–Meier estimation. The 25% and 75% probabilities respectively are shown in parentheses.
NS = not significant.

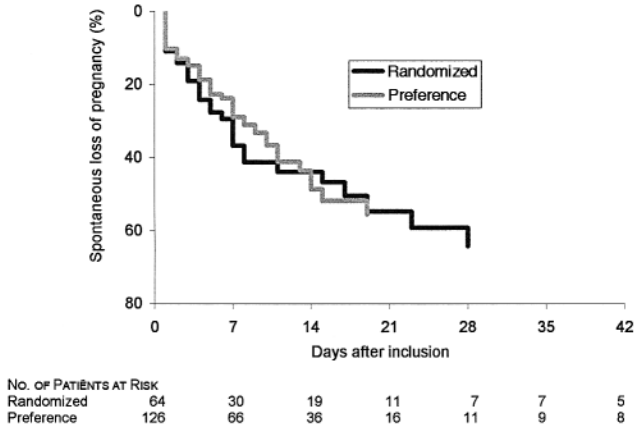

Figure 2. Kaplan–Meier estimates of the time until evacuation for expectant management (randomized and preference groups). Surgical evacuations were censored.

contents (including the waiting time of censored patients undergoing curettage) was 19 days, while 37% of the women had a spontaneous loss within seven days (Figure 2).

A successful evacuation of the uterus was reached in 55 of the 58 patients allocated to surgical evacuation (94.8%). In 10 women a spontaneous loss occurred before the scheduled curettage. A second curettage was needed in three cases (5.2%) because of incompleteness of the first procedure. The rate of emergency curettages and second curettages did not differ between the randomized groups. After 6 weeks, intention-to-treat analysis (including cross-overs) showed similar evacuation rates (92 versus 100%; P = NS).

The median duration of bleeding was 17 days for expectant management and 13 days for curettage (P = 0.04), while pain lasted for a median time of 14 versus 11 days (P = NS).

No difference was found in the efficacy of expectant management between women at >12 and ⩽12 weeks of gestation.

Preference groups

Baseline characteristics between randomized patients and those managed according to their preference did not differ (Table I). The complication rate was 4% for expectant management versus 6.2% for surgical evacuation (Table II).

Randomized versus preference groups

The efficacy was lower in the preference groups than in the trial (expectant 42.1%, curettage 89.4%), mainly because 12 women (9.5%) in the expectant group and seven women (3.9%) in the curettage group were lost to follow-up and were considered as failures in the present analysis. The rates of repeat curettages, emergency curettages and complications were similar in all groups.

Additional findings in all treatment groups

Approximately 25% of the women in each group did not have vaginal bleeding at inclusion. The outcomes (efficacy and complications), however, were identical to those in women with manifest vaginal bleeding at inclusion.

Discussion

The outcome of expectant management and surgical evacuation was studied in an unselected cohort of women with a diagnosis of early fetal demise or incomplete miscarriage. By conducting a randomized trial within this group, and by concomitantly accounting for the data of the observational study of women who refused randomization, the aim was to increase the generalizability of the study findings to the normal practice situation. No differences were found in the rate of emergency curettages or second curettages As expected according to the

literature, the complication rate was low and did not differ between the randomized groups.

The present study shows that a waiting period of 7 days after diagnosis results in a spontaneous loss in 37% of women randomized to expectant management. After 6 weeks, evacuation rates (including cross-overs) were about equal.

An unexpected finding was the high proportion of women expressing a strong preference for one of the management options. Consequently, the 162 randomized women required according to the power calculation was not reached within the pre-set study period, and as a result the study should be regarded formally as underpowered. However, in women, managed according their own preference, the study findings were similar to those identified in the randomized groups with regard to efficacy and complications. Whilst being aware that the combination of results from randomized and non-randomized patients might be challenged, in this case of high similarity of both patient characteristics and outcome data, the results would not be expected to change with larger numbers of randomized patients. It might be argued that patient data be combined in order to enhance power and to generalize findings (Torgerson and Sibbald, 1998; Mant, 1999; Pocock and Elbourne, 2000).

A short-term complication, namely haemorrhage, was registered only as a complication of surgery where the amount of blood loss was easy to assess. In the expectant management group, haemoglobin concentrations were measured only whenever indicated on clinical grounds; this did not result in a need for any blood transfusions.

The only previously reported randomized trial comparable with the present study (Nielsen and Hahlin, 1995) reported spontaneous complete miscarriages within 3 days in 79% of patients allocated to expectant management. By contrast, in the present study only 47% of patients reported spontaneous complete miscarriages during a much longer observation period. This difference between the two studies might be explained by differences in the interval between the onset of symptoms and inclusion of patients. The average time lapse between onset of bleeding and inclusion into the study was 3 days in the present investigation. Such a time lapse is controlled by the Dutch insurance system, where women with early pregnancy problems require formal referral to a fetal assessment unit by their general practitioner.

Of the 1101 women in the present study, 20% had already miscarried completely at baseline, and this might explain the difference between the present results and those reported by others (Nielsen and Hahlin, 1995). It is most likely that these authors included patients at an earlier stage and perhaps also included more patients with an incomplete miscarriage—a group virtually unrepresented in the present study.

Recently, expectant management was compared with medical treatment in a randomized study (Ngai *et al*., 2001), the success rate of 48.3% being comparable with that seen in the present investigation.

The average duration of bleeding and pain in the present study was also longer than was reported by Nielsen and Hahlin. This might be explained by the selection of patients (only a few incomplete miscarriages), the much longer period of expectant management in the present study, and the use of a standardized diary in which patients themselves, and not the investigators, registered vaginal bleeding that required sanitary protection.

A randomized study of 35 women, all with retained products of conception and with small diameters, was also performed (Chipchase and James, 1997). It should be noted that, in the present study, such patients were excluded, this situation being regarded as complete miscarriage.

In the present study, curettage was performed after several days, and not immediately, this being standard practice in the Netherlands. Clearly, if curettage had been performed earlier, i.e. immediately after inclusion into the study, fewer emergency (non-planned) curettages would have been required.

Until recently, medical treatment did not appear to offer any advantage in comparison with expectant or surgical management because of side effects, low efficacy (compared with curettage) and high costs. Two recent studies which compared vaginal misoprostol versus expectant management and curettage respectively, demonstrated an efficacy of 83.3% versus 48.3% (misoprostol versus expectant) and 82.5% versus 100% (misoprotol versus curettage) (Demetroulis *et al.*, 2001; Ngai *et al.*, 2001). However, as long as medical management requires patients to be hospitalized, this will most likely limit the preference of patients for this treatment.

For many years, the argument of safety has been used in justifying a surgical approach in the management of miscarriages. However, several large observational studies have indicated clearly that serious complications may result from surgical evacuation, i.e. laparotomy for uterine perforation (Hinshaw, 1997; Johnson *et al*., 1997; Ankum *et al*., 2001).

In conclusion, the success rate of expectant management is less favourable than has been reported earlier. Indeed, this approach fails in about half of cases, mainly because women are not prepared to wait for more than 2 weeks. However, up to 40% of surgical procedures can be prevented by awaiting the natural course of events within the first week. The generalizability of these findings is probably high, as all consecutive patients with first-trimester bleeding from a well-defined population were reported. Hence, expectant management of miscarriage can be offered to well-informed women who wish to avoid surgery.

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