Management of first trimester miscarriage; new insight in old dilemmas

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CHAPTER 10

General discussion and implications for further research

The studies in this thesis and the related thesis of Marike Lemmers focused on the short and long term effects and complications of currently available treatment options for women experiencing a first trimester miscarriage.

In women diagnosed with a miscarriage, expectant management leads to a complete expulsion of the products of conception in 37% of the women within the first week, and in 46% of the women within two weeks after diagnosis. (1, 2) In the past, the diagnosis of a miscarriage was often followed by immediate curettage with the underlying assumption that this decreased the risk of subsequent pelvic infection. A recent RCT suggested otherwise: no difference in pelvic infections was found between women undergoing expectant management, medical treatment or curettage. (1)

Curettage is highly effective in the treatment of first trimester miscarriage. (3) The procedure is considered safe and easy to perform, but serious complications may occur. Short term complications include cervical tears, bleeding, pelvic infection and perforation of uterus, bladder or bowel. (4-7) The exact incidence of these short term complications is low, <1% but these complications may lead to serious morbidity.

Miscarriage, but specifically surgically managed miscarriage, bears the risk of the formation of intra uterine adhesions (IUA), also known as Asherman’s syndrome. (8-10) In a systematic review we tried to assess the prevalence of IUA, possible contributing factors to the formation of IUA and the consequences of IUA on future fertility. (11) This systematic review revealed intra uterine adhesions to be present in one of every five women undergoing routine hysteroscopic examination after experiencing a recent miscarriage. In about half of the women with IUA these adhesions were judged to be mild to moderate, of which the clinical relevance is unknown. The risk on IUA is higher for women who experienced recurrent miscarriages (OR 1.99 (95% CI: 1.32–3.00)) or in women who underwent multiple curettages procedures compared to those with a history of only one curettage (OR 2.05 (95% CI: 1.35–3.12)). We found no papers assessing the consequences of IUA on future fertility, but reproductive outcome was similar for women who either underwent expectant, medical or surgical management for a first trimester miscarriage. (11) Another alarming long term complication of curettage for a first trimester miscarriage is the risk of preterm birth in a subsequent pregnancy as reported by recent large studies. (12-16) In a systematic review and meta-analysis we confirmed the risk of preterm birth in women with a history of curettage (OR 1.29 (95% CI 1.17; 1.42)). (17) Although absolute numbers on very or extreme preterm birth were lower, the OR for women with a history of curettage was even higher in these groups compared to women managed expectantly or medically (preterm birth < 32 weeks: OR of 1.69 (95% CI 1.20; 2.38) and preterm birth <28 weeks: OR of 1.68 (95% CI 1.47; 1.92)). (17) In this review we were unable to distinguish differences between various surgical procedures (dilation and curettage (sharp or blunt) or vacuum curettage). Since vacuum curettage is possibly less harmful than dilation and curettage, it is possible that the effect of curettage on preterm birth diminishes. Vacuum aspiration is now the standard surgical technique. However, large studies included in this review were published recently and presented similar effects of curettage on subsequent preterm birth. A Scottish study reported on the relationship between induced abortion and the risk of subsequent preterm birth. It showed that in the 1980s and 1990s there was an increased risk of preterm birth in women with a history of induced abortion. However, the risk diminished and
altogether disappeared by 2000. The authors hypothesized that this decrease was related to the use of vaginal misoprostol to prime the cervix prior to curettage, and the increased incidence of medical abortion by mifepristone and misoprostol.

Since its introduction for the treatment of miscarriages in the 1990s, misoprostol is being used ever more and more frequently. The safety and side-effects of misoprostol were the subject of previous studies. (18, 19) Depending on the definition of treatment success, rates in literature vary between 50-99%. (1, 19-23) When success of misoprostol treatment is evaluated 24 hours after initial treatment, success rates are lower, than when treatment success is evaluated later. This suggests that the effect of misoprostol carries on for a longer period of time. It is known that vaginal bleeding after misoprostol treatment may persist longer when compared to curettage. (24)

The implementation of misoprostol treatment is characterized by a large practice variation in dosage, regimen and route of administration. The most effective dose is subject of debate. A survey we performed in 92 Dutch hospitals showed that all academic hospitals offered misoprostol as a treatment option compared to 97.3% of non-academic teaching hospitals and 95.7% of nonteaching hospitals. (25) In comparison to a previous study performed in 2005, the proportion of clinics prescribing misoprostol for first trimester miscarriage had doubled. (26)

Although the percentage of gynecologists that are aware of the availability of misoprostol for miscarriage treatment doubled from 50% in 2005 to virtually 100% in 2013, there is still a large practice variation. In the absence of a guideline, a large number of hospitals still use local protocols for misoprostol treatment which are non-evidence-based. The most effective dosage, regimen and route of administration seemed to be subject of debate. In a Cochrane review that was published in 2006 different dose regimens of misoprostol were analyzed (19). Since publication of this review several new studies on misoprostol treatment of non-vital pregnancies were conducted. Therefore the review needed an update, which we performed. A total of thirty-eight studies (4188 women) were included. Our results showed that vaginally administered misoprostol speeds up the process of a miscarriage (complete or incomplete) when compared with placebo (RR 4.73, 95% CI 2.70 to 8.28), with less need for uterine curettage (RR 0.40, 95% CI 0.26 to 0.60). Lower-dose regimens of vaginal misoprostol (400 or 600mcg) tend to be less effective than higher-dose regimens (800mcg) in producing miscarriage but this was not significant (RR 0.91, 95% CI 0.74 to 1.11). Oral administration of misoprostol seemed to be less effective than the vaginal route in producing complete miscarriage but again this was not significant (RR 0.73, 95% CI 0.52 to 1.03); however it was slower in inducing complete miscarriage (weighted mean difference 4.10 hours, 95% CI 2.64 to 5.56). Sublingual misoprostol had equivalent efficacy to vaginal misoprostol in inducing complete miscarriage but was associated with more abdominal pain. The updated review revealed a large practice variation in misoprostol dosage: 27 different regimens were used in the included trials. We concluded that the available evidence supports the use of vaginal or sublingual misoprostol, especially in a higher dose.

However, still a proportion of patients does not have a complete miscarriage after misoprostol treatment. The diagnosis of incomplete evacuation is troublesome and subject to debate. Persisting blood loss whether or not accompanied by abdominal pain may suggest an incomplete evacuation. Transvaginal sonography is generally used to assess the presence of suspected intra uterine remnants. (27-30) However there is no relation between the bleeding patterns and the thickness of uterine contents as measured by sonography. (28) There is no consensus on sonographic criteria to diagnose incomplete evacuation of the uterus, and up to now no gold standard for this diagnosis has been established. Therefore, the MisoREST trial was developed to evaluate the effectiveness of
curettage versus expectant management in women with sonographic evidence of an incomplete evacuation of the uterus. Results of this trial showed curettage to be more effective than expectant management. But with expectant management still 5 out of every 6 women were prevented from having a curettage. The reason for women undergoing curettage in the expectant management group was mainly elective; these women were insecure or tired of the persisting blood loss and therefore either demanded or were thought to require a curettage. Remarkably the presence of pregnancy tissue could not be confirmed histologically in at least 35% of these women, which underlines the problematic diagnosis of incomplete miscarriage.

Alongside the MisoREST a cost-effectiveness and a quality of life analysis was performed. In women with an incomplete evacuation of the uterus after misoprostol treatment immediate curettage was not cost-effective over expectant management. Other studies assessing the cost-effectiveness of curettage compared with misoprostol for the primary treatment of miscarriage confirmed these results, but also showed the effect to diminish when curettage was performed in an outpatient setting. In our study, the additional costs per extra woman cured were €8,586 in the curettage group as compared to the expectant management group. Decision makers should make up if they are willing to pay this relatively high amount of money to be confident that curettage is cost-effective. We also investigated quality of life in women participating in the MisoREST trial. In this analysis, participating women filled out questionnaires on health-related quality of life at several moments in time, starting at study enrolment with a follow-up till 12 weeks. Women undergoing curettage were slightly more impaired in terms of mental health over time, compared to expectantly managed women. Levels of anxiety or depression were similar between both groups over time, as was their physical health status. Quality of life was not previously assessed for women with an incomplete evacuation after misoprostol treatment. Other studies reporting on quality of life and patient satisfaction in women diagnosed with a miscarriage, showed no differences between different treatment modalities.

The original sample size of the MisoREST trial (n=162) was not reached because of difficulties in recruiting patients for the RCT. This was caused by strong patient preferences. When the trial was ended, a total of 59 women were included in the RCT (curettage n = 30, expectant management n=29). The observational cohort alongside the RCT, in which women were treated according to their own preference, was relatively large compared to the RCT: it consisted of 65 women who preferred curettage, and 132 women who preferred expectant management. Since there was such a strong treatment preference among women diagnosed with incomplete miscarriages after primary misoprostol treatment, we decided to study the decisive factors involved in making these treatment choices. Women’s preferences were assessed using a discrete-choice experiment. A total of 128 women completed the survey (69% response rate). Analyses of their preferences revealed that two attributes were valued as most important in the choice between two treatment options (curettage or expectant management): the probability of success and the risk of reduced fertility. To our knowledge there has been no previous research on the specific topic of subsequent treatment for incomplete evacuation of the uterus after misoprostol treatment. However a few preference studies have been published about women’s preferences for miscarriage treatment in general. These showed treatment effects and the risk of (long term) complications were indeed judged as important by women treated for miscarriage. Another important attribute was the level of pain experienced during treatment. These factors, therefore, should be addressed when counselling women with a first trimester miscarriage about available treatment options.
Implications for future research

Over the past decade, miscarriage and its management were subject interest to our study group in the AMC. (40) Despite our efforts so far, there are several issues that need to be elucidated. Unfortunately, misoprostol is not effective in all women. Some women do not respond to medical treatment at all with a gestational sac remaining present, while other women have an incomplete evacuation of the uterus. Predictive factors involved in a successful outcome after misoprostol treatment still remain unknown. This should be a subject of future research, as knowledge about these prognostic factors would be helpful in the counselling of women diagnosed with a first trimester miscarriage.

There will always remain situations where curettage is required (e.g. excessive bleeding or infection). The introduction of vacuum aspiration caused a decline in major complications related to the curettage procedure, compared to dilatation and curettage. The use of misoprostol for cervical priming could add to the further reduction of surgery related complications. Likewise, the role of anti-adhesive agents in preventing intra uterine adhesions, is an interesting subject of ongoing future research.

At present, misoprostol treatment is being considered by most Dutch gynecologists as a treatment option for first trimester miscarriage. Although the use of misoprostol has been increasingly implemented into daily practice over the past years, there is still large practice variation and a relatively large proportion of women remains being treated primarily by curettage. This suggests that there are still barriers for some gynecologists to use misoprostol as a first-choice treatment for first trimester miscarriages. These possible barriers will impair further implementation of misoprostol and it is therefore crucial to address these obstacles, differences in financial compensation in the Dutch health insurance system between treatment options among these.

Development of a national guideline for the treatment of first trimester miscarriage

A national guideline for the treatment of first trimester miscarriage could reduce practice variation thus leading to effective treatment for more women, while reducing the amount of unnecessary interventions. This guideline should provide information on all the three treatment options which are currently available for miscarriage: expectant management, medical treatment and curettage. The guideline should describe the treatment effects, the risk of complications both short and long term complications, and the cost-effectiveness of the three options.

Curettage is effective but has specific risks of complications both on short and long term as we described in the theses. These complications can easily be prevented by not performing this procedure. The Hippocratic principle is at stake here: *Primum non nocere*, first do no harm. Medical treatment or expectant management in general do not lead to more complications i.e. infection or excessive bleeding with the need for blood transfusions when compared to curettage. (1) In medical treatment there is a risk of incomplete evacuation, but in 5 out of every 6 women this problem resolves spontaneously without a higher risk of complications when compared to curettage. This means that surgical intervention can be prevented in a large proportion of women experiencing a first trimester miscarriage. Furthermore, medical treatment is more cost-effective than curettage, while the quality of life of women undergoing these treatments is similar. (2, 31, 34) In our opinion a guideline should advise to offer expectant management or medical treatment for miscarriages as primary treatment option. Curettage then should be reserved for specific cases only, for example if a woman shows signs of infection or severe bleeding, or whenever non-invasive treatment has after a period has failed. In case of medical treatment, a vaginal or sublingual administration of a higher dose of misoprostol, i.e. 600
to 800 µg, seems to be most effective and should be provided to women opting for medical treatment. This is in line with international guidelines like the NICE guideline ‘Ectopic pregnancy and miscarriage: diagnosis and initial management’. (41)
References