MIFEPRISTONE
IN THE MANAGEMENT OF
EARLY PREGNANCY FAILURE

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MIFEPRISTONE
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1

Introduction

Introduction

Worldwide, the total number of miscarriages is estimated at more than 10 million yearly.[1] In the Netherlands, approximately 20,000 women annually have a miscarriage, of which approximately 50% will undergo medical or surgical treatment in order to remove the products of failed conception from the uterine cavity.[2] The incidence of early pregnancy failure (EPF) increases with age and, because of rising childbearing age in the Western world, EPF management will become of increasing importance.[3]

In today's era, health care demands preferably cost-effective and non-invasive over costly and invasive treatment options whenever possible, with more specifically high treatment efficacy, minimal side effects and short treatment duration. Also, during pre-treatment consultation, modern patient counseling calls for "shared decision making" on the basis of thorough informed consent about the pros and cons of different treatment options, i.e. patient preferences.
This thesis focuses on non-invasive medical treatment options in EPF: prostaglandin (misoprostol) treatment with or without pre-treatment of a progesterone receptor blocker (mifepristone).

Early pregnancy failure

EPF is a non-vital pregnancy in the first trimester, defined by the World Health Organization as a pregnancy between 6 and 12 to 14 weeks postmenstrual.[4] Other widely used terms for EPF are miscarriage, missed abortion or spontaneous abortion, not to be confused with medical abortion which implicates the intended termination of a vital pregnancy in the first trimester.

Nowadays, the diagnosis of EPF is usually made by ultrasound examination showing an intrauterine gestational sac with fetal parts and no cardiac activity or an "empty" gestational sac without embryonic pole (figure 1). Studies examining cut-off values for gestational sac diameter and embryo size, state that EPF can only be considered in case of an empty gestational sac with a mean diameter of ≥ 25mm, a missing yolk sac with a gestational sac diameter of ≥ 20 mm or a crown-rump length ≥ 7mm without cardiac activity.[5, 6] These cut-off values may be higher than one would expect based on clinical experience since there is inter-observer variability in measurements of sac diameter and crown-rump length.[7] If there is any doubt about the accuracy of the diagnosis on EPF or early vital pregnancy, for both healthcare professional and patient, a second ultrasound scan should be performed at least one week later to ensure a correct diagnosis.

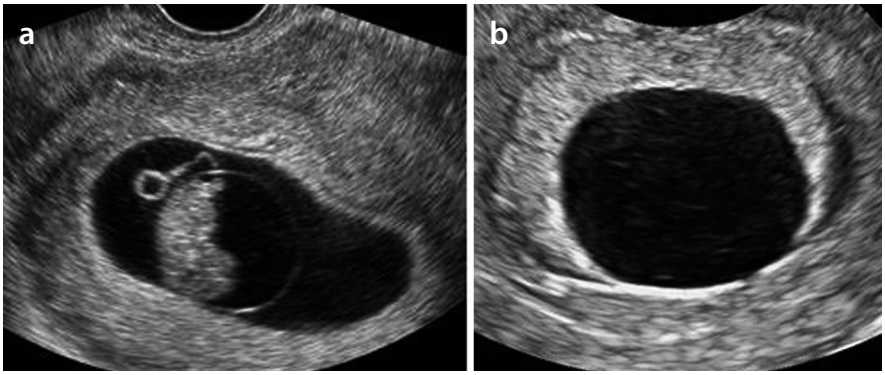

Figure 1 Embryo (**a**) and empty gestational sac (**b**) [8]

Epidemiology and pathophysiology

EPF (6-14 weeks) is a complication in 10-15% of all pregnancies; worldwide more than 20 million cases of EPF will occur. In the Netherlands, approximately 10,000 women per year visit a hospital because of EPF.[3, 9] The real incidence may be even higher, as not every case of EPF is being recognized clinically.[10] In more than 50% of the cases embryonic factors, mostly numerical chromosomal abnormalities, appear to be the cause of EPF.[11] The majority of chromosomal abnormalities (translocations) arise "de novo". Therefore in the Netherlands, in the search for an explanation of recurrent miscarriages, couples are eligible for chromosome analysis after two miscarriages.[11-13] In miscarriages after 12 weeks of gestation it is more likely that maternal factors play a role such as thrombophilia or other diseases.[11, 14-16]

Age is the most important risk factor for the occurrence of EPF (figure 2). The chance of EPF increases with age: 9% for women between 20-24 years, 20% at the age of 35-40 until 40% for women older than 40 years.[17] For women older than 45 years the risk may increase to 75%.[18]

Treatment options in EPF

Guidelines

There is a Dutch guideline for general practitioners and midwives, which provides recommendations for diagnosis and management in case of vaginal blood loss and / or abdominal pain up to 16 weeks of gestation. Unfortunately, there is no national guideline concerning

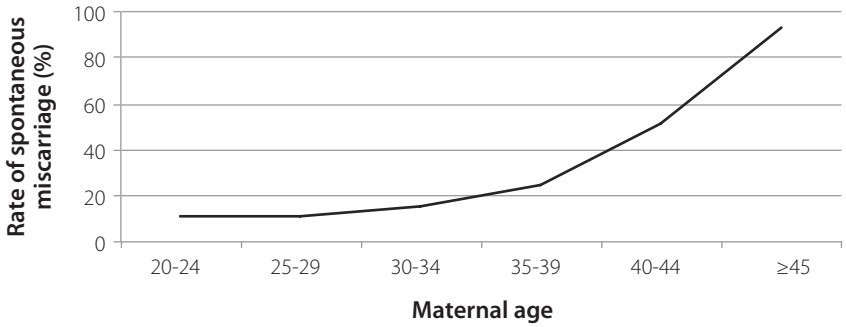

Figure 2 Miscarriage rates as a function of maternal age [19]

the treatment options for women with EPF.[3] The "Nederlandse Vereniging voor Obstetrie & Gynaecologie" (NVOG) has drafted a guideline for the termination of pregnancy before 24 weeks of gestation, however, it only includes termination of vital pregnancies.[16]

Worldwide, there are several guidelines describing the management options in case of EPF: expectant, medical or surgical management. The Royal College of Obstetricians and Gynecologists (RCOG) as well as the American College of Obstetricians and Gynecologists (ACOG), recommend medical methods (misoprostol) as a safe, effective and acceptable alternative to surgical treatment (evidence level A).[20, 21]

Due to the absence of a Dutch national guideline, there is a large practice variation between Dutch hospitals concerning the management of women with EPF. Despite the fact that for gynecologists the awareness of the availability to prescribe misoprostol doubled between 2005 and 2014, 23 different treatment regimens (including misoprostol alone) were used. Even without a national guideline, one third of the Dutch hospitals prescribed the combination of mifepristone and misoprostol in case of EPF.[22]

Expectant management

Spontaneous miscarriage i.e. expulsion of products of conception usually occur outside a clinical setting. It usually starts with little vaginal blood loss or spotting followed by several hours of heavy vaginal bleeding. At the same time, women experience an uncomfortable and intense pelvic cramping leading to expulsion of tissue. After the passage of pregnancy tissue, the bleeding and pain decreases (figure 3). Some patients may also experience nausea or vomiting. Complete miscarriage refers to cases in which the products of conception are expulsed entirely out of the uterus, after which the cervix is usually closed and the uterus is well contracted; vaginal bleeding and pain may only be mild or may have resolved.[23]

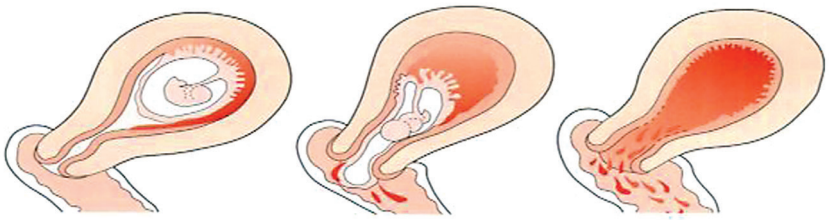

Figure 3 Spontaneous miscarriage [24]

By expectant management, spontaneous complete evacuation rates of the products of conception vary between 30-50% after one week and up to 60-75% after 6 weeks.[25-30] Therefore, expectant management is an option for women with EPF despite the risk of unplanned (or additional) surgical treatment, prolonged bleeding and/or the need for blood transfusion compared to immediate surgical treatment. At the same time, the risk of infection and psychological problems appear similar between expectant and surgical management.[31]

If there are no medical reasons to start immediate medical or surgical treatment, like heavy bleeding or intra-uterine infection, expectant management for at least one week should be advised. Given the high chance of spontaneous expulsion and the risk of complications due to interventions, expectant management and "watchful waiting" for at least one week, should definitely be discussed with women in case of EPF, which is standard procedure in the Netherlands.[3]

Curettage

Curettage was first described in 1950 and has been the preferred treatment option worldwide in the following years.[10, 32] Curettage mostly involves mechanical dilatation of the cervix and removal of the products of conception using a curette or suction cannula (dilatation and curettage, D&C) under general or regional local anesthesia. Nowadays, the most common form of suction curettage is called vacuum aspiration (figure 4). A blunt curette can be used afterwards to ensure the uterus is completely evacuated. This procedure can be performed under local (spinal or pudendal nerve block) or general anesthesia.[33]

Although having an effectiveness of 95-100%, curettage is accompanied by the risk of complications such as infections, uterine perforation and incomplete abortion (table 1). The incidence of such complications varies in the literature between 0,01% and 1,6%.[31, 35-37] Recent studies also reveal a high prevalence of intrauterine adhesions (Asherman syndrome), potentially interfering with subsequent child wish. Moreover, a higher risk of

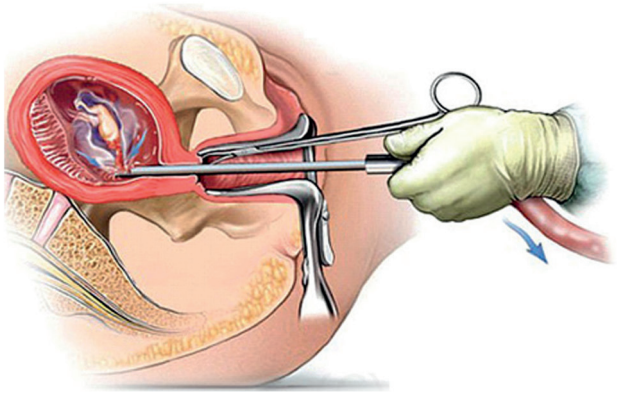

Figure 4 Vacuum aspiration/curettage [34]

premature delivery in future pregnancies has been reported. Mechanical dilatation of the cervix by force may lead to permanent cervical injury and cervical insufficiency.[38-40]

Table 1 Curettage and its risk of complications [31, 35-37, 39, 40]

	Incidence, %
Uterine perforation	1.01 – 1.0
Excessive bleeding	1.5
Infection	2.6 – 3.5
Additional surgery	4
Cervical lesion	1.0
Intrauterine adhesions (severe)	19.1 (13.7)
Premature delivery in subsequent pregnancy	9.4

Medical treatment with misoprostol

Misoprostol, a synthetic prostaglandin E1 (PGE_1, figure 5), was developed in 1973 to prevent and treat stomach ulcers. The first publication about sensitivity of the human pregnant uterus to prostaglandin analogues dates from 1987.[41] Misoprostol causes uterine contractions and softening and ripening of the cervix and may be used to achieve partial or complete expulsion of the products of conception or for the prevention and treatment of post-partum hemorrhage.[42, 43]

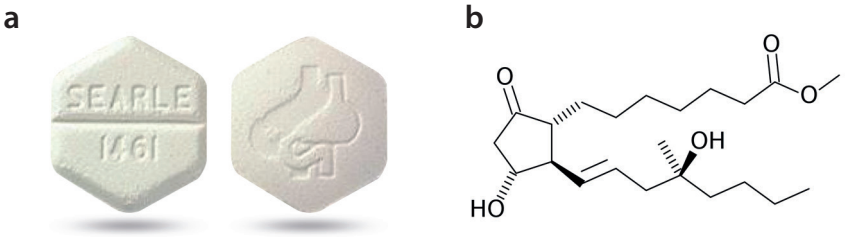

Figure 5 Misoprostol, prostaglandin E1; (**a**) 200 microgram tablet, (**b**) chemical structure [44, 45]

In 1992, el-Rafaey first described the use of medical methods, including misoprostol, for uterine evacuation in case of non-vital pregnancies.[46] The prostaglandin E1 analogue misoprostol has since then been used worldwide in case of EPF.[10]

Misoprostol (400-800µg/day) is approved and registered for the prophylaxis of NSAID-induced gastric ulcers and for the healing of duodenal and gastric ulcer. As mentioned before, due to uterotonic properties leading to myometrial contractions and ripening and dilatation of the cervix, it is also used for obstetric and gynecologic indications.[42] Despite the proven effectiveness, it has never been officially registered for these indications.[4, 47] The prescription of misoprostol in case of EPF is therefore called "off-label use": the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration. Off-label use, after obtaining informed consent of the patient, is legal unless it violates ethical guidelines or safety regulations. The off-label prescription is generally based on scientific research or guidelines and widely accepted to provide patients the most optimal treatment regimen.[41, 43]

Due to low costs (in the Netherlands 1.02 euro for one tablet) and stability at room temperature, it may also be an attractive treatment option in low-resource countries.[48] It has few systemic side effects, which are seldom severe and self-limiting (table 2).[42] Misoprostol can be swallowed orally, placed vaginally or sublingually.[49]

Different effective treatment regimens have been advocated which showed wide ranges of success rates due to different inclusion criteria, routes of administration dosage and success criteria. The International Federation of Gynecology and Obstetrics (FIGO) recommends the prescription of two doses misoprostol 800µg administered vaginally (three hours apart) or two doses misoprostol 600µg sublingual (three hours apart).[10, 49] However, a decline in serious infection rate has been reported in case of medical abortion after changing the regime of vaginal to buccal administration.[50] In case of EPF, a Cochrane

Table 2 Misoprostol, side effects [42]

	Incidence, %
Diarrhea	> 10
Nausea, vomiting, abdominal pain, headache	1 – 10
Fever	0.1 – 1

review described a study comparing 800µg oral with the same dose of vaginal misoprostol with no difference in efficacy, although the mean time to expulsion was significantly longer in the oral group.[10] At the same time several clinical studies comparing oral and vaginal misoprostol have found increased patient satisfaction with the oral route.[51]

In contrast to other Western world countries, in the Netherlands medical treatment starts after minimally one week of expectant management.[3] One week of expectant management will lead to a spontaneous complete miscarriage in approximately 50%.[25, 32] Unfortunately, misoprostol treatment after minimal one week of expectant management, may lead in only 50-60% of the cases to complete miscarriage (endometrial thickness < 15mm on ultrasonography). Thus, after two weeks, half of the women treated with misoprostol alone still have to undergo D&C and may still be exposed to the risks of complications associated with surgery.[32] Therefore, a more effective, non-invasive, alternative to misoprostol is wanted.

Medical treatment with mifepristone

Mifepristone, also known as RU-486, was developed in France in 1980 and approved for medical abortion in 1987.[52] In response to anti-abortion protests the distribution of mifepristone was stopped one month later. However, the French minister of Health ordered to distribute mifepristone in the interests of public health: "I could not permit the abortion debate to deprive women of a product that represents medical progress." In France, mifepristone was first distributed free of charge for 34.000 women and since February 1990 Mifegyne (mifepristone) was sold to hospitals.[53] Although approval in other European countries followed quickly, it took until 2000 before mifepristone was approved as an oral medical abortion agent in the USA.[54]

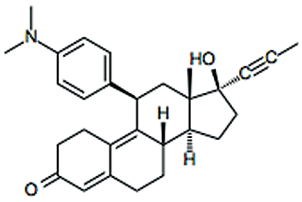

Figure 6 Mifepristone, chemical structure [15]

Mifepristone is a synthetic steroid, binding tightly to the progesterone receptor leading to degeneration of the uterine lining (decidua) and softening of the cervix (figure 6). In vital pregnancies it causes detachment of the blastocyst, which leads to decreased production of the hormone hCG: human chorionic gonadotropin (hCG inhibits the disintegration of the corpus luteum, which produces progesterone). Decreased progesterone production results in further breakdown of the decidua. Furthermore, prostaglandin levels are increased and the sensitivity of the uterus towards prostaglandins is enhanced leading to uterine contractions that may cause expulsion of the detached blastocyst (figure 7). Mifepristone is absorbed rapidly (t_{max} 1-2 hours) and has a long half-live of 26-48 hours.[52, 55, 56]

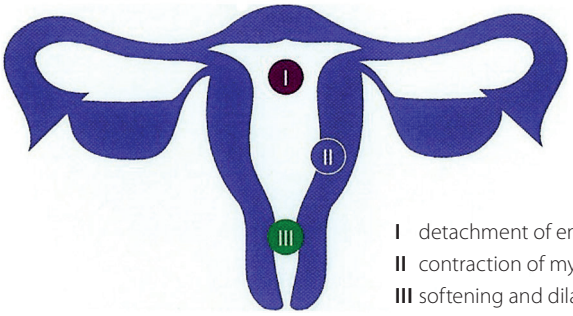

Figure 7 Mifepristone, mechanisms of action [57]

A highly effective combination for medical abortion of mifepristone and a prostaglandin analogue (gemeprost) was first reported in 1986.[58] The effect of the administration of mifepristone and oral PGE_1 (misoprostol) on uterine contractions in a double blinded, randomized, controlled efficacy trial was described in 1989 by Swahn et al.[59] Since then, the sequential combination of mifepristone with misoprostol (M&M) has been shown superior to the use of misoprostol alone for four indications: medical termination of vital

pregnancy (abortion) up tot 63 days of gestation, termination of vital pregnancy beyond first trimester, preparation for surgical abortion in the first trimester and labor induction in fetal death in utero in the second and third trimester (table 3).[4, 60-62]

Table 3 Indications mifepristone [4, 60-62]

	Recommended dose, mg	Success rate, %
Preparation for surgical abortion	200	-
Medical abortion first trimester	600	92.5 – 98.7
Termination of vital pregnancy beyond first trimester	600	99
Labor induction, fetal death in utero second/third trimester	600	95 – 99

In case of termination of a vital pregnancy in the first trimester, the World Health Organization advises mifepristone 200mg in combination with misoprostol starting 36-48 hours later. Up to 9 weeks of gestation a single dose misoprostol 800µg can be administered vaginal, buccal or sublingual or 400µg oral. Between 9 and 12 weeks up to 5 doses misoprostol (every 3 hours) can be administered, starting with one dose of 800µg vaginal, then 400µg vaginal or sublingual.[4] An explanation for the prescription of low dose mifepristone (200mg) is not described in the guideline; one could imagine it's because of the high costs of mifepristone in the context of low-income countries. However, two phase 2 trials showed that 600mg mifepristone is superior to the 200mg dose in terms of complete abortion in case of medical abortion of vital pregnancies (89% versus 63%).[63, 64] And since the patent on mifepristone has expired, the costs are decreasing drastically.[60, 65] Given the current evidence-based indications for mifepristone, it appears reasonable to assume that also for EPF, misoprostol with pre-treatment of mifepristone may lead to superior treatment results compared to misoprostol alone.

Defining successful treatment & follow-up after medical treatment

With regards to the follow-up of women receiving medical treatment: ultrasonography seems to be of limited value in predicting the presence of intrauterine remnants one week after medical treatment. Previous studies do not provide any clear evidence which endometrial thickness corresponds best to the presence of intrauterine pregnancy remnants.[66] A study by Rulin et al concludes that a maximum anterior-posterior diameter of 15 mm or less, genuine retained products are less likely to be confirmed histologically.[67] Also a recent study by Lavecchia et al also reported that a cavity anterior posterior distance of

more than 15mm was associated with the need for D&C and an unplanned return to the emergency department.[68] Another study by Creinin showed a wide range of endometrial thickness (1-31mm) two weeks after expulsion of the gestational sac and that endometrial thickness generally decreasing with time. These authors suggest that only clinical signs and symptoms should guide treatment decisions after medical treatment.[69]

Concerning the follow-up after medical treatment for EPF, the recent Dutch "MisoREST" study investigated whether curettage is more effective than expectant management in case of an incomplete evacuation after misoprostol treatment. In a randomized controlled trial, curettage was more successful than expectant management: 97% versus 76%. Successful treatment was defined as a maximum diameter of any contents of the uterine cavity less than 10 millimeters six weeks after study entry. The risk of complications was comparable between both groups. Only one third of the calculated sample size of patients was included because the trial was stopped prematurely due to strong patient preferences for expectant management.[66] At the same time, a cohort study by the same research group included 203 women who were treated according to their treatment preference. The same results were shown compared to the randomized trial: a significant difference in efficacy between curettage and expectant management (95% versus 85%) and no difference in complication rates.[70] Because expectant management was effective in approximately 80%, the authors advise that expectant management should be considered first line treatment in women with a suspected incomplete evacuation after medical treatment.

Patient preferences

When considering any treatment, woman's preferences are important and should be included in the decision-making process. If it's a physician intention to achieve complete evacuation without any invasive methods, possibly leading to a time consuming treatment, than that may be in conflict with the patient's wish to get pregnant again as soon as possible. For women, pain-related factors and ''time'' of the treatment process (time to achieve complete miscarriage) are most important.[71] The decision making process is also influenced by acceptance of pregnancy loss (desire for closure), timing and control of the process (home or clinical-based, length of treatment), home and work responsibilities, pain and physical aversions, prior experiences with spontaneous or medical abortion, health and safety of the procedures and opinions of their physician, family and friends.[72-74] Additionally, the number of days of bleeding, the overall safety and risk of complications are weighed. Nevertheless, the physician's recommendation is still crucial in the decision-making process.[71]

Preferences in case of early pregnancy failure

Concerning medical treatment with mifepristone and misoprostol in case of EPF, only one trial was found. This study concluded that 88% of women were satisfied with the received medical treatment and 70% would choose this same method again if necessary.[75]

However, in EPF, several studies about the acceptability and quality of life in case of medical treatment with misoprostol alone are performed. Women deliberately choosing medical treatment are satisfied with their treatment in approximately 70-75%.[76, 77] In randomized trials comparing medical versus surgical treatment, women receiving medical treatment reported more pain. All other dimensions of the quality of life questionnaire and acceptability were not significant different, there were also no significant differences between successful or failed medical treatment.[78] However, another study showed that women who received surgical treatment after failed medical treatment were less satisfied compared to women directly randomized to surgical treatment.[79]

A Dutch study by Graziosi reported that women may be willing to accept some disadvantages of medical treatment to avoid curettage; treatment inconvenience may be accepted as long as the complete evacuation rate is high.[80] Women prefer medical treatment as long as the success rate exceeds 65% and approximately 85% of women would prefer medical treatment if its complete evacuation rate would reach 80% (figure 8).[81]

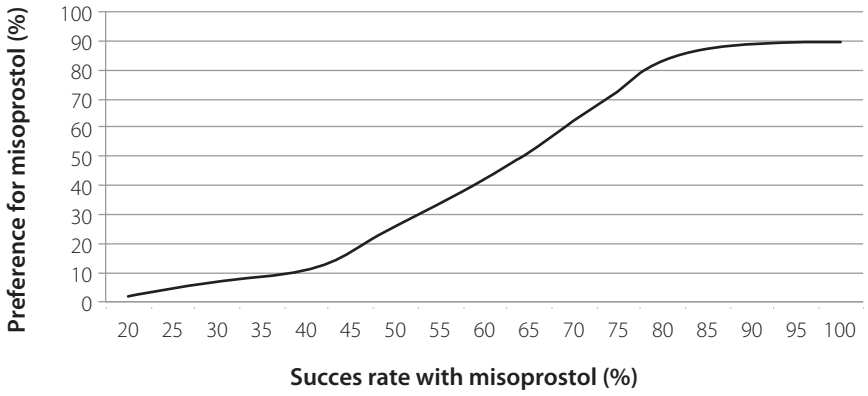

Figure 8 Women's preferences for misoprostol relative to curettage [81]

Besides effectiveness, also complication rate and days of bleeding influences patient treatment preference. Another Dutch study by Wieringa showed that by decreasing the complication rate of expectant management the percentage of women preferring curettage declined from 58% to 35% in case of a difference in complication rate of 8%.[74]

Cost-effectiveness

Several studies conclude that effective medical treatment options for EPF may be less expensive than surgical treatment.[36, 82-84] Direct costs per case appear significantly lower but indirect costs may be equal for both groups.[85] By increasing the complete evacuation rates of the medical treatment, by adding mifepristone, the total direct costs per patient may be reduced compared to the curettage group. Since the costs of mifepristone will drop drastically as the patent has expired, even more cost reduction can be expected. At the same time, women will not be exposed to surgery and its risk of complication on short- and long-term. However, healthcare costs are not only dependent on guidelines or protocols, but are also determined by the preferences of the patient. When a woman prefers medical treatment and the desire to avoid surgery is high, medical therapy becomes less costly and even more efficacious.[81, 83]

Thesis

In this thesis, several medical treatment options in EPF are analyzed, which may lead to higher complete evacuation rates: the combination of mifepristone with misoprostol versus misoprostol alone. By demonstrating the effectiveness of this combination, it may be possible to

- offer women with a miscarriage an effective alternative to surgery
- increase patient satisfaction
- limit the number of hospital admissions
- reduce the number of short- and long-term complications
- prevent overtreatment and thereby increase the quality of health care
- realize cost savings for healthcare services
- create a promising therapy for low-resource countries

Aims of this thesis

- To review the available literature on the added value of mifepristone to current non-surgical treatment regimens in women with EPF (chapter 2).
- To compare the success rates of sequential use of mifepristone and misoprostol versus misoprostol alone in a single center retrospective cohort study (chapter 3).
- To analyze the current use in the Netherlands of medical treatment in early pregnancy failure and estimate the willingness to prescribe mifepristone in the future depending on effectiveness and costs: a nationwide questionnaire (chapter 4).
- To investigate the effectiveness and health-related quality of life of the sequential combination of mifepristone with misoprostol versus the use of misoprostol alone in terms of complete evacuation of the products of conception from the uterus, a pilot study (chapter 5).
- To compose a research protocol of a sufficiently powered, multi-center, randomized, double blinded and placebo-controlled trial to test whether, in EPF, the sequential combination of mifepristone with misoprostol is superior to misoprostol only (chapter 6).

References

1. Sedgh G, Singh S, Hussain R. Intended and unintended pregnancies worldwide in 2012 and recent trends. Stud Fam Plann. 2014;45:301-14.
2. Open data van de Nederlandse Zorgautoriteit (2014-2016) [25-05-2017]. Available from: http://www.opendisdata.nl/.
3. Van Asselt KM BA, Engelsman N, Hammers-Cupido RJ, Landskröner I, Opstelten W, De Vries CJH. NHG-Standaard Miskraam (Derde herziening). 2017. Available from: https://www.nhg.org/standaarden/volledig/nhg-standaard-miskraam.
4. Clinical Practice Handbook for Safe Abortion. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2014.
5. Bourne T, Bottomley C. When is a pregnancy nonviable and what criteria should be used to define miscarriage? Fertil Steril. 2012;98:1091-6.
6. Jeve Y, Rana R, Bhide A, Thangaratinam S. Accuracy of first-trimester ultrasound in the diagnosis of early embryonic demise: a systematic review. Ultrasound Obstet Gynecol. 2011;38:489-96.
7. Pexsters A, Luts J, Van Schoubroeck D, Bottomley C, Van Calster B, Van Huffel S, et al. Clinical implications of intra- and interobserver reproducibility of transvaginal sonographic measurement of gestational sac and crown-rump length at 6-9 weeks' gestation. Ultrasound Obstet Gynecol. 2011;38:510-5.
8. Miscarriage Ultrasound 6 weeks. Available from: https://www.healthtap.com/user_questions/506640.
9. Prismant Landelijke LMR informatie [Internet]. 2008-2010 [cited 30-08-2012]. Available from: http://cognos-server.prismant.nl.
10. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2009;3:CD002253.
11. Herhaalde miskraam. Richtlijn Nederlandse Vereniging voor Obstetrie & Gynaecologie. 2007. Available from: http://www.nvog.nl.
12. Mishell DR, Jr. Recurrent abortion. J Reprod Med. 1993;38:250-9.
13. Goddijn M, Leschot NJ. Genetic aspects of miscarriage. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000; 14:855-65.
14. van Oppenraaij RH, Goddijn M, Lok CA, Exalto N. De jonge zwangerschap: revisie van de Nederlandse benamingen voor klinische en echoscopische bevindingen. Ned Tijdschr Geneeskd. 2008;152:20-4.
15. Boogaard Evd. Optimizing quality of care for couples with recurrent miscarriage. [S.l]: [s.n.]; 2014.
16. Zwangerschapsafbreking tot 24 weken. Richtlijn Nederlandse Vereniging voor Obstetrie & Gynaecologie. 2015 [08-06-2017]. Available from: https://www.nvog.nl.
17. Knudsen UB, Hansen V, Juul S, Secher NJ. Prognosis of a new pregnancy following previous spontaneous abortions. Eur J Obstet Gynecol Reprod Biol. 1991;39:31-6.
18. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ. 2000;320:1708-12.
19. Heffner LJ. Advanced maternal age--how old is too old? N Engl J Med. 2004;351:1927-9.
20. Hinshaw K, Fayyad A, Munjuluri P. The management of early pregnancy loss. Royal College of Obstetricians and Gynaecologists, Green-top Guideline No. 25. http://www.rcog.org.uk/. 2006.
21. Committee on Practice B-G. The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. Obstet Gynecol. 2015;125:1258-67.
22. Verschoor MA, Lemmers M, Wekker MZ, Huirne JA, Goddijn M, Mol BW, et al. Practice variation in the management of first trimester miscarriage in the Netherlands: a nationwide survey. Obstet Gynecol Int. 2014;2014:387860.
23. Tulandi T, Al-Fozan H. Spontaneous abortion: Management. 2017. Available from: http://www.uptodate.com/home.
24. Bleeding in pregnancy. Available from: https://www.studyblue.com/ - flashcard/view/7065346.
25. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002;324:873-5.
26. Wieringa-de Waard M, Vos J, Bonsel GJ, Bindels PJ, Ankum WM. Management of miscarriage: a randomized controlled trial of expectant management versus surgical evacuation. Hum Reprod. 2002;17:2445-50.
27. Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP. Expectant, medical, or surgical management of first-trimester miscarriage: a meta-analysis. Obstet Gynecol. 2005;105:1104-13.

28. Trinder J, Brocklehurst P, Porter R, Read M, Vyas S, Smith L. Management of miscarriage: expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial). BMJ. 2006;332:1235-40.
29. El-Sayed MM, Mohamed SA, Jones MH. Expectant management of first-trimester miscarriage. J Obstet Gynaecol. 2009;29:681-5.
30. Casikar I, Bignardi T, Riemke J, Alhamdan D, Condous G. Expectant management of spontaneous first-trimester miscarriage: prospective validation of the '2-week rule'. Ultrasound Obstet Gynecol. 2010;35:223-7.
31. Nanda K, Lopez LM, Grimes DA, Peloggia A, Nanda G. Expectant care versus surgical treatment for miscarriage. Cochrane Database Syst Rev. 2012;3:CD003518.
32. Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Hum Reprod. 2004;19:1894-9.
33. Callahan TL, Caughey AB. Blueprints obstetrics & gynecology2017.
34. Partial-birth abortion more respectfull than vacuum aspiration? [23-05-2017]. Available from: http://clinicquotes.com/partial-birth-abortion-more-respectful-that-vacuum-aspiration/.
35. Verschoor MAC. Management of first trimester miscarriage; new insight in old dilemmas2017.
36. You JH, Chung TK. Expectant, medical or surgical treatment for spontaneous abortion in first trimester of pregnancy: a cost analysis. Hum Reprod. 2005;20:2873-8.
37. Tristan SB, Gilliam M. First trimester surgical abortion. Clin Obstet Gynecol. 2009;52:151-9.
38. Lemmers M, Verschoor MA, Hooker AB, Opmeer BC, Limpens J, Huirne JA, et al. Dilatation and curettage increases the risk of subsequent preterm birth: a systematic review and meta-analysis. Hum Reprod. 2016;31:34-45.
39. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2013.
40. Saccone G, Perriera L, Berghella V. Prior uterine evacuation of pregnancy as independent risk factor for preterm birth: a systematic review and metaanalysis. Am J Obstet Gynecol. 2016;214:572-91.
41. Rabe T, Basse H, Thuro H, Kiesel L, Runnebaum B. [Effect of the PGE1 methyl analog misoprostol on the pregnant uterus in the first trimester]. Geburtshilfe Frauenheilkd. 1987;47:324-31.
42. Cytotec UK SPC (Summary of Product Characteristics). [21-10-2016]. Available from: http://www.medicines.org.uk/emc/medicine/9352.
43. Hofmeyr GJ, Gülmezoglu AM, Novikova N, Lawrie TA. Postpartum misoprostol for preventing maternal mortality and morbidity. Cochrane Database of Systematic Reviews. 2013.
44. Prostaglandin E2 [23-05-2017]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Dinoprostone - section=Top.
45. Misoprostol, oral tablet. [23-05-2017]. Available from: http://www.healthline.com/drugs/misoprostol/oral-tablet - SideEffects2.
46. el-Refaey H, Hinshaw K, Henshaw R, Smith N, Templeton A. Medical management of missed abortion and anembryonic pregnancy. BMJ. 1992;305:1399.
47. Kulier R, Gulmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2008:CD002855.
48. Misoprostol tablet 200 microgram. 2017. [23-05-2017]. Available from: https://www.medicijnkosten.nl.
49. FIGO. Misoprostol Recommendations. International Federation of Gynecology and Obstetrics (FIGO). 2017 [24-04-2017]. Available from: http://www.figo.org/publications/miscellaneous_publications/Misoprostol_Recommendation_2012.
50. Fjerstad M, Trussell J, Sivin I, Lichtenberg ES, Cullins V. Rates of serious infection after changes in regimens for medical abortion. N Engl J Med. 2009;361:145-51.
51. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev. 2006:CD001338.
52. Corey EJ CB, Kürti L. Molecules and Medicine. Wiley; 2007.
53. Mifepriston [23-05-2017]. Available from: http://www.pharmawiki.ch/wiki/index.php?wiki=Mifepriston.
54. Goldman MB, Troisi R, Rexrode KM. Women and health. London; Waltham, MA: Academic Press; 2013.
55. Heikinheimo O. Clinical pharmacokinetics of mifepristone. Clin Pharmacokinet. 1997;33:7-17.
56. Heikinheimo O, Kekkonen R, Lahteenmaki P. The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestin action. Contraception. 2003;68:421-6.
57. Pharma N. Mifegyne (Mifepristone) - Scientific information and guide to use2010.

58. Cameron IT, Michie AF, Baird DT. Therapeutic abortion in early pregnancy with antiprogestogen RU486 alone or in combination with prostaglandin analogue (Gemeprost). Contraception. 1986;34:459-68.
59. Swahn ML, Ugocsai G, Bygdeman M, Kovacs L, Belsey EM, Van Look PF. Effect of oral prostaglandin E2 on uterine contractility and outcome of treatment in women receiving RU 486 (mifepristone) for termination of early pregnancy. Hum Reprod. 1989;4:21-8.
60. Exelgyn. Mifegyne 200mg tablets: Summary of Product Characeteristics (SmPC) [24-04-2017]. Available from: https://www.exelgyn.com.
61. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011:CD005216.
62. Hapangama D, Neilson JP. Mifepristone for induction of labour. Cochrane Database Syst Rev. 2009:CD002865.
63. Maria B, Chaneac M, Stampf F, Ulmann A. [Early pregnancy interruption using an antiprogesterone steroid: Mifepristone (RU 486)]. J Gynecol Obstet Biol Reprod (Paris). 1988;17:1089-94.
64. Grimes DA, Mishell DR, Jr., Shoupe D, Lacarra M. Early abortion with a single dose of the antiprogestin RU-486. Am J Obstet Gynecol. 1988;158:1307-12.
65. Mifepristone tablet 200ug 2017. Available from: https://www.medicijnkosten.nl.
66. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Opmeer BC, Bossuyt PM, et al. MisoREST: surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: a randomized controlled trial. Hum Reprod. 2016;31:2421-7.
67. Rulin MC, Bornstein SG, Campbell JD. The reliability of ultrasonography in the management of spontaneous abortion, clinically thought to be complete: a prospective study. Am J Obstet Gynecol. 1993;168:12-5.
68. Lavecchia M, Klam S, Abenhaim HA. Effect of Uterine Cavity Sonographic Measurements on Medical Management Failure in Women With Early Pregnancy Loss. J Ultrasound Med. 2016;35:1705-10.
69. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J, Trial NMoEPF. Endometrial thickness after misoprostol use for early pregnancy failure. Int J Gynaecol Obstet. 2004;86:22-6.
70. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Bossuyt PM, Huirne JA, et al. MisoREST: Surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: A cohort study. Eur J Obstet Gynecol Reprod Biol. 2017;211:83-9.
71. Wallace RR, Goodman S, Freedman LR, Dalton VK, Harris LH. Counseling women with early pregnancy failure: utilizing evidence, preserving preference. Patient Educ Couns. 2010;81:454-61.
72. Schreiber CA, Chavez V, Whittaker PG, Ratcliffe SJ, Easley E, Barg FK. Treatment Decisions at the Time of Miscarriage Diagnosis. Obstet Gynecol. 2016;128:1347-56.
73. Petrou S, McIntosh E. Women's preferences for attributes of first-trimester miscarriage management: a stated preference discrete-choice experiment. Value Health. 2009;12:551-9.
74. Wieringa-de Waard M, Bindels PJ, Vos J, Bonsel GJ, Stalmeier PF, Ankum WM. Patient preferences for expectant management vs. surgical evacuation in first-trimester uncomplicated miscarriage. J Clin Epidemiol. 2004;57:167-73.
75. Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. Fertil Steril. 2006;86:367-72.
76. Tang OS, Lau WN, Ng EH, Lee SW, Ho PC. A prospective randomized study to compare the use of repeated doses of vaginal with sublingual misoprostol in the management of first trimester silent miscarriages. Hum Reprod. 2003;18:176-81.
77. Tanha FD, Feizi M, Shariat M. Sublingual versus vaginal misoprostol for the management of missed abortion. Journal of Obstetrics and Gynaecology Research. 2010;36:525-32.
78. Harwood B, Nansel T. Quality of life and acceptability of medical versus surgical management of early pregnancy failure. BJOG. 2008;115:501-8.
79. Lee DT, Cheung LP, Haines CJ, Chan KP, Chung TK. A comparison of the psychologic impact and client satisfaction of surgical treatment with medical treatment of spontaneous abortion: a randomized controlled trial. Am J Obstet Gynecol. 2001;185:953-8.
80. Graziosi GC, Bruinse HW, Reuwer PJ, van Kessel PH, Westerweel PE, Mol BW. Misoprostol versus curettage in women with early pregnancy failure: impact on women's health-related quality of life. A randomized controlled trial. Hum Reprod. 2005;20:2340-7.

81. Graziosi GC, Bruinse HW, Reuwer PJ, Mol BW. Women's preferences for misoprostol in case of early pregnancy failure. Eur J Obstet Gynecol Reprod Biol. 2006;124:184-6.
82. Xia W, She S, Lam TH. Medical versus surgical abortion methods for pregnancy in China: a cost-minimization analysis. Gynecol Obstet Invest. 2011;72:257-63.
83. Rausch M, Lorch S, Chung K, Frederick M, Zhang J, Barnhart K. A cost-effectiveness analysis of surgical versus medical management of early pregnancy loss. Fertil Steril. 2012;97:355-60.
84. Dalton VK, Liang A, Hutton DW, Zochowski MK, Fendrick AM. Beyond usual care: the economic consequences of expanding treatment options in early pregnancy loss. Am J Obstet Gynecol. 2015;212:177 e1-6.
85. Graziosi GC, van der Steeg JW, Reuwer PH, Drogtrop AP, Bruinse HW, Mol BW. Economic evaluation of misoprostol in the treatment of early pregnancy failure compared to curettage after an expectant management. Hum Reprod. 2005;20:1067-71.

2

The added value of mifepristone to non-surgical treatment regimens for uterine evacuation in case of early pregnancy failure: a systematic review of the literature

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Abstract

Objectives

Early pregnancy failure (EPF) is a common complication of pregnancy. Surgical intervention carries a risk of complications and, therefore, medical treatment appears to be a safe alternative. Unfortunately, the current medical treatment with misoprostol alone has complete evacuation rates between 53% and 87%. Some reports suggest that sequential treatment with mifepristone and misoprostol leads to higher success rates than misoprostol alone.

Study design

To evaluate the added value of mifepristone to current non-surgical treatment regimens in women with EPF we performed a systematic literature search. Electronic databases were searched: PubMed, Cochrane Library, Current Controlled Trials, and ClinicalTrials.gov. Clinical studies, both randomized and non-randomized trials, reporting on the added value of mifepristone to current nonsurgical treatment regimens in women with EPF were included. Data of sixteen studies were extracted using a data extraction sheet (based on the Cochrane Consumers and Communication Review Group's data extraction template). The methodological quality was assessed using the Cochrane Collaboration Risk of Bias tool.

Results

In five randomized and eleven non-randomized trials, success rates of sequential treatment with mifepristone and misoprostol in case of EPF varied between 52% and 95%. Large heterogeneity existed in treatment regimens and comparators between studies.

Conclusions

The existing evidence is insufficient to draw firm conclusions about the added value of mifepristone to misoprostol alone. A sufficiently powered randomized, double blinded placebo-controlled trial is urgently required to test whether, in EPF, the sequential combination of mifepristone with misoprostol is superior to misoprostol only.

Introduction

Early pregnancy failure (EPF) is a common complication of pregnancy, as approximately 15% of all clinical pregnancies will end in a non-viable pregnancy (6–14 weeks). The real incidence might be even higher, as not every case of EPF is being recognized clinically. The incidence increases with age and because of rising childbearing age in the Western world, EPF will become of increasing importance. If expectant management does not lead to spontaneous miscarriage, a surgical or medical treatment may be chosen in order to remove the products of conception from the uterus.[1-4]

For many years, surgical evacuation has been the preferred option for treating EPF, as it is associated with complete evacuation rates of 93–98%.[5-7] However, surgical evacuation is associated with high costs and carries a small risk of complications such as pelvic infection, cervical injury, uterine perforation, excessive bleeding, and cervical insufficiency in following pregnancies. The incidence of such complications varies in the literature between 0,01% and 1,2%.[8-10] Worrying may also be the findings reported by a recent systematic review revealing a high prevalence of intrauterine adhesions (19,1%) after surgical evacuation, potentially interfering with subsequent child wish.[11]

An alternative to surgical evacuation is therefore worth considering. In EPF, expectant management for at least one week is a reasonable and successful approach leading to a spontaneous complete evacuation in around 50% of woman.[12] There are no serious medical risks associated with this watchful waiting strategy.[12]

In first trimester termination of a viable pregnancy, medical methods are proven effective, safe and described by patients as a natural and highly acceptable method.[13-19] Medical treatment for EPF using the prostaglandin E1 analogue misoprostol was first described in 1992 by El-Refaey.[20] Complete evacuation rates after two doses of misoprostol vary between 53% and 87%. This variation may be explained by differences in the duration of expectant management before medical treatment was started.[3, 5, 21]

Complete evacuation rates after medical treatment might be improved by adding mifepristone to misoprostol.[5, 21] Mifepristone, a synthetic steroid, is a competitive progesterone receptor antagonist and a glucocorticoid receptor antagonist. Mifepristone is licensed for four indications, including medical termination of a viable pregnancy up to 63 days of gestation leading to complete evacuation rates of 95%.[22, 23] The sequential combination has also already been shown superior to the use of misoprostol alone for labor induction in case of fetal death in the second and third trimester.[24, 25] Therefore it might be that also for EPF, mifepristone with misoprostol is more effective than misoprostol alone.

The aim of the present study was to systematically review whether addition of mifepristone to current non-surgical treatment regimens in women with EPF is beneficial.

Materials and methods

We reviewed the available literature on the added value of mifepristone to current non-surgical treatment regimens in women with EPF. EPF was defined as either an anembryonic gestation with a blighted ovum or as an early embryonic/fetal demise showing an embryo without cardiac activity. Two reviewers systematically searched the literature from 1983 (first use of mifepristone by WHO) to May 2015 to retrieve all trials, randomized or non-randomized, reporting data on the use of mifepristone in non-surgical treatment regimens for EPF. PubMed and Cochrane Library electronic databases were searched and reference lists were scanned. Databases of current clinical trials were checked: Current Controlled Trials (http://controlled-trials.com/) and ClinicalTrials.gov (http://clinicaltrials.gov/).

The following Mesh terms or keywords were used to search all trial registers and databases: (Abortion, spontaneous OR Abortion, missed OR Miscarriage OR Pregnancy failure) AND mifepristone AND misoprostol AND humans.

Two reviewers performed eligibility assessment independently. Methods of the analysis and inclusion criteria were specified and documented in advance. Disagreements between reviewers were resolved by consensus. All clinical studies, both randomized and non-randomized trials, reporting on the added value of mifepristone to non-surgical treatment regimens in women in case of EPF were included. Reviews, case reports and studies for which no full text was available were excluded. Studies including vital pregnancies, pregnant women in second or third trimester or including only incomplete miscarriages were also excluded. Articles were first checked for eligibility and relevance by screening title and abstract and second by examining the full text of potentially relevant studies.

A data extraction sheet (based on the Cochrane Consumers and Communication Review Group's data extraction template) was developed. Items assessed included design, participants, treatment, (assessment of) primary and secondary outcomes, follow-up and complications. The methodological quality of the included studies was assessed using the Cochrane Collaboration Risk of Bias tool.

Results

The search resulted in 154 articles (figure 1). One Cochrane review was available describing two trials using mifepristone treatment for EPF.[3] These trials were already found in the PubMed search. A search of the Cochrane Library did not yield any additional useful articles. In the clinical trials register (www.clinicaltrials.gov) one randomized, double blinded placebo-controlled trial was found.

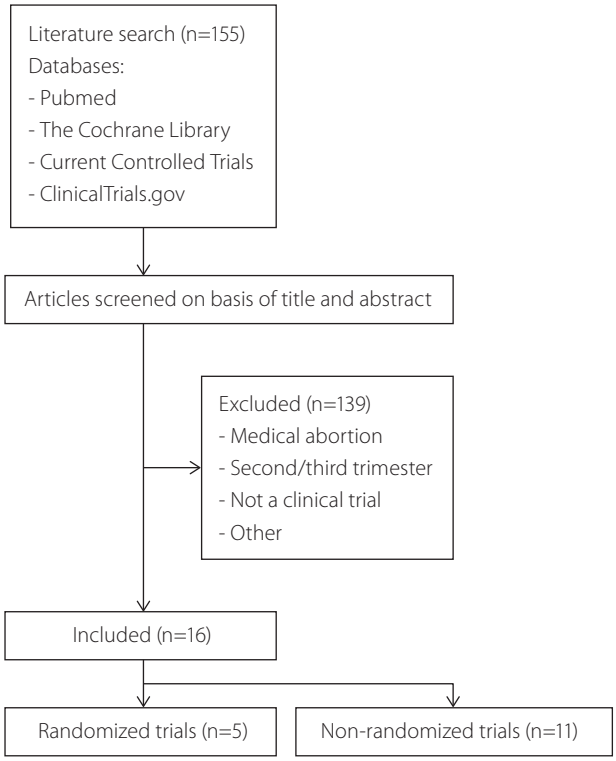


Figure 1 Flowchart

Thus, a total of 155 articles were found, of which 139 were excluded for reasons mentioned in figure 1. In total, sixteen articles were included in our analysis consisting of five randomized controlled trials and eleven non-randomized trials. Meta-analysis could not be performed due to the heterogeneity in treatment protocols.

Randomized controlled trials, non-blinded

Five randomized controlled trials using mifepristone with misoprostol as a treatment for EPF were analyzed (tables 1 and 2). In general, the methodological quality of included studies was mediocre at best as illustrated per study in figure 2.

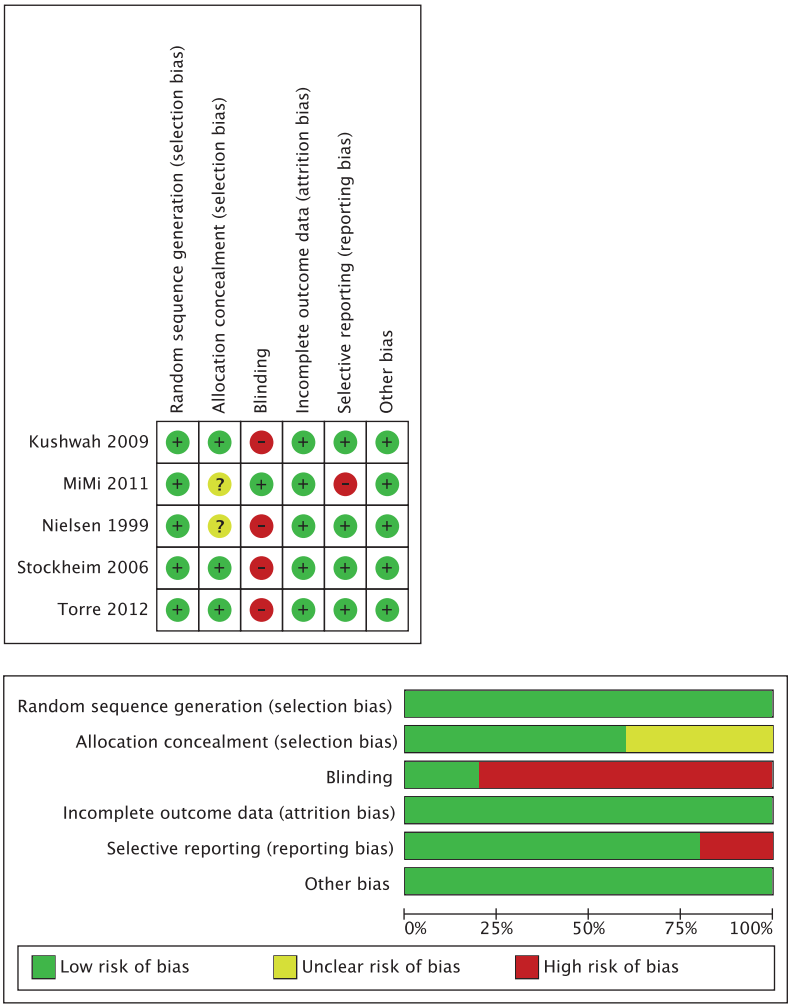


Figure 2 Overview of methodological quality of reporting of included RCT studies

The first randomized controlled trial performed by Nielsen et al. in 1999 included both women with EPF and incomplete miscarriages. Nielsen et al. compared sequential mifepristone and oral misoprostol treatment with expectant management reporting complete evacuation rates of 82% versus 76%.[26]

The studies performed by Stockheim et al. and Kushwah et al. included only women with EPF. The treatment regimen in the study of Stockheim et al. consisted in the intervention group of mifepristone 600µg followed by one dose of oral misoprostol 800µg, and was successful in 65,5%. The control group received no mifepristone but two doses of oral misoprostol 800µg leading to a complete evacuation rate of 73,6%.[27] Kushwah et al. included women with EPF between six and fourteen weeks of gestation. 48 h after receiving mifepristone 200mg orally, women were randomized to receive misoprostol sublingually or orally. Complete evacuation rates after 22 h of 92% versus 84% were described which was not statistically significant.[28]

A fourth study by Torre et al. compared immediate versus delayed medical treatment with sequential mifepristone and vaginal misoprostol leading to a statistically significant difference in success rates. Immediate treatment was started directly after diagnosis leading to a complete evacuation rate of 81%. The delayed treatment regimen was started after one week of expectant management. During this week 23% of women experienced a spontaneous complete evacuation; delayed medical treatment was successful in 53% of the remaining women. Vacuum aspiration in the immediate treatment group was required in 19,1% versus 43,5% of the women in the delayed treatment group. The rate of emergency vacuum aspiration was higher in the sequential treatment arm; however, vacuum aspiration performed on patient request was also recorded as an emergency procedure. The rate of vacuum aspiration in case of retained products of conception was not significantly different between both groups.[29]

In the clinical trials register (www.clinicaltrials.gov) one randomized, double blinded placebo-controlled trial was found comparing two combinations of drugs in case of EPF, sequential mifepristone with buccal misoprostol versus placebo with buccal misoprostol. Seventeen patients were included; combined mifepristone and buccal misoprostol treatment led to success rates of 62,5% while success rates of 55,6% were described in the placebo group after 24–48 h. One week after randomization complete evacuation rates increased to 87,5% and 66,7%. The trial was prematurely terminated because of poor enrolment.[30]

Table 1 Randomized controlled trials where mifepristone and misoprostol was used for treatment of EPF

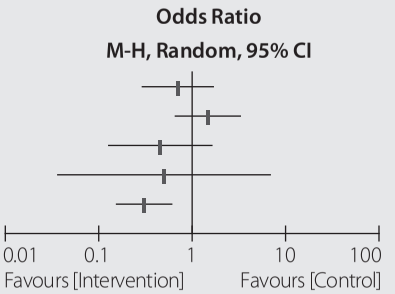
First author (Year)	Inclusion criteria	N	Intervention group		Control group	Outcome measure	Assessment of outcome	Success rates (intervention vs. control)	OR (95% CI) or P-value
			mifepristone	misoprostol					
Nielsen (1999)	EPF or incomplete miscarriage < 13 weeks	122	400mg	400µg oral	Expectant management	US - APD < 15 mm	After 5 days	82% vs. 76%	OR 1.42 (0.59-3.41)
Stockheim (2006)	EPF < 9 weeks	115	600mg	800µg oral (one day)	Misoprostol 800µg oral (two days)	US - APD < 15 mm No need for surgical intervention	After 10 -14 days	65,5% vs. 73,6%	OR 1.47 (0.61-3.55)
Kushwah (2009)	EPF > 6 weeks and < 13 weeks	100	200mg	600µg sublingual + 400µg sublingual every 3h (max three doses)	Mifepristone 200mg and misoprostol 600µg oral + 400µg oral every 3h (max three doses)	US - empty uterine cavity No bleeding Closed cervical os	After 22 hours	92% vs. 84%	NS
MiMi (2011) *Prematurely terminated*	EPF	17	200mg	800µg buccally	Placebo and misoprostol 800µg buccally	Not specified	After 24 - 48 hours	62,5% vs. 55,6%	-
						Ultrasound	After 1 week	87,5% vs. 66,7%	-
Torre (2012)	EPF or incomplete miscarriage < 14 weeks	174	200mg	400µg vaginal	Same treatment after one week (delayed)	US - APD < 15 mm No need for surgical intervention	1 week after medical treatment	81% vs. 53%	P < 0.001

EPF = early pregnancy failure. US = ultrasound. APD = anterior-posterior (double) layer endometrial diameter.

Table 2 Complete evacuation using mifepristone and misoprostol in case of EPF

	Intervention		Control		Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**M-H, Random, 95% CI**
Nielsen 1999	11	60	15	62	0.70 [0.29, 1.69]
Stockheim 2006	20	58	15	57	1.47 [0.66, 3.28]
Kushwah 2009	4	50	8	50	0.46 [0.13, 1.63]
MiMi 2011	1	8	2	9	0.50 [0.04, 6.86]
Torre 2012	17	89	37	85	0.31 [0.16, 0.60]

Heterogeneity: $I^2 = 66\%$



Non-randomized trials

Eleven non-randomized controlled trials using mifepristone with misoprostol as a treatment for EPF were analyzed (table 3). An overview of the methodological quality per study of included studies is shown in figure 3. In 1992, El-Refaey was the first to report a prospective

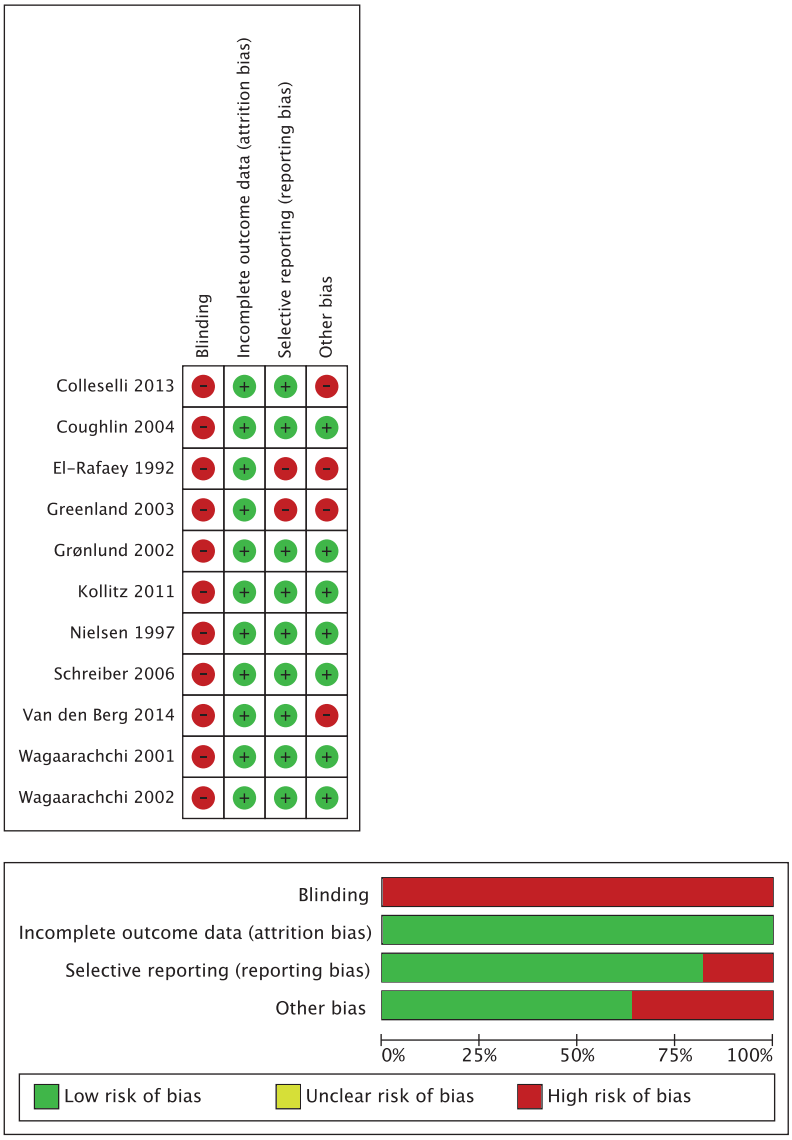


Figure 3 Overview of methodological quality of reporting of included non-RCT studies

study on the management of 60 women with EPF with a combination of mifepristone and oral misoprostol. Despite the short interval between treatment and determination of the outcome (4 h), this treatment regimen appeared successful in 95% of the cases.[20] Five years later, Nielsen described a prospective trial including 31 women with EPF receiving sequential mifepristone and oral misoprostol treatment. Success rates of 52% were reached. Authors concluded that these results do not support the use of mifepristone and misoprostol in women wishing the miscarriage to be evacuated quickly.[31] However, from 2001 on, nine non-randomized trials were published and these reports demonstrated that a medical treatment of sequential mifepristone and misoprostol is effective in 67–93% without serious adverse events.

Wagaarachchi et al. described a consecutive series of 220 women with EPF before thirteen weeks of gestation. All women had chosen to undergo medical treatment (combined mifepristone with vaginal misoprostol) leading to an overall success rate of 84,1%. After excluding all women who had surgical evacuation by choice after medical treatment was started, the success rate was 86,4%.[32] One year later, Wagaarachchi reported another prospective trial using mifepristone in combination with sublingual misoprostol. Fifty-six women with EPF were included both with (43,9%) and without (66,1%) symptoms of vaginal bleeding or pain. The overall success rate was 83,9%. The medical treatment regimen failed in 10,5% of the women having symptoms at presentation compared to 18,9% of the women who were asymptomatic ($p = 0.704$).[33] In 2002, Grønlund et al. reported on a prospective trial including 176 women with alternating treatment regimens every four months. Patients were randomized to medical treatment with sequential mifepristone and vaginal misoprostol, medical treatment with vaginal misoprostol only or surgical evacuation. Concerning medical treatment, no improvement in the expulsion rate by pretreatment with mifepristone was reported (74% versus 71%). Although significantly more women needed acute evacuation because of heavy bleeding in the intervention group (11% versus 1%, $p < 0.05$), no patient in either study group needed a blood transfusion.[34]

Coughlin et al. assessed the efficacy of a lower and higher dose of mifepristone in a small, prospective study in 103 women. With either drug regime (sequential mifepristone 200mg or 600mg followed by oral misoprostol) an initial success rate of 66–70% was reached. In case of incomplete evacuation ten days after treatment, a further 13–14% raise in success rates was achieved after another ten-day period of expectant management or a second dose of oral misoprostol. Both drug regimens were well tolerated; there was no statistically significant difference in overall success rates between both groups. A significant reduction in the amount of bleeding was seen in the 200mg mifepristone group versus the 600mg mifepristone group. However, only one patient required emergency evacuation because of heavy bleeding; this patient received 200mg mifepristone.[35]

Table 3 Non-randomized trials where mifepristone and misoprostol was used for treatment of EPF

First author (year)	Design	Inclusion criteria	N	Intervention group		Control group	Outcome measure	Assess-ment of outcome	Success rates (intervention vs. control)
				Mifepristone	Misoprostol				
El-Refaey (1992)	Prospective	EPF < 13 weeks	60	600mg	600µg oral + (optional) 600µg oral	-	US - no GS	After 4 hours	95%
Nielsen (1997)	Prospective	EPF	31	400mg	400µg oral	-	US - APD < 15mm	After 6 days	52%
Wagaarachchi (2001)	Prospective	EPF < 13 weeks	220	200mg	800µg vaginal + 2 doses 400µg at 3 hours interval After 24 hours another 1600µg or D&C	-	No need for surgical intervention	After 2 weeks	84,1%
Wagaarachchi (2002)	Prospective	EPF > 6 weeks and < 13 weeks	56	200mg	800µg sublingually + (optional) 2 doses 400µg at 3 hours interval After 24 hours another 1200µg or D&C	-	No need for surgical intervention	Within 2 weeks	83,9%
Grønlund (2002)	Prospective	EPF	176	600mg	600µg vaginal	600µg misoprostol vaginal OR curettage	US - APD < 20 mm	After 1 week	74% vs. 71% vs. 96%
Coughlin (2004)	Prospective	EPF < 13 weeks	103	600mg	800µg oral	200 mg mifepristone and 800µg misoprostol oral	US - empty uterus - no bleeding	After 10 days	70,5% vs. 66,7%

Schreiber (2006)	Prospective	EPF	30	200mg	800µg vaginal	-	US - no GS	After 24 hours After 1 week	90% 93%
Kollitz (2011)	Prospective	EPF or incomplete abortion	123	200mg	800µg vaginal + (optional) 800µg vaginal	-	US - no GS - APD < 30 mm	After 1 week	83%
Colleselli (2013)	Retrospective	EPF < 13 weeks	168	600mg	400µg oral + 400µg vaginal every 6h (max three doses)	-	US - APD No need for surgical intervention	Not specified	61%
Greenland (2003)	Retrospective	EPF < 12 weeks or incomplete abortion	207	200mg	600µg oral	-	US - no criteria defined No need for surgical intervention	After 1 week	88%
Van den Berg (2014)	Retrospective	EPF < 14 weeks	301	200mg	800µg vaginal (two days)	800µg misoprostol vaginal (twice)	Clinical signs Empty uterus - US or hysteroscopy Histology report	Different time points	66,8% vs. 54,9%

EPF = early pregnancy failure. US = ultrasound. GS = gestational sac. D&C = dilatation and curettage. APD = anterior-posterior (double) layer endometrial diameter.

A pilot study including 30 women all receiving sequential mifepristone and vaginal misoprostol treatment was performed by Schreiber et al. Besides reporting success rates of 93%, also the acceptability of medical management was studied. The overall experience and acceptability of the participants was classified as "positive" (54%) and "neutral" (32%). Regarding patient preference, 86% of the women would prefer medical treatment again if this would be needed in the future and 89% would recommend medical treatment to a friend.[36]

Kollitz et al. published a prospective study including 123 patients with EPF and incomplete miscarriage. An overall success rate of 83% using mifepristone and vaginal misoprostol (two doses) was achieved; treatment success occurred in 80% after a single dose of misoprostol. Adverse outcomes, mostly infection, were observed in only 2% of cases.[37]

Three retrospective studies were retrieved. First, Colleselli et al. included 168 women in a retrospective chart review. The treatment consisted of 600mg mifepristone followed by oral misoprostol and subsequent administration of vaginal misoprostol every 6 h, with a maximum of three doses total. A complete evacuation rate of 61% was reached.[38] Second, a retrospective cohort analysis by Greenland et al. described success rates of 88% in 207 women receiving mifepristone followed by oral misoprostol in case of EPF before twelve weeks of gestation.[39] A third retrospective study on 301 women was recently published by our group, comparing sequential mifepristone and vaginal misoprostol treatment to vaginal misoprostol alone in women with EPF before fourteen weeks of gestation. This study showed complete evacuation rates of 67% versus 54%.[21]

Comment

Main findings

In case of EPF, this systematic review reveals complete evacuation rates with sequential treatment with mifepristone and misoprostol of 52–95%. No serious adverse events were reported in the included trials.

Strengths and limitations

Our systematic review was the first to evaluate the added value of mifepristone to current non-surgical treatment regimens in case of EPF. However, due to the limitations of the included studies, firm conclusions cannot be drawn. The studies analyzed may be criticized because of small sample size and non-blinded design. Meta-analysis could not be performed due to the heterogeneity in treatment protocols; particularly treatment of women in the control group was different in each trial.

Since the definition of EPF is not well defined, inclusion of women in the reported trials was based on heterogeneous inclusion criteria. There is no international consensus on the definition of EPF; for example, the RCOG and FIGO use a limit of 12 weeks amenorrhea whereas the World Health Organization maintains a limit of 14 weeks amenorrhea. Since there is also no consensus on the definition of successful treatment, the reported trials determined the study outcome at different time points and based on various criteria such as an empty uterus seen on ultrasound or whether surgical intervention had been performed.

Interpretation

Expectant management

In all trials reported, the treatment started immediately after diagnosis. However, there are no serious medical risks associated with a watchful waiting strategy. Luise followed more than 1000 women with EPF for up to four weeks after diagnosis. Successful spontaneous miscarriage occurred in 52% of women within fourteen days of inclusion. Complications occurred in 1% of expectantly managed patients.[12] In the Netherlands medical or surgical treatment is started generally after a minimum of one week of expectant management, because of an expected spontaneous complete evacuation rate of around 50% during this expectant management.[12]

Mifepristone

In some studies a low dose of 200mg mifepristone was used; this may have resulted in lower complete evacuation rates.[29, 32] A dose of 600mg mifepristone is advised by the manufacturer based on phase 2 trials for medical termination of a viable pregnancy up to 63 days gestation.[24] These trials revealed that mifepristone 600mg is superior to mifepristone 200mg in terms of complete evacuation in case of medical abortion of a viable pregnancy: 89% versus 63%.[40, 41] Moreover, there is no difference in side effects compared with lower doses of mifepristone.[22, 24, 42] However, Birgerson et al. and the World Health Organization Task Force compared low and high doses of mifepristone in case of medical termination of a viable pregnancy, and found similar failure rates.[43, 44]

At this moment, the World Health Organization and the ''Dutch Society for Obstetrics and Gynecology'' advises mifepristone 200mg in case of termination of a viable pregnancy in the first trimester.[45, 46] Although inferiority of the 200mg dose is reported, this low-dose regimen may be probably due to the relatively high costs of mifepristone. In the context of low-resource countries, the discrete inferiority is considered to be acceptable. However, in order to achieve an optimal effect, based on phase 2 trials, a dose of 600mg mifepristone may be preferred in further trials.[40, 41]

Misoprostol

Regarding misoprostol, it should also be noticed that the optimal regimen, dose and route of administration has not yet been established.[3] Different misoprostol regimens in the reported studies of this review could have influenced the complete evacuation rates. For example, the different misoprostol regimen in the trial of Stockheim et al., 800µg once in the intervention group versus 800µg twice in the control group, may explain higher success rates in the control group.[27] It has been shown that a higher dose of misoprostol increases success rates. Hamoda et al. showed that the mean dose misoprostol needed to achieve abortion in case of medical termination of a viable pregnancy was 1324µg.[47] Another study performed by Tang et al. showed that the mean dose of misoprostol needed to achieve abortion was 2460µg.[48]

Successful treatment

In all existing guidelines, there are no recommendations concerning the follow-up of early pregnancy failure, also literature is limited.[45, 46, 49] Since the rate of clearance of serum hCG is dependent on the initial concentration, this should not be used to define complete evacuation.[50] The rate of decline does not guarantee that the evacuation is complete.[51] Follow-up based on clinical judgment and ultrasonography appears to be justified.[52] It is unclear which follow-up period is most appropriate. Complete evacuation rates of 89,7% may be reached seven days after medical treatment with misoprostol.[53] A period of one week is common practice in the Netherlands.

Costs

According to Graziosi, 85% of women would prefer medical treatment if its complete evacuation rate would reach 80%.[54] If complete evacuation rates could be increased by adding mifepristone to misoprostol, the total direct costs per patient can be lowered. Since the patent on mifepristone has expired recently, it is expected that also the pharmaceutical costs per patient will drop drastically.

Graziosi showed that the use of misoprostol for early pregnancy failure after failed expectant management is less costly than curettage. The direct costs per case were significantly lower (mean difference € 250; 95% CI 184–316, $p < 0.001$), indirect costs were equal for both groups (mean € 457). Differences in direct costs in favor of misoprostol treatment were large for women who had complete evacuation after initial medical treatment (direct costs € 137) as compared to those who needed additional curettage after failed misoprostol (direct costs € 788).[55]

Practical and research recommendations

A sufficiently powered prospective, randomized, double blinded and placebo-controlled trial on this subject is urgently needed.

Conclusion

The available evidence shows that medical treatment appears to be a safe alternative to surgical evacuation, leading to savings and a reduced number of serious complications. It represents an option of a less invasive management and gives women more control, and is especially suited for women not wanting hospital admission or surgical procedures or for patients in low resource countries. Unfortunately, medical treatment with misoprostol alone reaches complete evacuation in only half of the women. Adding mifepristone to current non-surgical treatment regimens might increase success rates and thereby reduce the number of surgical interventions. However, the evidence from the existing literature is insufficient to draw firm conclusions concerning the added value of mifepristone.

Declarations

Disclosure of interests statement

No conflicting interests to declare.

Contribution to authorship

JB and MS conceived and developed the idea for the article. JB and BG analyzed the data. SC and FV assisted in data analysis. All authors took part in drafting the article and revising it for critically important intellectual content. All authors gave final approval for publication.

Details of ethics approval

Ethics approval was not required for this review.

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References

1. Warburton D, Fraser FC. Spontaneous Abortion Risks in Man: Data from Reproductive Histories Collected in a Medical Genetics Unit. Am J Hum Genet. 1964;16:1-25.
2. Edmonds DK, Lindsay KS, Miller JF, Williamson E, Wood PJ. Early embryonic mortality in women. Fertil Steril. 1982;38:447-53.
3. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2009;3:CD002253.
4. Prismant Landelijke LMR informatie [Internet]. 2008-2010 [cited 30-08-2012]. Available from: http://cognosserver.prismant.nl.
5. Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Hum Reprod. 2004;19:1894-9.
6. Jurkovic D, Overton C, Bender-Atik R. Diagnosis and management of first trimester miscarriage. BMJ. 2013;346:f3676.
7. Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management in Early Pregnancy of Ectopic Pregnancy and Miscarriage. National Institute for Health and Clinical Excellence: Guidance. London2012.
8. You JH, Chung TK. Expectant, medical or surgical treatment for spontaneous abortion in first trimester of pregnancy: a cost analysis. Hum Reprod. 2005;20:2873-8.
9. Soulat C, Gelly M. [Immediate complications of surgical abortion]. J Gynecol Obstet Biol Reprod (Paris). 2006;35:157-62.
10. Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. Fertil Steril. 2006;86:367-72.
11. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2013.
12. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002;324:873-5.
13. Beckman LJ, Harvey SM. Experience and acceptability of medical abortion with mifepristone and misoprostol among U.S. women. Womens Health Issues. 1997;7:253-62.
14. Mamers PM, Lavelle AL, Evans AJ, Bell SM, Rusden JR, Healy DL. Women's satisfaction with medical abortion with RU486. Med J Aust. 1997;167:316-7.
15. Clark S, Ellertson C, Winikoff B. Is medical abortion acceptable to all American women: the impact of socio-demographic characteristics on the acceptability of mifepristone-misoprostol abortion. J Am Med Womens Assoc. 2000;55:177-82.
16. Elul B, Pearlman E, Sorhaindo A, Simonds W, Westhoff C. In-depth interviews with medical abortion clients: thoughts on the method and home administration of misoprostol. J Am Med Womens Assoc. 2000;55:169-72.
17. Arvidsson C, Hellborg M, Gemzell-Danielsson K. Preference and acceptability of oral versus vaginal administration of misoprostol in medical abortion with mifepristone. Eur J Obstet Gynecol Reprod Biol. 2005;123:87-91.
18. Lohr PA, Wade J, Riley L, Fitzgibbon A, Furedi A. Women's opinions on the home management of early medical abortion in the UK. J Fam Plann Reprod Health Care. 2010;36:21-5.
19. Ngo TD, Park MH, Shakur H, Free C. Comparative effectiveness, safety and acceptability of medical abortion at home and in a clinic: a systematic review. Bull World Health Organ. 2011;89:360-70.
20. el-Refaey H, Hinshaw K, Henshaw R, Smith N, Templeton A. Medical management of missed abortion and anembryonic pregnancy. BMJ. 1992;305:1399.
21. van den Berg J, van den Bent JM, Snijders MP, de Heus R, Coppus SF, Vandenbussche FP. Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study. Eur J Obstet Gynecol Reprod Biol. 2014;183:16-9.
22. Kulier R, Gulmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2008:CD002855.
23. Say L, Kulier R, Gulmezoglu M, Campana A. Medical versus surgical methods for first trimester termination of pregnancy. Cochrane Database Syst Rev. 2005:CD003037.
24. Pharma N. Mifegyne (Mifepristone) - Scientific information and guide to use2010.

25. Mifepriston - Mifegyne http://www.fk.cvz.nl [06-10-2011]. http://www.fk.cvz.nl]. Available from: http://www.farmacotherapeutischkompas.nl.
26. Nielsen S, Hahlin M, Platz-Christensen J. Randomised trial comparing expectant with medical management for first trimester miscarriages. Br J Obstet Gynaecol. 1999;106:804-7.
27. Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, et al. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. Fertil Steril. 2006;86:956-60.
28. Kushwah B, Singh A. Sublingual versus oral misoprostol for uterine evacuation following early pregnancy failure. Int J Gynaecol Obstet. 2009;106:43-5.
29. Torre A, Huchon C, Bussieres L, Machevin E, Camus E, Fauconnier A. Immediate versus delayed medical treatment for first-trimester miscarriage: a randomized trial. Am J Obstet Gynecol. 2012;206:215 e1-6.
30. Betstadt S. MiMi: A Randomized Trial of Mifepristone and Misoprostol for Treatment of Early Pregnancy Failure. 2011.
31. Nielsen S, Hahlin M, Platz-Christensen JJ. Unsuccessful treatment of missed abortion with a combination of an antiprogesterone and a prostaglandin E1 analogue. Br J Obstet Gynaecol. 1997;104:1094-6.
32. Wagaarachchi PT, Ashok PW, Narvekar N, Smith NC, Templeton A. Medical management of early fetal demise using a combination of mifepristone and misoprostol. Hum Reprod. 2001;16:1849-53.
33. Wagaarachchi PT, Ashok PW, Smith NC, Templeton A. Medical management of early fetal demise using sublingual misoprostol. BJOG. 2002;109:462-5.
34. Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidegaard O. Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark. Acta Obstet Gynecol Scand. 2002;81:1060-5.
35. Coughlin LB, Roberts D, Haddad NG, Long A. Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? J Obstet Gynaecol. 2004;24:69-71.
36. Schreiber CA, Creinin MD, Reeves MF, Harwood BJ. Mifepristone and misoprostol for the treatment of early pregnancy failure: a pilot clinical trial. Contraception. 2006;74:458-62.
37. Kollitz KM, Meyn LA, Lohr PA, Creinin MD. Mifepristone and misoprostol for early pregnancy failure: a cohort analysis. Am J Obstet Gynecol. 2011;204:386 e1-6.
38. Colleselli V, Schreiber CA, D'Costa E, Mangesius S, Wildt L, Seeber BE. Medical management of early pregnancy failure (EPF): a retrospective analysis of a combined protocol of mifepristone and misoprostol used in clinical practice. Arch Gynecol Obstet. 2013.
39. Greenland H, Ogunbiyi I, Bugg G, Tasker M. Medical treatment of miscarriage in a district general hospital is safe and effective up to 12 weeks' gestation. Curr Med Res Opin. 2003;19:699-701.
40. Maria B, Chaneac M, Stampf F, Ulmann A. [Early pregnancy interruption using an antiprogesterone steroid: Mifepristone (RU 486)]. J Gynecol Obstet Biol Reprod (Paris). 1988;17:1089-94.
41. Grimes DA, Mishell DR, Jr., Shoupe D, Lacarra M. Early abortion with a single dose of the antiprogestin RU-486. Am J Obstet Gynecol. 1988;158:1307-12.
42. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. World Health Organisation Task Force on Post-ovulatory Methods of Fertility Regulation. BJOG. 2000;107:524-30.
43. Birgerson L, Odlind V. The antiprogestational agent RU 486 as an abortifacient in early human pregnancy: a comparison of three dose regimens. Contraception. 1988;38:391-400.
44. Termination of pregnancy with reduced doses of mifepristone. World Health Organisation Task Force on Post-ovulatory Methods of Fertility Regulation. BMJ. 1993;307:532-7.
45. Tang J, Kapp N, Dragoman M, de Souza JP. WHO recommendations for misoprostol use for obstetric and gynecologic indications. Int J Gynaecol Obstet. 2013;121:186-9.
46. Zwangerschapsafbreking tot 24 weken. In: Richtlijn Nederlandse Vereniging voor Obstetrie & Gynaecologie; 2005. Available from: https://www.nvog.nl.
47. Hamoda H, Ashok PW, Flett GM, Templeton A. A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. BJOG. 2005;112:1102-8.
48. Tang OS, Miao BY, Lee SW, Ho PC. Pilot study on the use of repeated doses of sublingual misoprostol in termination of pregnancy up to 12 weeks gestation: efficacy and acceptability. Hum Reprod. 2002;17:654-8.

49. Hinshaw K, Fayyad A, Munjuluri P. The management of early pregnancy loss. Royal College of Obstetricians and Gynaecologists, Green-top Guideline No. 25. http://www.rcog.org.uk/. 2006.
50. Barnhart K, Sammel MD, Chung K, Zhou L, Hummel AC, Guo W. Decline of serum human chorionic gonadotropin and spontaneous complete abortion: defining the normal curve. Obstet Gynecol. 2004;104:975-81.
51. Creinin MD. Change in serum beta-human chorionic gonadotropin after abortion with methotrexate and misoprostol. Am J Obstet Gynecol. 1996;174:776-8.
52. Dayananda I, Maurer R, Fortin J, Goldberg AB. Medical abortion follow-up with serum human chorionic gonadotropin compared with ultrasonography: a randomized controlled trial. Obstet Gynecol. 2013;121:607-13.
53. Bagratee JS, Khullar V, Regan L, Moodley J, Kagoro H. A randomized controlled trial comparing medical and expectant management of first trimester miscarriage. Hum Reprod. 2004;19:266-71.
54. Graziosi GC, Bruinse HW, Reuwer PJ, Mol BW. Women's preferences for misoprostol in case of early pregnancy failure. Eur J Obstet Gynecol Reprod Biol. 2006;124:184-6.
55. Graziosi GC, van der Steeg JW, Reuwer PH, Drogtrop AP, Bruinse HW, Mol BW. Economic evaluation of misoprostol in the treatment of early pregnancy failure compared to curettage after an expectant management. Hum Reprod. 2005;20:1067-71.

3

Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study

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Abstract

Objective

Is treatment of early pregnancy failure (EPF) with sequential use of mifepristone and misoprostol more effective than treatment with misoprostol alone?

Study design

In a retrospective cohort study at the Department of Obstetrics and Gynecology of the Radboud University Medical Centre, 301 women with early pregnancy failure receiving medical treatment between January 2008 and March 2013 were included. Of these, 199 women were pre-treated with 200mg mifepristone (orally) followed by 2 consecutive doses of 800µg misoprostol (vaginally) and 102 women were treated with 2 consecutive doses of 800µg misoprostol (vaginally) alone.

Results

Complete expulsion was achieved in 66,8% of the women treated with a sequential combination of mifepristone and misoprostol versus 54,9% of the women treated with misoprostol alone. The difference in rates of complete expulsion was 11,9% ($p < 0.05$; 95% CI 0.3–23,6%).

Conclusions

Medical treatment of early pregnancy failure with a sequential combination of mifepristone and misoprostol was more effective than treatment with misoprostol alone. Our findings will have to be confirmed by a large prospective multicenter double blinded-randomized trial.

Introduction

Early pregnancy failure (EPF) is a common complication of pregnancy, as 10% to 20% of all clinically recognized pregnancies will end in EPF.[1] For many years surgical evacuation was the standard treatment, but more recently medical management has gained a substantial role in treatment of EPF. Medical management of EPF with the prostaglandin E1 analogue misoprostol has been the subject of many studies showing complete expulsion rates using between 53% and 87%.[2-5] As evidence is growing that surgical management may have major long-term consequences, such as intra-uterine adhesions and increased spontaneous preterm birth rates in subsequent pregnancies, the potential of successful medical treatment of EPF is of utmost importance.[6, 7]

Mifepristone is an anti-progesterone and anti-glucocorticoid drug and is registered for induction of abortion in viable pregnancies up to a gestational age of 63 day.[8] The sequential combination of mifepristone (200mg) with misoprostol (800µg) has been shown superior to the use of misoprostol alone (800µg) for medical termination of viable pregnancies.[9] The rate of complete abortion after treatment with a combination of mifepristone and misoprostol is reported to be as high as 95%.[10]

Several studies examined the combination of mifepristone and misoprostol in cases of EPF and found it an effective and safe alternative to surgical treatment, with success rates ranging between 65,5% and 93%.[11-15] Unfortunately, these studies had limitations due to study design, small sample size and heterogeneous inclusion criteria. Therefore, conflicting findings about the value of mifepristone need to be resolved by additional studies.[3] In preparation for this trial we conducted a retrospective study to compare complete expulsion rates with a combination of mifepristone and misoprostol versus misoprostol alone in women with early pregnancy failure.

Methods

We performed a single-center retrospective cohort study of women treated in the Radboud University Medical Centre between January 2008 and March 2013, to study the effectiveness of mifepristone in women treated for early pregnancy failure. Ethics approval was not required for this study; this was confirmed by our local medical ethics committee.

Patient selection

Mifepristone (Mifegyne1, Exelgyn France, Nordic Pharma, The Netherlands) is registered for induction of abortion in the Netherlands. It is solely available in clinics authorized by an explicit jurisdictional approval of the Minister of Health. Therefore a strict registration of

distributed mifepristone is used in the outpatient clinic. This registration was used to identify women treated with mifepristone between April 2010 and March 2013. The use of misoprostol (Cytotec1, Pfizer The Netherlands) for the indication EPF is "off label" and also registered. To search for patients potentially not listed in these registrations, electronic patient records were searched between January 2008 and March 2010 for variables such as absent fetal heartbeat and gestational age less than 14 weeks.

Inclusion criteria for this cohort study were the presence of a non-viable pregnancy before 14 weeks' gestation and an indication for medical treatment. A non-viable pregnancy was defined either as an anembryonic gestation with a blighted ovum or as early embryonic/fetal demise showing an embryo without cardiac activity. In The Netherlands, expectant management for at least one week after the diagnosis has been established is common practice, because spontaneous complete expulsion rates of 50% are to be expected during this first week.[16]

Exclusion criteria were imminent miscarriage (products of conception passing through the cervical os at presentation at the outpatient department) and incomplete miscarriage, which was defined as retained products of conception (endometrial lining >15 mm) after expulsion of an intrauterine pregnancy.

Treatment protocols

At our clinic, women with early pregnancy failure are counseled according to a local protocol with respect to three options: expectant management, or medical or surgical treatment. Before April 2010 medical treatment of EPF consisted solely of administration of two consecutive doses of misoprostol 800µg vaginally (time interval of 24 h) without mifepristone. Thereafter, medical treatment consisted of 200mg mifepristone orally followed by 800µg misoprostol vaginally 36 h later administered at home. When cramps or vaginal bleeding do not occur within 24 h after the first dosage of misoprostol, women are instructed to use another dosage of 800µg misoprostol vaginally the next day.

Outcome measures

The primary outcome parameter was complete expulsion, defined as asymptomatic women after clinical signs of a complete miscarriage, or an empty uterine cavity seen on vaginal ultrasound, or an empty uterine cavity seen during hysteroscopy, or a histology report after surgical evacuation describing the absence of the products of conception. The study outcome was determined at different time points depending on the policy of the treating physician. Secondary outcome parameters were the different reasons for failure of treatment (no expulsion of products, persistent gestational sac, suspected residue, excessive blood loss or suspected infected residue) and factors that could affect the rate of complete expulsion like gestational age and parity.

Statistical analyses

SPSS version 20.0 was used for data analysis. Differences between groups were analyzed using Pearson's chi-square test or Fisher's exact test for categorical variables. The Mann–Whitney U test was used for non-normally distributed metric variables. Logistic regression analysis was performed to identify factors that were associated with treatment success. P values smaller than 0.05 were considered significant.

Results

Baseline characteristics were not significantly different between the treatment groups (table 1). A total of 311 women were medically treated for early pregnancy failure at the Radboud University Medical Centre in the period between January 2008 and March 2013. Ten cases were excluded because there were no exact data on the primary outcome. A total of 102 women were treated with misoprostol alone and 199 women were treated with the sequential combination of mifepristone and misoprostol.

Table 1 Baseline characteristics

	Misoprostol (N=102)	**Mifepristone and misoprostol (N=199)**	***P* value**
Age (years), mean SD	32,6 4.5	33,0 4.9	0.44
Anembryonic gestation Embryonic / fetal demise	28 (27,5%) 74 (72,5%)	54 (27,1%) 145 (72,9%)	1.00
Gestational age amenorrhea (days), mean SD	71,8 9.8	74,1 10.1	0.08
Ultrasound gestational age (days), mean SD	53,0 9.8	52,9 10.2	0.99
Nulliparous	39 (38,2%)	81 (40,7%)	0.62
Previous miscarriage	40 (39,2%)	60 (30,2%)	0.15
Previous elective abortion (APLA)	13 (12,7%)	26 (13,1%)	1.00
Previous caesarean section	6 (5,9%)	27 (13,6%)	0.06

Complete expulsion (table 2) was achieved in 66,8% of the women treated with a sequential combination of mifepristone and misoprostol compared to 54,9% of the women treated with misoprostol alone. The difference in rates of complete expulsion was 11,9% ($p < 0.05$; 95% CI 0,3%–23,6%). In women diagnosed with an anembryonic gestation (AG) the rate of complete miscarriage did not differ significantly between the two treatment groups. In women diagnosed with embryonic/fetal demise (EFD) the rate of complete expulsion after treatment with a sequential combination of mifepristone and misoprostol was 64,1%, compared to 44,1% in women treated with misoprostol alone ($p < 0.01$, difference 20%, 95%CI: 5,8%–33,3%).

Table 2 Outcome measures of consecutive combination of mifepristone and misoprostol versus misoprostol alone

	Misoprostol, n/N (%)	**Mifepristone and misoprostol, n/N (%)**	***P* value**
Complete expulsion rate (total)	56/102 (54,9)	133/199 (66,8)	< 0.05
Complete expulsion rate (AG)	21/28 (75)	40/54 (74,1)	1.00
Complete expulsion rate (EFD)	33/74 (44,6)	93/145 (64,1)	< 0.01

AG= Anembryonic gestation, EFD= Embryonic or fetal demise

In 113 women who needed a surgical intervention after medical treatment, two were diagnosed with an empty uterine cavity during hysteroscopy. Hysteroscopy was performed in women presenting more than six weeks after medical treatment with a suspicion of retained products of gestation. In three women treated with dilatation and curettage the pathologist reported absence of gestational products.

Table 3 shows indications for surgical management after failed medical treatment. Most women were surgically treated due to a suspicion of retained products of gestation. In women treated with misoprostol alone 30% of the indications for surgical intervention were because of a persistent gestational sac, compared to 9% in the group treated with a sequential combination of mifepristone and misoprostol (difference 21%, $p < 0.01$, 95%CI: 6,6%–35,5%). Ten women treated with a sequential combination of mifepristone and misoprostol had a surgical intervention because of excessive bleeding. Among the patients treated with misoprostol alone, one patient needed an intervention due to hemorrhage.

Table 3 Indications for surgical intervention after failed medical treatment

	Misoprostol, n/N (%)	Mifepristone and misoprostol, n/N (%)	*P* value
Surgical intervention (total)	50/102 (49)	67/199 (33,7)	< 0.05
Suspected residua	31/50 (62)	44/67 (65,7)	0.70
Persistent gestational sac	15/50 (30)	6/67 (9)	< 0.01
Suspected residua with signs of infection	3/50 (6)	5/67 (7,5)	1.00
Hemorrhage	1/50 (2)	10/67 (14,9)	< 0.05

After adjusting for gestational age a non-significant declining rate of complete expulsion was observed, as shown in Fig. 1 (p = 0.06). No differences in primary outcome were observed after adjusting for the difference between time since last menstrual period and ultrasound gestational age, parity, prior miscarriages, prior elective abortions or prior dilatation and curettage.

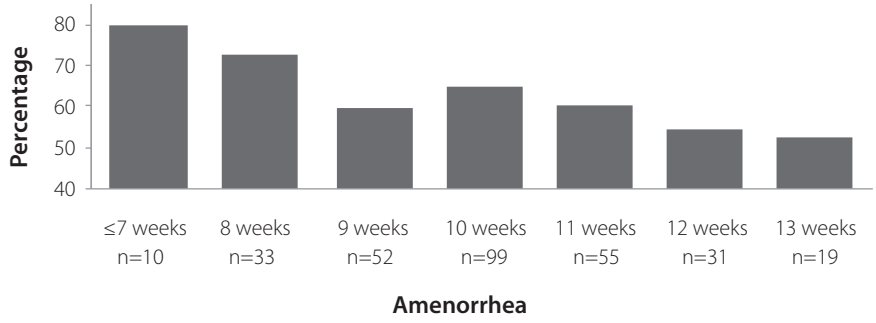

Figure 1 Complete expulsion rate

Comment

Main findings

This retrospective study compared rates of complete expulsion of EPF after medical treatment with sequential mifepristone and misoprostol to those after treatment with misoprostol alone after at least one week of expectant management. Sequential treatment with mifepristone and misoprostol resulted in a 66,8% complete expulsion rate and treatment with misoprostol alone resulted in a 54,9% complete expulsion rate. The difference in rates of complete expulsion was statistically significant.

Strengths and limitations

EPF is a common complication of pregnancy, and therefore we were able to include a large group of women. Our baseline data showed no significant difference between the two treatment groups. Diagnosis of early pregnancy failure, therapy counseling and patient information was standardized. A uniform treatment protocol was available and there was a clear and objective outcome definition.

A limitation of our findings is the retrospective study design. The data were collected directly from patient charts, which could be inconclusive or incomplete. The allocation to the two treatment groups was caused by a protocol change in April 2010, but a minority of women was still treated according to the old protocol after 2010.

Interpretation

Success rates of the use of misoprostol alone vary from 53% to 88%.[2, 5, 14, 17-20] These studies are heterogeneous in their definition of complete abortion, duration of follow-up period and doses of misoprostol.[11-13, 21, 22] As an example, in the studies of Wagaarachchi et al. up to 1600µg misoprostol for two consecutive days was given.[21, 22] Others used different frequencies of administration such as two consecutive doses of 800µg misoprostol followed by an additional dose after one week if necessary.[20] Regarding follow-up, Kollitz and Petersen used an endometrial lining of < 30 mm to diagnose complete miscarriage after one week.[5, 12] In essence, there is no consensus on the diagnosis of a complete miscarriage. Some clinicians or researchers use clinical symptoms like the cessation of vaginal blood loss and cramps. Others use ultrasonographic criteria such as the absence of a gestational sac or an endometrial lining of less than 15 or 30 mm. Some data show that there is no relationship between increasing endometrial residue-thickness and the need for surgical intervention in women treated with misoprostol for early pregnancy failure.[23, 24] In our center, clinicians use a maximum endometrial lining of 15 mm with absence of vaginal bleeding to diagnose complete miscarriage one week after treatment. This may have led to a lower success rate of treatment compared to other studies using less stringent criteria for complete miscarriage. We are eagerly awaiting

the results of the Dutch "MisoREST" study, ultimately defining the effectiveness of expectant management and curettage in symptom-free women with sonographic evidence of incomplete evacuation of a miscarriage after misoprostol treatment.

Graziosi et al. found a success rate of misoprostol after one week of expectant management of 53,2%, comparable with 54,9% found in our study. Graziosi concluded that these lower success rates might be due to this patient selection after one week of expectant management.[2] Indeed, Torre et al. conducted a randomized trial to compare delayed treatment with direct medical treatment and concluded that delayed treatment is less effective than direct treatment.[25] In women treated with mifepristone and misoprostol we found a 66,8% rate of complete expulsion after one week expectant management, which is comparable with the percentage success found by several other studies (66–74%).[14, 15, 26]

Additional findings

The difference in expulsion rates between the two treatment regimens in women with an anembryonic gestation (AG) and women having an early embryonic/fetal demise (EFD) have not been described in earlier studies. Wagaarachchi et al. described the two groups separately but found no significant difference in treatment success.[21] Kollitz et al. described a difference between AG and EFD, showing that women with an AG had a success rate of 69% compared to 88% in the group of women with EFD.[12] The data of Zhang et al. showed that the success rate of treatment of AG was lower compared to the success rate of treatment of women having an EFD.[4]

Practical and research recommendations

Reflecting on cost-effectiveness, it may already be clear that medical treatment delivered at an outpatient department, with the intention of spontaneous miscarriage at home, will decrease costs substantially compared to clinical surgical treatment. Besides, since the patent on mifepristone has expired, the costs of mifepristone are already decreasing drastically. Because of the decreasing costs of mifepristone, even a small increase in the rate of complete expulsion may lead to a decrease in overall treatment costs.

Based on the results of our study, treatment of early pregnancy failure with the sequential combination of mifepristone and misoprostol appears to be more effective than misoprostol alone. A randomized, double blind placebo-controlled trial is urgently needed. Such a trial could confirm that treatment with mifepristone and misoprostol may lead to higher complete evacuation rates and thus a significant reduction of costs.

Conclusion

In our retrospective study, treatment of early pregnancy failure with a sequential combination of mifepristone and misoprostol was significantly more effective than treatment with misoprostol alone. These findings should be confirmed by a multicenter double blinded-randomized trial.

Declarations

Conflict of interest statement

No conflicting interests to declare.

Contribution to authorship

JB, RH, MS and FV conceived and developed the idea for the article. JB and JMB were responsible for the acquisition and analysis of the data. SC and RH assisted in data analysis. All authors took part in drafting the article or revising it for critically important intellectual content and all gave final approval of the version to be published.

Details of ethics approval

Ethics approval was not required for this study; this was confirmed by our local medical ethics committee.

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References

1. Sur SD, Raine-Fenning NJ. The management of miscarriage. Best Pract Res Clin Obstet Gynaecol. 2009;23:479-91.
2. Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Hum Reprod. 2004;19:1894-9.
3. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2009;3:CD002253.
4. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med. 2005;353:761-9.
5. Petersen SG, Perkins A, Gibbons K, Bertolone J, Devenish-Meares P, Cave D, et al. Can we use a lower intravaginal dose of misoprostol in the medical management of miscarriage? A randomised controlled study. Aust N Z J Obstet Gynaecol. 2013;53:64-73.
6. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2013.
7. McCarthy FP, Khashan AS, North RA, Rahma MB, Walker JJ, Baker PN, et al. Pregnancy loss managed by cervical dilatation and curettage increases the risk of spontaneous preterm birth. Hum Reprod. 2013;28:3197-206.
8. Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. Contraception. 2010;82:442-52.
9. Kulier R, Kapp N, Gulmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2011:CD002855.
10. Baird DT. Medical abortion in the first trimester. Best Pract Res Clin Obstet Gynaecol. 2002;16:221-36.
11. Schreiber CA, Creinin MD, Reeves MF, Harwood BJ. Mifepristone and misoprostol for the treatment of early pregnancy failure: a pilot clinical trial. Contraception. 2006;74:458-62.
12. Kollitz KM, Meyn LA, Lohr PA, Creinin MD. Mifepristone and misoprostol for early pregnancy failure: a cohort analysis. Am J Obstet Gynecol. 2011;204:386 e1-6.
13. Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. Fertil Steril. 2006;86:367-72.
14. Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, et al. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. Fertil Steril. 2006;86:956-60.
15. Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidegaard O. Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark. Acta Obstet Gynecol Scand. 2002;81:1060-5.
16. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002;324:873-5.
17. Muffley PE, Stitely ML, Gherman RB. Early intrauterine pregnancy failure: a randomized trial of medical versus surgical treatment. Am J Obstet Gynecol. 2002;187:321-5; discussion 5-6.
18. Wood SL, Brain PH. Medical management of missed abortion: a randomized clinical trial. Obstet Gynecol. 2002;99:563-6.
19. Creinin MD, Moyer R, Guido R. Misoprostol for medical evacuation of early pregnancy failure. Obstet Gynecol. 1997;89:768-72.
20. Barcelo F, De Paco C, Lopez-Espin JJ, Silva Y, Abad L, Parrilla JJ. The management of missed miscarriage in an outpatient setting: 800 versus 600 mug of vaginal misoprostol. Aust N Z J Obstet Gynaecol. 2012;52:39-43.
21. Wagaarachchi PT, Ashok PW, Narvekar N, Smith NC, Templeton A. Medical management of early fetal demise using a combination of mifepristone and misoprostol. Hum Reprod. 2001;16:1849-53.
22. Wagaarachchi PT, Ashok PW, Smith NC, Templeton A. Medical management of early fetal demise using sublingual misoprostol. BJOG. 2002;109:462-5.
23. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J, Trial NMoEPF. Endometrial thickness after misoprostol use for early pregnancy failure. Int J Gynaecol Obstet. 2004;86:22-6.
24. Grossman D, Grindlay K. Alternatives to ultrasound for follow-up after medication abortion: a systematic review. Contraception. 2011;83:504-10.

25. Torre A, Huchon C, Bussieres L, Machevin E, Camus E, Fauconnier A. Immediate versus delayed medical treatment for first-trimester miscarriage: a randomized trial. Am J Obstet Gynecol. 2012;206:215 e1-6.
26. Coughlin LB, Roberts D, Haddad NG, Long A. Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? J Obstet Gynaecol. 2004;24:69-71.

4

Current and future expectations of mifepristone treatment in early pregnancy failure: a survey among Dutch gynecologists

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Abstract

Objective

To investigate the current and future addition of mifepristone to misoprostol treatment (M&M) in case of early pregnancy failure (EPF).

Study design

A digital questionnaire was distributed to a representative sample of all Dutch hospitals (25/79). Gynecologists with focus on early pregnancy of eight academic hospitals, ten teaching hospitals, six non-teaching hospitals and one private practice center were approached to fill in the survey. The questionnaire consisted of 25 questions concerning current practice in EPF with a focus on the use of mifepristone.

Results

All 25 questionnaires were returned. In non-teaching centers the presence of a local protocol was significantly lower compared to academic and teaching hospitals (p 0.012). If a local protocol was present, first choice of treatment was medical in 54,5%. Four respondents (16%) always prescribed mifepristone in case of EPF. The most common reason not prescribing mifepristone was the lack of sufficient scientific evidence. An average increase in success rate of 21,7% was desired to prescribe mifepristone in the future for EPF. Completeness of evacuation of products of conception from the uterus was usually assessed after one week by ultrasonography combined with clinical signs. The cut-off point for total endometrial thickness used to diagnose (in) complete evacuation varied from 4 until 15 millimeters. If a complete evacuation was not achieved by the initial medical treatment, expectant management was proposed just as often as surgical intervention (24%). Follow-up after additional expectant management was usually planned after the first menstruation.

Conclusions

For EPF, there is still a large practice variation in the Netherlands concerning treatment of patients. The use of M&M in EPF is not common practice, due to the lack of sufficient evidence. Physicians are willing to prescribe pre-treatment with mifepristone before misoprostol in the future if proven effective.

Introduction

Early pregnancy failure (EPF) is a common complication of pregnancy. In the Netherlands, approximately 10,000 women per year will undergo some form of treatment, in order to remove the products of conception from the uterus.[1] The Dutch guideline for general practitioners and midwives advise expectant management for a minimum of one week, because this leads to a spontaneous complete evacuation rate of approximately 50%.[2-4] Surgical treatment (dilatation and curettage, D&C) is associated with high (>95%) efficacy rates, but also with higher cost, short- and long-term risks of complications, and possible consequences for following pregnancies.[3, 5-10] Medical treatment for EPF with misoprostol (a synthetic prostaglandin E1 analogue) started after one week of expectant management, is a less invasive alternative, but results in a lower complete evacuation rate of approximately 50%.[3, 11, 12]

A new medical treatment option combines pre-treatment with mifepristone, an anti-progesterone and anti-glucocorticoid drug, to misoprostol (M&M) and this combination appears more effective.[13, 14] Up until now, mifepristone is licensed in the Netherlands for four indications namely medical termination of a vital pregnancy up tot 63 days of gestation, termination of vital pregnancy beyond first trimester, preparation for surgical abortion in the first trimester, and labor induction in fetal death in utero in the second and third trimester.[15-18] So, it appears reasonable to consider that, also for EPF (non-vital pregnancy in the first trimester), M&M is superior to misoprostol alone.[11, 15] Unfortunately, until now the existing evidence is insufficient to draw firm conclusions regarding M&M treatment.[13]

In the Netherlands, there is no national guideline for gynecologists describing diagnostic, treatment and follow up options for EPF. Verschoor et al reporting on a national survey in 2014 concerning treatment options in the Netherlands showed a large practice variation between hospitals. The awareness to prescribe misoprostol doubled between 2005 and 2014 to nearly 100%. However, up until 2014, 23 different treatment regimens (dosages and routes of administration) were used, and in many hospitals even more than one treatment regimen existed simultaneously. The aforementioned questionnaire focused mainly on the use of misoprostol. Mifepristone was prescribed in approximately 37% of the hospitals with no further details mentioned.[19]

This survey was conducted in the context of preparation of a randomized controlled trial to test the hypothesis that M&M is superior to the use of misoprostol alone in case of EPF. We investigated the presence of a local protocol, the current prescription of mifepristone, and possible future intention to prescribe mifepristone in case of EPF. Since evidence based literature regarding follow up and optimal diagnostics defining (un) successful treatment after medication is lacking, we also focused on these items.[20, 21]

Materials and methods

An online questionnaire was developed using Google Forms. Twenty-five questions were compiled about a local protocol, the current prescription of medical treatment and mifepristone, the intention to use M&M in the future, and follow-up procedures (diagnostic tools and time period). In the Netherlands, a representative sample of gynecologic centers was approached (25/79, 32%) consisting of 8 academic centers, 10 teaching hospitals, 6 non-teaching hospitals and 1 private practice center. Gynecologists with focus on early pregnancy working in these centers were contacted beforehand by telephone and/or e-mail and informed about the following questionnaire. Questionnaires were sent between February and July 2017. An email once again explained the purpose of the survey and the confidentiality, and provided a direct link to the digital questionnaire. One reminder was sent out after two weeks. The survey was based on voluntary participation and patients were not involved, therefore ethical approval was not necessary.

Statistical analyses

Data collection was confidential and anonymous. Data were automatically entered into a spreadsheet after completion of the questionnaire. Analysis was performed per type of hospital (academic versus (non-) teaching hospitals), and between centers with and without a local protocol. The private practice center was analyzed as a non-teaching hospital. SPSS version 24 was used for data analysis. Differences between groups were analyzed using the Pearson's chi-square test or the Fisher's exact test for categorical variables. P values smaller than .05 were considered significant.

Results

All twenty-five questionnaires were returned (response 25/25, 100%), two questionnaires from non-academic centers were incomplete; they were included in the analysis up to the point where they were completed. A local protocol for EPF was present in 88% of all responding hospitals, in 100% of academic and teaching hospitals versus 57,1% in non-teaching hospitals (p 0.012, table 1). In the remaining 12% of the centers, so-called agreements about the preferred treatment method exist, but not documented in a protocol. One week of expectant management was not significant different between academic or non-academic centers, or hospitals with or without a local protocol. If a local protocol was present, the first choice of treatment was medical in 12/22 (54,5%), and mifepristone was described in 9/22 (41%). Of non-teaching hospitals with a local protocol, 3/4 (75%) recommended the prescription of mifepristone compared to 6/18 (33,3%) of the academic and teaching hospitals (p 0.125).

Table 1 Local protocol for early pregnancy failure

	Type of clinic n/N (%)		
	Academic	**Teaching**	**Non-teaching**
Local protocol present?			
Yes	8/8 (100)	10/10 (100)	4/7 (57,1)
No	0	0	3/7 (42,9)
First choice of treatment			
Medical	6/8 (75)	5/10 (50)	1/4 (25)
Patient and/or doctor preference	2/8 (25)	5/10 (50)	3/4 (75)
One week of expectant management			
Always	3/8 (37,5)	3/10 (30)	0
Usually	4/8 (50)	7 (70)	4/7 (57,1)
Only when indicated	1/8 (12,5)	0	3/7 (42,9)
Mifepristone recommended in protocol			
Yes	2/8 (25)	4/10 (40)	3/4 (75)
No	6/8 (75)	5/10 (50)	0
Unknown	0	1/10 (10)	1/4 (25)

When analyzing all hospitals, mifepristone was prescribed 'always' by 4/25 (16%), 'usually' by 1/25 (4%), 'only when indicated' by 9/25 (36%), and 'never' by 9/25 (36%) respondents (table 2). The most mentioned reason (26,1%) for not prescribing mifepristone in case of EPF was lack of evidence of effectiveness. Although the Dutch drug leaflet of mifepristone recommends taking mifepristone in the presence of a physician or one of his/her employees, two hospitals followed this advice. The complete evacuation rate after mifepristone and misoprostol treatment was estimated between 50% and 100% with similar side effects compared to treatment with misoprostol alone. The required average increase in success rate for physicians to prescribe mifepristone as part of the standard medical treatment in case of EPF was 21,7%.

The mean time period between medical treatment and first follow-up visit was 1,3 weeks, with a median of 1 week (table 3). To determine complete evacuation of the products of conception from the uterus, most centers used the combination of clinical signs and ultrasonography 16/25 (64%). When ultrasonography was used, whether or not combined with clinical signs, complete evacuation was most often based on evaluation of the sonographic impression by the physician without any measurements (11/25, 44%). When measuring the total endometrial thickness, the used cut-off point for maximum anteri-

Table 2 Use of mifepristone

	Type of clinic		
	Academic	**Teaching**	**Non-teaching**
Prescription of mifepriston n/N (%)			
Always	0	2/10 (0)	2/7 (28,6)
Usually	1/8 (12,5)	0	0
Only when indicated	3/8 (37,5)	4/10 (40)	2/7 (28,6)
Never	4/8 (50)	3/10 (30)	2/7 (28,6)
Unknown	0	1/10 (10)	1/7 (14,3)
Dosage mifepristone n/N (%)			
200mg	1/1 (100)	1/2 (50)	2/2 (100)
600mg	0	1/2 (50)	0
Time interval mifepristone – misoprostol			
Mean (hours)	36	32	30
Range	36	8 – 48	24 – 36
Estimated success rate n/N (%)			
0 – 25 %	0	0	0
25 – 50 %	0	0	0
50 – 75 %	0	1 (50)	1 (50)
75 – 100 %	1 (100)	1 (50)	1 (50)
Side effects compared to misoprostol alone n/N (%)			
More	1 (100)	0	0
Similar	0	1 (100)	1 (50)
Less	0	0	1 (50)
Required increase rate to prescribe mifepristone			
Mean	21,9	18,9	24,2
Range	5 – 35%	10 – 35%	15 – 30%

or-posterior diameter varied from four up to fifteen millimeters, with a median of ten millimeters. If retained products of conception were suspected after medical treatment, 24% of the centers proposed expectant management, 24% administration of misoprostol, and 24% an invasive treatment option (hysteroscopy or curettage). In case of expectant management, a second follow-up visit was arranged after the first spontaneous menstruation in 15/25 clinics (60%). Other time points used by the remaining centers were divergent between two and six weeks or only in case of symptoms. All of the variables mentioned above, regarding follow-up and if necessary further treatment, showed no

Table 3 Evaluation of treatment effect

	Type of clinic		
	Academic	**Teaching**	**Non-teaching**
Time period			
Mean (weeks)	1,8	1,1	1,2
Range	1 – 6	1 – 2	1 – 2
Diagnostic tool n/N (%)			
Ultrasonography, no measurements	1/8 (12,5)	2/10 (20)	0
Measurement of ET by ultrasonography	0	1/10 (10)	2/7 (28,6)
Clinical signs	1/8 (12,5)	0	
Ultrasonography and clinical signs	6/8 (75)	6/10 (60)	4/7 (57,1)
Unknown	0	1/10 (10)	1/7 (14,3)
Cut-off point ET			
Mean (millimeters)	8,8	11,25	8,2
Range	4 – 12	8 – 15	4 – 15
Treatment in case of retained products of conception n/N (%)			
Expectant management	4/8 (50)	1/10 (10)	1/7 (14,3)
Misoprostol	1/8 (12,5)	2/10 (20)	3/7 (42,9)
D&C	0	2/10 (20)	1/7 (14,3)
Hysteroscopy	1/8 (12,5)	1/10 (10)	1/7 (14,3)
Patient and/or doctor preference	2/8 (25)	3/10 (30)	0
Unknown	0	1/10 (10)	1/7 (14,3)
Planned follow-up visit n/N (%)			
After first menstruation	5/8 (62,5)	7/10 (70)	3/7 (42,9)
Other	2/8 (25)	3/10 (30)	3/7 (42,9)
Unknown	1/8 (12,5)	1/10 (10)	1/7 (14,3)

ET: endometrial thickness

significant differences between academic, teaching and non-teaching centers, neither when comparing centers with or without a local protocol.

Comment

Main findings

In our sample of gynecologic centers in the Netherlands (32%), a local protocol was present in 88% with a significant difference between academic and teaching (100%) versus non-teaching centers (57,1%). The first choice of treatment was medical in 54,5%. Only 20% of the respondents always or usually prescribe M&M in case of EPF, estimating the complete evacuation rate between 50% and 100% with similar side effects compared to treatment with misoprostol alone. The most given reason for not prescribing mifepristone for EPF, is lack of sufficient scientific evidence of effectiveness. An average increase in success rate of 21,7% is required to prescribe mifepristone in the future for EPF. Treatment effect is usually assessed by ultrasonography and clinical signs (64%). The cut-off point for total endometrial thickness used to diagnose complete evacuation varies from 4 until 15 millimeters. If complete evacuation is not achieved by the initial medical treatment, expectant management including a second follow-up visit after the first following menstruation was proposed just as often as surgical intervention.

Strengths and Limitations

All questionnaires sent were returned by a representative sample of all gynecologic centers in the Netherlands. The fact that we used a self-constructed survey, may have led to common method bias. However, based upon the questions asked, we believe this has not influenced the results.

Interpretation

The large practice variation in the Netherlands reported in our survey is comparable to earlier results reported by Verschoor et al in 2014.[19] The percentages described in our study of academic, teaching and non-teaching hospitals reporting medical methods as first treatment option in case of EPF are comparable with their results. Up until now, there is national guideline of gynecologists describing the treatment options in case of EPF. However, recommendations are made in a Dutch guideline for general practitioners and midwives, which advises expectant management for one or two weeks after sonographic diagnosis of EPF. At follow-up, ultrasonography will determine (in) complete evacuation and whether referral to a gynecologists is necessary.[4] Despite these recommendations, only 24% of our respondents (i.e. gynecologists) always follow this advice before starting any treatment.[4] Because this guideline is specifically made for general practitioners and midwives, it is possible that part of the gynecologists is not aware of the existence of this guideline, causing physicians to start treatment immediately after diagnosis. However, this guideline advises an expectant management. Further, also patient preferences could also have major influence on the time of referral to a gynecologic center. If women do not want to wait any longer for spontaneous miscarriage to occur, i.e. because of their wish to

get pregnant again as soon as possible or inconvenience of impending expulsion or blood loss, this may persuade a physician to start treatment immediately. Also financial components in the Dutch reimbursement system may potentially drive physicians to start treatment immediately since interventions still yield higher remunerations than an expectant policy.[22]

Although previous studies do not provide sufficient evidence about time period and diagnostic tool to define success, and since there is no Dutch guideline, it's interesting to notice that assessment of treatment success appears similar in almost every center in the Netherlands.[21] Most respondents planned a visit at the outpatient department one week after medical treatment. Ultrasonography combined with clinical signs was mostly used to determine treatment effect. An average cut-off point of 10mm for endometrial thickness to suspect retained products of conception is reported, which in our opinion might lead to the unjustified diagnosis of incomplete evacuation. A study by Rulin et al conclude already in 1993 that in case of a maximum anterior-posterior diameter of 15 mm or less, retained products are less likely to be confirmed histologically.[23] Also a recent study by Lavecchia et al demonstrated that in women with a cavity anterior-posterior distance of less than 15 mm, 87,1% did not need D&C afterwards.[24] Despite the fact that the results by the MisoREST-study have just recently been published, recommending that expectant management should be considered first line treatment in women with suspected incomplete evacuation after initial medical treatment, already 26% of our respondents propose an expectant management until the first following menstruation. [20] Seventeen of our twenty-five respondents participated in the MisoREST-study of which one respondent answered that their follow-up protocol was recently changed based on these results.

The amount of hospitals prescribing mifepristone "always" or "usually" in case of EPF is lower in our survey compared to the numbers mentioned by Verschoor: 20% versus 38%. [19] This difference might be due to our selection of hospitals.[13] It is interesting that all non-teaching hospitals describe M&M in their protocol (when existing), compared to only one third of the academic and teaching hospital protocols. Possibly, academic and teaching hospitals work more often according to evidence based principles of medicine approach. Although several studies do report higher complete evacuation rates after M&M treatment compared to misoprostol alone, there is insufficient evidence to draw firm conclusions.[13]

All respondents were willing to prescribe M&M treatment in the future with sufficient evidence that the success rate increases with an average of 21,7%. It should be mentioned that the current costs of mifepristone might be taken into account, so it may be that, since its costs are still decreasing, also lower success rates will be accepted in the near future.

Dutch women prefer medical treatment as long as the success rate exceeds 65%, and approximately 85% of women would prefer medical treatment if its complete evacuation rate would reach 80%.[25] This all together, assuming that a randomized controlled trial may confirm the superiority of M&M compared to misoprostol alone in case of EPF, implementation of M&M treatment will proceed fast.

Practical and research recommendations

Up until now, there is no Dutch guideline for treatment of EPF despite earlier recommendations made by Verschoor et al.[19] Foreign guidelines concerning treatment in case of EPF exist, for example by the Royal College of Obstetricians and Gynecologist (RCOG) or the American College of Obstetricians and Gynecologists (ACOG). In contrast to other countries worldwide, it is standard procedure to wait for at least one week before starting any treatment because of a high change of spontaneous expulsion.[4, 26, 27] We therefore strongly advise to develop a national guideline describing the most optimal treatment regimen for the Dutch population. Preferably, this guideline should be developed by the Dutch association for Obstetrics and Gynecology (NVOG).

As mentioned before, a substantial part of the Dutch hospitals already prescribes mifepristone in case of EPF. A sufficiently powered, multi-center, randomized, double blinded, and placebo-controlled trial will start second half of 2017 (http://www.clinicaltrials.gov: NCT03212352). This trial is necessary to confirm the hypothesis that M&M is superior to the use of misoprostol alone in terms of effectiveness (reduction of surgical interventions), risks of complications, patient satisfaction and costs.

Conclusion

Although in most centers in the Netherlands a local protocol is present, there is still a large practice variation in the treatment of EPF. The use of M&M in EPF is not common practice, due to the lack of sufficient evidence. A proven increase in effectiveness of approximately 20% after addition of mifepristone to the current treatment with misoprostol alone may cause all doctors to prescribe M&M in the future.

Declarations

Disclosure of Interests statement

No conflicting interests to declare.

Contribution to authorship

JB and SC conceived and developed the idea for the article. JB, CH, SC and MS were mainly responsible for the acquisition and analysis of the data. All authors took part in drafting the

article or revising it critically for content, all authors gave final approval of the version to be published.

Details of ethics approval

Ethics approval was not required for this study.

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References

1. Open data van de Nederlandse Zorgautoriteit (2014-2016) [25-05-2017]. Available from: http://www.opendisdata.nl/.
2. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002;324:873-5.
3. Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Hum Reprod. 2004;19:1894-9.
4. Van Asselt KM BA, Engelsman N, Hammers-Cupido RJ, Landskröner I, Opstelten W, De Vries CJH. NHG-Standaard Miskraam (Derde herziening). 2017. Available from: https://www.nhg.org/standaarden/volledig/nhg-standaard-miskraam.
5. Graziosi GC, van der Steeg JW, Reuwer PH, Drogtrop AP, Bruinse HW, Mol BW. Economic evaluation of misoprostol in the treatment of early pregnancy failure compared to curettage after an expectant management. Hum Reprod. 2005;20:1067-71.
6. You JH, Chung TK. Expectant, medical or surgical treatment for spontaneous abortion in first trimester of pregnancy: a cost analysis. Hum Reprod. 2005;20:2873-8.
7. Soulat C, Gelly M. [Immediate complications of surgical abortion]. J Gynecol Obstet Biol Reprod (Paris). 2006;35:157-62.
8. Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. Fertil Steril. 2006;86:367-72.
9. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2013.
10. McCarthy FP, Khashan AS, North RA, Rahma MB, Walker JJ, Baker PN, et al. Pregnancy loss managed by cervical dilatation and curettage increases the risk of spontaneous preterm birth. Hum Reprod. 2013;28:3197-206.
11. Nielsen S, Hahlin M, Platz-Christensen J. Randomised trial comparing expectant with medical management for first trimester miscarriages. Br J Obstet Gynaecol. 1999;106:804-7.
12. Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, et al. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. Fertil Steril. 2006;86:956-60.
13. van den Berg J, Gordon BB, Snijders MP, Vandenbussche FP, Coppus SF. The added value of mifepristone to non-surgical treatment regimens for uterine evacuation in case of early pregnancy failure: a systematic review of the literature. Eur J Obstet Gynecol Reprod Biol. 2015;195:18-26.
14. van den Berg J, van den Bent JM, Snijders MP, de Heus R, Coppus SF, Vandenbussche FP. Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study. Eur J Obstet Gynecol Reprod Biol. 2014;183:16-9.
15. Exelgyn. Mifegyne 200mg tablets: Summary of Product Characeteristics (SmPC) [24-04-2017]. Available from: https://www.exelgyn.com.
16. Mifepriston - Mifegyne http://www.fk.cvz.nl [06-10-2011]. http://www.fk.cvz.nl]. Available from: http://www.farmacotherapeutischkompas.nl.
17. Say L, Kulier R, Gulmezoglu M, Campana A. Medical versus surgical methods for first trimester termination of pregnancy. Cochrane Database Syst Rev. 2005:CD003037.
18. Kulier R, Gulmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2008:CD002855.
19. Verschoor MA, Lemmers M, Wekker MZ, Huirne JA, Goddijn M, Mol BW, et al. Practice variation in the management of first trimester miscarriage in the Netherlands: a nationwide survey. Obstet Gynecol Int. 2014;2014:387860.
20. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Bossuyt PM, Huirne JA, et al. MisoREST: Surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: A cohort study. Eur J Obstet Gynecol Reprod Biol. 2017;211:83-9.
21. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Opmeer BC, Bossuyt PM, et al. MisoREST: surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: a randomized controlled trial. Hum Reprod. 2016;31:2421-7.

22. Gezondheidsraad. De kunst van het nee zeggen. Factoren die bijdragen aan onnodige zorg. 2014. [cited 03-08-2017].
23. Rulin MC, Bornstein SG, Campbell JD. The reliability of ultrasonography in the management of spontaneous abortion, clinically thought to be complete: a prospective study. Am J Obstet Gynecol. 1993;168:12-5.
24. Lavecchia M, Klam S, Abenhaim HA. Effect of Uterine Cavity Sonographic Measurements on Medical Management Failure in Women With Early Pregnancy Loss. J Ultrasound Med. 2016;35:1705-10.
25. Graziosi GC, Bruinse HW, Reuwer PJ, Mol BW. Women's preferences for misoprostol in case of early pregnancy failure. Eur J Obstet Gynecol Reprod Biol. 2006;124:184-6.
26. Hinshaw K, Fayyad A, Munjuluri P. The management of early pregnancy loss. Royal College of Obstetricians and Gynaecologists, Green-top Guideline No. 25. http://www.rcog.org.uk/. 2006.
27. Committee on Practice B-G. The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. Obstet Gynecol. 2015;125:1258-67.

5

Mifepristone followed by misoprostol for uterine evacuation in early pregnancy failure: a randomized, double blinded, placebo controlled pilot study

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Submitted.

Abstract

Study question

Is pre-treatment with mifepristone followed by misoprostol (M&M) superior to the use of misoprostol alone in terms of complete evacuation of the products of conception in early pregnancy failure?

Summary answer

The sequential combination of M&M in case of early pregnancy failure appears more effective than treatment with misoprostol alone regarding complete evacuation measured one week after treatment. This pilot study protocol reassured the methodology to confirm these findings by a large, prospective, randomized, and double-blinded trial.

What is known already

Several studies have been investigating the M&M treatment option, revealing success rates of 66 – 93% without serious adverse events. Unfortunately, these data are all derived from studies with a number of weaknesses including study design, inclusion criteria, and medical treatment starting directly after diagnosis without at least one week of expectant management.

Study design, size, duration

Two-centered, prospective, two-armed, randomized, double blinded, placebo-controlled trial at the department of Obstetrics and Gynecology of the Radboud University Medical Centre and Canisius-Wilhelmina Hospital in Nijmegen, the Netherlands. Forty women were randomized after giving informed consent between October 2016 and May 2017. Participants were randomized in a 1:1 ratio using computerized randomization tables. The randomization was conducted using block randomization and was stratified by hospital.

Participants/materials, setting, methods

Forty women with early pregnancy failure (6-14 weeks) wishing medical treatment after at least one week of expectant management were randomized. At day one, women were pre-treated with mifepristone 600mg or placebo tablets (both orally). At day three all women took standard medical treatment, which consisted of two doses of misoprostol 400µg (four hours apart, orally). If no tissue was lost at day four, another two doses of misoprostol 400µg (four hours apart, orally) were taken. Ultrasound evaluation of treatment result was performed six to nine days after medical treatment started. Three digital questionnaires about quality of life and patient satisfaction were sent at baseline, four days and four weeks after treatment started.

Main results and the role of chance

This pilot study confirmed feasibility of the study protocol. Complete evacuation was achieved in 13/19 (68,4%) of women in the M&M group versus 8/20 (40%) of women in the placebo group, which is not significantly different (p 0.057). The need for surgical intervention, was significantly lower in the M&M group as compared to the placebo group: 10,5% versus 50% respectively (RR 1.789, 95% CI 1.124-2.848). No serious adverse events were reported in either group. Quality of life was similar in both groups. The majority of women, 84,6%, in the M&M group versus 62,6% of women in the placebo group, would choose medical treatment again. In the M&M group 92,3% and in the placebo group 75% of women would recommend medical treatment to a friend in case of EPF.

Limitations, reasons for caution

A limitation of the pilot study is the small number of patients included.

Wider implications of the findings

Expectant management of at least one week is common practice in the Netherlands. In other countries treatment is started immediately after diagnosis. Therefore, our study results may not be globally generalizable for clinical practice. However, M&M treatment may also be superior to the use of misoprostol alone if started immediately after diagnosis.

Study funding/competing interest(s)

This research was partly funded by Exelgyn (Groupe Nordic Pharma). The funders provided mifepristone and placebo tablets, and the costs of the pharmacy and CMO Arnhem-Nijmegen. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The authors have no conflicts of interest.

Introduction

Early pregnancy failure (EPF) is a common complication of pregnancy, as approximately 15% of all clinical pregnancies end in a miscarriage (6-14 weeks). The real incidence may be even higher, as not every case is being recognized clinically.[1-3] The incidence of EPF increases with age and because of rising childbearing age in the Western world, EPF is of increasing importance.

In the Netherlands, approximately 10,000 women per year undergo surgical or medical treatment after a minimum of one week of expectant management (prescribed in national guidelines) in order to remove the products of conception from the uterus.[4, 5] Surgical treatment (dilatation and curettage, D&C) is associated with risks of complications (0,01-1,2%; pelvic infection, cervical injury, uterine perforation, excessive bleeding, anesthesia, cervical insufficiency in following pregnancies) and costs.[6-8] Misoprostol is a synthetic prostaglandin E1 analogue and is widely used in the management of EPF.[9-11] In the Netherlands, treatment is started after a minimum of one week of expectant management, because of an expected spontaneous complete evacuation rate of around 50% during the first weeks after diagnosis.[5, 12, 13] Unfortunately, after medical treatment with misoprostol, circa 50% of the women may still need a form of second treatment due to retained products of conception.[13, 14]

A new medical treatment option combining mifepristone, an anti-progesterone and anti-glucocorticoid drug, followed by misoprostol (M&M treatment) seems more effective.[14, 15] Mifepristone increases the production of endogenous prostaglandin by the endometrium, as well as the sensitivity of the gravid uterus to exogenous prostaglandin, thus causing contractility of the myometrium, cervical softening and dilatation.[16, 17] At present, mifepristone is licensed for four indications: medical termination of vital pregnancy (abortion) up tot 63 days of gestation, termination of vital pregnancy beyond first trimester, preparation for surgical abortion in the first trimester, and labor induction in fetal death in utero in the second and third trimester.[18] It appears reasonable to consider that, also for EPF, the sequential combination of mifepristone and misoprostol may be superior to misoprostol alone.[14-16]

Retrospective and anecdotal studies have been investigating the M&M treatment option, revealing success rates of 66 – 93% without serious adverse events.[3, 8, 19-25] All studies concluded that the combination of mifepristone and misoprostol might be an effective and safe alternative to surgical treatment. Unfortunately, these data are all derived from studies with a number of weaknesses including study design, inclusion criteria, and medical treatment starting directly after diagnosis without at least one week of expectant management.

A randomized, double blinded, placebo-controlled trial with a sufficient number of patients is required to test the hypothesis that the sequential combination of mifepristone with misoprostol is superior to misoprostol alone in case of EPF.[14, 15] The aim of this pilot study is to test feasibility and recruitment in order to improve quality of the final protocol of a larger study.

Methods

A two-centered, prospective, two-armed, randomized, double blinded and placebo-controlled pilot trial was started, situated in a large academic (Radboud University Medical Centre) and a large teaching hospital (Canisius-Wilhelmina Hospital) in Nijmegen, the Netherlands, between October 2016 and May 2017. For this study, ethics approval (CMO Arnhem-Nijmegen, file number 2015-2264, NL 57892.091.16) and local approval by the Board of Directors of the two hospitals was obtained. All women gave written informed consent before study entry. Forty participants were followed in an outpatient clinic; hospital admission followed only if medically necessary. The trial was registered in the Dutch trial register, part of the Dutch Cochrane Centre (NTR6109), and in the European Clinical Trials Database (EudraCT, 2013-001554-10).

Patient selection and randomization

Woman with a diagnosis of EPF between 6 and 14 weeks of gestation, who had been managed expectantly for at least one week, were eligible for the trial. EPF was defined by transvaginal ultrasonography as an intra-uterine pregnancy and a crown-rump length ≥ 6mm and no cardiac activity, or a gestational sac without embryonic pole. Women could be included one week after diagnosis or immediately in case of a discrepancy of at least one week between crown-rump length and calendar gestational age. Exclusion criteria were age < 18 years, hemodynamic instability, sign of infection, incomplete miscarriage, high risk of thrombosis, contra-indications for mifepristone or misoprostol, interaction between study-medication and other medication or the inability to give informed consent. A computerized randomization list was prepared by an independent medical doctor not working at or connected to the trial. Participants were randomized in a 1:1 ratio to mifepristone or placebo using computerized randomization tables. The randomization was conducted using block randomization and was stratified by hospital to prevent any imbalance between groups in aspects of maternal care that may differ between centers.

Treatment protocols

After informed consent and randomization, each patient received three (blinded) tablets containing 200mg mifepristone each or placebo (day 1). The mifepristone tablets and placebo were identical in appearance so neither the patient nor the physician knew which

product was taken. Both groups took the standard treatment with misoprostol at day three: two doses of misoprostol 400µg orally (four hours apart). If no tissue was lost by day four, again two doses of misoprostol 400µg orally (four hours apart) were taken. A transvaginal ultrasonography was performed six to nine days after treatment. Women were asked to document the amount of misoprostol tablets taken each day and possible side effects using a registration form (diary). Standard, validated questionnaires (Short Form 36, EuroQol-VAS and CSQ) were sent by e-mail at baseline (day 1), four days (day 5) and four weeks (day 29) after treatment started. The blinding of patients and physicians for treatment arm was maintained until the follow-up (questionnaire four weeks after treatment) of the last included patient was completed.

Outcome measures

Primary and secondary outcome measures were extracted from the patient medical record, diary, digital questionnaires and/or case report form. The primary outcome parameter, complete (success) or incomplete (failure) evacuation, was determined by transvaginal ultrasonography one week (six to nine days) after medical treatment. An endometrial thickness < 15mm (maximum anterior-posterior diameter) or no evidence of retained products of conception using only the allocated therapy by randomization was considered as complete evacuation.[9, 13, 26-28]

Secondary outcome parameters included complications, side effects and patient satisfaction. Each patient received a registration form (diary) to document the amount of misoprostol tablets taken and possible side effects. The treating gynecologist documented complications and side effects using the case report form (CRF). Quality of life was measured at baseline, four days and four weeks after treatment started using standard, validated questionnaires: EuroQol-VAS and Short Form 36. Patient satisfaction with treatment was measured four weeks after treatment using the Client Satisfaction Questionnaire (CSQ-8).

Statistical analyses

Data were analyzed according to intention to treat method. The main outcome variable was complete evacuation after medical treatment and was assessed by calculating success rates, relative risks and 95% confident intervals in both groups. To evaluate the potential of each of the strategies, we also performed a per protocol analysis, taking into account only those cases that were treated according to protocol.

SPSS version 24 was used for data analysis. Differences between groups were analyzed using the Pearson's chi-square test or the Fisher's exact test for categorical variables. Mann-Whitney U test was used for non-normally distributed metric variables. Logistic regression, univariate, and multivariate analysis were performed to identify factors that were associated with treatment success. P-values smaller than 0.05, were considered significant.

Results

Forty women were included and randomized: twenty women were allocated to mifepristone and twenty to placebo (figure 1). Since both arms are followed by misoprostol, treatment arms will further be called as "M&M" and "placebo" group. Baseline characteristics of the two groups were comparable (e.g. not significant, table 1). One woman in the M&M group was excluded post-randomization because she did not meet the inclusion criteria, which was detected after randomization. She was included after only one day of expectant management instead of at least one week (figure 2). So, 39 women were included in the intention to treat analysis.

Two women, one in each arm, who gave informed consent, experienced spontaneous miscarriage before medical treatment started. In the M&M group, one woman, who was included after informed consent, changed her mind afterwards and did not take the study medication. Another woman in the M&M group was not treated conform treatment protocol; she inserted misoprostol vaginally (two doses of 800µg) 22 hours after taking the study medication instead of swallowing misoprostol orally (400µg) 36-48 hours later. So, taken into account two spontaneous miscarriages and two protocol deviations, 35 women were treated conform study protocol and included in per protocol analysis (figure 2).

One woman in the M&M group did not show up at the appointment six to nine days after treatment; she visited the hospital five weeks later and underwent transvaginal ultrasonography showing an endometrial thickness < 15mm without additional therapy. In the placebo group, one woman had an ultrasound at day 4 because she didn't want to wait any longer. A gestational sac was still intra-uterine; D&C was performed at day 11. The mean time between the start of medical treatment and performing ultrasonography to determine treatment success was 9.37 days (range 3 – 34 days).

In the M&M group, 13/19 (68,4%) had a complete evacuation one week after medical treatment. In the placebo group, 8/20 (40,0%) had a complete evacuation after one week, which is not significantly different (p 0.057, table 2). In addition to intention-to-treat analysis, per protocol analysis revealed success rates of 10/16 (62,5%) in the M&M group versus 7/19 (36,8%) in the placebo group (p 0.139). No differences in primary outcome were observed after adjusting for the difference between ultrasound gestational age, duration of expectant management, parity, prior miscarriages or prior successful misoprostol treatment.

At the time of determining the main study outcome and the need for additional treatment in case of an incomplete evacuation (one week after treatment), physician and patient were both still blinded. In total, 18 women underwent additional treatment and reached complete evacuation afterwards (table 3). In 1/19 (5,2%) of the M&M group versus 9/20

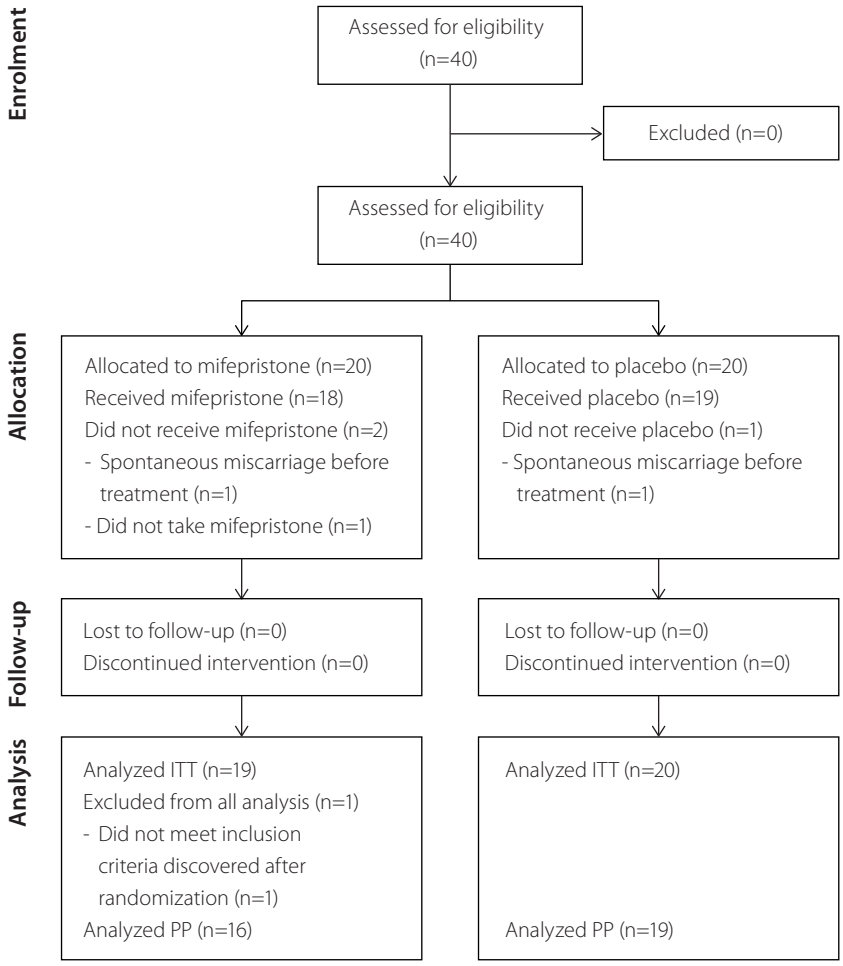

Figure 1 CONSORT flow diagram

(45%) of the placebo group a gestational sac was still intrauterine, concluding that medical treatment has had no effect at all. Five women (5/18, 27,8%) reached complete evacuation after expectant management until approximately six weeks after treatment. Two women were treated with misoprostol treatment again and received two more doses of misoprostol (800µg vaginally), of which one woman (placebo group) underwent emergency D&C because of heavy vaginal bleeding after the second misoprostol treatment. The need for D&C was significantly lower in the M&M group as compared to the placebo group: 2/19 (10,5%) versus 10/20 (50%) respectively (p 0.008, RR 1.789, 95% CI 1.124-2.848). D&C

Table 1 Baseline characteristics

Baseline characteristics	M&M N=19	Placebo N=20	Significance (P-value)
Age (years)			
Mean (SD)	30,53 (5,274)	32,00 (2,772)	0.288
Range	21 – 39	28 –37	
Unknown	0	0	
Diagnosis			
Embryo without cardiac activity	13 (85%)	17 (85%)	0.219
Anembryonic gestation	6 (15%)	3 (15%)	
Gestational age based on amenorrhea (days)			
Mean (SD)	73,76 (11,503)	73,50 (10,541)	0.760
Range	56 – 96	56 – 100	
Unknown	2	0	
Gestational age based on ultrasound (days)			
Mean (SD)	52,05 (10,799)	49,00 (7,688)	0.438
Range	36 – 78	38 – 64	
Unknown	0	1	
Duration expectant management (days)			
Mean (SD)	20,94 (12,235)	24,21 (9,953)	0.302
Range	7 – 53	12 – 50	
Exact period unknown	2	1	
Number of previous pregnancies			
0	8 (42,1%)	10 (50%)	0.857
1	5 (26,3%)	4 (20%)	
≥2	6 (31,6%)	6 (30%)	
Parity			
0	12 (63,2%)	11 (55%)	0.361
1	6 (31,6%)	5 (25%)	
2	1 (5,3%)	4 (20%)	
Prior miscarriage			
Yes	8 (40%)	6 (30%)	0.507
No	12 (60%)	14 (70%)	
Prior misoprostol treatment			
Yes, successful	2 (N=8, 25%)	1 (N=6, 20%)	1.000
Yes, unsuccessful	0	0	
No	6 (N=8, 75%)	5 (N=6, 80%)	

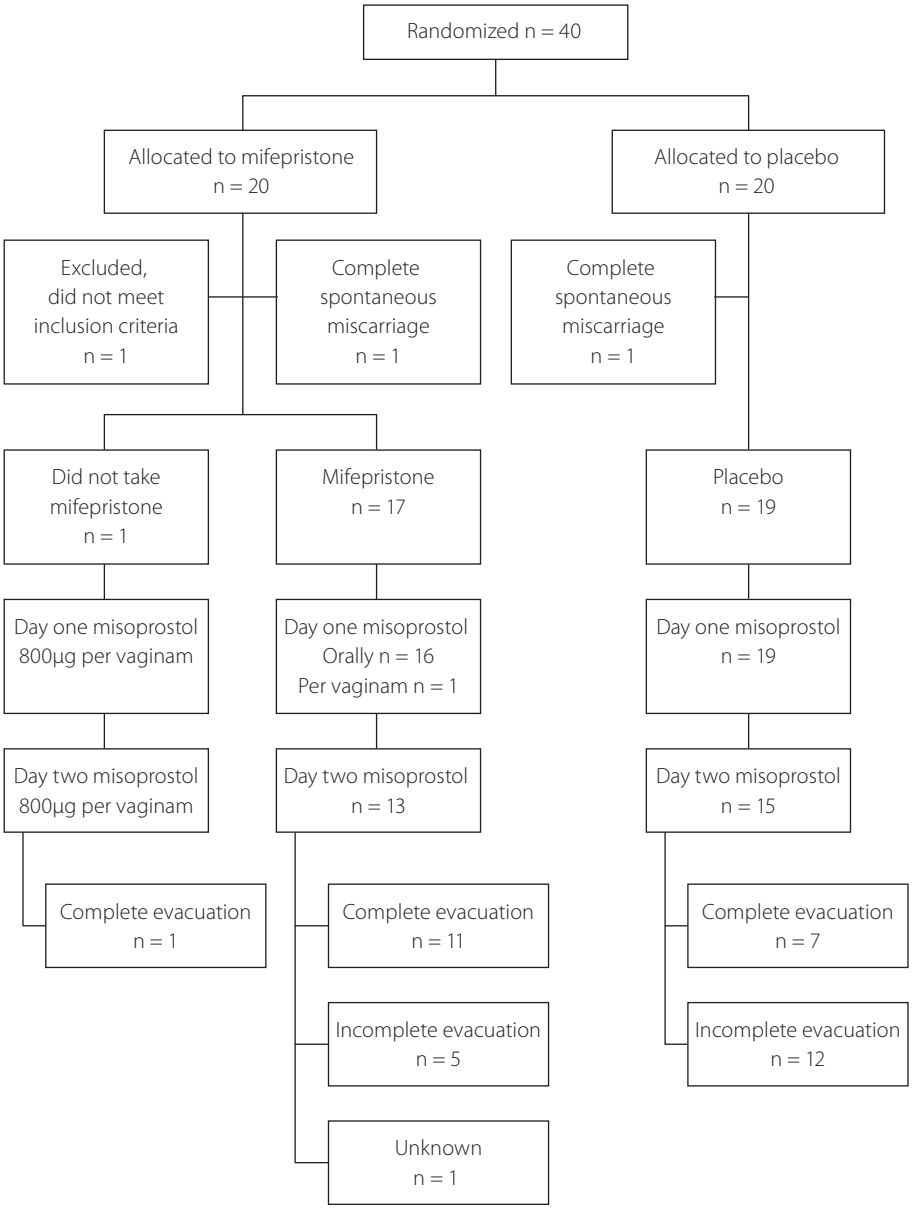

Figure 2 Flow of participants until one week after treatment

Table 2 Complete evacuation rates

	M&M group, n/N (%)	Placebo group, n/N (%)	*P* value
Complete evacuation rate, total	13/19 (68,4)	8/20 (40)	0.057
Anembryonic gestation	4/6 (66,7)	2/3 (66,7)	1.000
Embryo without cardiac activity	9/13 (66,7)	6/17 (35,3)	0.070

Table 3 Additional treatment resulting in complete evacuation

	M&M group, n/N (%)	Placebo group, n/N (%)	*P* value
Expectant management	4/19 (21,2)	1/20 (5)	0.134
Residua	4/4 (100)	-	-
Persistent gestational sac	-	1/1 (100)	-
Medical treatment	0/19 (0)	1/20 (5)	-
Persistent gestational sac	-	1/1 (100)	-
D&C	2/19 (10,5)	10/20 (50)	0.008
Residua	1/2 (50)	0/100 (0)	0.487
Persistent gestational sac	1/2 (50)	7/10 (70)	0.044
Hemorrhage	-	3/10 (30)	0.23

was mainly performed (8/12, 66,7%) because of a persistent intrauterine gestational sac, this was significant different between both groups: only one woman in the M&M group versus seven women in the misoprostol group (p 0.044). Three women in the placebo group needed D&C because of heavy vaginal bleeding, of which one woman underwent D&C at day three because of heavy vaginal bleeding (750cc) and sonographic retained products of conception. Another woman was scheduled for D&C a few days after determining the main study outcome, however, in the meantime she underwent emergency D&C because of heavy vaginal bleeding. Also, per protocol analysis revealed a significant difference between the need for D&C in the M&M and placebo group: 2/16 (12,5%) versus 10/19 (52,5%, p 0.013).

During treatment, women in the M&M group reported significantly more blood loss than women in the placebo group (p 0.007, figure 3). In the M&M group, 15/19 (78,9%) described their blood loss as "more than a menstruation" and 1/19 (5,3%) as "less than a menstruation".

In the placebo group, 8/20 (40%) classified their blood loss as "more than a menstruation" and 9/20 (45%) as "less than a menstruation". However, one week later, during follow-up, this difference was no longer seen (p 0.081). The bleeding had stopped or was described as less than a menstruation in the M&M group in 16/18 (84,2%) and in the placebo group in 14/20 (70%). No blood transfusions during treatment and follow-up were needed.

Side effects in both groups were mainly experienced at day three and four during misoprostol treatment (figure 3). Nausea and gastrointestinal side effects were most reported in both groups. Concerning the reported side effects, only dizziness was significantly higher in the placebo group (p 0.047). The use of analgesics was not significant different between both groups.

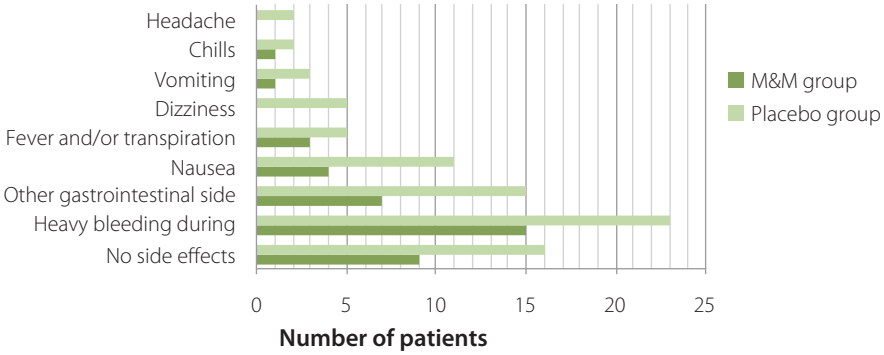

Figure 3 Side effects during medical treatment. *Defined by patients as more than a menstruation

Client satisfaction questionnaire

In total, 115 digital questionnaires were sent of which 75,4% in the M&M group, and 89,7% in the placebo group were completed. Women in both groups were equally satisfied with medical treatment (figure 4). In case of EPF, 11/13 (84,6%) women in the M&M group versus 10/16 (62,6%) women in the placebo group would choose the same treatment again. In the M&M group 12/13 (92,3%) and in the placebo group 12/16 (75%) would recommend medical treatment to a friend in case of EPF.

Short Form-36 and EuroQol visual analogue scale

Health related quality of life, measured using short-form 36 (SF-36) and EuroQol-VAS as baseline, four days and four weeks after treatment started, was not significant different between the M&M and placebo group. In both groups, six dimensions of SF-36 were significantly different over time, and were most impaired four days after treatment (figure 5).

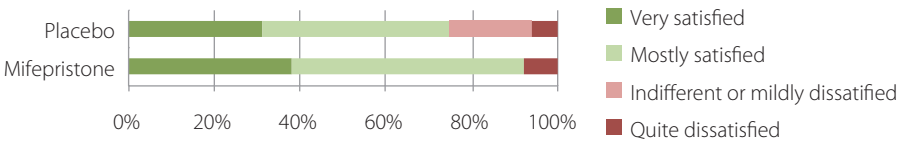

Figure 4 Satisfaction with treatment

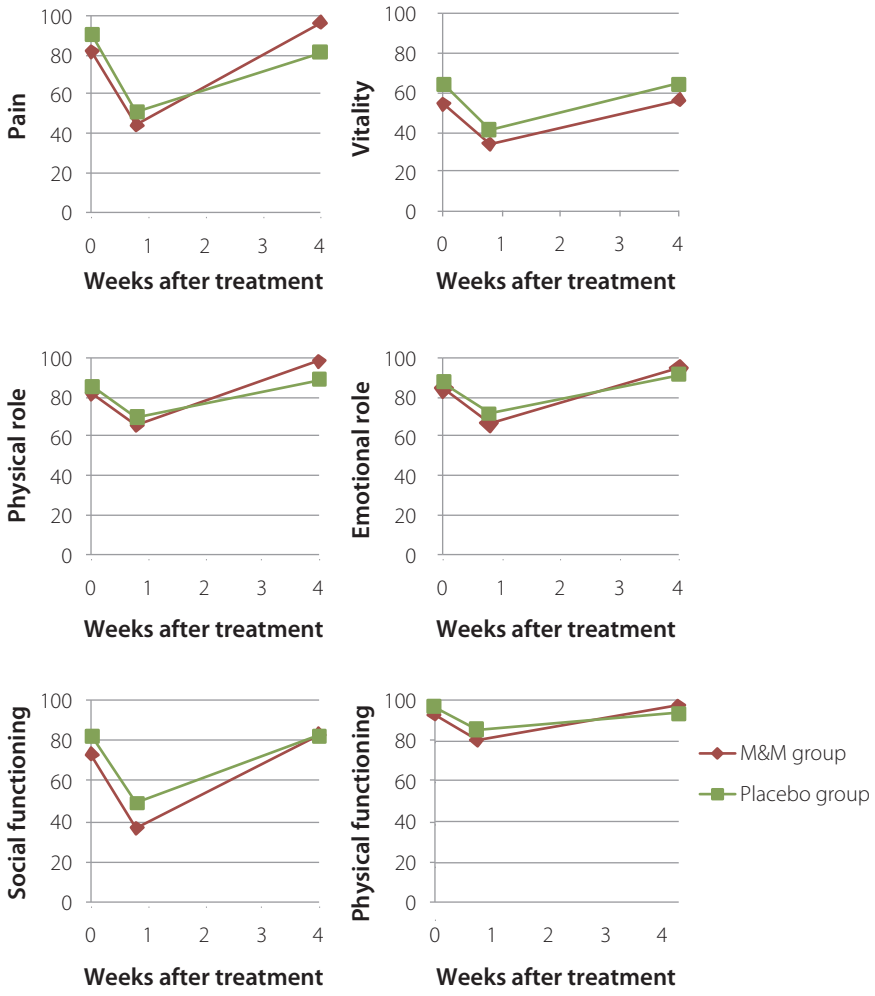

Figure 5 Dimensions of Short Form 36

Mental health, general health and general health change were not significant different over time. In the M&M group, no significant differences in health dimensions were seen between successful and unsuccessful treatment. Women in the placebo group with an unsuccessful treatment had significantly more pain, more impaired physical functioning and lower scores at the EuroQol-VAS compared to women with a successful treatment.

Discussion / comment

Main findings

This randomized, double blinded, placebo controlled pilot study was designed to prepare for a sufficiently powered definitive trial, comparing pre-treatment with mifepristone versus placebo followed by misoprostol in women with EPF between 6 and 14 weeks of gestation after a minimum of one week of expectant management. Accrual of study patients was as expected with completion of forty patients within seven months in one academic and one teaching hospital in the Netherlands. This pilot clinical trial showed an inclusion rate as expected, and almost no data loss: only one patient didn't show up at the follow-up appointment. Complete evacuation measured one week after treatment was not significantly different: 68,4% in the M&M group versus 40% in the placebo group. The need for D&C after medical treatment was significantly different, 10,5% in the M&M group versus 50% in the placebo group. A significant difference was reported between the incidence of persistent gestational sac: 1 woman in the M&M group versus 9 women in the placebo group. No serious adverse events were reported. More than 80% of the digital questionnaires were completed. Concerning patient preferences, 84,6% women in the M&M group versus 62,6% women in the placebo group, would choose medical treatment again and 92,3% in the M&M group versus 75% in the placebo group would recommend medical treatment to a friend in case of EPF.

Strengths and Limitations

This pilot study was randomized, double blinded and placebo controlled. Our baseline data showed no significant differences between the two treatment groups. A uniform treatment protocol and CRF were available describing diagnosis of early pregnancy failure, therapy counseling and patient information. There was a clear and objective primary and secondary outcome definition. A limitation of the pilot study is of course the small number of patients included.

Interpretation

Regarding medical treatment regimens, different doses of mifepristone and misoprostol and routes of administration of misoprostol are described in literature. Until now, the World Health Organization (WHO) advises 200mg mifepristone in case of termination of a

vital pregnancy in the first trimester.[29] However, based on phase 2 trials for medical termination of a vital pregnancy up to 63 days gestation, a dose of mifepristone 600mg is advised by the manufacturer Exelgyn (Groupe Nordic Pharma, France).[16] Phase 2 trials showed that 600mg mifepristone was superior to the 200mg dose in terms of complete abortion in case of medical abortion of a vital pregnancy (89% versus 63%).[30, 31] A Cochrane review included only one trial comparing low and high doses of mifepristone in case of medical abortion, reporting no significant difference in failure and side effects.[32, 33] The recommendation of 200mg mifepristone by the WHO is probably due to formerly high costs (approximately 20 euro for one tablet containing 200mg) in the context of low-resource countries. Since the patent on mifepristone has expired, the costs of mifepristone are decreasing drastically (current price in the Netherlands € 11,66). To achieve the desired optimal effect, a dose of 600mg mifepristone was used in our pilot trial. The effect of mifepristone develops over a time period of 24-48 hours; therefore prostaglandins were administered 36-48 hours later.[16, 32]

Misoprostol is part of the standard treatment and different treatment regimens (dose and route of administration) are described in literature. In case of EPF, the International Federation of Obstetrics and Gynecology (FIGO) advises misoprostol 800µg per vaginam every 3 hours (maximum of 2 doses) or 600µg sublingual every 3 hours (maximum of 2 doses).[29] However, recent reviews conclude that further research is necessary to determine the most optimal treatment regimen.[34-36] Vaginal application of misoprostol is widely accepted. However, oral misoprostol is advised by the manufacturer of mifepristone (Exelgyn) if combined with mifepristone, based on a significant lower infection rate in case of medical abortion after changing the regime of vaginal to oral administration.[37] When pharmacologically comparing oral and vaginal administration of misoprostol, oral misoprostol leads to a more rapid absorption and higher peak levels.[37] Gastrointestinal side effects are dose and interval dependent, higher doses and short intervals may lead to an increase in symptoms.[38, 39] Although one would suspect that oral misoprostol leads to more side effects due to higher peak concentrations, a similar incidence of vomiting, nausea, diarrhea and fever was found in a recent Cochrane review.[40] However, it should be mentioned that the quality of evidence is low. In contrast to this recent review regarding EPF, Cochrane reviews including incomplete miscarriages or termination of vital pregnancies in the first trimester, report significantly more nausea and diarrhea after oral misoprostol.[32, 41] Regarding effectiveness, a Cochrane review reported that misoprostol 800µg orally is equally effective compared to misoprostol 800µg vaginally.[3, 40] A split dosage of misoprostol (two or three doses of 400µg) has been reported to be similar in success rates as a protocol using 800µg at once.[32, 40] However, the mean time to expulsion was longer after oral intake of misoprostol compared to vaginal application.[41, 42] Clinical studies comparing oral and vaginal misoprostol have found increased satisfaction with the oral route because it is easy to use and avoids any unnecessary vaginal examinations.[44, 45]

Taken all together, we have chosen oral administration of misoprostol because it seems equally effective compared to vaginal application, is easy to use, and is preferred by patients. Since a split-dose regimen is equally effective, but would possibly lead to a lower incidence of side effects, we have chosen a split dose of misoprostol 400µg.

The main study endpoint was determined by ultrasonography one week after medical treatment was started. With regards to the follow-up of women receiving medical treatment: there are no clear recommendations about the time period and optimal diagnostic tool to define success. Assessment after one week was common practice in the Netherlands at the time of drafting the study protocol (J. van den Berg, Dutch survey 2017, unpublished data). And as reported in our results section, there was a significant difference in persistent intrauterine gestational sac one week after treatment between both groups. Therefore, performing ultrasonography shortly after medical treatment (one or two weeks) is important to determine treatment failure and to offer further treatment to patients on short-term.

Regarding the presence of intrauterine remnants, ultrasonography seems to be of limited value. Recent studies do not provide any clear evidence which endometrial thickness corresponds best to the presence of intrauterine pregnancy remnants.[46, 47] A study by Rulin concludes that in case of a maximum anterior-posterior diameter of 15 mm or less, retained products are less likely to be confirmed histologically.[26] Also a recent study by Lavecchia et al demonstrated that in women with a cavity anterior-posterior distance of less than 15 mm, 87,1% did not need D&C afterwards.[27] In contrast, a study by Creinin reported a wide range of endometrial thickness (1-31mm) two weeks after expulsion of the gestational sac and a decreasing endometrial thickness over time, suggesting that clinical signs and symptoms should guide treatment decisions after medical treatment.[48]

Evidence is growing that D&C may have major long-term consequences such as intra-uterine adhesions and increased spontaneous preterm birth rates in subsequent pregnancies. [13, 49, 50] The recent Dutch "MisoREST" study compared D&C and expectant management in case of an incomplete evacuation after misoprostol treatment defined as intra-uterine remnants at ultrasonography or an anterior-posterior diameter exceeding 10 mm.[46] These authors conclude that expectant management should be considered as first line treatment in women with incomplete evacuation after misoprostol treatment for EPF.[51] As a result of the aforementioned, we have made adjustments in the definitive protocol concerning the primary endpoint.

Practical and research recommendations

Based on current data, we have made recommendations for improvements of the definitive, sufficiently powered study protocol for a multicenter, randomized, double blind and placebo controlled trial.

- Ultrasonography will be performed two weeks after medical treatment to evaluate the uterine cavity shortly after medical treatment. In case of a so-called empty uterus by ultrasonography (TED < 15mm), no further evaluation is necessary. In case of suspected retained products of conception, expectant management is advised for another four weeks. Ultrasonography will be performed six weeks after medical treatment to determine complete or incomplete evacuation.
- During six weeks after treatment, clinical signs and symptoms should guide treatment decisions. In case of asymptomatic patients, no additional examination or treatment is necessary until six weeks later. Additional treatment could be necessary in case of: no reaction after treatment (no bleeding or tissue loss), heavy or continuous bleeding, persistent abdominal pain, intra-uterine infection or on patient request.

A longer period of expectant management is in line with patient preferences in the Netherlands as shown by the recent "MisoREST-study", which was stopped prematurely because of strong preferences for expectant management instead of D&C in case of incomplete miscarriage after medical treatment.[46, 51] For expectant management to be safe, patients have to be able to contact and visit a nearby hospital immediately.

Conclusion

The sequential combination of mifepristone and misoprostol in case of early pregnancy failure appears more effective than treatment with misoprostol alone regarding complete evacuation after one week. This pilot study protocol reassured the methodology to confirm these findings by a large, prospective, randomized, and double-blinded trial, which will start second half of 2017.

Declarations

Conflict of interest statement

No conflicting interests to declare.

Contribution to authorship

JB, MS, SC and FV conceived and developed the idea for the article. JB and MS mainly responsible for the acquisition and analysis of the data. All authors took part in drafting the article or revising it for critically important intellectual content and all gave final approval of the version to be published.

Details of ethics approval

Ethics approval was required for this study, and obtained by CMO Arnhem-Nijmegen (file number 2015-2264).

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References

1. Warburton D, Fraser FC. Spontaneous Abortion Risks in Man: Data from Reproductive Histories Collected in a Medical Genetics Unit. Am J Hum Genet. 1964;16:1-25.
2. Edmonds DK, Lindsay KS, Miller JF, Williamson E, Wood PJ. Early embryonic mortality in women. Fertil Steril. 1982;38:447-53.
3. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2009;3:CD002253.
4. Prismant Landelijke LMR informatie [Internet]. 2008-2010 [cited 30-08-2012]. Available from: http://cognosserver.prismant.nl.
5. Van Asselt KM BA, Engelsman N, Hammers-Cupido RJ, Landskröner I, Opstelten W, De Vries CJH. NHG-Standaard Miskraam (Derde herziening). 2017. Available from: https://www.nhg.org/standaarden/volledig/nhg-standaard-miskraam.
6. You JH, Chung TK. Expectant, medical or surgical treatment for spontaneous abortion in first trimester of pregnancy: a cost analysis. Hum Reprod. 2005;20:2873-8.
7. Soulat C, Gelly M. [Immediate complications of surgical abortion]. J Gynecol Obstet Biol Reprod (Paris). 2006;35:157-62.
8. Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. Fertil Steril. 2006;86:367-72.
9. Hinshaw K, Fayyad A, Munjuluri P. The management of early pregnancy loss. Royal College of Obstetricians and Gynaecologists, Green-top Guideline No. 25. http://www.rcog.org.uk/. 2006.
10. Newbatt E, Beckles Z, Ullman R, Lumsden MA. Ectopic pregnancy and miscarriage: summary of NICE guidance. BMJ. 2012;345:e8136.
11. Committee on Practice B-G. The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. Obstet Gynecol. 2015;125:1258-67.
12. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002;324:873-5.
13. Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Hum Reprod. 2004;19:1894-9.
14. van den Berg J, van den Bent JM, Snijders MP, de Heus R, Coppus SF, Vandenbussche FP. Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study. Eur J Obstet Gynecol Reprod Biol. 2014;183:16-9.
15. van den Berg J, Gordon BB, Snijders MP, Vandenbussche FP, Coppus SF. The added value of mifepristone to non-surgical treatment regimens for uterine evacuation in case of early pregnancy failure: a systematic review of the literature. Eur J Obstet Gynecol Reprod Biol. 2015;195:18-26.
16. Exelgyn. Mifegyne 200mg tablets: Summary of Product Characeteristics (SmPC) [24-04-2017]. Available from: https://www.exelgyn.com.
17. Mifepriston - Mifegyne http://www.fk.cvz.nl [06-10-2011]. http://www.fk.cvz.nl]. Available from: http://www.farmacotherapeutischkompas.nl.
18. Pharma N. Mifegyne (Mifepristone) - Scientific information and guide to use2010.
19. Wagaarachchi PT, Ashok PW, Narvekar N, Smith NC, Templeton A. Medical management of early fetal demise using a combination of mifepristone and misoprostol. Hum Reprod. 2001;16:1849-53.
20. Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidegaard O. Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark. Acta Obstet Gynecol Scand. 2002;81:1060-5.
21. Coughlin LB, Roberts D, Haddad NG, Long A. Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? J Obstet Gynaecol. 2004;24:69-71.
22. Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, et al. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. Fertil Steril. 2006;86:956-60.
23. Schreiber CA, Creinin MD, Reeves MF, Harwood BJ. Mifepristone and misoprostol for the treatment of early pregnancy failure: a pilot clinical trial. Contraception. 2006;74:458-62.

24. Kollitz KM, Meyn LA, Lohr PA, Creinin MD. Mifepristone and misoprostol for early pregnancy failure: a cohort analysis. Am J Obstet Gynecol. 2011;204:386 e1-6.
25. Torre A, Huchon C, Bussieres L, Machevin E, Camus E, Fauconnier A. Immediate versus delayed medical treatment for first-trimester miscarriage: a randomized trial. Am J Obstet Gynecol. 2012;206:215 e1-6.
26. Rulin MC, Bornstein SG, Campbell JD. The reliability of ultrasonography in the management of spontaneous abortion, clinically thought to be complete: a prospective study. Am J Obstet Gynecol. 1993;168:12-5.
27. Lavecchia M, Klam S, Abenhaim HA. Effect of Uterine Cavity Sonographic Measurements on Medical Management Failure in Women With Early Pregnancy Loss. J Ultrasound Med. 2016;35:1705-10.
28. Jauniaux E, Johns J, Burton GJ. The role of ultrasound imaging in diagnosing and investigating early pregnancy failure. Ultrasound Obstet Gynecol. 2005;25:613-24.
29. FIGO. Misoprostol Recommendations. International Federation of Gynecology and Obstetrics (FIGO). 2017 [24-04-2017]. Available from: http://www.figo.org/publications/miscellaneous_publications/Misoprostol_Recommendation_2012.
30. Maria B, Chaneac M, Stampf F, Ulmann A. [Early pregnancy interruption using an antiprogesterone steroid: Mifepristone (RU 486)]. J Gynecol Obstet Biol Reprod (Paris). 1988;17:1089-94.
31. Grimes DA, Mishell DR, Jr., Shoupe D, Lacarra M. Early abortion with a single dose of the antiprogestin RU-486. Am J Obstet Gynecol. 1988;158:1307-12.
32. Kulier R, Gulmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2008:CD002855.
33. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. World Health Organisation Task Force on Post-ovulatory Methods of Fertility Regulation. BJOG. 2000;107:524-30.
34. Wu HL, Marwah S, Wang P, Wang QM, Chen XW. Misoprostol for medical treatment of missed abortion: a systematic review and network meta-analysis. Sci Rep. 2017;7:1664.
35. Chen BA, Creinin MD. Medical management of early pregnancy failure: efficacy. Semin Reprod Med. 2008;26:411-22.
36. Doggrell SA. Misoprostol for the treatment of early pregnancy failure. Curr Clin Pharmacol. 2007;2:1-9.
37. Fjerstad M, Trussell J, Sivin I, Lichtenberg ES, Cullins V. Rates of serious infection after changes in regimens for medical abortion. N Engl J Med. 2009;361:145-51.
38. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. Rev Obstet Gynecol. 2009;2:159-68.
39. Shannon C, Winikoff B. Misoprostol as a single agent for medical termination of pregnancy [cited 14-07-2017]. Available from: https://www.uptodate.com.
40. Verschoor MAC. Management of first trimester miscarriage; new insight in old dilemmas2017.
41. Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. Cochrane Database Syst Rev. 2017;1:CD007223.
42. Marwah S, Gupta S, Batra NP, Bhasin V, Sarna V, Kaur N. A Comparative Study to Evaluate the Efficacy of Vaginal vs Oral Prostaglandin E1 Analogue (Misoprostol) in Management of First Trimester Missed Abortion. J Clin Diagn Res. 2016;10:QC14-8.
43. Ngoc NT, Blum J, Westheimer E, Quan TT, Winikoff B. Medical treatment of missed abortion using misoprostol. Int J Gynaecol Obstet. 2004;87:138-42.
44. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev. 2006:CD001338.
45. Ho PC, Ngai SW, Liu KL, Wong GC, Lee SW. Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. Obstet Gynecol. 1997;90:735-8.
46. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Opmeer BC, Bossuyt PM, et al. MisoREST: surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: a randomized controlled trial. Hum Reprod. 2016;31:2421-7.
47. Debby A, Golan A, Sadan O, Rotmensch S, Malinger G. Sonographic characteristics of the uterine cavity following first-trimester uterine evacuation. Ultrasound Obstet Gynecol. 2008;31:555-9.
48. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J, Trial NMoEPF. Endometrial thickness after misoprostol use for early pregnancy failure. Int J Gynaecol Obstet. 2004;86:22-6.
49. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2013.

50. McCarthy FP, Khashan AS, North RA, Rahma MB, Walker JJ, Baker PN, et al. Pregnancy loss managed by cervical dilatation and curettage increases the risk of spontaneous preterm birth. Hum Reprod. 2013;28:3197-206.
51. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Bossuyt PM, Huirne JA, et al. MisoREST: Surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: A cohort study. Eur J Obstet Gynecol Reprod Biol. 2017;211:83-9.

6

Mifepristone and misoprostol versus misoprostol alone for uterine evacuation after early pregnancy failure: a randomized double blinded placebo-controlled comparison (M&M trial)

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Abstract

Background

Early pregnancy failure (EPF) is a common complication of pregnancy. If women do not abort spontaneously, they undergo medical or surgical treatment in order to remove the products of conception from the uterus. Curettage, although highly effective, is associated with risks of complications; medical treatment with misoprostol is a safe and less expensive alternative. Unfortunately, after one week of expectant management, the current treatment with misoprostol has a complete evacuation rate of approximately 50%. Medical treatment may be improved by pre-treatment with mifepristone; its effectiveness has already been proven for other indications of pregnancy termination. This study will test the hypothesis that, in EPF, the sequential combination of mifepristone with misoprostol is superior to the use of misoprostol alone in terms of complete evacuation (primary outcome), patient satisfaction, complications, side effects and costs (secondary outcomes).

Methods

The trial will be performed multi-centered, prospectively, two-armed, randomized, double-blinded and placebo-controlled. Women with confirmed EPF by ultrasonography (6-14 weeks), managed expectantly for at least one week, can be included and randomized to pre-treatment with oral mifepristone (600mg) or oral placebo (identical in appearance). In both arms pre-treatment will be followed by oral misoprostol, which will start 36-48 hours later consisting of two doses 400µg (four hours apart), repeated after 24 hours if no tissue is lost. 460 women will be randomized in a 1:1 ratio, stratified by center.
Ultrasonography two weeks after treatment will determine treatment effect on short term. An expectant management is advised until six weeks after treatment when the primary endpoint, complete or incomplete evacuation, will be determined. A sonographic endometrial thickness < 15mm and no evidence of retained products of conception using only the allocated therapy by randomization, is considered as successful treatment result. Secondary outcome measures (patient satisfaction, complications, side effects and costs) will be registered using a case report form, patient diary and validated questionnaires (Short Form 36, EuroQol-VAS, Client Satisfaction Questionnaire).

Discussion

This trial will answer the question if, in case of EPF, medical management with sequential mifepristone and misoprostol is more effective than misoprostol alone to achieve complete evacuation of the products of conception.

Trial registration

EudraCT number:	2017-002694-19	Clinicaltrials.gov:	NCT03212352
Trialregister.nl:	NTR 6550	Toetsingonline.nl:	NL 62449.091.17

Background

In the Netherlands, every year more than 10.000 women with early pregnancy failure (EPF) undergo surgical or medical treatment in order to remove the products of conception from the uterus.[1] For many years, surgical treatment (dilatation and curettage, D&C) has been standard treatment.[2] However, D&C is associated with risks of complications (uterine perforation, pelvic infection, excessive bleeding, anesthesia, intra-uterine adhesions, cervical injury or cervical insufficiency in following pregnancies) and high costs.[3-7]

The Royal College of Obstetricians and Gynecologists as well as the "American College of Obstetricians and Gynecologists" recommend medical methods as a safe, effective and acceptable alternative (evidence level A).[8, 9] Misoprostol is used for several obstetric and gynecologic indications, including EPF, due to uterotonic properties leading to myometrial contractions and ripening and dilatation of the cervix.[10] For medical treatment, the International Federation of Gynecology and Obstetrics (FIGO) recommends the prescription of two doses misoprostol 800µg administered vaginally (three hours apart) or two doses misoprostol 600µg sublingual (three hours apart).[11, 12] Unfortunately, if a minimum of one week of expectant management is followed by misoprostol treatment, half of the women still have to undergo D&C due to retained products of conception and thus still may be exposed to the risks of complications associated with D&C.[2, 13-15]

Mifepristone is a progesterone antagonist and its administration during pregnancy increases the production of endogenous prostaglandin by the endometrium, the sensitivity of the gravid uterus to exogenous prostaglandin, the contractility of the myometrium, and cervical softening and dilatation.[16, 17] For other indications, such as labor induction in case of fetal death after the first trimester, and also for medical termination of vital pregnancy (medical abortion), the sequential combination of mifepristone with misoprostol has been shown superior to the use of misoprostol alone.[18, 19] So, it appears reasonable to consider mifepristone with misoprostol to be superior to misoprostol alone in case of EPF (non-vital pregnancy in the first trimester).

Several groups have been investigating the sequential combination of mifepristone with misoprostol in EPF, and reported success rates of 66 – 93% without any serious adverse events.[7, 11, 13, 20-27] Unfortunately, these studies were small and flawed by different inclusion criteria and treatment regimens or retrospective study design.[13] A retrospective study performed by our research group including 301 women with EPF between 6-14 weeks of gestation, reported success rate of 67% in the intervention group (mifepristone + misoprostol, M&M) versus 40% in the control group (placebo + misoprostol). However, to develop evidence based treatment regimen, a sufficiently powered, randomized, double blinded, and placebo-controlled trial is required.

Methods / Design

Study aim and design

The aim of this study is to compare addition of mifepristone to the standard treatment with misoprostol in terms of complete evacuation of products of conception from the uterus, patient satisfaction, complications, side effects and costs. The trial will be performed multi-centered in the Netherlands and will be conducted prospectively, two-armed, randomized (1:1 ratio), double blinded and placebo-controlled. Participating hospitals can be district, teaching or third referral (academic) hospitals. Participants are followed in an outpatient clinic; hospital admission follows only if medically necessary. Ethical approval to conduct the study is obtained at the regional medical-ethical commission (CMO Arnhem-Nijmegen).

Participants and eligibility criteria

We will study women aged above 18 years with a diagnosis of EPF between 6 and 14 weeks of gestation. EPF is diagnosed by transvaginal ultrasonography describing:

- A crown-rump length ≥ 6mm and no cardiac activity OR
- A crown-rump length < 6mm and no fetal growth at least one week later OR
- A gestational sac with absent embryonic pole for at least one week.

A minimum of one week of expectant management results in spontaneous complete abortion rates of 50%, and is common practice in the Netherlands.[2, 28] Therefore, women can only be included at least one week after diagnosis. However, in case of a discrepancy of at least one week between crown-rump length and the calendar gestational age, patients can be included immediately because the one-week of expectant management has already passed.

Exclusion criteria are age < 18 years, hemodynamic instability, sign of infection, incomplete miscarriage, high risk of thrombosis, contra-indications for mifepristone or misoprostol, interaction between study-medication and other medication or the inability to give informed consent.

Procedures, recruitment, randomization, and collection of baseline data

Women visiting a hospital in case of EPF are identified and approached to participate in the trial by their treating physician. Trained staff will counsel patients, inform about the aims, methods, reasonable anticipated benefits and potential hazards of the study, hand out the patient information letter, and offer 24 hours to reflect. Patients will also be informed about the off-label use of mifepristone and misoprostol. Participation is voluntary and patients may withdraw consent to participate at any time during the study. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Baseline demographics, obstetric and medical history are recorded for all women

at the time of randomization using a case report form. After obtaining written informed consent, randomization can be performed.

The Clinical Trial Unit of the Radboudumc will coordinate randomization. Subjects will be randomized in a 1:1 ratio to mifepristone 600mg oral or placebo using computerized randomization tables. The randomization will be conducted using block randomization and will be stratified by hospital. After randomization a unique study number will be assigned corresponding with a study package available in the participating center containing the blinded study medication. The placebo and mifepristone tablets are identical in appearance so neither the patient nor the physician will know which product is taken. Only the pharmacy will know which medication or placebo the patient receives. Blinding, distribution and labeling of the study medication packages will be coordinated by the clinical trial unit in the Radboudumc (Nijmegen). A sealed list with the label codes will be available in case of emergencies. These data will be disclosed to the principal investigators only after data on all outcome parameters have been collected. Regarding misoprostol, the treating physician will prescribe these tablets as usual, which woman can retrieve at their own pharmacy.

Interventions and follow-up

After informed consent and randomization, each patient receives three (blinded) tablets containing 200mg mifepristone each or placebo (day 1, figure 1). Apart from the study medication, management of participants will be similar in both groups. At day three (36-48 hours later), two doses of misoprostol 400µg orally (four hours apart) will be taken at home. If no tissue is lost by day four, two more doses of oral misoprostol 400µg orally (four hours apart) will be taken at home.

Regarding mifepristone, the World Health Organization advises mifepristone (200mg) in combination with misoprostol in case of termination of a vital pregnancy in the first trimester.[29] Reasons for the lower dosage of mifepristone are not mentioned in their guideline; one could imagine it's because of the, until recent, high costs of mifepristone in the context of low-resource countries. However, two phase 2 trials showed that 600mg mifepristone was superior to the 200mg dose in terms of complete abortion in case of termination of a vital pregnancy (89% versus 63%).[30, 31]

Concerning misoprostol, many different treatment regimens have been described with various routes of administration and doses. Up until 2014, 23 different treatment regimens (dosages and routes of administration) were used in the Netherlands, and in many hospitals even more than one treatment regimen existed simultaneously.[32] Several reviews conclude that research is still necessary to determine the most optimal treatment regimen.[33, 34] Vaginal application of misoprostol is widely accepted. However, oral

misoprostol is advised by the manufacturer of mifepristone (Exelgyn) if combined with mifepristone, based on a significant lower infection rate in case of medical abortion after changing the regime of vaginal to oral administration.[35] When pharmacologically comparing oral and vaginal administration of misoprostol, oral misoprostol leads to a more rapid absorption and higher peak levels.[36] Gastrointestinal side effects are dose and interval dependent, higher doses and short intervals may lead to an increase in symptoms.[36, 37] Although one would suspect that oral misoprostol leads to more side effects due to higher peak concentrations, an equal incidence of vomiting, nausea, diarrhea and fever was reported in a recent Cochrane review (submitted).[38] However, it should be mentioned that the quality of the included studies is low. In contrast to this recent Cochrane review concerning EPF, reviews including incomplete miscarriages or termination of vital pregnancies in the first trimester do report significantly more nausea and diarrhea after oral misoprostol.[19, 39]

Regarding effectiveness of misoprostol treatment, a Cochrane review reported that misoprostol 800µg orally is equally effective compared to misoprostol 800µg vaginally.[11, 38] A split dosage of misoprostol (two or three doses of 400µg) has been reported to be similar in success rates as a protocol using 800µg at once.[19, 38] However, the mean time to expulsion was longer after oral intake of misoprostol compared to vaginal application.[40, 41] Clinical studies comparing oral and vaginal misoprostol have found increased satisfaction with the oral route because it is easy to use and avoids any unnecessary vaginal examinations.[42, 43] In our study protocol, the oral route is chosen because it appears equally effective compared to vaginal application, is easy to use, and an increased patients satisfaction.[42] Since a split-dose regimen is equally effective, but may lead to a lower incidence of side effects, we have chosen a split dose of misoprostol 400µg. Thereby, if the first dose of misoprostol 400µg leads to complete expulsion of the gestational sac, the second dose doesn't have to be taken.

With regards to the follow-up of women receiving medical treatment, there are no clear recommendations about the time period and optimal diagnostic tool to define success. Ultrasonography seems to be of limited value in predicting the presence of intrauterine remnants. Recent studies do not provide any clear evidence which endometrial thickness corresponds best to the presence of intrauterine pregnancy remnants.[15, 44] A study by Rulin concludes that in case of a maximum anterior-posterior diameter of 15 mm or less, retained products are less likely to be confirmed histologically.[45] Also a recent study by Lavecchia et al reported that a cavity anterioposterior distance of more than 15mm was associated with the need for D&C and an unplanned return to the emergency department.[46] However, another study by Creinin showed a wide range of endometrial thickness (1-31mm) two weeks after expulsion of the gestational sac and a decreasing endometrial thickness over time. The authors suggest that clinical signs and symptoms should guide

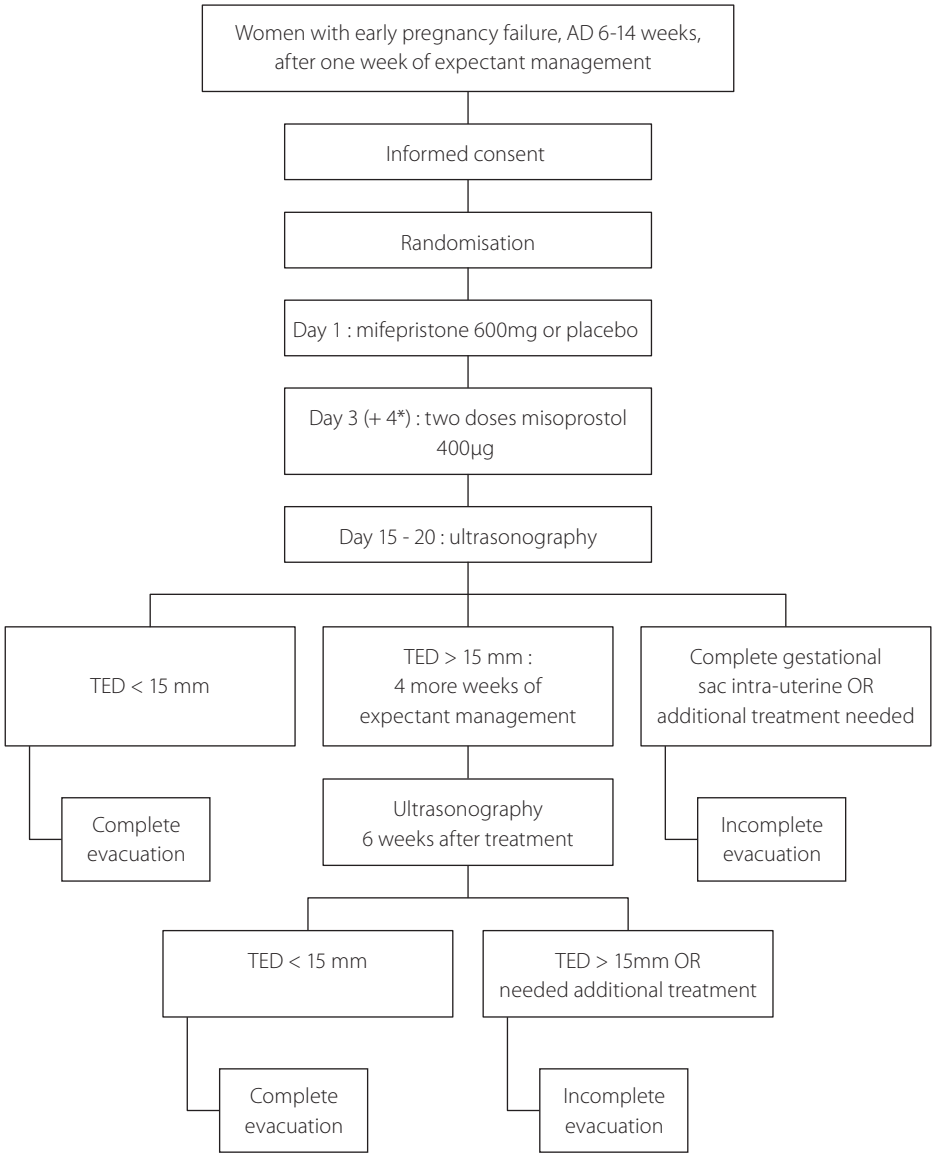

Figure 1 Flowchart of study procedures. *If no tissue is lost by day four, two more doses of misoprostol will be taken at day four

treatment decisions after medical treatment.[47] An expectant management in case of an endometrial thickness more than 15mm one week after medical treatment is advised on the basis of recent findings by the Dutch nationwide MisoREST-study,[14, 15] The MisoREST-study investigated whether curettage is more effective than expectant management in case of an incomplete evacuation (sonographic endometrial thickness > 10mm) one week after misoprostol treatment. The MisoREST-study concludes that expectant management until six weeks after medical treatment is safe, effective in approximately 80% of patients, and that women have a clear preference for expectant management instead of curettage.[14]

In our trial, ultrasonography will be performed between day 15 and 20 to evaluate the first treatment effect (figure 1). In case of a total endometrial thickness (TED) < 15mm by ultrasonography, no further evaluation is necessary and treatment is considered as successful. In case of retained products of conception (TED > 15mm) expectant management is advised, with consent from the patient, for another four weeks. Patients are able to contact their hospital 24h a day in case of any questions, complaints or emergencies. During these weeks of expectant management, clinical signs and symptoms should determine whether additional treatment (curettage) is necessary. If successful curettage has been performed after medical treatment, no further examinations for the purposes of the study project are necessary. Six weeks after treatment, ultrasonography will be performed to evaluate endometrial thickness. In case of an endometrial thickness > 15mm six weeks after treatment, further treatment will be according to local protocol and patient preferences. Additional treatment may be expectant, medication or surgical (hysteroscopy or D&C).
Anti-D prophylaxis will be given if necessary as part of the standard treatment, following the NVOG-guideline "Erytrocytenimmunisatie en zwangerschap".[48]

Outcome measures

Primary and secondary outcome measures will be extracted from routine clinical parameters in the patient medical record and patient diary and recorded in a digital case report form. A two-step method will be used to determine treatment success. Ultrasonography will be performed two weeks after medical treatment to determine treatment failure defined as a complete gestational sac intrauterine. The definite primary study outcome, complete (success) or incomplete (failure) evacuation, will be determined six weeks after treatment. [2, 8, 45, 47, 49-51] A successful medical treatment will be considered in case of an ultrasonography showing a TED < 15mm (maximum anterior-posterior diameter), two or six weeks after medical treatment and no evidence of retained products of conception using only the allocated therapy by randomization.

Secondary outcomes include patient satisfaction, complications, side effects and costs. Secondary outcome measures are subtracted from the medical record, patient diary

and (validated) digital questionnaires. At baseline, day five, and two and six weeks after treatment started, questionnaires will be sent by email. To measure the quality of the health status of the patients, two so-called health-related quality of life (HRQoL) instruments will be used: the Short Form 36 health survey and the EuroQol-5D, both available in a Dutch translation. Patient preferences and satisfaction with treatment will be measured using The Client Satisfaction Questionnaire (CSQ-8, digital) two and six weeks after treatment.

Economic evaluation

A cost-effectiveness analysis will be performed, from a societal perspective. To evaluate which medical treatment strategy is cost-effective, volumes of health care consumed will additionally be measured prospectively alongside the clinical trial together with cost associated with productivity losses. Costs of medical interventions (direct costs) and costs resulting from productivity loss (indirect costs) will be taken into account. Resource uses will be recorded in the case report forms. Standardized unit costs will be calculated using the Dutch manual for costing in economic evaluations.

Statistical issues

Sample size calculation

Based on retrospective data in the Radboud University Medical Centre (Nijmegen) that are compatible with data from the literature, we found a complete evacuation rate of 67% in the M&M group versus 54% in the placebo group.[20] We used these rates for the calculation of the sample size with an overall significance level of 5%, $\alpha = 0.05$, in combination with a power of 80%, $\beta = 0.20$. Based on an improvement of complete evacuation rates from 54% to 67%, the trial requires 221 patients in each arm. Considering 3-4% patients lost-to-follow-up, 230 patients per arm have to be included (total 460).

Data analysis

Data handling will be done anonymized, with the patient code only available to the treating physician and local investigator. Data will initially be analyzed according to intention to treat method. The main outcome variable will be assessed by calculating success rates in both groups, relative risks, and 95% confidence intervals. A per protocol analysis will be performed to evaluate the potential of both strategies, taking into account only those cases that were treated according to protocol. Differences between groups will be analyzed using the Pearson's chi-square test or the Fisher's exact test for categorical variables and the Students t-test for continuous variables. Mann-Whitney U test will be used for non-normally distributed metric variables and univariate and multivariate logistic regression analysis to identify individual factors that are associated with treatment success. Economic analysis will be done according to intention to treat principle. Differences in total costs between the intervention and control group will be calculated.

Interim analysis and safety monitoring

A data safety monitoring board will be installed, and after including 100 patients in each arm, an interim analysis will be done using O'Brien-Fleming stopping rules. This means that if M&M treatment (mifepristone followed by misoprostol) is particularly beneficial or harmful compared to the control group, the investigators will be able to make a deliberate consideration of terminating the study earlier. Local investigators will report (serious) adverse events as soon as possible to the sponsor. The sponsor is responsible to report serious adverse events (SAE's) within 15 days to the ethical committee CMO Arnhem-Nijmegen.

Discussion

Yearly in the Netherlands, 10.000 women with EPF do not abort spontaneously and do undergo medical or surgical treatment, after a minimum of one week of expectant management, in order to remove the products of conception from the uterus. Medical treatment is a safe and a less expensive alternative to D&C. However, since there is no national guideline describing the treatment options for EPF, there is a large practice variation between Dutch hospitals.[32]. The current medical treatment with misoprostol only after a minimum of one week of expectant management has a complete evacuation rate of circa 50%. Thus, 50% of women are still exposed to the risks of complications and costs associated with surgery.[2, 13-15]

Medical treatment for EPF may be improved by pre-treatment with mifepristone followed by the current treatment with misoprostol alone. The superiority of the combination has been demonstrated for termination of vital pregnancy in the first trimester, preparation for surgical abortion in the first trimester, termination of vital pregnancy beyond first trimester, and induction of labor in case of fetal death after the first trimester.[16, 52, 53] Therefore, it is reasonable to consider that also for EPF mifepristone with misoprostol will be superior to misoprostol alone.

A randomized, double blinded placebo-controlled trial is required to deliver the ultimate evidence that in EPF the sequential combination of mifepristone with misoprostol is superior to the use of misoprostol alone with respect to complete evacuation of products of conception, side effects, complications, patient preferences, and costs.

Declarations

Conflict of interest statement

The authors declare that they have no competing interests.

Contribution to authorship

All authors were involved in the conception and design of the study. All authors took part in developing the study protocol and drafting the article or revising it for critically important intellectual content and all gave final approval of the version to be published.

Details of ethics approval

Ethics approval for this study by CMO region Arnhem-Nijmegen and the National Central Committee on Research involving Human Subjects (CCMO) is obtained.

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References

1. Open data van de Nederlandse Zorgautoriteit (2014-2016) [25-05-2017]. Available from: http://www.opendisdata.nl/.
2. Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Hum Reprod. 2004;19:1894-9.
3. You JH, Chung TK. Expectant, medical or surgical treatment for spontaneous abortion in first trimester of pregnancy: a cost analysis. Hum Reprod. 2005;20:2873-8.
4. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2013.
5. Lemmers M, Verschoor MA, Hooker AB, Opmeer BC, Limpens J, Huirne JA, et al. Dilatation and curettage increases the risk of subsequent preterm birth: a systematic review and meta-analysis. Hum Reprod. 2016;31:34-45.
6. Soulat C, Gelly M. [Immediate complications of surgical abortion]. J Gynecol Obstet Biol Reprod (Paris). 2006;35:157-62.
7. Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. Fertil Steril. 2006;86:367-72.
8. Hinshaw K, Fayyad A, Munjuluri P. The management of early pregnancy loss. Royal College of Obstetricians and Gynaecologists, Green-top Guideline No. 25. http://www.rcog.org.uk/. 2006.
9. Committee on Practice B-G. The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. Obstet Gynecol. 2015;125:1258-67.
10. Cytotec UK SPC (Summary of Product Characteristics). [21-10-2016]. Available from: http://www.medicines.org.uk/emc/medicine/9352.
11. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2009;3:CD002253.
12. FIGO. Misoprostol Recommendations. International Federation of Gynecology and Obstetrics (FIGO). 2017 [24-04-2017]. Available from: http://www.figo.org/publications/miscellaneous_publications/Misoprostol_Recommendation_2012.
13. van den Berg J, Gordon BB, Snijders MP, Vandenbussche FP, Coppus SF. The added value of mifepristone to non-surgical treatment regimens for uterine evacuation in case of early pregnancy failure: a systematic review of the literature. Eur J Obstet Gynecol Reprod Biol. 2015;195:18-26.
14. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Bossuyt PM, Huirne JA, et al. MisoREST: Surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: A cohort study. Eur J Obstet Gynecol Reprod Biol. 2017;211:83-9.
15. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Opmeer BC, Bossuyt PM, et al. MisoREST: surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: a randomized controlled trial. Hum Reprod. 2016;31:2421-7.
16. Exelgyn. Mifegyne 200mg tablets: Summary of Product Characeteristics (SmPC) [24-04-2017]. Available from: https://www.exelgyn.com.
17. Mifepriston - Mifegyne http://www.fk.cvz.nl [06-10-2011]. http://www.fk.cvz.nl]. Available from: http://www.farmacotherapeutischkompas.nl.
18. Say L, Kulier R, Gulmezoglu M, Campana A. Medical versus surgical methods for first trimester termination of pregnancy. Cochrane Database Syst Rev. 2005:CD003037.
19. Kulier R, Gulmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2008:CD002855.
20. van den Berg J, van den Bent JM, Snijders MP, de Heus R, Coppus SF, Vandenbussche FP. Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study. Eur J Obstet Gynecol Reprod Biol. 2014;183:16-9.
21. Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, et al. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. Fertil Steril. 2006;86:956-60.

22. Wagaarachchi PT, Ashok PW, Narvekar N, Smith NC, Templeton A. Medical management of early fetal demise using a combination of mifepristone and misoprostol. Hum Reprod. 2001;16:1849-53.
23. Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidegaard O. Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark. Acta Obstet Gynecol Scand. 2002;81:1060-5.
24. Coughlin LB, Roberts D, Haddad NG, Long A. Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? J Obstet Gynaecol. 2004;24:69-71.
25. Schreiber CA, Creinin MD, Reeves MF, Harwood BJ. Mifepristone and misoprostol for the treatment of early pregnancy failure: a pilot clinical trial. Contraception. 2006;74:458-62.
26. Kollitz KM, Meyn LA, Lohr PA, Creinin MD. Mifepristone and misoprostol for early pregnancy failure: a cohort analysis. Am J Obstet Gynecol. 2011;204:386 e1-6.
27. Torre A, Huchon C, Bussieres L, Machevin E, Camus E, Fauconnier A. Immediate versus delayed medical treatment for first-trimester miscarriage: a randomized trial. Am J Obstet Gynecol. 2012;206:215 e1-6.
28. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002;324:873-5.
29. Clinical Practice Handbook for Safe Abortion. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2014.
30. Maria B, Chaneac M, Stampf F, Ulmann A. [Early pregnancy interruption using an antiprogesterone steroid: Mifepristone (RU 486)]. J Gynecol Obstet Biol Reprod (Paris). 1988;17:1089-94.
31. Grimes DA, Mishell DR, Jr., Shoupe D, Lacarra M. Early abortion with a single dose of the antiprogestin RU-486. Am J Obstet Gynecol. 1988;158:1307-12.
32. Verschoor MA, Lemmers M, Wekker MZ, Huirne JA, Goddijn M, Mol BW, et al. Practice variation in the management of first trimester miscarriage in the Netherlands: a nationwide survey. Obstet Gynecol Int. 2014;2014:387860.
33. Chen BA, Creinin MD. Medical management of early pregnancy failure: efficacy. Semin Reprod Med. 2008;26:411-22.
34. Doggrell SA. Misoprostol for the treatment of early pregnancy failure. Curr Clin Pharmacol. 2007;2:1-9.
35. Fjerstad M, Trussell J, Sivin I, Lichtenberg ES, Cullins V. Rates of serious infection after changes in regimens for medical abortion. N Engl J Med. 2009;361:145-51.
36. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. Rev Obstet Gynecol. 2009;2:159-68.
37. Shannon C, Winikoff B. Misoprostol as a single agent for medical termination of pregnancy [cited 14-07-2017]. Available from: https://www.uptodate.com.
38. Verschoor MAC. Management of first trimester miscarriage; new insight in old dilemmas. Thesis. 2017.
39. Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. Cochrane Database Syst Rev. 2017;1:CD007223.
40. Marwah S, Gupta S, Batra NP, Bhasin V, Sarna V, Kaur N. A Comparative Study to Evaluate the Efficacy of Vaginal vs Oral Prostaglandin E1 Analogue (Misoprostol) in Management of First Trimester Missed Abortion. J Clin Diagn Res. 2016;10:QC14-8.
41. Ngoc NT, Blum J, Westheimer E, Quan TT, Winikoff B. Medical treatment of missed abortion using misoprostol. Int J Gynaecol Obstet. 2004;87:138-42.
42. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev. 2006:CD001338.
43. Ho PC, Ngai SW, Liu KL, Wong GC, Lee SW. Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. Obstet Gynecol. 1997;90:735-8.
44. Debby A, Golan A, Sadan O, Rotmensch S, Malinger G. Sonographic characteristics of the uterine cavity following first-trimester uterine evacuation. Ultrasound Obstet Gynecol. 2008;31:555-9.
45. Rulin MC, Bornstein SG, Campbell JD. The reliability of ultrasonography in the management of spontaneous abortion, clinically thought to be complete: a prospective study. Am J Obstet Gynecol. 1993;168:12-5.
46. Lavecchia M, Klam S, Abenhaim HA. Effect of Uterine Cavity Sonographic Measurements on Medical Management Failure in Women With Early Pregnancy Loss. J Ultrasound Med. 2016;35:1705-10.
47. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J, Trial NMoEPF. Endometrial thickness after misoprostol use for early pregnancy failure. Int J Gynaecol Obstet. 2004;86:22-6.

48. Erytrocytenimmunisatie en zwangerschap. Versie 2.1, 2009. [10-06-2017]. Available from: http://nvog-documenten.nl/.
49. Chung TK, Cheung LP, Sahota DS, Haines CJ, Chang AM. Evaluation of the accuracy of transvaginal sonography for the assessment of retained products of conception after spontaneous abortion. Gynecol Obstet Invest. 1998;45:190-3.
50. Jauniaux E, Johns J, Burton GJ. The role of ultrasound imaging in diagnosing and investigating early pregnancy failure. Ultrasound Obstet Gynecol. 2005;25:613-24.
51. Mol BW. MisoREST: What should be done in women with an incomplete evacuation of the uterus after treatment with misoprostol for miscarriage? An analysis of effects. http://www.studies-obsgyn.nl/misorest2012.
52. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011:CD005216.
53. Hapangama D, Neilson JP. Mifepristone for induction of labour. Cochrane Database Syst Rev. 2009:CD002865

7

General discussion and topics for future research

Mifepristone and misoprostol: M&M

Since the fifties of the last century, surgical intervention (e.g. dilatation and curettage, D&C) was the preferred treatment option worldwide in case of early pregnancy failure (EPF).[1-3] Although prostaglandins (i.e. misoprostol) were developed in 1973 and the anti-progesterone mifepristone in 1980, it took approximately a decade before drug treatment regimens were introduced for termination of vital pregnancies or EPF.[4-7] Due to the risks of short and long term complications after D&C, medical treatment options will become of increasing importance.[8-10] Concurrently, patients have developed a strong preference for medical treatment options; they are willing to accept some disadvantages to avoid D&C.[11, 12] Also in the Netherlands, health care providers and insurance companies are searching for the most cost-effective treatment options and substitution of health care from the hospital towards homecare by general practitioners whenever possible.[13, 14]

In this thesis we focus on a medical treatment option for the evacuation of the products of conception in women with EPF: the sequential combination of mifepristone and misoprostol (M&M). To provide insight into the hypothesis that M&M is more effective than standard misoprostol treatment, we have conducted:

- A systematic review concerning mifepristone in the treatment of EPF, concluding that the addition of mifepristone to current misoprostol treatment regimens might increase success rates, and thereby reducing the number of surgical interventions. However, the evidence from the existing literature is insufficient to draw firm conclusions.[15]
- A single-center retrospective cohort study including patients in the period before and after a protocol change (addition of mifepristone to misoprostol), reporting that treatment of EPF with M&M was significantly more effective than treatment with misoprostol alone: 66,8 versus 54,9%.[16]
- A survey among 25 gynecologic centers in the Netherlands (2017), evaluating the use and expectations of mifepristone, which reveals a large practice variation regarding treatment of patients with EPF. Mifepristone prescription for EPF in the Netherlands appears scarce because of lack of sufficient evidence. Physicians are willing to prescribe M&M in the future if scientifically evidence-based superior to the use of misoprostol alone.[17]
- A two-centered, prospective, randomized, double blinded, placebo controlled pilot study, comparing M&M versus misoprostol alone, showing fluent accrual of patients, feasibility of the study protocol and measurement of primary and secondary outcomes. With this pilot encouraging treatment results in terms of effectiveness (68,4% versus 40%) and patient satisfaction (84,6% versus 62,6%) are reported, with no serious adverse events and significantly less surgical interventions (10,5% versus 50%) after M&M.[18]

- The composition of the definitive study protocol for a sufficiently powered, multicenter, randomized, double blinded and placebo controlled trial to confirm the hypothesis that the sequential treatment with M&M is more effective than misoprostol alone, is patient preferred, and results in less surgical interventions and significant reduction of healthcare costs (www.clinicaltrials.gov, NCT03212352).[19]

Implications for current practice

Terminology

We suggest using the universal term "early pregnancy failure" (EPF), or in Dutch "miskraam", when describing a non-vital pregnancy until 14 weeks of gestation. It should be attempted to maintain a uniform definition to prevent confusion between physicians and patients, to compare treatment results in the best possible way, to improve implementation of research results in daily practice, and to reach similarity in inclusion criteria for future research.[20, 21]

Treatment in case of EPF

Treatment of women with EPF may be improved by protocol-based care preferably directed by a nationwide guideline. We recommend starting medical treatment only after at least one week of expectant management.[22] Physicians should explain to the patient with EPF that expectant management for at least one week leads to complete spontaneous miscarriage in approximately 50% of women.[23, 24] After unsuccessful expectant management, women then should be thoroughly counseled between medical and surgical treatment options.

The first choice after unsuccessful expectant management, after excluding contra-indications for prostaglandins, should be medical treatment, because it is a safe alternative compared to surgical treatment with lower short and long term complication rates and costs.[3, 9, 10, 25] Up until now, we advise misoprostol 800µg, followed by a second dose of 800µg 24 hours later if no tissue is lost. Ultrasonography should be performed after 1 or 2 weeks to evaluate whether the gestational sac has been expulsed or is still intra-uterine. If the gestational sac has been expulsed, in general, expectant management until six weeks after medical treatment is advised, based on the results of the MisoREST-study reporting that expectant management is effective in approximately 80% of patients. Furthermore, it is safe, and even more important, women have a clear preference for expectant management instead of curettage.[26, 27] Curettage is accompanied by the risk of complications on short and long term, the incidence of complications varies between 0,01% and 1,6%.[8, 9, 28-30] Recent studies also reveal a high prevalence of intrauterine adhesions (Asherman syndrome), potentially interfering with subsequent

child wish.[10] Moreover, a higher risk of premature delivery in future pregnancies has been reported.[9, 31] Therefore, it appears of utmost importance to reduce the need for curettage in women with EPF. As reported in our pilot study, M&M treatment may lead to significantly less interventions.[18]

Unfortunately, the current medical treatment with misoprostol alone, after one week of expectant management, is successful in approximately 50%. To achieve a substantial reduction of surgical interventions it is urgently needed to increase the success rates of medical treatment.[2, 16] Besides reduction of complications, effective medical treatment is also cost reducing as already shown by Graziosi et al., so, an even more reduction in costs is expected when success rates increase.[25] Thereby, approximately 85% of women would prefer medical treatment if its complete evacuation rate would reach 80%.[12]

Concluding, if M&M appears superior to the use of misoprostol alone, M&M may lead to less surgical interventions, reduction of complications and costs, and may increase patient satisfaction. Although our thesis is already showing very promising results after M&M treatment, we must wait for the results of the sufficiently powered randomized, double blinded, and placebo-controlled trial (starting second half of 2017, NCT03212352) to draw any firm conclusions.[19]

Dutch situation: general practitioner, midwife and early pregnancy unit

In the Netherlands, with a condense medical infrastructure, medical treatment (both mifepristone and misoprostol) in case of EPF could be a suitable opportunity for home-based care. In the Netherlands, most women primarily visit their local GP or midwife in case of a pregnancy. So, if miscarriage is diagnosed in the first trimester of pregnancy, and medical treatment may be necessary, this kind of relatively safe treatment with a very low complication rate seems highly suitable to GPs and midwifes to deliver.

In the Netherlands, physicians may only prescribe medication for termination of a vital pregnancy (i.e. abortus provocatus) if they are authorized and licensed to provide such treatment. Actually, this is done by doctors working in so-called specific "abortion clinics". Besides, informed consent is always necessary because of off-label use of misoprostol. At this moment, the debate is still going on whether GP's may prescribe "the abortion pill" i.e. mifepristone, in termination of vital pregnancies.[32] If it is allowed for GP's to prescribe mifepristone also in case of EPF, women can visit their GP who knows their complete medical record and social context without extra hospital-visit related costs. Of course, for future use by GP's it is required that they are familiar with the contra-indications and possible complications of mifepristone and misoprostol use. In case of an emergency, like excessive bleeding, the possibility for immediate hospital admission (in a collaborative network) is an obligatory condition for substitution of this kind of health care towards GPs.

Within this new concept of care, one should also be aware that ultrasonography is necessary to confirm the diagnosis of a non-vital pregnancy in utero and its gestational age. In the Dutch situation midwifes are, in contrast to GP's, educated and licensed to perform and interpret ultrasonography to diagnose EPF. However, midwives are and probably will not be authorized to prescribe mifepristone or misoprostol for the treatment of EPF. Therefore, after determining the correct diagnosis, at this moment women are still referred to the hospital. This could be changed into referral back to the GP after determining diagnosis, ensuring that women are treated by their own GP. In conclusion, the aforementioned EPF treatment concept (see figure 1) may lead to an increase in patient satisfaction, improvement of health care quality and substantial reduction of costs (i.e. substitution of health care).[33-36]

In England, the care for women during early pregnancy is centralized in more than 200 specialized "early pregnancy units" (EPU).[37] Treatment of women with EPF takes place in these EPUs if available in the nearby area, because the logistical improvements and bundling of expertise lead to expert guidance of women by a dedicated team of physicians, and improvement of health care quality. Women are guided by physicians who also have an extra focus on the differential diagnosis of EPF, for example bleeding in a vital pregnancy, extra-uterine pregnancy or pregnancy of unknown location. Also guidance in case of recurrent miscarriages can be given by the same dedicated team of physicians. In the Netherlands only two EPUs have been opened until now, causing that referral to an EPU is not an option for many Dutch women.[38]

Global health: EPF care in low-resource countries

Differences in healthcare between high- (like the Netherlands) and low-resource countries are well known. Costs and distance to healthcare providers have major influences on the opportunities for primary healthcare. Surgical methods may be scarce and may be even more hazardous in low-income countries due to lack of trained staff, lack of material or inadequate transportation to centers where surgical procedures are performed. Also cultural norms, community beliefs, financial aspects, distance to the hospital, education, and lack of knowledge determine whether women seek medical help at all.[39, 40]

In places with limited resources, medical treatment options may be extremely helpful to reduce both morbidity and mortality rates.[39, 41] Compared to surgical, medical treatment has even more advantages in low than in high-resource countries, for example by its low-costs (in the Netherlands 1.02 euro for one misoprostol tablet), easy availability and storage at room temperature. A one-stop-shop EPF approach, to determine diagnosis and start treatment on the same day, could be very useful. However, if it's not secured that patients return for follow-up, high treatment efficacy is essential. Since the sequential combination of mifepristone and misoprostol may lead to higher success rates, reducing

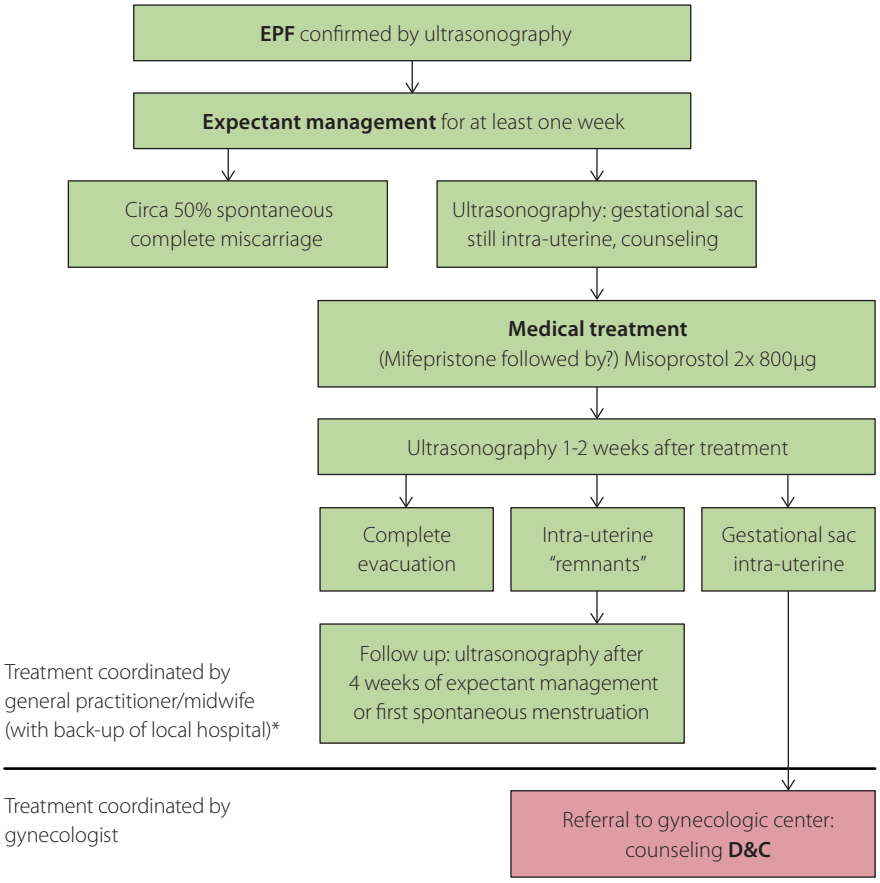

Figure 1 Proposed treatment protocol for early pregnancy failure

* Uncomplicated cases (referral to EPU or local hospital in case of uncertain diagnosis, i.e. extra-uterine pregnancy or pregnancy of unknown location)

the need for additional surgical intervention, M&M in case of EPF could be of utmost importance in low-resource countries. Certainly, since the costs of mifepristone are decreasing drastically (current costs in the Netherlands 11.66 euro per tablet), this treatment option may have significant impact on health care safety and costs in low-resource countries.[42]

Topics for future research

Conception of a nationwide guideline for EPF

A sufficiently powered, multicenter, randomized, double blinded, and placebo-controlled trial will start at the end of 2017, funded by "Innovatiefonds Zorgverzekeraars", Canisius-Wilhelmina Hospital and Radboud University Medical Centre (NCT03212352). Definitely, a robust RCT is necessary to obtain evidence to confirm the hypothesis that sequential treatment with mifepristone and misoprostol is superior to the use of misoprostol alone in terms of effectiveness (reduction of surgical interventions), risks of complications, patient satisfaction and preference, and costs.

After establishing the most optimal treatment regimen, a national guideline should be developed as soon as possible to minimize the current practice variation in het Netherlands.[17, 43] Besides describing the specific diagnostic and treatment regimen in case of EPF, recommendations must be made where patients are treated. To our opinion, women may preferably be treated by their own GP and/or midwife backed up by the local hospital, united in a collaborative network (figure 1). This guideline should be developed by the NVOG (the Dutch association for Obstetrics and Gynecology) in close collaboration with the NHG (the Dutch College of General Practitioners) and KNOV (Royal Dutch association of Midwives). Also, if our hypothesis is confirmed by the above-mentioned trial, the recommendations made by the World Health Organization regarding the medical treatment of EPF should be adjusted to M&M.

Development of decision aid

Miscarriage may lead to higher levels of anxiety, depression and post-traumatic stress.[44, 45] The development of a decision aid describing expectant, medical, and (preferably only if strictly necessary) surgical treatment options, could be very helpful for both patient and physician in a shared decision making process to reduce this stress. Patient preferences should be taken seriously during the process of establishing the most optimal treatment regimen. Especially the woman's own opinions concerning the timing of examination and follow-up after treatment is unknown yet. After studying women's preferences and considerations, a thorough and evidence based decision aid can be created, followed by evaluation of the implementation and its effects in clinical practice.

Individualized medicine

Future research should furthermore focus on a risk model and risk factors, on the basis of a multivariate analysis. Predicting successful medical treatment in EPF, i.e. to estimate a woman's individual chance of reaching complete evacuation, will contribute to the correct selection of patients for medical treatment and minimize the risk of complications.[46-49] Recent reports mention that medical treatment may be more effective in case of non-Hispanic ethnicity, null parity, non-obesity, high hCG levels (> 4000 mIU/mL), and high progesterone levels (> 10 nmol/); however, further research is necessary.[48, 49]

Improvement of outcome measurement

With regards to the follow-up of women receiving medical treatment: ultrasonography seems to be of limited value in predicting the presence of intrauterine remnants shortly (1-2 weeks) after medical treatment. Previous studies do not provide any clear evidence which endometrial thickness corresponds best to the presence of intrauterine pregnancy remnants.[27, 50, 51] Further evaluation is needed to see which diagnostic tool is best in determining retained products of conception, for example: clinical signs and symptoms, vaginal examination of the cervix (open or closed ostium internum), (Doppler) ultrasonography, blood tests (hCG) or any combination of these aspects. Also the time period to determine treatment success should be studied.

References

1. Macfarlane KT. The Indications for Dilatation and Curettage. Can Med Assoc J. 1964;90:364-9.
2. Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Hum Reprod. 2004;19:1894-9.
3. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2009;3:CD002253.
4. Rabe T, Basse H, Thuro H, Kiesel L, Runnebaum B. [Effect of the PGE1 methyl analog misoprostol on the pregnant uterus in the first trimester]. Geburtshilfe Frauenheilkd. 1987;47:324-31.
5. el-Refaey H, Hinshaw K, Henshaw R, Smith N, Templeton A. Medical management of missed abortion and anembryonic pregnancy. BMJ. 1992;305:1399.
6. Corey EJ CB, Kürti L. Molecules and Medicine. Wiley; 2007.
7. Mifepriston [23-05-2017]. Available from: http://www.pharmawiki.ch/wiki/index.php?wiki=Mifepriston.
8. Verschoor MAC. Management of first trimester miscarriage; new insight in old dilemmas [dissertation]. Amsterdam: University of Amsterdam; 2017.
9. Lemmers M, Verschoor MA, Hooker AB, Opmeer BC, Limpens J, Huirne JA, et al. Dilatation and curettage increases the risk of subsequent preterm birth: a systematic review and meta-analysis. Hum Reprod. 2016;31:34-45.
10. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update. 2013.
11. Graziosi GC, Bruinse HW, Reuwer PJ, van Kessel PH, Westerweel PE, Mol BW. Misoprostol versus curettage in women with early pregnancy failure: impact on women's health-related quality of life. A randomized controlled trial. Hum Reprod. 2005;20:2340-7.
12. Graziosi GC, Bruinse HW, Reuwer PJ, Mol BW. Women's preferences for misoprostol in case of early pregnancy failure. Eur J Obstet Gynecol Reprod Biol. 2006;124:184-6.
13. Nivel Nivovdg. Substitutie in de zorg is mogelijk. 2016 [cited 08-08-2017]. Available from: https://www.nivel.nl/nl/nieuws/substitutie-de-zorg-mogelijk.
14. Rijksoverheid. Substitutie van zorg. 2008 [cited 08-08-2017.]. Available from: https://www.rijksoverheid.nl/documenten/kamerstukken/2008/09/12/substitutie-van-zorg.
15. van den Berg J, Gordon BB, Snijders MP, Vandenbussche FP, Coppus SF. The added value of mifepristone to non-surgical treatment regimens for uterine evacuation in case of early pregnancy failure: a systematic review of the literature. Eur J Obstet Gynecol Reprod Biol. 2015;195:18-26.
16. van den Berg J, van den Bent JM, Snijders MP, de Heus R, Coppus SF, Vandenbussche FP. Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study. Eur J Obstet Gynecol Reprod Biol. 2014;183:16-9.
17. van den berg J, Hamel CC, Snijders MP, Coppus SF, Vandenbussche FP. Current and future expectations of mifepristone treatment in early pregnancy failure: a survey among Dutch gynecologists. *Submitted*. 2017.
18. Van den Berg J, Snijders MP, Coppus SF, Vandenbussche FP. Mifepristone followed by misoprostol for uterine evacuation in early pregnancy failure: a randomized, double blinded, placebo controlled pilot study. *Submitted*. 2017.
19. Van den Berg J, Hamel CC, Snijders MP, Coppus SF, Vandenbussche FP. Mifepristone and misoprostol versus misoprostol alone for uterine evacuation after early pregnancy failure: a randomized double blinded placebo-controlled comparison (M&M trial). *Submitted*. 2017.
20. van Oppenraaij RH, Goddijn M, Lok CA, Exalto N. [Early pregnancy: revision of the Dutch terminology for clinical and ultrasound findings]. Ned Tijdschr Geneeskd. 2008;152:20-4.
21. Jurkovic D, Overton C, Bender-Atik R. Diagnosis and management of first trimester miscarriage. BMJ. 2013;346:f3676.
22. Van Asselt KM BA, Engelsman N, Hammers-Cupido RJ, Landskröner I, Opstelten W, De Vries CJH. NHG-Standaard Miskraam (Derde herziening). 2017. Available from: https://www.nhg.org/standaarden/volledig/nhg-standaard-miskraam.

23. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002;324:873-5.
24. Wieringa-de Waard M, Vos J, Bonsel GJ, Bindels PJ, Ankum WM. Management of miscarriage: a randomized controlled trial of expectant management versus surgical evacuation. Hum Reprod. 2002;17:2445-50.
25. Graziosi GC, van der Steeg JW, Reuwer PH, Drogtrop AP, Bruinse HW, Mol BW. Economic evaluation of misoprostol in the treatment of early pregnancy failure compared to curettage after an expectant management. Hum Reprod. 2005;20:1067-71.
26. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Bossuyt PM, Huirne JA, et al. MisoREST: Surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: A cohort study. Eur J Obstet Gynecol Reprod Biol. 2017;211:83-9.
27. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Opmeer BC, Bossuyt PM, et al. MisoREST: surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: a randomized controlled trial. Hum Reprod. 2016;31:2421-7.
28. Nanda K, Lopez LM, Grimes DA, Peloggia A, Nanda G. Expectant care versus surgical treatment for miscarriage. Cochrane Database Syst Rev. 2012;3:CD003518.
29. Tristan SB, Gilliam M. First trimester surgical abortion. Clin Obstet Gynecol. 2009;52:151-9.
30. You JH, Chung TK. Expectant, medical or surgical treatment for spontaneous abortion in first trimester of pregnancy: a cost analysis. Hum Reprod. 2005;20:2873-8.
31. Saccone G, Perriera L, Berghella V. Prior uterine evacuation of pregnancy as independent risk factor for preterm birth: a systematic review and metaanalysis. Am J Obstet Gynecol. 2016;214:572-91.
32. NHG. Medicamenteuze overtijdbehandeling veilig en effectief in de eerste lijn, maar mag nog niet worden toegepast door de huisarts. 2016 [cited 08-08-2017]. Available from: https://www.nhg.org/actueel/nieuws/medicamenteuze-overtijdbehandeling-veilig-en-effectief-de-eerste-lijn-maar-mag-nog.
33. Westra D, Kroese M, Ruwaard D. [Substitution of care: what do we know, what should we know, and what should we do?]. Ned Tijdschr Geneeskd. 2017;161:D1354.
34. van Hoof SJ, Kroese ME, Spreeuwenberg MD, Elissen AM, Meerlo RJ, Hanraets MM, et al. Substitution of Hospital Care with Primary Care: Defining the Conditions of Primary Care Plus. Int J Integr Care. 2016;16:12.
35. van Hoof SJ, Spreeuwenberg MD, Kroese ME, Steevens J, Meerlo RJ, Hanraets MM, et al. Substitution of outpatient care with primary care: a feasibility study on the experiences among general practitioners, medical specialists and patients. BMC Fam Pract. 2016;17:108.
36. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. Health Aff (Millwood). 2008;27:759-69.
37. The Association of Early Pregnancy Units (AEPU). [06-07-2017]. Available from: http://www.aepu.org.uk/.
38. Goddijn M, de Jager F, Kaaijk EM, van der Veen F, Ankum WM, Hajenius PJ. Problemen vroeg in de zwangerschap vereisen speciale zorg: 'Jonge zwangerschapsunits'. Ned Tijdschr Geneeskd. 2009;153:A601.
39. Shochet T, Diop A, Gaye A, Nayama M, Sall AB, Bukola F, et al. Sublingual misoprostol versus standard surgical care for treatment of incomplete abortion in five sub-Saharan African countries. BMC Pregnancy Childbirth. 2012;12:127.
40. Elmusharaf K, Byrne E, O'Donovan D. Strategies to increase demand for maternal health services in resource-limited settings: challenges to be addressed. BMC Public Health. 2015;15:870.
41. Tulandi T, Al-Fozan H. Spontaneous abortion: Management. 2017. Available from: http://www.uptodate.com/home.
42. Mifepristone tablet 200ug 2017. Available from: https://www.medicijnkosten.nl.
43. Verschoor MA, Lemmers M, Wekker MZ, Huirne JA, Goddijn M, Mol BW, et al. Practice variation in the management of first trimester miscarriage in the Netherlands: a nationwide survey. Obstet Gynecol Int. 2014;2014:387860.
44. Nikcevic AV, Tunkel SA, Nicolaides KH. Psychological outcomes following missed abortions and provision of follow-up care. Ultrasound Obstet Gynecol. 1998;11:123-8.
45. Farren J, Jalmbrant M, Ameye L, Joash K, Mitchell-Jones N, Tapp S, et al. Post-traumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study. BMJ Open. 2016;6:e011864.
46. Jauniaux E, Johns J, Burton GJ. The role of ultrasound imaging in diagnosing and investigating early pregnancy failure. Ultrasound Obstet Gynecol. 2005;25:613-24.

47. Creinin MD, Huang X, Westhoff C, Barnhart K, Gilles JM, Zhang J, et al. Factors related to successful misoprostol treatment for early pregnancy failure. Obstet Gynecol. 2006;107:901-7.
48. Banerjee AK, Emembolu JO, Habiba M. The association between serum progesterone and outcome of medical management of early fetal demise: a pilot study. J Obstet Gynaecol. 2013;33:384-6.
49. Schreiber CA, Ratcliffe SJ, Quinley KE, Miller C, Sammel MD. Serum biomarkers may help predict successful misoprostol management of early pregnancy failure. Reprod Biol. 2015;15:79-85.
50. Rulin MC, Bornstein SG, Campbell JD. The reliability of ultrasonography in the management of spontaneous abortion, clinically thought to be complete: a prospective study. Am J Obstet Gynecol. 1993;168:12-5.
51. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J, Trial NMoEPF. Endometrial thickness after misoprostol use for early pregnancy failure. Int J Gynaecol Obstet. 2004;86:22-6.

8

Summary

Nederlandse samenvatting

Summary

In **chapter 1** the *background, rationale and aims of this thesis* are described. In the Netherlands, approximately 10,000 women per year undergo some form of treatment in case of early pregnancy failure (EPF). Dilatation and curettage (D&C), although resulting in a high effectiveness of 95-100%, is accompanied by the risk of complications. A non-invasive, medical treatment is misoprostol, used for EPF since approximately 1985. Unfortunately, after one week of expectant management, only in 50-60% of the cases a complete miscarriage is achieved. A new medical treatment option may be pretreatment with mifepristone followed by misoprostol (M&M). This combination has already been proven superior to treatment with misoprostol alone for other indications of termination of pregnancy. In this thesis more insight is provided into the effectiveness of M&M in case of EPF.

A *systematic review* of the existing literature is described in **chapter 2**, evaluating the added value of mifepristone in women with EPF. Electronic databases were searched and all relevant clinical studies reporting on the added value of mifepristone to current nonsurgical treatment regimens were included. Data of sixteen studies (five randomized and eleven non-randomized trials) were extracted using a data extraction sheet (based on the Cochrane Consumers and Communication Review Group's data extraction template). The methodological quality was assessed using the Cochrane Collaboration Risk of Bias tool. The available evidence revealed that medical treatment appears to be a safe alternative to surgical evacuation, leading to savings and a reduced number of (serious) complications. Success rates of M&M in case of EPF varied between 52% and 95%. Unfortunately, large heterogeneity existed in treatment regimens between studies. Therefore, up until now the existing evidence appears insufficient to draw firm conclusions about the added value of mifepristone to misoprostol in case of EPF.

Chapter 3 describes a *retrospective study*, which has been performed at the Radboud University Medical Center. Between 2008 and 2013, patients were already pretreated with mifepristone (200 – 600mg) followed by misoprostol (400 – 800µg). A total number of 301 patients with EPF between 6-14 weeks were included. 199 patients received M&M, and 102 patients received misoprostol alone. Complete expulsion of the products of conception in women treated with M&M was 67%; in women treated with misoprostol alone a success rate of 54% was reported ($p = 0.045$). M&M treatment appeared more effective in case of EPF compared to misoprostol alone, however, these findings have to be confirmed by a sufficiently powered, multicenter, randomized, and placebo-controlled trial.

In **chapter 4** the current and future expectations of M&M in case of EPF are evaluated, using a digital *questionnaire* sent to a representative sample of gynecologic centers in the Netherlands (25/79 = 32%). Questions were asked regarding the presence of a local

protocol, the current prescription of medical treatment, and the use and future expectations of mifepristone in case of EPF. We also focused on follow-up procedures after medical treatment since literature concerning the most optimal follow-up period and diagnostic tool is lacking. A local protocol was present in 88% with a significant difference between academic and teaching (100%) versus non-teaching centers (57,1%). The first choice of treatment was medical in 54,5% of centers. Only 20% of the respondents "always" or "usually" prescribed M&M in case of EPF, estimating the complete evacuation rate between 50% and 100% with similar side effects compared to treatment with misoprostol alone. The most given reason for not prescribing mifepristone for EPF was lack of sufficient evidence of effectiveness. An average increase in success rate of 21,7% was required to prescribe mifepristone in the future for EPF. Treatment effect was usually assessed by clinical signs and ultrasonography; using 4 – 15 millimeters cut-off points for total endometrial thickness to diagnose complete evacuation. If a complete evacuation was not achieved by the initial medical treatment, expectant management was proposed just as often as direct surgical intervention (i.e. dilatation and curettage or hysteroscopy). Concluding, although in most centers in the Netherlands a local protocol is present, there is still a large practice variation in the treatment of EPF. The use of M&M in EPF is not common practice, due to the lack of sufficient evidence. However, a scientifically proven increase in effectiveness may lead to prescription of M&M in more centers in the future.

In **chapter 5** a two-centered, prospective, two-armed, randomized, double blinded, placebo-controlled *pilot study* is described evaluating M&M treatment in case of EPF, and to test feasibility and recruitment of the proposed study protocol. In the Radboud University Medical Centre and Canisius-Wilhelmina Hospital in Nijmegen (the Netherlands), women with a diagnosis of EPF between 6 and 14 weeks of gestation were included after at least one week of expectant management. 40 women were included; on day one 20 women were pre-treated with 600mg mifepristone (orally) and 20 women received placebo pretreatment. In both groups this was followed by misoprostol 800µg (oral) on day 3, and if necessary on day 4. A transvaginal ultrasonography six to nine days after treatment determined the primary outcome. Successful treatment was defined by an endometrial thickness < 15mm or no evidence of retained products of conception using only the allocated therapy by randomization. Complete evacuation was achieved in 68,4% of women in the M&M group versus 40% of women in the placebo group. The need for surgical intervention, was significantly lower in the M&M group as compared to the placebo group: 10,5% versus 50% respectively. No serious adverse events were reported in either group. Quality of life was similar in both groups. The majority of women, 84,6%, in the M&M group versus 62,6% of women in the placebo group, would choose medical treatment again if necessary. In the M&M group 92,3% and in the placebo group 75% of women would recommend medical treatment to a friend in case of EPF. Feasibility of the study protocol was confirmed and recruitment of patients was as expected.

Chapter 6 describes the definitive *study protocol* with a sufficient number of patients to compare addition of mifepristone (M&M) to the standard treatment with misoprostol alone in terms of complete evacuation of products of conception from the uterus, patient satisfaction, complications, side effects and cost-effectiveness (NL 62449.091.17, NCT03212352). Due to our data from the retrospective and pilot study we were able to optimize the study protocol; the multicenter trial will start second half of 2017.

A *general discussion* is presented in **chapter 7**, evaluating the findings of this thesis. Implications for current practice and recommendations of future research are made to improve the treatment of women with early pregnancy failure including the substation of health care towards general practitioners and midwifes.

Samenvatting

In **hoofdstuk 1** worden de *achtergrond en doelstellingen* van dit proefschrift beschreven. In Nederland ondergaan ongeveer 10.000 vrouwen per jaar een behandeling vanwege een miskraam. (Zuig)curettage onder enige vorm van anesthesie in een kliniek of ziekenhuis gaat ondanks een hoog slagingspercentage van 95-100%, gepaard met een risico op korte en lange termijn complicaties. Een inmiddels veel toegepaste niet-operatieve, medicamenteuze behandeling bestaat uit het gebruik van misoprostol tabletten. Helaas wordt, na ruim 1 week afwachten op een spontane miskraam, met misoprostol slechts in 50-60% van de vrouwen een volledige miskraam bereikt. Een nieuwe optie is de combinatiebehandeling: voorbehandeling met mifepriston gevolgd door misoprostol tabletten (M&M). Deze combinatie blijkt bewezen superieur in vergelijking met de behandeling met alleen misoprostol voor andere indicaties voor het beëindigen van zwangerschappen zoals bij abortus provocatus. Dit proefschrift verschaft verder inzicht in de effectiviteit van M&M bij vrouwen met een miskraam.

Een *systematisch literatuuroverzicht* wordt beschreven in **hoofdstuk 2** waarin de toegevoegde waarde van mifepriston bij vrouwen met een miskraam wordt geëvalueerd. Diverse elektronische databanken werden systematisch doorzocht en studies, welke rapporteren over de toegevoegde waarde van mifepriston aan huidige niet-chirurgische behandelmethoden, werden geanalyseerd. Gegevens van zestien studies (vijf gerandomiseerde en elf niet-gerandomiseerde studies) werden geëxtraheerd met behulp van een data-extractie sheet (op basis van de "Cochrane Consumers and Communication Review Group's data extraction template"). De methodologische kwaliteit werd beoordeeld met behulp van de "Cochrane Collaboration Risk of Bias tool". De slagingspercentages van de behandeling met mifepriston én misoprostol varieerden tussen 52% en 95%. Helaas bestond er een grote diversiteit in de behandelschema's tussen deze studies. Concluderend is er tot op heden nog onvoldoende wetenschappelijk bewijs omtrent de toegevoegde waarde van mifepriston aan misoprostol bij de behandeling van vrouwen met een miskraam.

Hoofdstuk 3 beschrijft een *retrospectieve studie* welke is uitgevoerd in het Radboud Universitair Medisch Centrum te Nijmegen. Tussen 2008 en 2013 werden aldaar reeds patiënten met miskraam behandeld met de combinatie van mifepriston voorbehandeling (200 - 600mg) gevolgd door misoprostol (400 - 800µg). Een totaal aantal van 301 patiënten met een miskraam werd geïncludeerd bij een zwangerschapsduur tussen 6 en 14 weken. 199 patiënten kregen de M&M combinatie voorgeschreven en 102 patiënten kregen alleen misoprostol. Een succespercentage (d.w.z. een complete miskraam) van 67% in de M&M groep versus 54% in de groep die alleen misoprostol kreeg resulteerde in een significant verschil ($p = 0.045$).

In **hoofdstuk 4** worden de huidige ervaringen en toekomstige verwachtingen van M&M bij vrouwen met een miskraam geëvalueerd m.b.v. een digitale *enquête* verzonden naar een representatieve sample van gynaecologische centra in Nederland (25/79 = 32%). In deze elektronische enquête zijn vragen omtrent de aanwezigheid van een lokaal protocol, het voorschrijven van een medicamenteuze behandeling, het huidige gebruik en de toekomstige verwachtingen van mifepriston bij vrouwen met een miskraam gesteld. Daarnaast lag de focus van enkele vragen op de evaluatie/follow-up procedure na medicamenteuze behandeling. Een lokaal protocol was aanwezig in 88% van de centra, met een significant verschil tussen academische en perifere opleidingsklinieken (100%) versus perifere niet-opleidingsklinieken (57,1%). De eerste keus van behandeling was medicamenteus in 54,5%. Slechts 20% van de respondenten schreven M&M "altijd" of "meestal" voor aan vrouwen met een miskraam, waarbij het slagingspercentage tussen 50% en 100% werd geschat zonder toename van het aantal bijwerkingen. De meest gegeven reden om mifepriston (nog) niet voor te schrijven was gebrek aan wetenschappelijk bewijs voor deze indicatie. Een gemiddelde toename van het slagingspercentage van 21,7% was gewenst om mifepriston in de toekomst wel voor te voorschrijven in geval van een miskraam. Het effect van de behandeling werd meestal beoordeeld m.b.v. echoscopie in combinatie met klinische symptomen (64%). De echoscopisch vast te stellen afkapwaarde van de totale endometrium (baarmoederslijmvlies) dikte waarbij men een complete miskraam diagnosticeerde varieert tussen 4 en 15 millimeter. Als er sprake was van een zodanig geconstateerde "incomplete" miskraam, werd een expectatief beleid in de diverse klinieken even vaak voorgesteld als een chirurgische interventie (curettage). Concluderend, alhoewel er in de meeste centra in Nederland een lokaal protocol aanwezig is, bestaat er nog steeds een grote praktijkvariatie in de behandeling van vrouwen met een miskraam in NL. Het gebruik van M&M is (nog) niet gebruikelijk voor deze indicatie door een reeds eerder vermeld gebrek aan wetenschappelijk bewijs. Echter, een bewezen toename van de effectiviteit kan ervoor zorgen dat gynaecologen M&M in de toekomst wel gaan voorschrijven.

Een prospectief, gerandomiseerd, dubbelblind, placebo-gecontroleerd *pilotstudie* werd uitgevoerd in twee centra om M&M-behandeling bij vrouwen met een miskraam wetenschappelijk te evalueren en om de haalbaarheid van het voorgestelde definitieve studieprotocol te toetsen (**hoofdstuk 5**). Vrouwen met miskraam tussen 6 en 14 weken zwangerschap werden na minstens één week expectatief beleid geïncludeerd in het Radboud Universitair Medisch Centrum en het Canisius-Wilhelmina Ziekenhuis te Nijmegen. In totaal werden 40 vrouwen geïncludeerd, 20 vrouwen werden behandeld met 600mg mifepriston (oraal), 20 vrouwen kregen een placebo tablet. In beide groepen werd dit gevolgd door de medicamenteuze behandeling bestaande uit misoprostol 800µg oraal. Een transvaginale echoscopie zes tot negen dagen na behandeling, werd verricht om de primaire uitkomstmaat vast te stellen. Een succesvolle behandeling was gedefinieerd als

een totale endometrium (baarmoederslijmvlies) dikte minder dan 15mm zonder dat de vrouw een andere behandeling naast de toegewezen behandeling door randomisatie had ondergaan. Een complete miskraam werd bereikt in 68,4% van de vrouwen in de M&M groep versus 40% van de vrouwen in de placebo groep. De noodzaak voor een aanvullende chirurgische interventie (curettage) was significant lager in de M&M groep in vergelijking met de placebogroep: respectievelijk 10,5% en 50%. Er werden geen ernstige bijwerkingen gerapporteerd en de gemeten kwaliteit van het leven was vergelijkbaar in beide groepen. De meerderheid van de vrouwen, 84,6%, in de M&M-groep versus 62,6% van de vrouwen in de placebogroep, zou indien noodzakelijk bij een volgende miskraam weer dezelfde behandeling verkiezen. In de M&M groep zou 92,3% en in de placebogroep 75% van de vrouwen deze medicamenteuze behandeling aanbevelen aan een vriendin. De pilotstudie, waarbij haalbaarheid en de inclusie van patiënten was zoals verwacht, leidde tot enkele aanpassingen in het definitieve protocol.

Hoofdstuk 6 beschrijft het definitieve multicenter *studieprotocol* (NL 62449.091.17) waarin de toevoeging van mifepriston aan de behandeling met misoprostol wordt vergeleken voor wat betreft effectiviteit (= primaire uitkomstmaat), patiënttevredenheid, complicaties, bijwerkingen en kosteneffectiviteit. Op basis van gegevens en resultaten verkregen uit de in dit proefschrift beschreven (retrospectieve- en pilot) studies, is het studieprotocol geoptimaliseerd, hetgeen najaar 2017 zal leiden tot start van deze zogenaamde multicenter M&M trial.

In **hoofdstuk 7** wordt een *algemene discussie* beschreven, waarbij de bevindingen van dit proefschrift worden geëvalueerd in het licht van de huidige behandelmogelijkheden van vrouwen met een miskraam. Implicaties voor de huidige praktijk en aanbevelingen voor toekomstig onderzoek worden gedaan om de behandeling verder kwalitatief en kosteneffectief te verbeteren, waarbij onzes inziens een transitie van tweede naar eerstelijns zorg is aangewezen.

Abbreviations
Questionnaires
Data management
Dankwoord
Curriculum vitae
Portfolio

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
AG	Anembryonic gestation
APD	Anterior-posterior (double) layer endometrial diameter
CRF	Case report form
CSQ	Client satisfaction Questionnaire
D&C	Dilatation and curettage
EFD	Embryonic or fetal demise
EPF	Early pregnancy failure
EPU	Early pregnancy unit
EuroQol-VAS	EuroQol visual analogue scale
FIGO	International Federation of Gynecology and Obstetrics
GP	General practitioner
GS	Gestational sac
M&M	mifepristone and misoprostol
NVOG	Nederlandse Vereniging voor Obstetrie & Gynaecologie
RCOG	Royal College of Obstetricians and Gynecologists
SF-36	Short Form 36
US	Ultrasound
WHO	World Health Organization

Questionnaires

A Dutch survey among gynecologists (chapter 4)

De medicamenteuze behandeling van vrouwen met een miskraam is vooralsnog niet optimaal. Hierdoor worden nog veel curettages verricht met het bijkomende risico op complicaties. Deze enquête is bedoeld om meer inzicht te krijgen in het gebruik van mife-priston in Nederland. Schrijft u weleens mifepriston voor?

1. Wat is uw geslacht?
   - o Man
   - o Vrouw

2. Wat is uw leeftijd?
   ……

3. Hoeveel jaar bent u gynaecoloog?
   ……

4. In welke kliniek bent u werkzaam?
   - o Academisch centrum
   - o Perifeer opleidingsziekenhuis
   - o Perifeer ziekenhuis

5. De naam van de kliniek waar u werkzaam bent is:
   ……

Lokaal protocol

6. Is er in uw ziekenhuis een lokaal protocol miskraambehandeling?
   - o Ja
   - o Nee

7. Wat is de eerste keus behandeling bij een miskraam (na een expectatieve periode) volgens het lokale protocol van uw ziekenhuis?
   - o Medicamenteus
   - o Chirurgie
   - o Voorkeur van patiënte en/of arts
   - o Er is geen lokaal protocol

Lokaal protocol / afspraken

Alle vragen gaan over de behandeling van vrouwen met een miskraam zónder lichamelijke klachten zoals buikpijn of bloedverlies.

8. Zijn er in uw ziekenhuis mondelinge afspraken omtrent de eerste keus van behandeling?
   - o Ja, medicamenteus
   - o Ja, chirurgie
   - o Ja, voorkeur van patiënte en/of arts
   - o Nee

Keuze behandeling

Alle vragen gaan over de behandeling van vrouwen met een miskraam zónder lichamelijke klachten zoals buikpijn of bloedverlies.

9. Start u de behandeling na minstens één week expectatief beleid? Deze week afwachten kan ook in de eerste lijn hebben plaats gevonden.
   - o Altijd
   - o Meestal wel
   - o Alleen op indicatie
   - o Nooit

10. Schrijft u weleens een medicamenteuze behandeling voor?
    - o Ja
    - o Nee

11. Vanwege welke reden bespreekt u geen medicamenteuze behandeling? Meerdere antwoorden zijn mogelijk.
    - o Lage effectiviteit
    - o Langer behandeltraject
    - o Staat niet in lokaal protocol beschreven c.q. is niet volgens lokale afspraken
    - o Medico-legaal: i.v.m. off-label gebruik misoprostol en/of mifepriston
    - o Ik bespreek wel een medicamenteuze behandeling

Mifepriston

Alle vragen gaan over de behandeling van vrouwen met een miskraam zónder lichamelijke klachten zoals buikpijn of bloedverlies.

12. Wordt mifepriston in uw lokale protocol beschreven?
    - o Ja
    - o Nee, dit wordt niet beschreven
    - o Nee, er is geen lokaal protocol

13. Schrijft u mifepriston voor?
    - o Altijd
    - o Meestal wel
    - o Alleen op indicatie
    - o Nooit

14. Waarom schrijft u geen mifepriston voor? Meerdere antwoorden zijn mogelijk.
    - o Ontbreken van wetenschappelijk bewijs
    - o Medico-legaal: is hier niet voor geregistreerd
    - o Kosten
    - o Bijwerkingen
    - o Ik schrijf wel mifepriston voor
    - o Anders, namelijk …

15. Welke dosering mifepriston schrijft u voor?
    - o 200mg
    - o 400mg
    - o 600mg
    - o Anders, namelijk …

16. De bijsluiter beschrijft dat mifepriston onder toezicht van een arts of één van diens medewerkers moet worden ingenomen. Hoe is de inname in uw ziekenhuis?
    - o Onder toezicht van een arts of andere medewerker
    - o Inname vind niet onder toezicht plaats maar wel in het ziekenhuis
    - o Inname vind thuis plaats

17. Welk tijdsinterval hanteert u tussen inname van mifepriston en start van misoprostol?
    ……

18. Kunt u het effect inschatten van de behandeling met mifepriston en misoprostol? Het aantal complete miskramen ligt tussen:
    - o 0 – 25 %
    - o 25 – 50 %
    - o 50 – 75 %
    - o 75 – 100%

19. Kunt u een inschatting maken van de frequentie van bijwerkingen bij het gebruik van mifepriston?
    - o Meer dan bij de behandeling met alleen misoprostol
    - o Evenveel als bij de behandeling met alleen misoprostol
    - o Minder dan bij de behandeling met alleen misoprostol

Kosten

20. Een medicamenteuze behandeling met alleen misoprostol kost ongeveer 2 euro. Mifepriston is, afhankelijk van de dosering, circa 12 tot 36 euro. Bij welke effectiviteit zou u besluiten mifepriston wel voor te schrijven? Ga hierbij uit van een effectiviteit van een behandeling met alleen misoprostol van 55%. Bij een totale effectiviteit (in procent) van: ……

Follow-up

21. Wanneer spreekt u een eerste controle na een medicamenteuze behandeling af?
    - o Na 1 week
    - o Na 6 weken
    - o Na de eerstvolgende menstruatie
    - o Niet, alleen bij klachten
    - o Anders, namelijk…

22. Hoe bepaald u of de miskraam compleet is?
    - o Echoscopie
    - o Klinisch beeld i.c.m. echoscopie
    - o Alleen o.b.v. klinisch beeld
    - o Anders, namelijk…

23. Hoe beoordeeld u bij echoscopie of de uterus leeg is?
    - o "Op het oog": beeld wel/niet passend bij een rest
    - o Meting van totale endometrium dikte (TED)
    - o Er wordt geen echo gemaakt
    - o Anders, namelijk…

24. Vanaf welke totale endometrium dikte spreekt u van een complete miskraam?
    ……

25. Wat is uw beleidsvoorstel in geval van een rest? Ga hierbij uit van een hemodynamisch stabiele patiënt zonder tekenen van infectie.
    - o Expectatief
    - o Curettage
    - o Curettage onder echogeleide
    - o Hysteroscopie
    - o Nogmaals behandeling met misoprostol
    - o Anders, namelijk…

26. Indien u een afwachtend beleid afspreekt, wanneer ziet u patiënte weer terug voor controle?
    - o Na de eerstvolgende menstruatie
    - o Niet, alleen bij klachten
    - o Anders, namelijk…

Wij willen u hartelijk bedanken voor het invullen van deze vragenlijst.

Quality of life and patient satisfaction: a pilot study (chapter 5)

U heeft toestemming gegeven om deel te nemen aan de M&M-studie. In het kader van deze studie willen we graag in kaart brengen hoe uw gezondheidstoestand en tevredenheid op dit moment is. Door het beantwoorden van deze vragenlijst draagt u eraan bij dat we de zorg rondom miskramen kunnen verbeteren. Daarom vragen we u om de vragenlijst in te vullen, dit zal u enkele minuten van uw tijd kosten. U wordt verzocht alle vragen te beantwoorden. Als vragen niet helemaal duidelijk zijn kunt u contact opnemen met uw ziekenhuis. Deze vragenlijst zal strikt vertrouwelijk en anoniem verwerkt worden.

Short-form 36

In deze vragenlijst wordt naar uw gezondheid gevraagd. Wilt u alstublieft elke vraag beantwoorden door het juiste antwoord aan te klikken? Wanneer u twijfelt, probeer dan het antwoord te geven dat het meest van toepassing is.

1. Wat vindt u, over het algemeen genomen, van uw gezondheid?
   - o uitstekend
   - o zeer goed
   - o goed
   - o matig
   - o slecht

2. In vergelijking met een jaar geleden, hoe zou u nu uw gezondheid beoordelen?
   - o veel beter dan een jaar geleden
   - o iets beter dan een jaar geleden
   - o ongeveer hetzelfde als een jaar geleden
   - o iets slechter dan een jaar geleden
   - o veel slechter dan een jaar geleden

3. De volgende vragen gaan over dagelijkse bezigheden. Wordt u door uw gezondheid op dit moment beperkt bij deze bezigheden? Zo ja, in welke mate?

	Ja, ernstig beperkt	Ja, een beetje beperkt	Nee, helemaal niet beperkt
Forse inspanning zoals hardlopen, zware voorwerpen tillen, inspannend sporten	o	o	o
Matige inspanning zoals het verplaatsen van een tafel, stofzuigen, fietsen	o	o	o
Tillen of boodschappen dragen	o	o	o
Een paar trappen oplopen	o	o	o
Eén trap oplopen	o	o	o
Buigen, knielen of bukken	o	o	o
Meer dan een kilometer lopen	o	o	o
Een halve kilometer lopen	o	o	o
Honderd meter lopen	o	o	o
Uzelf wassen of aankleden	o	o	o

4. Had u, ten gevolge van uw lichamelijke gezondheid de afgelopen 4 weken één van de volgende problemen bij uw werk of andere dagelijkse bezigheden? Vink aan wat van toepassing is, meerdere antwoorden zijn mogelijk.
   - o Ja, u heeft minder tijd kunnen besteden aan werk of andere bezigheden
   - o Ja, u heeft minder bereikt dan u zou willen
   - o Ja, u was beperkt in het soort werk of het soort bezigheden
   - o Ja, u had moeite met het werk of andere bezigheden (het kostte u bijvoorbeeld extra inspanning)
   - o Nee

5. Had u, ten gevolge van een emotioneel probleem (bijvoorbeeld doordat u zich depressief of angstig voelde), de afgelopen 4 weken één van de volgende problemen bij uw werk of andere dagelijkse bezigheden? Vink aan wat van toepassing is, meerdere antwoorden zijn mogelijk.
   - o Ja, u heeft minder tijd kunnen besteden aan werk of andere bezigheden
   - o Ja, u heeft minder bereikt dan u zou willen
   - o Ja, u heeft het werk of andere bezigheden niet zo zorgvuldig gedaan als u gewend bent
   - o Nee

6. In hoeverre heeft uw lichamelijke gezondheid of hebben uw emotionele problemen u de afgelopen 4 weken belemmerd in uw normale sociale bezigheden met gezin, vrienden, buren of anderen?
   - o helemaal niet
   - o enigszins
   - o nogal
   - o veel
   - o heel erg veel

7. Hoeveel pijn had u de afgelopen 4 weken?
   - o geen
   - o heel licht
   - o licht
   - o nogal
   - o ernstig
   - o heel ernstig

8. In welke mate heeft pijn u de afgelopen 4 weken belemmerd bij uw normale werkzaamheden (zowel werk buitenshuis als huishoudelijk werk)?
   - o helemaal niet
   - o enigszins
   - o nogal
   - o veel
   - o heel erg veel

De volgende vragen gaan over hoe u zich de afgelopen 4 weken heeft gevoeld. Wilt u bij elke vraag het antwoord aankruisen dat het beste aansluit bij hoe U zich heeft gevoeld?

9. Hoe vaak gedurende de afgelopen 4 weken:

	Voortdurend	Meestal	Vaak	Soms	Zelden	Nooit
Voelde u zich levenslustig	o	o	o	o	o	o
Voelde u zich erg zenuwachtig	o	o	o	o	o	o
Zat u zo erg in de put dat niets u kon opvrolijken	o	o	o	o	o	o
Voelde u zich kalm en rustig	o	o	o	o	o	o
Voelde u zich erg energiek	o	o	o	o	o	o
Voelde u zich neerslachtig en somber	o	o	o	o	o	o
Voelde u zich uitgeblust	o	o	o	o	o	o
Voelde u zich gelukkig	o	o	o	o	o	o
Voelde u zich moe	o	o	o	o	o	o

10. Hoe vaak hebben uw lichamelijke gezondheid of emotionele problemen gedurende de afgelopen 4 weken uw sociale activiteiten (zoals bezoek aan vrienden of naaste familieleden) belemmerd?

o voortdurend
o meestal
o soms
o zelden
o nooit

11. Wilt u bij de volgende vragen het antwoord kiezen dat het beste weergeeft hoe juist of onjuist u elke uitspraak voor uzelf vindt?

	Volkomen juist	Groten-deels juist	Weet ik niet	Groten-deels onjuist	Volkomen onjuist
Ik lijk gemakkelijker ziek te worden dan andere mensen	o	o	o	o	o
Ik ben net zo gezond als andere mensen die ik ken	o	o	o	o	o
Ik verwacht dat mijn gezondheid achteruit zal gaan	o	o	o	o	o
Mijn gezondheid is uitstekend	o	o	o	o	o

EuroQol-VAS

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent "100" de beste gezondheidstoestand die u zich kunt voorstellen, en "0" de slechtste gezondheidstoestand die u zich kunt voorstellen. Geef hiernaast aan welk punt op de meetschaal volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand vandaag is. Uw gezondheidstoestand vandaag is.

|----------|----------|----------|----------|
0 25 50 75 100

Client Satisfaction Questionnaire

Met deze vragenlijst kunnen we de behandeling evalueren en verder verbeteren. We zijn geïnteresseerd in uw oprechte mening, positief of negatief, over de behandeling die u hebt ontvangen. Gelieve alle vragen te beantwoorden.

1) Hoe zou je de kwaliteit van de behandeling die je kreeg beoordelen?
   - o Uitstekend
   - o Goed
   - o Redelijk
   - o Slecht

2) Kreeg je de soort behandeling die je wou?
   - o Neen, zeker niet
   - o Neen, niet echt
   - o Ja, over het algemeen wel
   - o Ja, ongetwijfeld

3) In welke mate kwam de behandeling aan jouw noden tegemoet?
   - o Al mijn behoeften zijn vervuld
   - o De meeste van mijn behoeften zijn vervuld
   - o Slechts een klein deel van mijn behoeften is vervuld
   - o Geen van mijn behoeften zijn vervuld

4) Als een vriend gelijkaardige hulp nodig heeft, zou je hem of haar deze behandeling aanraden?
   - o Zeker niet
   - o Niet echt
   - o Over het algemeen wel
   - o Ongetwijfeld

5) Hoe tevreden ben je met de behandeling die je hebt gekregen?
   - o Redelijk ontevreden
   - o Onverschillig/licht ontevreden
   - o Grotendeels tevreden
   - o Heel tevreden

6) Heeft de behandeling die je kreeg je geholpen om effectiever om te gaan met je problemen?
   - o Ja, ze hielpen enorm
   - o Ja, ze hielpen een beetje
   - o Neen, ze hielpen echt niet
   - o Neen, ze maakten het erger

7) In het algemeen, hoe tevreden ben je met de behandeling die je hebt gekregen?
   - o Heel tevreden
   - o Grotendeels tevreden
   - o Onverschillig/licht ontevreden
   - o Redelijk ontevreden

8) Als je opnieuw hulp zou zoeken, zou je opnieuw kiezen voor deze behandeling?
   - o Zeker niet
   - o Niet echt
   - o Over het algemeen wel
   - o Ongetwijfeld

Wij willen u hartelijk bedanken voor het invullen van deze vragenlijst. Nogmaals wijzen wij u erop dat deze gegevens strikt vertrouwelijk en anoniem worden verwerkt.

Research data management according to the FAIR principles

Handling of all study data concerning this thesis "Mifepristone in the management of early pregnancy failure" is the responsibility of the coordinating investigator and the Radboud University Medical Center Nijmegen, the Netherlands.

The pilot study protocol is open, free and universally accessible at:
1) http://toetsingonline.nl (NL 57892.091.16)
2) http://www.trialregister.nl (NTR 6109)

Data was retrieved from paper and electronic patient records, and directly entered into a validated digital database (Castor EDC). Data was organized under anonymous coding (consecutively assigned study number). The data was stored apart from the person's identifying information. Digital questionnaires were sent using Castor EDC and directly stored in this database. During the clinical trial, a sealed envelope containing the code list was locked in a GCP-compliant cabinet at the Clinical Trials Unit of Radboudumc (route 864, AKF-number 1830).

The validated digital data management system Castor EDC was used to collect and store all (meta)data. (Meta)data are stored on secure Castor servers as well as on the secure Radboudumc computer network.

Anonymous data was analyzed using SPSS version 24.0. A list containing the person's identifying information was stored in a GCP-compliant cabinet. The data and analysis files, as well ass the code list, were archived after completion of the trial on a locked folder of the secure Radboudumc computer network.

Dankwoord

Eindelijk is het einde van mijn onderzoek in zicht, waarmee ik niet alleen een proefschrift maar ook een ander doel heb bereikt: een opleidingsplek tot gynaecoloog! Zonder de hulp, steun en aanmoedigingen van vele mensen om mij heen was dit nooit gelukt, bedankt!

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Curriculum Vitae

Joyce van den Berg werd geboren op 27 oktober 1984 te Nijkerk waar zij samen met haar jongere broer Roy is opgegroeid. In 2002 behaalde zij haar vwo-diploma (profiel Natuur & Gezondheid met Latijn) aan 't Hooghe Landt College te Amersfoort waarna zij startte met de studie Geneeskunde aan de Vrije Universiteit te Amsterdam. Van begin af aan is er interesse geweest in de gynaecologie, echter wekte ook de neurologie haar interesse wat ertoe leidde dat zij het profiel Neurowetenschappen met goed gevolg afrondde. Tijdens de co-schappen bleek haar hart bij de obstetrie en gynaecologie te liggen, en het oudste co-schap werd met goed succes op deze afdeling afgerond (Kennemer Gasthuis, Haarlem). Het keuze co-schap volgde zij bij een eerstelijns verloskundigen praktijk (Laan van de Helende Meesters, Amstelveen) waar nog meer ervaring met verloskunde werd opgedaan. Na afronding van de studie Geneeskunde eind 2008 begon zij begin 2009 als ANIOS Obstetrie & Gynaecologie in het Medisch Centrum Alkmaar (opleider dr. A.H. Adriaanse). Medio 2010 begon zij als ANIOS Obstetrie en Gynaecologie in het Canisius-Wilhelmina Ziekenhuis te Nijmegen (opleiders dr. J.M.J. Sporken en dr. M.P.L.M. Snijders). Alhier begon zij naast haar klinische taken als ANIOS dit promotieonderzoek in samenwerking met het Radboud Universitair Medisch Centrum te Nijmegen. Na afronding van het promotie-traject zal zij starten met de opleiding tot gynaecoloog. Tijdens de studie en ANIOS-tijd in Alkmaar woonde Joyce van den Berg in Amsterdam, daarna is zij is terugverhuisd naar haar geboortestad Nijkerk waar zij samenwoont met Marco Schuurman. Samen maakten ze de website: joycevandenberg.doctor.

Portfolio

Name PhD student:	Joyce van den Berg
PhD period:	August 2013 – August 2017
Name PhD supervisors	prof. dr. F.P.H.A. Vandenbussche, dr. M.P.M.L. Snijders, dr. S.F.P.J. Coppus

List of publications

The added value of mifepristone to non-surgical treatment regimens for uterine evacuation in case of early pregnancy failure: a systematic review of the literature.
***Van den Berg J**, Gordon BB, Snijders MP, Vandenbussche FP, Coppus SF.*
Eur J Obstet Gynecol Reprod Biol. 2015 Sep 30;195:18-26.

Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study.
***Van den Berg J**, van den Bent JM, Snijders MP, de Heus R, Coppus SF, Vandenbussche FP.*
Eur J Obstet Gynecol Reprod Biol. 2014 Dec;183:16-9.

Bicyclist's vulva.
***Van den Berg J**, Franssen AM.*
NTOG 2014 Okt;127:394-96.

Oral presentations	**Year**
Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study. Avond van de Wetenschap, CWZ Nijmegen. Winnaar publieksprijs.	2016
Aankondiging M&M-trial. Kwartaalbijeenkomst Consortiumbestuur Benigne Gynaecologie.	2013
Mifepristone én misoprostol bij een miskraam – M&M Trial. Symposium Jonge Zwangerschap, Erasmus MC Rotterdam.	2013

Courses

E-BROK (electronische Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers)	2016
Good Clinical Practice (herregistratie)	2012 (2016)
Schrijven van een wetenschappelijke publicatie, KNMG.	2012
SPSS	2012