Outcomes of treatment for first trimester miscarriage
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Citation for published version (APA):

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CHAPTER 1

General Introduction

Miscarriage: definition, incidence and treatment options
First trimester miscarriage is the most common complication in pregnancy which occurs in 10-15% of pregnant women.\(^1\) This results in approximately 20,000 miscarriages in the Netherlands each year.\(^2\) A miscarriage is defined as an intra-uterine pregnancy demise confirmed by ultrasound or histology up to 13 weeks of gestation.\(^3\) Women may present with vaginal blood loss and abdominal pain, but as a result from the increased use of first trimester ultrasounds, many women are diagnosed with a non-vital pregnancy before the onset of any clinical signs and symptoms.\(^4\) Sonographically non-vital pregnancies are intra uterine pregnancies which are either anembryonic (empty gestational sac with a diameter >15-20mm), with a yolk sac but without an embryo or embryonic (embryo without cardiac activity).\(^5\)

Several treatment options are available for women with a first trimester miscarriage: expectant management; removing the non-vital pregnancy surgically i.e. curettage; or medical treatment with misoprostol. Historically women with a miscarriage were either managed expectantly, with complete expulsion of the pregnancy known to occur in 37% of the women within the first week \(^6\), or were offered a curettage. The surgical procedure to which the word curettage refers has changed over the years. In the late 19th century dilation and curettage was performed for several indications including first trimester miscarriage. The indication for this procedure was to avoid pelvic infection or heavy bleeding.\(^7\) Dilation of the cervical canal is performed using Hegar dilators after which the uterine content is removed using a curette (sharp or blunt) by scraping and scooping. A variant to dilation and curettage is dilation and evacuation. A term mostly reserved for surgical approach of second trimester abortions. After dilation, all uterine contents are removed using various instruments e.g. graspers and curettes. Vacuum aspiration as a means of removing a miscarriage was pioneered in 1958 by two Chinese doctors, Y. Wu and X. Wu. Recognition for their work took over 50 years when their original paper was translated into English.\(^8\) The same technique was developed in Canada by Morgentaler. He was the first North American physician to use vacuum aspiration, resulting in a decline in complication rates.\(^9\) The most recent development was the introduction cervical priming before curettage procedure. Several methods for cervical priming were described of which mifepristone and misoprostol were the most effective.\(^10\) Curettage is highly effective, but also bears the risk of short term complications: excessive blood loss, cervical tears, perforation of the uterus, bladder or bowel, and pelvic infections.\(^11-14\) Possible long term complications include the formation or intra uterine adhesions, also known as Asherman’s syndrome, and the risk of preterm birth in subsequent pregnancies.\(^15, 16\) It is possible that adverse events such as intra uterine adhesions have become less frequent since the introduction of vacuum aspiration, but it is known that also after vacuum aspiration intra uterine adhesions can occur.\(^17\)

Medical alternatives to curettage have been developed since the 1990s and include prostaglandins, mifepristone in combination with prostaglandin, methotrexate in combination with prostaglandin and oxytocin, of which the prostaglandin Misoprostol is used most commonly.\(^18, 19\) Misoprostol is a synthetic prostaglandin E1 analogue. When administered it causes uterine contractions, thereby inducing the expulsion of miscarriage. Misoprostol is easily available, simple to use, it is well tolerated
and had an acceptable adverse effect and safety profile. Furthermore, initial treatment with misoprostol seems to be more cost-effective than immediate curettage. The efficacy of misoprostol treatment varies between 50-99% in the literature which largely depends on the chosen definition e.g. time to complete evacuation of the uterus, ultrasound criteria, need for additional curettage. A general problem in this area is the lack of consensus about the diagnosis of an incomplete evacuation of the uterus. We face a therapeutic dilemma for women with minor or no clinical symptoms at all, but with a sonographically incomplete evacuation of the uterus. Is additional curettage necessary, or is expectant management a safe and effective alternative?

**Current Guidelines**

Although miscarriage is a frequent complication of pregnancy, the Dutch association of Obstetricians and Gynecologists (NVOG: Nederlandse Vereniging van Obstetrie en Gynaecology) have not (yet) developed a guideline for its management. It is unclear why a guideline has not been developed yet. One possible explanation is that the NVOG is divided in four pillars that represent the various sub-disciplines in gynecology and obstetrics: general gynecology, reproductive medicine, fetomaternal medicine and oncology. Miscarriage and its management however represent a problem that can be found in three of the four disciplines, i.e. reproductive medicine, fetomaternal medicine and general gynecology. This division in sub disciplines could pose a barrier in developing and implementing a multidisciplinary guideline, because it takes time to overcome differences in insight between the various disciplines.

In absence of a national guideline, Dutch gynecologists counsel women with a miscarriage for either expectant management, medical treatment with misoprostol or a curettage. The decision for either one of the treatment options is based on the personal experience of the gynecologist, the availability of a local protocol, and the preference of the woman concerned.

Over the past years misoprostol was increasingly used by Dutch gynecologists. In 2005 a national survey on the use of misoprostol indicated that 50% of the gynecologists considered misoprostol for the treatment of first trimester miscarriage. A similar survey in 2012 showed that by then 100% of the Dutch gynecologists considered misoprostol for the treatment of a miscarriage.

The Dutch association of general practitioners (NHG: Nederlands Huisartsen Genootschap) have a guideline on the management of first trimester miscarriage. This guideline was developed in 1997 and last updated in 2004. This guideline advises general practitioners to refer women for sonographic examination of the uterus. In case of a miscarriage, general practitioners counsel women either for expectant management, or curettage. The option of medical treatment with misoprostol is not discussed in their guideline. The Dutch association of midwives (KNOV: Koninklijke Nederlandse Organisatie van Verloskundigen) and the NHG have a national agreement about the guidance, treatment and referral of women with a first trimester miscarriage. This agreement briefly mentions the option of medical treatment after referral to the gynecologist, but does not specify this type of treatment any further.

In the international field, there are several guidelines for the management of miscarriage available. The RCOG (Royal College of Obstetricians and Gynaecologists) published the NICE guideline: “ectopic pregnancy and miscarriage: diagnosis and initial management”, which was last revised in 2012. This guideline advises expectant management for 7-14 days as the initial option for women with a sonographically confirmed diagnosis of miscarriage. Medical treatment may be considered when expectant management is not acceptable to the woman. Surgical treatment for miscarriage is offered.
whenever clinically appropriate, i.e. if the risks of hemorrhage or the effects of hemorrhage are considered unacceptable, or in case of infection.

The latest “practice bulletin” (a clinical management guideline) of the ACOG (American College of Obstetricians and Gynecologists) on the management of first trimester miscarriage was released in 2015.(31) According to this guideline gynecologists should inform women with a miscarriage about the three available treatment options: expectant management, medical management with misoprostol, or curettage. This guideline reports all options to be safe, reasonably effective and accepted by patients and states that there is no evidence of any difference in long-term outcomes between the various options. According to the ACOG practice bulletin women should receive treatment of their own choice. Neither one of the existing guidelines mentions the follow-up of women after misoprostol treatment. There is no consensus on the necessity of preforming a (routine) ultrasound during follow-up, nor the implications of abnormalities found on ultrasound scanning.

**Aims of this thesis**

In counselling women with a first trimester miscarriage it is necessary to be fully informed about the effectivity, risk of complications, and possible consequences for future fertility of the three available management options: expectant management, medical treatment or curettage. Numerous reports have addressed the treatment of miscarriage. Several issues however, still have to be elucidated which is why the research leading to this thesis was initiated.

Our main questions were:

- What are the currently available treatment options for women facing a first trimester miscarriage?
- Which medical treatment options are momentarily available and which treatment is most effective?
- How is misoprostol treatment for miscarriage implemented in the Dutch health care system?
- What is the incidence of short term complications of surgical treatment for first trimester miscarriage, in comparison to expectant or medical management?
- What is the influence of a miscarriage on the formation of intra uterine adhesions, and how does curettage contribute to this?
- What are the reproductive consequences of these uterine adhesions?
- Does curettage for first trimester miscarriage increase the risk of preterm birth in a subsequent pregnancy?
- Is expectant management a safe and effective alternative for curettage in women with an incomplete evacuation of the uterus after misoprostol treatment?
- Does the quality of life differ between women undergoing curettage versus expectant management in case of an incomplete evacuation after primary misoprostol treatment?
Is curettage cost-effective compared to expectant management in women with an incomplete evacuation after primary misoprostol treatment?

Is there a difference in subsequent fertility and obstetric outcome in women with either curettage of expectant management for an incomplete evacuation of the uterus after primary misoprostol treatment?

What are the treatment preferences of women who are diagnosed with an incomplete evacuation of the uterus after misoprostol treatment?

Outline of this thesis

Part I: Long term complications of surgical treatment

Chapter 2 reports on the prevalence, risk factors and reproductive outcome in women with intrauterine adhesions also known as Asherman’s syndrome, subsequent to the event of a miscarriage.

Chapter 3 provides a systematic review and meta-analysis which assesses the risk of preterm birth in the pregnancy subsequent to the event of a miscarriage or induced abortion.

Part II: Management of incomplete evacuation after medical treatment

Chapter 4 describes the study protocol of the MisoREST trial. The aim of this trial was to compare women undergoing curettage versus expectant management for efficacy, safety, quality of life, costs and subsequent fertility.

Chapter 5 reports on the results of a multicenter randomized controlled trial. In the MisoREST trial, women were allocated to curettage or expectant management in case of an incomplete evacuation after misoprostol treatment for first trimester miscarriage. Six weeks after enrollment in the study women underwent a sonographic examination, to assess the uterine cavity for pregnancy remains.

Chapter 6 reports on the results of a prospective cohort. In the MisoREST trial, women declining randomization were asked to participate in a cohort and underwent treatment of their own choice (curettage or expectant management). Follow-up was similar to the randomized women.

Chapter 7 evaluates the quality of life in the women who participated in the MisoREST trial. We performed a linear multilevel analysis to compare health related quality of life between women who underwent curettage compared to expectant management, over time.

Chapter 8 displays the results of a cost effectiveness study performed alongside the MisoREST trial. During the first 4 weeks of follow-up all costs, including indirect costs and loss of productivity were assembled. A cost-effectiveness analysis was performed from a societal perspective.

Chapter 9 evaluates the fecundity and the outcome of the pregnancy subsequent to participation in the MisoREST trial.

Part III Implications for practice

Chapter 10 and 11 provide a summary of the data presented in this thesis and present implications for future research

Note: this thesis represents research that was embedded in a larger research project, the MisoREST trial. This trial was conducted by two researchers: Marike Lemmers and Marianne Verschoor. Since they both contributed equally to the project, there is overlap in some of the content of their theses.
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References