Bleeding in the first trimester of pregnancy
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CHAPTER 4

Management of miscarriage

*a randomised controlled trial of expectant management versus surgical evacuation*

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Abstract

OBJECTIVES To determine safety and efficacy of either expectant management or surgical evacuation for miscarriages.

DESIGN Randomised controlled trial.

SETTING Two Amsterdam hospitals.

PARTICIPANTS Patients with a non-viable pregnancy or incomplete miscarriage at a gestational age of less than 16 completed weeks.

INTERVENTION Allocation to either expectant management or surgical evacuation. Patients who refused randomisation were managed according to their own preference.

MAIN OUTCOME MEASURES Safety, complications, efficacy, success of intended treatment, duration of clinical symptoms.

RESULTS One hundred and twenty-two patients were randomised and 305 were managed according to their choice. No differences were found in the number of emergency curettages and complications between expectant management and surgical evacuation between the randomised groups. Intention-to-treat analysis showed similar efficacy (92% versus 100%) for the randomised groups after six weeks. The success rate of intended treatment at six weeks was 30/64 (47%) in women allocated to expectant management with a median time to evacuation after inclusion of 19 days. After seven days, 37% of women in this group had a spontaneous complete miscarriage. Results in the preference groups were comparable with the randomised groups.

CONCLUSIONS In randomised patients the efficacy of expectant management and surgical evacuation is similar. A waiting period of seven days after diagnosis may prevent about 40% of surgical procedures without loss of safety.
**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.\(^1\) Just one randomised clinical trial compared both management options in a hospital setting, suggesting the outcomes to be similar.\(^2\) However, the duration of expectant management in this study was restricted to only three days. From a clinical and health policy point of view we regard this information as important but insufficient to base guidelines and individual decisions upon. 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.

We conducted a randomised controlled trial comparing expectant management with surgical evacuation. Eligible women who refused randomisation because of a strong preference for either surgery or expectant management were managed according to their choice, and evaluated similarly to randomised patients. By using this particular study design, we aimed to enhance the generalisability of our findings.

**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 a non-viable pregnancy or incomplete miscarriage at a gestational age of less than 16 completed weeks were included in the study. Transvaginal sonographic criteria for non-viability 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 seven-days interval.\(^4\),\(^5\) 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: under 18 years of age, 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 randomly allocated by the attending physician to expectant management or surgical evacuation (randomised groups) using central electronic randomisation. Randomisation was stratified for referral setting (directly by GPs versus outpatient clinics) and for gestational age (4-8, 8-12, and 12-16 weeks of amenorrhea). Eligible women who expressed a strong preference for one of the treatment options and refused informed consent for randomisation, 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 randomised 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 (randomised or preference). Local anaesthesia was attained by paracervical injection of scandicaine, after premedication with intravenous atropine. Occasionally, this was combined with midazolam for sedation. General anaesthesia was used whenever cardio-pulmonary monitoring was required or when requested by the patient. General anaesthesia was attained by the administration of propofol intravenously. The cervical canal was dilated to a maximum of Hegar 12. Vacuum aspiration was done using 8, 10, or 12 mm curettes (Rocket of London Ltd, UK). Rhesus negative patients received 625 IU anti-D immunoglobulin. Patients left the hospital after two to four hours 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 as yet, were scheduled to undergo curettage within a week.

All women (randomised 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 three months.
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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, available on request). All patients were asked to report the amount of bleeding, the degree of abdominal pain and the ability to work in a standardised diary. Bleeding was registered daily on a validated pictorial blood loss assessment chart; pain was scored on a visual analogue scale.6
During the bi-weekly visits, diaries were taken in, and patients received instructions about the diary for the next interval.

Outcome measures
We applied the following hierarchy in comparing the outcomes of both strategies: safety, complications, efficacy, success rate and duration of vaginal bleeding and pain.

Safety: this was defined as the absence of excessive bleeding requiring a blood transfusion, or, in case of curettage, the absence of uterine perforation necessitating laparotomy.

Complications: we considered excessive bleeding (> 500 cc, not requiring a blood transfusion), ascending genital tract infection, cervical tear and uterine perforation (not necessitating laparotomy) as short-term complications. Intra-uterine 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 hypomenorrhea, dysmenorrhea or amenorrhea, a hysteroscopy was performed.7

Efficacy: expectant management and surgical evacuation were considered to have been effective in case of sonographic evidence of RPOC < 15 mm (AP diameter) at six weeks after inclusion in the study. The analysis followed the intention-to-treat principle.

Success of intended treatment: expectant management was considered to be successful if a spontaneous loss had occurred within six weeks. Surgical evacuation was successful if the curettage was performed without the need of a repeat curettage within six weeks. Women with a spontaneous loss before the scheduled curettage were considered as failures.

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 randomised trial in terms of safety and complications, we aimed to
A randomised controlled trial of expectant versus surgical management

demonstrate a 20% difference in success rate of intended treatment (65% for expectant management and 85% for curettage). To reach a power of 0.80 we needed 162 patients to be randomised.

**Statistical analysis**
The randomised groups were primarily analysed according to the intention-to-treat principle.
Safety and efficacy were analysed using descriptive statistics, with the application of the t-test, Chi-square and Wilcoxon-Mann-Whitney tests as appropriate. For the analysis of time until evacuation and time until stop bleeding or pain, we applied conventional survival analysis methods and appropriate comparative tests (log-rank test).
Medians are 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**
Out of 1101 women referred for an early pregnancy assessment, 449 were eligible for the study (Figure 4.1). Twenty-two women were excluded because of severe bleeding or pain necessitating immediate curettage. Of the 427 remaining women, 122 accepted randomisation while 305 expressed their own treatment preference and gave consent for data collection and follow-up.

![Trial profile](image)

**Figure 4.1.** Trial profile.
### Table 4.1. Patient characteristics at inclusion according to treatment allocation and preference.

<table>
<thead>
<tr>
<th>Age-yr, mean</th>
<th>Randomised group</th>
<th>Preference group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expectant (n=64)</td>
<td>Curettage (n=58)</td>
</tr>
<tr>
<td>32.1</td>
<td>33.4</td>
<td>32.5</td>
</tr>
</tbody>
</table>

**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)

**Gestational age**
- < 8 wk: 9 (14.1) | 8 (13.8) | 9 (7.1) | 18 (10.1)
- 8-12 wk: 36 (56.3) | 29 (50.0) | 65 (51.6) | 93 (52.0)
- 12-16 wk: 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—median days**
- 3 (0-9) | 2.5 (1-6) | 2 (0-6) | 2 (0-7)

**Pain until inclusion—median days**
- 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)

*a* Values are numbers with percentages in parentheses.

*b* True median and 25-75 percentiles in parentheses.
Analysis
Randomised groups
No significant differences in patient characteristics were present between the two randomised groups (Table 4.1). Also, no difference in prior experience with one of the management options was observed. Safety of both treatment arms was excellent: only one case of excessive bleeding requiring a blood transfusion occurred in the expectantly managed group. The complication rate in randomised patients was low and did not differ significantly between the two management strategies (4.7% versus 3.4%) (Table 4.2). According to intention-to-treat analysis the efficacy rates at 6 weeks did not differ significantly and reached 92% (59/64) in the expectant group versus 100% in the curettage group (p=0.06); median time until complete evacuation was 7 days versus 5 days (p<0.001), respectively. 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>0.10). Success of intended treatment: in the group allocated to expectant management 30 out of 64 women (46.9%) actually underwent a spontaneous loss within six 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 7 (10.9%) as an emergency procedure because of intolerable bleeding or pain.

![Figure 4.2. Kaplan-Meier estimates of the time until evacuation for expectant management (randomised and preference group). Surgical evacuations are censored.](Image)
### Table 4.2. Outcome measures according to treatment allocation and preference; intention to treat analysis.

<table>
<thead>
<tr>
<th></th>
<th>Randomised group</th>
<th></th>
<th>Preference group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expectant (n=64)</td>
<td>Curettage (n=58)</td>
<td>P&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Expectant (n=126)</td>
</tr>
<tr>
<td><strong>Curettage performed</strong></td>
<td>32 (50.0)</td>
<td>48 (82.8)</td>
<td>&lt;0.001</td>
<td>61 (48.4)</td>
</tr>
<tr>
<td>Second curettage</td>
<td>2 (3.1)</td>
<td>3 (5.2)</td>
<td>&gt;0.10</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Emergency curettage</td>
<td>7 (10.9)</td>
<td>6 (10.3)</td>
<td>&gt;0.10</td>
<td>19 (15.1)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding, transfusion needed</td>
<td>1 (1.6)</td>
<td>-</td>
<td>&gt;0.10</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage (&gt;500cc)</td>
<td>2 (3.1)</td>
<td>1 (1.7)</td>
<td>&gt;0.10</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td>Cervical tear</td>
<td>1 (1.6)</td>
<td>-</td>
<td>&gt;0.10</td>
<td>-</td>
</tr>
<tr>
<td>Uterine perforation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Infection</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Asherman's syndrome</td>
<td>1 (1.6)</td>
<td>1 (1.7)</td>
<td>&gt;0.10</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>3 (4.7)</td>
<td>2 (3.4)</td>
<td>&gt;0.10</td>
<td>5 (4.0)</td>
</tr>
<tr>
<td><strong>Efficacy at six weeks</strong></td>
<td>59 (92.2)</td>
<td>58 (100)</td>
<td>0.06</td>
<td>106 (84.1)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Median time until evacuation</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (3-16)</td>
<td>5 (2-7)</td>
<td>&lt;0.001</td>
<td>10 (4-18)</td>
</tr>
<tr>
<td><strong>Median time to stop bleeding</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17 (10-26)</td>
<td>13 (9-17)</td>
<td>0.04</td>
<td>22 (15-35)</td>
</tr>
<tr>
<td><strong>Median time to stop pain</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14 (7-24)</td>
<td>11 (6-26)</td>
<td>&gt;0.10</td>
<td>17 (7-24)</td>
</tr>
<tr>
<td><strong>Success of Intended treatment at 6 weeks</strong></td>
<td>30 (46.9)</td>
<td>45 (77.6)</td>
<td>0.001</td>
<td>53 (42.1)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are the percentages.

<sup>a</sup> Randomised groups.

<sup>b</sup> Median time after inclusion defined as the 50% probability of evacuation, cessation of bleeding or pain following Kaplan-Meier estimation. In parentheses the 25% probability and 75% probability respectively.

<sup>c</sup> Women who were lost to follow-up were treated as failures (12 in the expectant group, 7 in the curettage group).
The median time to reach complete evacuation of uterine contents (including the waiting time of censored patients undergoing curettage) analysed according to the intended treatment was 19 days, while 37% of the women had a spontaneous loss within seven days (Figure 4.2).

A successful evacuation of the uterus was reached in 45 of the 58 patients allocated to surgical evacuation (77.6%). In ten women (17%) a spontaneous loss occurred before the scheduled curettage. If these 10 women were not considered failures of the intended treatment, the success rate of surgical evacuation was 93.8% (45/48). 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 randomised groups.

Preference groups
Base-line characteristics between randomised patients and those managed according to their preference did not differ (Table 4.1). With regard to safety, bleeding requiring a blood transfusion occurred three times. The complication rate was 4% for expectant management versus 6.2% for surgical evacuation (Table 4.2).

Randomised versus preference groups
The efficacy (intention-to-treat analysis) was lower in the preference groups than in the trial (expectant: 84.1%, curettage: 95.5%), because 12 (9.5%) women in the expectant group and 7 (3.9%) in the curettage group were lost to follow-up and were considered as failures in the present analysis. The rate of repeat curettages, emergency curettages and complications was similar in all groups. The success rates of intended treatment of expectant versus surgical management in the preference groups (42.1% versus 78.8% respectively) were comparable to those in randomised patients.

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
We studied the outcome of expectant management and surgical evacuation in an unselected cohort of women with a diagnosis of a non-viable pregnancy or incomplete miscarriage. By conducting a randomised trial within this group, and by concomitantly accounting for the data of the observational study of women who refused randomisation, we aimed to increase the generalisability of our findings to the normal practice situation. We compared within and between the randomised and preference groups and did not find any differ-
enches in the rate of serious adverse events, emergency curettages, second curettages or complications.

Intention-to-treat analysis showed the efficacy in both randomised arms to be similar (92% in the expectant and 100% in the curettage group). In patients treated according to their preference the efficacy was lower, i.e. 84% versus 95%, mainly because women who were lost to follow-up were considered to be failures.

When analysed according the intended treatment, our study shows expectant management to be safe, while a waiting period of seven days after diagnosis resulted in a spontaneous loss in 37% of women.

An unexpected finding was the high proportion of women expressing a strong preference for one of the management options. As a consequence, the 162 randomised women required according to our power calculation was not reached within the pre-set study period. As a result, formally our study should be regarded underpowered. However, in women, managed according their own preference, our findings were similar to those in the randomised groups with regard to efficacy, effect of intended treatment and safety. While aware that combining of the results of randomised and non-randomised patients might be challenged, in this case of high similarity of both patient characteristics and outcome data, we don't expect the results to change with larger numbers of randomised patients. One might argue to combine patient data to enhance power and to generalise findings.8-10

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

The only randomised trial comparable to the present study, earlier published by Nielsen and Hahlin, reported spontaneous complete miscarriages within three days in 79% of patients allocated to expectant management.3 In contrast, we found only 47% during a much longer observation period. This difference might be explained by a different interval between the onset of symptoms and inclusion of patients in their and our study. Time lapse between the onset of bleeding and inclusion in our study was three days on average. This time lapse is explained by the Dutch insurance system, where women with early pregnancy problems require a formal referral by their GP to a fetal assessment unit.

Of the 1101 women in our study, 20% had already miscarried completely at base-line and this might explain the difference with Nielsen and Hahlin. Probably, they included patients at an earlier stage and possibly included more patients with an incomplete miscarriage, a group virtually not represented in our study.

The average duration of bleeding and pain was also longer compared to Nielsen and Hahlin's findings. This might be explained by the selection of
patients (only a few incomplete miscarriages), the much longer period of expectant management in our study and the use of a standardised diary, in which patients themselves, not the investigators, registered vaginal bleeding requiring sanitary protection.

Chipchase also performed a randomised study of 35 women, all with retained products of conception with small diameters, which in our study were not even included but regarded as complete miscarriages.\textsuperscript{11}

We performed our curettages after several days, not immediately. This is standard practice in the Netherlands. Obviously, if curettages would have been performed earlier, i.e. immediately after entrance in the study, the number of emergency curettages (not-planned curettage) would have been less.

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 made clear that serious complications may result from surgical evacuation, i.e. laparotomy for uterine perforation.\textsuperscript{12-14}

In conclusion, the success rate of expectant management is less favourable than earlier reported by other studies. It fails in about half of cases, mainly because women are not prepared to wait for more than two weeks. Expectant management, however, is safe and up to 40\% of surgical procedures can be prevented by awaiting the natural course of events within the first week. The generalisability of these findings is probably high, because we reported on all consecutive patients with first-trimester bleeding from a well defined population.

Expectant management of miscarriage can be offered as a safe option to well-informed women who wish to avoid surgery.

References


