Bleeding in the first trimester of pregnancy
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CHAPTER 8
General discussion and implications for future research

General discussion

This thesis describes the diagnostic and therapeutic challenges in pregnant women with first-trimester bleeding. In case of a proven miscarriage we studied the natural course of expectant management, assessed the safety and efficacy of expectant versus surgical management, the health-related quality of life during the three months after treatment, and the preferences of women for one of the two treatment options. A cost effectiveness analysis was also part of the study, but these data will be published separately at a later stage.

The evidence presented in this thesis will be helpful in solving the controversies in the existing guidelines with regard to the diagnostic work-up and therapeutic management of women with first-trimester bleeding. We conclude that neither statistical prediction models based on signs and symptoms, nor clinical judgement can validly replace ultrasonographic assessment in establishing a diagnosis in first-trimester bleeding. When a non-viable pregnancy or an incomplete miscarriage is diagnosed, expectant and surgical management are both safe. In an RCT and in women managed according to their own preference we did not find differences in the complications and safety between expectant and surgical management. Expectant management was successful within a week after inclusion in 38% of the women. The mental health of women randomised to expectant management showed better and earlier improvement compared to women randomised to surgical evacuation. Mental health scores were significantly better in women preferring than in women randomised to curettage. Women's treatment preference 12 weeks after treatment showed that women with an outspoken initial preference for one particular management option held on to this preference regardless of the actual treatment they had received. Women who accepted randomisation tended to prefer the treatment they had received.

We established the natural course of a miscarriage among women who were managed expectantly. An increasing bleeding pattern was predictive of a quicker spontaneous loss in women already bleeding at inclusion. Data from the patients' diaries, reporting on bleeding patterns and pain during expectant management, were used to construct a graphic representation of the spontaneous course of miscarriages. As a result, a graphic representation of
the natural course of a miscarriage is now for the first time available to inform women about what can be expected.

The large sample size, the unselected cohort, the availability of randomised and preference data and the coverage of preferences, allows for the following conclusions:

- Ultrasonography is essential for making a diagnosis in pregnant women with first-trimester bleeding.
- In non-viable pregnancies or incomplete miscarriages expectant management is a safe treatment option.
- An increasing bleeding pattern is predictive for a relatively quick spontaneous loss in first-trimester miscarriage.
- Mental health is better in women randomised to expectant management compared to those randomised to surgical evacuation.
- A free treatment choice improves mental health. Therefore, women expressing a treatment preference should be allowed to follow their choice.
- Women without a treatment preference should be encouraged to initially follow expectant management.
- Information on the outcomes of both treatment options over time should be made available to patients to facilitate informed-shared decision-making.

We studied the outcome of expectant management and surgical evacuation in an unselected cohort of women with a diagnosis of non-viable pregnancy or incomplete miscarriage, a case-mix as it appears in real practice, i.e. without exclusion of any specific type of patients. 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. At the beginning of this project we expected that about 50% of eligible patients would accept randomised treatment allocation. To our surprise, however, despite the absence of evidence in favour of either expectant or surgical management, 70% of the women expressed a strong treatment preference. This preference could not be explained by earlier experiences of these women with one of the treatment options. Possibly, preferences were influenced by cultural background or information given by GPs or gynaecologists, but we did not analyse this. The women who refused randomisation (n=305) and were managed according their own choice were analysed in our observational part of the study. Our findings support the views of earlier reports, that RCTs and non-randomised studies can provide complementary evidence. In our study, the patient characteristics of the randomised groups did not dif-
fer from those of the women managed according to their own preference and findings were identical with regard to efficacy, effect of intended treatment, and safety. Although we are aware that combining the results of the RCT and the observational study may raise criticism from a strictly methodological viewpoint, we consider it unlikely that our findings would have been different with larger numbers of randomised patients. Our specific design, including all presenting patients with first-trimester problems, makes the results applicable to a normal practice situation. Arguably, our study is an example of valuable use of observational methods.4

Almost 50% of the women randomised to expectant management or choosing this treatment asked for a curettage (cross-over) after a variable period of time. For most women it seemed unacceptable to wait longer than two weeks for a spontaneous loss. It is most likely that the implementation of findings from our study in the management of future patients, may decrease cross-over and encourage women opting for expectant management to accept a longer period of waiting.

Recommendations for research

Women from non-Western-European origin were relatively under-represented in our RCT, the health-related quality of life study and the preference study, because these women were unable to read the English or Dutch questionnaires used for these parts of the study. However, we do not expect that the clinical results from the RCT (i.e. efficacy and safety) would have been different if we had been able to also include this group of women. Health-related quality of life and treatment preference are possibly different in other cultures. Future research is needed to determine the influence of ethnicity on preferences and health-related quality of life in miscarriages.

Until recently, medical treatment did not seem to offer any advantage in comparison with expectant or surgical management because of side effects, low effectiveness (compared with curettage) and costs. Two recent studies comparing 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% (misoprostol versus curettage).5, 6 The role of medical management of miscarriages needs further exploration.

Determinants of HRQL of women with a non-viable pregnancy need future attention in order to select women at risk of a worse HRQL after treatment for a miscarriage. Further research into the long-term treatment effects on HRQL is needed, including the influence of a next pregnancy thereupon.

The new multi-disciplinary guideline on first-trimester bleeding which is to be
developed has to be implemented and evaluated. Also the need for the initiation of Early Pregnancy Units, with easy access for women with first-trimester bleeding in primary care, needs further exploration.

Recommendations for practice

Based on our findings the following diagnostic and therapeutic recommendations can now be given.

By acknowledging the essential role of ultrasonography, this facility becomes a basic diagnostic requirement. The availability of ultrasonography may vary widely, depending on the health care system and geographical setting. In many countries, pregnant women with first-trimester bleeding are initially cared for by GPs and sometimes by midwives. For a safe and effective management of these women, transvaginal ultrasonography should be easily accessible to pregnant women with first-trimester bleeding under primary care. In Primary Health Centers (U.K.), where ultrasonographic examinations were performed by a trained physician or midwife, this diagnostic service has proven to be of use. In the Netherlands, however, ultrasonographic equipment and expertise are virtually only available in Obstetric/Gynaecologic outpatient clinics and Radiology departments. The open access to these facilities for women under primary care, and the details and responsibilities for their further management still need to be defined. An agreement on these issues must be reached between the involved health care professionals and insurance companies, both on a local and national level.

We recommend expectant policy for at least a week after sonographical confirmation of the diagnosis in women with a non-viable pregnancy or incomplete miscarriage, unless the woman expresses an existing strong preference for surgical evacuation.

We conclude that a multi-disciplinary guideline of GPs, midwives and gynaecologists on the management of miscarriages has to be developed for collaboration in the field of miscarriage.

Based on the results of this thesis, the time is ripe for a new guideline which should include the following acknowledgments:

- Transvaginal ultrasonography is a basic requirement for establishing a diagnosis in first-trimester bleeding. A correct diagnosis is essential in guiding further management decisions.
- When a non-viable pregnancy is diagnosed, expectant management during at least one week is feasible and useful without loss of safety.
- Patients must be well-informed about the natural course of a miscarriage.
In case of a strong preference for either expectant or surgical management women should be advised to follow their preference.

Women without a strong preference should be encouraged to follow expectant management.

Gynaecologists should acknowledge the role of primary care in the expectant management of miscarrying women. GPs/midwives should acknowledge a strong preference for curettage in many women with a non-viable pregnancy or incomplete miscarriage.

GPs/midwives and gynaecologists should provide detailed information to their patients about all aspects of expectant and surgical management in order to give patients the opportunity to make well-informed decisions.\textsuperscript{8-10}

For a successful implementation of the guideline, the possible hindrances and practical consequences need to be addressed in multi-disciplinary seminars.\textsuperscript{11} Apart from these educational efforts the willingness to change among the health-care providers involved, is an essential prerequisite for a successful implementation of the new guideline.\textsuperscript{12}

**References**


