LUND UNIVERSITY

Aspects of Miscarriage Management. Efficiency, safety, psychological impact and future fertility.

Fernlund, Anna

2021

Document Version:
Publisher's PDF, also known as Version of record

[Link to publication](#)

Citation for published version (APA):
Fernlund, A. (2021). *Aspects of Miscarriage Management. Efficiency, safety, psychological impact and future fertility.* [Doctoral Thesis (compilation), Department of Clinical Sciences, Malmö]. Lund University, Faculty of Medicine.

Total number of authors:
1

Aspects of miscarriage management

Efficiency, safety, psychological impact and future fertility

ANNA FERNLUND
DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY | LUND UNIVERSITY

Aspects of miscarriage management

Aspects of Miscarriage Management

Efficiency, safety, psychological impact and future fertility

Anna Fernlund

LUND UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended in the Library of the Dept. of Obstetrics and Gynecology, Skåne University Hospital, Malmö. October 29th 2021 at 13:00.

Faculty opponent
Professor Christina Bergh, Gothenburg University

Organization LUND UNIVERSITY	Document name DOCTORIAL DISSERTATION	
	Date of issue October 21 2021	
Author(s): Anna Fernlund	Sponsoring organization	

Title and subtitle
Aspects of miscarriage management, Efficiency, safety, psychological impact and future fertility

Abstract

Aims: To compare treatment with vaginal misoprostol and expectant management in women with early miscarriage reporting vaginal bleeding. Treatment efficiency, complications, side effects, psychological reactions, patient satisfaction and subsequent fertility were compared. Variables were explored with respect to their ability to predict treatment success. **Methods:** Randomized controlled trial. Women with embryonic or anembryonic miscarriage and vaginal bleeding were randomized (1:1) to expectant management or treatment with vaginal misoprostol, 800μg single dose. Scheduled follow up until complete miscarriage (no gestational sac in uterus and maximum diameter of intracavitary contents < 15 mm) was achieved, at most 31 days. Analysis was by intention to treat. Main outcome measure: rate of complete miscarriage without D&E ≤10days. Predefined secondary outcomes: complications, side-effects, rate of complete miscarriage within 17, 24, and 31 days after randomization, levels of anxiety, depressive symptoms, grief and satisfaction with treatment from randomization until 14 months after complete miscarriage and reproductive outcome at 14 months after complete miscarriage. Multivariable regression analysis of pre-defined variables in relation to their ability to predict treatment success in. **Results:** 94 women were randomized to misoprostol and 90 women to expectant management. More women in the misoprostol group than in the expectant group achieved complete miscarriage within 10 days: 62/94 (66.0%) *vs* 39/90 (43.3%) (risk difference (RD)=22.6%; 95% CI, 7.5–36.5%). The cumulative rate of complete miscarriage was higher in the misoprostol group at all time points - 17, 24 and 31days. At 31 days, complete miscarriage was achieved by 81/94 (86.2%) of women treated with misoprostol *vs* 55/90 (61.1%) of the women in the expectantly managed group (RD=25.1%; 95% CI, 11.6–37.5%). 11% (10/94) of women in the misoprostol group underwent D&E *vs* 34% (31/90) in the expectantly managed group (RD = -23.8; 95% CI, -35.8 to -11.1). Treatment success after expectant management was more common in embryonic than in anmebryonic miscarriages: complete miscarriage within 10 days 53.8% (28/52) versus 33.0% (11/33) (*P*=0.06). No variable predicted success after misoprostol treatment. Variables independently associated with treatment success after expectant management were gestational age according to LMP, mean gestational sac diameter and CRL (or type of miscarriage). The AUCs of the models ranged from 0.71 to 0.77. Psychometric scores and patient satisfaction were similar in the two treatment groups at all assessment points. Symptom scores for anxiety and depression were significantly higher at inclusion than after treatment and remained low. At inclusion, 37% (34/92) of the women treated with misoprostol and 41% (35/86) of the women managed expectantly had STAI-state scores indicating "high levels of anxiety" and 10% (9/91) and 9% (8/86) had symptoms indicating moderate/severe depression. Grief reactions were mild and patients' satisfaction with treatment was high in both groups. The reproductive outcome at 14 months after complete miscarriage did not differ between the groups; 75% of the women (67/89 and 62/83) had achieved at least one clinical pregnancy. Sixty-three percent (56/89) of the women in the misoprostol group and 55% (46/83) of those in the expectantly managed group delivered a live baby after a pregnancy conceived within 14 months after the index miscarriage (MD=7.5%; 95% CI, -7.9 to 22.4). **Conclusions:** Misoprostol treatment is more effective than expectant management for treatment of embryonic or anembryonic miscarriage in women with vaginal bleeding. Both methods are safe. Spontaneous resolution is significantly more likely in embryonic miscarriage than in anembryonic miscarriage. In terms of treatment satisfaction, psychological effects and subsequent fertility the treatments are equivalent and women's' preferences should guide treatment decisions.

Key words: Randomized controlled trial, pregnancy complications, misoprostol, expectant management, logistic models prediction, anxiety, depression, psychology, grief, fertility

Classification system and/or index terms (if any)

Recipient's notes	**Number of pages 94**	Price
	Security classification	

Signature   Date 2021-09-23

Aspects of Miscarriage Management

Efficiency, safety, psychological impact and future fertility

Anna Fernlund

LUND UNIVERSITY

Till Pappa

Contents

Abbreviations

AP diameter	anteroposterior diameter
AUC	area under the receiver operating characteristic curve
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
CI	confidence interval
CRP	C-reactive protein
D&E	dilatation and evacuation
GA	gestational age
GW	gestational week
Hb	haemoglobin
IUA	intrauterine adhesions
IVF	in vitro fertilization
LMP	last menstrual period
MGS	mean gestational sac
MD	mean difference
OR	odds ratio
PI	pulsatility index
PSV	peak systolic velocity
RCT	randomized controlled trial
RD	risk difference
RI	resistance index
SD	standard deviation
TVS	transvaginal ultrasound

List of original papers

The thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I.   A. Fernlund, L. Jokubkiene, P. Sladkevicius and L. Valentin
Misoprostol treatment *vs* expectant management in women with early non-viable pregnancy and vaginal bleeding: a pragmatic randomized controlled trial.

Ultrasound in Obstetrics & Gynecology 2017; 51; 24-32

II.   A. Fernlund, L. Jokubkiene, P. Sladkevicius and L. Valentin
Predictors of complete miscarriage after expectant management or misoprostol treatment of non-viable early pregnancy in women with vaginal bleeding.

Archives of Gynecology and Obstetrics 2020; 302(5): 1279–1296

III.   A. Fernlund, L. Jokubkiene, P. Sladkevicius, L. Valentin and K. Sjöström
Psychological impact of early miscarriage and client satisfaction with treatment: a comparison between expectant management and misoprostol treatment in a randomized controlled trial.

Ultrasound in Obstetrics & Gynecology Open access; First published 02 April 2021

IV.   A. Fernlund, L. Jokubkiene, P. Sladkevicius and L. Valentin
Reproductive outcome after early miscarriage: comparing vaginal misoprostol treatment with expectant management in planned secondary analysis of randomized controlled trial
Ultrasound in Obstetrics & Gynecology Open access; First published 15 September 2021

Preface

Spontaneous early miscarriage is the most common complication of pregnancy and by the age of 39, 25% of all women that have been pregnant have experienced a first trimester miscarriage[1]. Symptoms and complications associated with early miscarriage are frequent causes of referral to gynaecological emergency care units.

During the last decades, management of early miscarriage has evolved significantly. Historically, early miscarriage was associated with significant risks and at times the presumed miscarriage was the result of illegal termination of pregnancy. Surgical procedures used to be first line of treatment as to avoid infections and major blood loss frequently associated with early miscarriage. Several factors have since contributed to a change of perspectives. Legalization of medical termination, antibiotics and increased availability of high standard care have made complications decrease. Thanks to easy access to simple and sensitive urinary pregnancy tests and the general availability of ultrasound in primary health care service, at least in developed countries, miscarriage is usually diagnosed at an early stage. Urgent surgical procedures are less needed and alternative management methods have been explored. Medical management with different uterotonic substances as well as expectant management, i. e. "no treatment" are accepted alternatives[2]. Compared to surgical management, the effect of non-surgical management may be more unpredictable, more often leading to incomplete miscarriage, but may also be appreciated as less invasive and more physiological.

Many women experience psychological distress in response to miscarriage and emotional aspects of early miscarriage have been increasingly recognized. Feelings of grief, low mood and anxiety are reactions commonly described.

The purpose of this thesis was to compare two different non-surgical treatments for early miscarriage in a randomized trial – medical treatment with vaginal misoprostol and expectant management. Efficiency, complications and side effects as well as psychological reactions and treatment satisfaction were evaluated in relation to miscarriage treatment. Demographic and clinical variables were explored with respect to their potential power to predict treatment success. Finally reproductive outcome after miscarriage and miscarriage treatment was investigated.

Introduction

Early miscarriage

Prevalence

The prevalence of spontaneous early miscarriage is generally estimated to 15-20% of all clinical recognized pregnancies[3]. One in four women will be affected during her lifetime[4]. According to data (1978-2017) from the Danish National health register about 23% of all women of reproductive ages experienced at least one pregnancy loss during the period. The miscarriage rate increases with increasing maternal age[5, 6] and the prevalence ranges from 10% in women aged 20 to 24 years to more than 50% in women above 45 years[7]. In women up to 40 years, slightly more losses occur in pregnancies achieved after assisted reproduction than after spontaneous conceptions, but in women above 40 years there are more losses in spontaneous pregnancies.

Nomenclature and definition

According to the European Society of Human Reproduction and Embryology (ESHRE), miscarriage is the spontaneous loss of a pregnancy before 22 weeks' of gestation, i e when the fetus is capable of surviving outside the womb or before the weight of the fetus is more than 500g. Miscarriages may be classified as early or late losses. Previously, "early" or "late" separated losses in the first trimester, before 13 weeks of gestation, from losses in the second trimester, i.e. losses at or after 13 weeks of gestation. However, this classification was not based on ultrasound or histological findings. According to ESHRE, recommended nomenclature should be evidence-based and reflect biological landmarks of pregnancy development. Early miscarriage should be reserved for demise of intrauterine pregnancies before 10 weeks' of gestation[8].

According to the terminology of ESHRE, *clinical miscarriage* is the term for losses in which ultrasound examination or histological analysis confirmed that an intrauterine pregnancy has existed. A pregnancy loss confirmed neither by ultrasound nor by histopathology may be called a *non-visualized pregnancy loss*.[8] Under normal circumstances beta human chorionic gonadotropin (β-hCG) is exclusively produced by the syncytiotrophoblasts and the loss of a pregnancy that

has been diagnosed only by serum or urine beta human chorionic gonadotropin (β-hCG), not by ultrasound or histological analysis, is termed *biochemical loss*[8].

Depending on if an embryo is visualized at ultrasound examination, early miscarriages are classified as embryonic or anembryonic. An early miscarriage with a visible embryo is termed *embryonic miscarriage* and an early miscarriage with no visible embryo is termed *anembryonic miscarriage*.[8]
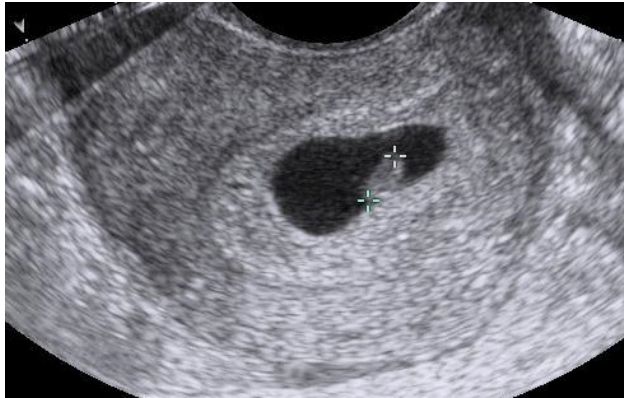
Figure 1. Early pregnancy with embryonic pole

Figure 2. Empty gestational sac
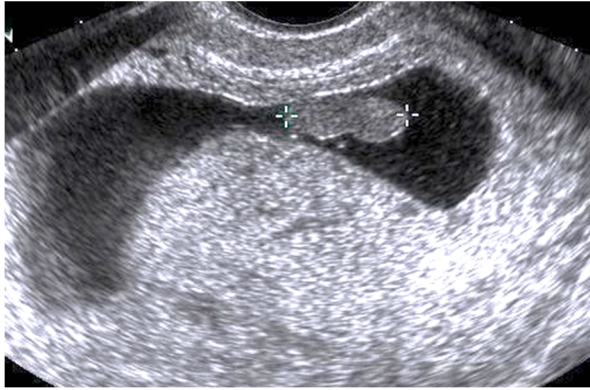
Figure 3. Early pregnancy with embryonic pole and collapsed gestational sac

By the end of the ninth gestational week, which corresponds to the end of the seventh developmental week, the organogenesis is completed and losses after the ninth week is appropriately termed *fetal miscarriage*.[8] A yolk sac is sometimes visible in the absence of an embryo and the term *yolk sac miscarriage*[8] may be used although the definition has minor clinical significance. Early miscarriage covers all three types of intrauterine pregnancies - embryonic, anembryonic or yolk sac.

Incomplete miscarriage is usually defined as the passage of some, but not all, of the pregnancy tissue and retained tissue (without an identifiable gestational sac) is visible at ultrasound examination[8].

The term *inevitable abortion* signifies an intrauterine early pregnancy complicated by active vaginal bleeding and in which clinical examination reveals an open cervical os[8].

In the first paper within this thesis, early fetal or embryonic loss and anembryonic loss are sometimes referred to as non-viable pregnancies. In Paper II-IV the terms recommended by ESHRE[8] were used. No upper limit of gestational length was used. Instead the maximum crown-rump-length allowed was 33 mm, which corresponds to gestational week 10+1[9]. For briefness, all miscarriages in which an embryonic or fetal pole could be visualized were termed embryonic miscarriage.
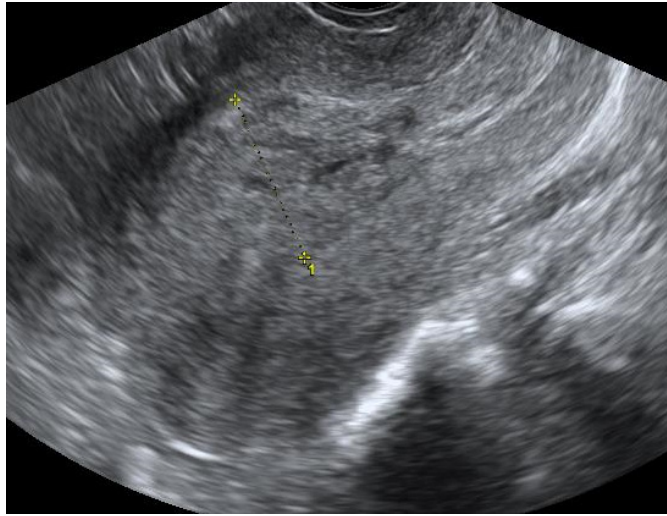
Figure 4. Heterogeneous intrauterine tissue indicating incomplete miscarriage.

Early pregnancy

The different stages of early pregnancy – pre-implantation, implantation and placentation - are delicately regulated. Interruption of any step will cause implantation failure or inadequate placentation leading to miscarriage, as well as later gestation pregnancy disorders. Most miscarriages occur in the first trimester.

Pre-implantation

As soon as the egg is fertilized, the embryo starts to divide and develops into a blastocyst. Prior to implantation, the endometrium must undergo important structural changes to enable the implantation, 'decidualization'. Under the influence of oestrogen and progesterone endometrial vascularization increases and endometrial stromal cells differentiate into decidual stromal cells. Lymphocytes infiltrate the endometrial lining. Five to seven days after fertilization, implantation begins as the blastocyst adheres to and invades the decidual lining. The decidua is receptive for implantation of the free-lying blastocyst for only a brief period, usually 5 days and if implantation fails, 'the decidua' will degenerate.

Implantation

Mutual interaction between decidua and blastocyst is requisite for successful implantation. During implantation, signals from the decidual epithelial cells promote the differentiation of the trophoblasts in the outer cell layer of the blastocyst, into cytotrophoblasts, syncytiotrophoblasts and extravillous trophoblasts. Conversely, enzymes and hormones secreted by the differentiated trophoblasts, e.g. β-hCG secreted by syncytiotrophoblasts, interact with the decidua

16

and prepare the endometrial wall for deep invasion by the syncytiotrophoblasts. Immunological pathways must regulate the interface between the maternal immune system and the embryo in order to prevent rejection of the embryo.

Placentation
A thick layer of syncytiotrophoblasts surrounds the blastocyst that is embedded by the decidualized endometrium. Maternal blood vessels form lacunae between the syncytiotrophoblasts and placental villi develop from the syncytiotrophoblasts and cytotrophoblasts. The placental membrane develops from these. Spiral arteries in the endometrium are invaded by extravillous trophoblasts that form trophoblastic plugs. Extravillous trophoblasts cause remodelling of the spiral arteries into dilated, non-vasoactive vessels. Through the placental membrane and the trophoblastic plugs, a barrier between maternal blood in the intervillous space and the embryo is established. Erythrocytes (and supposedly other blood cells) are stowed by the trophoblast plug, letting only maternal blood plasma to seep through[10]. In that way, the supply of nutrients and oxygen to the embryo, are regulated[11]. It is supposed that both trophoblastic differentiation and artery remodelling are dependent on the hypoxic environment. Elevated oxygen levels during the first trimester may cause pregnancy complications and spontaneous abortion[12, 13]. Eight to ten days after fertilization implantation is complete and the embryonic disc and the yolk sac are formed about one week later. Prior to the establishment of the placenta, the yolk sac is the main source of nutritional supply to the embryo[14]. The oxygen gradient between maternal blood and the embryo is maintained until the end of the first trimester (gw 10) when the trophoblastic plugs are dissolved, and maternal blood flow enter the intervillous space without resistance[11]. From the second trimester nutrients and oxygen are delivered to the fetus by placenta.

Aetiology and risk factors
It is generally accepted that 50% or more of spontaneous early losses are caused by random numeric chromosomal errors of the embryo, primary trisomies[15, 16]. The arrest of development is supposed to be an important "physiological" mechanism to prevent abnormal embryos to progress to viability and the majority of losses probably occur before the pregnancy is clinically recognized - approximately 30% at the implantation stage and another 30% after implantation but before the first missed menses[18]. These losses will not result in clinical symptoms and could only be detected by falling levels of human chorionic gonadotropin[17, 18].

Only losses occurring after the first missed menses will result in *clinical* miscarriage. In clinical miscarriages, embryos with abnormal karyotype may have escaped early quality control and implantation has continued long enough to let the

pregnancy present clinically before failing. Only clinical miscarriages are within the scope of this thesis.

Sporadic early miscarriage is usually separated from recurrent early losses, defined as more than two or three losses in a row. Recurrent miscarriage affects 1-3%, depending on definition, of women in reproductive age. The aetiology behind recurrent early losses is believed to be more diverse than that behind spontaneous early miscarriage and the risk of detecting an aneuploidy has been shown to decrease as the number of previous miscarriages increases[19]. In *in vitro* studies, decidualized stromal cells have been demonstrated to act as a biosensor for embryonic derived signals and may thus be capable of 'selecting' embryos for implantation on the basis of their quality[18]. In women suffering from recurrent losses, impaired function of decidual cells has been reported to allow implantation of low-quality embryos, causing both euploidic and aneuploidic pregnancy losses[18].

As the implanted blastocyst contains genetical material from the father coding for "foreign" proteins in relation to the immune system of the mother, immunological dysregulation is another possible cause of both sporadic and recurrent miscarriages[18]. However, the mechanisms behind miscarriage are supposed to be multifactorial and probably result from a complex interplay between parental age, genetic, hormonal, immunological, and environmental factors[18, 20].

Risk factors
The risk of aneuploidy increases with age and advanced maternal age is the strongest clinical risk factor for early miscarriage. A previous miscarriage is another documented risk factor. According to a Norwegian population-based register study the adjusted odds ratio for miscarriage, in relation to no previous pregnancy, was 1.5 after one miscarriage, and 2.2 after two previous miscarriages[21]. Several lifestyle factors have been associated with sporadic early miscarriage, e.g. smoking, intake of alcohol and coffee. Maternal obesity is related to a higher risk of both sporadic and recurrent miscarriages[22, 23]. Trombophilic disorders, various endocrine disturbances, parental genetic anomalies, anatomical defects, e.g. congenital uterine septum or acquired intrauterine adhesions are risk factors mainly related to recurrent miscarriage.[20, 24]

Ultrasound

Ultrasound is high-frequency sound waves, generated when electrical signals are transformed into acoustic energy by piezoelectric crystals in the ultrasound transducer. The piezoelectric crystals transform electrical signals into sound waves and conversely they produce an electrical field when hit by a sound wave. Ultrasound waves are directed into the organ or tissue of interest. Different tissue has different acoustic impendence, which is determined by tissue density. When the sound waves hit the interface between adjacent tissues part of the ultrasound is reflected, as an echo, and the other part is transmitted. How much of the ultrasound that is reflected depends on the difference of impedances between adjacent tissues. A large difference in density (as between soft tissue and bone) will generate a large echo. A minimal echo will result if the difference is small. The intensity of the echo is also dependent on how the sound waves hit the interface, i.e. the angle between the beam and the tissue of interest. The time it takes until the echo reaches the probe will depend on how far from the probe the tissue interface is located. The reflecting sound waves hit the piezoelectrical crystals in the transducer and each echo is transformed into electrical signals. In B-mode ultrasound the transducer contains a linear array of multiple piezoelectrical crystals. A two-dimensional image of the tissue or organ is generated when the electrical signals are processed to display each echo as dots of different brightness.

Some of the ultrasound waves will be absorbed; i.e. converted into heat. Absorption is higher for higher frequencies and thus low frequencies have better penetration. The resolution is proportional to the wavelength and low frequencies have better penetration but at the cost of lower resolution. The quality of ultrasound imaging is dependent not only on the technical standard of the ultrasound equipment, but also on the experience and expertise of the operator.

Doppler ultrasound

Both velocity and direction of blood flow can be assessed by Doppler ultrasound. The frequency of sound waves is altered if the source of the sound is moving. This is called the Doppler effect, first described in 1843. Correspondingly, if sound waves hit a moving object the frequency of the sound waves will be changed. When a stationary object reflects the sound wave the returning echo will be the same from pulse to pulse. In contrast, when sound waves encounter moving objects, there will be a slight variation in how the pulse waves hit the objects. The time it takes for the returning signal to reach the transducer will differ between subsequent pulses. These differences result in a phase shift, the Doppler shift. In Doppler ultrasound the frequency of the emitted sound waves change when they are reflected by red blood

cells. The Doppler shift is dependent on the velocity of the moving object (the blood cells), the frequency of the transmitted beam and the angle of insonation i.e. the angle between the emitted pulse signals and the direction of the flow. To achieve a strong Doppler signal the beam has to be aligned to the flow direction, i.e. blood cells moving either to or away from the transducer. If the blood flow is perpendicular to the transmitted beam (insonation angle of 90°) there will be no relative motion from pulse to pulse and the Doppler signals will be weak. The size of the phase shift is proportional to the velocity of the moving object. However, to correctly estimate the blood flow velocity it is important that the insonation angle does not exceed 60°. Increasing velocity of blood flow, a more aligned beam (smaller insonation angle) or a higher frequency of the transmitted signal will cause increasing Doppler frequencies.

Two types of transducers are used for Doppler ultrasound:

Continuous wave Doppler: Two separate piezoelectrical crystals transmit and receive the pulse waves. A continuous sound wave pulse is transmitted by one crystal and the returning echo is received and recorded by the other crystal. All signals, reflected along the ultrasound beam, will be registered, which makes it non-selective and blood vessels cannot be visualized with continuous wave Doppler.

Pulsed wave Doppler: A single crystal both transmits and receives the pulse waves and the subsequent signal is not initiated before the return signal is recorded. This makes it possible to position the depth of the reflection. By colour Doppler both direction and velocity of blood flow can be visualized. In colour flow imaging, the blood flow is assessed along multiple beam lines (in the beam width) and the mean frequency shift created by each small area of measurement (depending on the mean velocity of all the refractors within the scan line) - is displayed as a colour pixel. The frequency shifts are usually assigned different colours to display direction and size. By convention, red is for blood flow towards the transducer and blue for blood flow away from the transducer. Brighter shades depict faster flow (higher frequency shift). Multiple pixels build up the colour image. The transducer switches rapidly between B-mode and colour flow imaging and the colour-coded image is superimposed onto the B-mode ultrasound image to produce an image of the blood flow and the surrounding structures.

In *spectral Doppler*, the blood flow in a specific area of interest can be visually and numerically evaluated. A range gate circuit is set at the targeted area. As the different components of blood do not move with an identical fixed velocity the sampled volume of blood flow will reflect a multiple of different Doppler frequencies. The returning signal is made up by all of the different frequencies. Through spectral analysis the different Doppler frequencies can be separated and

the entire spectrum of frequencies is displayed graphical as the flow velocity waveform. The flow velocity waveform represents the flow velocity over time and different types of blood flow, e.g. arterial or venous yield different typical waveforms.

In this work colour Doppler (**Fig 5a**) and spectral Doppler (**Fig 5b**) were used to evaluate blood flow in the intravillous space in early miscarriages.
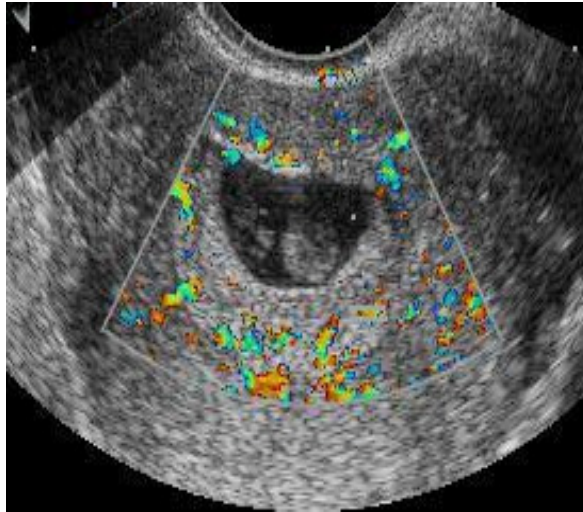

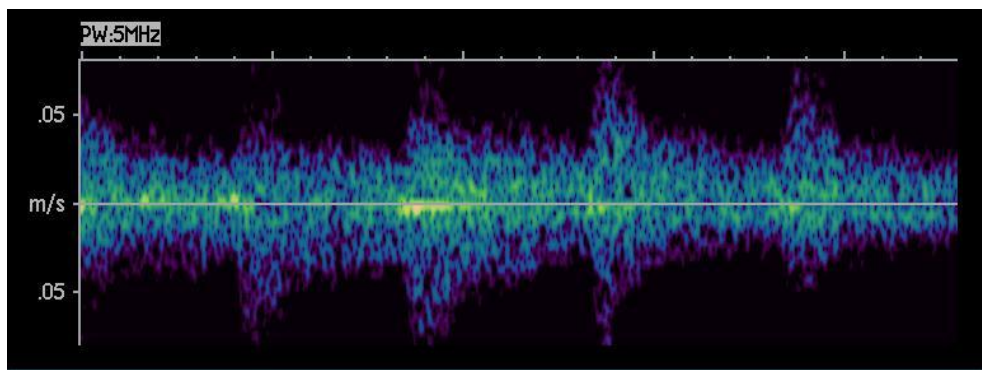**Figure 5a.** Colour Doppler Ultrasound

Figure 5b Spectral Doppler waveform

Ultrasound in early miscarriage

Ultrasound in early pregnancy
In a normally developing pregnancy there are several developmental landmarks that are possible to visualize by transvaginal ultrasound. The gestational sac is usually visible 4.5-5 weeks from the last menstrual period (LMP), and the yolk sac appears 5.5 weeks after LMP. The mean gestational sac diameter (MSD) is possible to calculate about 35 days from LMP. The gestational sac is measured in three perpendicular dimensions, the longitudinal, the transversal and the anterior-posterior and MSD is the average of the measurements. When the MSD is 25 mm an embryo should be identifiable, although in most normal pregnancies, an embryo or "fetal pole" is visible much earlier. Usually, an embryo may be identified with cardiac pulsations as early as 6 weeks after LMP, which is the time when the embryonic heart tube starts to beat[25]. However, in 5-10% of embryos measuring between 2 and 4 mm, which correspond to the beginning of 6th gestational week, cardiac pulsations may not be evident, although the pregnancy develops normally later on[26]. Current guidelines state that fetal heartbeats should be recognized when the embryo measures 7 mm or more[26]. Gestational age is more accurately estimated from the length of the embryo than from the size of the gestational sac as the growth of the embryo is more regular and predictable than the growth of the gestational sac. The average growth of the embryo is approximately 1 mm of length per day[26].

Ultrasound criteria defining early miscarriage
Miscarriage is usually diagnosed by ultrasound. In most cases a pregnancy is wanted and early pregnancy failure causes distress. Obviously, ultrasound criteria must be unambiguous, so as not to mistake a viable early pregnancy for a failed one. All pregnancies do not exhibit uniform growth in the first trimester[17] and the visual landmarks, identifiable on ultrasound, previously described do not apply in all, otherwise normal, pregnancies. Ultrasound criteria defining early miscarriage must take this into account.

In 2011, a series of publications pointed out that current ultrasound criteria for deciding upon viability of an early pregnancy were poorly validated. Considerable intra- and interobserver variability of measurements was reported. As an example, a mean gestational sac diameter of 20 mm as estimated by one observer, was assigned a range of 16.8-24.5 mm by a second observer[27]. The CRL also varied in relation to different observers. As a consequence, a substantial number of viable pregnancies could be at risk of misclassification[27]. If a viable pregnancy should wrongly be diagnosed as a failed one, it might be terminated if medical treatment or surgical management was prescribed[28, 29]. As a consequence, the cut-offs were significantly widened to account for variations of measurement accuracy and to

minimize risks. A repeat scan was recommended when measurements were around decision boundaries. New safe cut-offs were suggested, and several national guidelines revised their ultrasound criteria for defining early miscarriage [30-34].

Current ultrasound criteria for early miscarriage recommended by the national speciality association for Swedish gynaecologists and obstetricians (Svensk Förening för Obstetrik och Gynekologi, SFOG).

(1) intracavitary gestational sac with a mean diameter ≥ 26 mm with no embryonic pole, or

(2) intracavitary gestational sac with an embryo with crown-rump-length ≥ 7 mm without cardiac pulsations, or

(3) if the above criteria are not fulfilled, no significant development at a repeat scan after 10-14 days

Definition of complete miscarriage

In clinical trials, treatment success is usually defined as complete miscarriage without any additional (surgical) treatment. However, treatment success is dependent on what definition of complete miscarriage is used and the rate of success of any treatment will depend on the definition of complete miscarriage[35]. Complete miscarriage is typically defined by sonographic criteria. No distinguishable gestational sac in the uterine cavity combined with a maximum anterior-posterior diameter of the intracavitary contents, e.g. 15 mm[36-40], are criteria used in many trials. However, there is no consensus on a specific cut-off for endometrial thickness to define treatment success. Endometrial thickness alone may not be a reliable test for diagnosing retained products of conception[41, 42]. In studies evaluating endometrial thickness after miscarriage management (medical or expectant), no association was found between endometrial thickness 2-4 weeks after treatment and the need of surgical evacuation[41, 43]. When endometrial thickness was evaluated in women with retained products of conception (RPOC) and persistent significant bleeding after miscarriage, no identifiable cut-off for endometrial thickness could be used to differentiate between retained products of conception and decidua only, verified by histopathological analysis[42]. Authors concluded that signs and symptoms, rather than endometrial thickness, should guide decisions[41, 42] and all symptomatic women with measurable tissue should be offered intervention[42]. For clinical purposes, the definition of "successful treatment" is usually not restricted to a specific cut-off value for endometrial thickness but to a more clinical definition such as "no signs of residual products of conception"[42].

Early miscarriage management

The most common complications associated with early miscarriage are bleeding and infections. Both infections and major blood-loss are unusual and for the majority of women presenting with early miscarriage there are no pressing medical reasons for urgent evacuation[44]. Surgical management used to be the cornerstone of miscarriage management. Before easy access to simple high-sensitive pregnancy tests and ultrasound in acute and office settings, it may be assumed that patients with early miscarriage typically would present for care with considerable time delay. Moreover, some presumed miscarriages might have been the result of unsafe illegal abortions. In contrast, most miscarriages today are sporadic early miscarriages entailed with small risks. In some cases, women are diagnosed with miscarriage on a routine scan prior to the onset of symptoms. Accordingly, expectant and medical management are first line alternatives to surgical evacuation[2, 6].

There are a large number of randomized trials evaluating different management alternatives – surgical, medical or expectant. However, it is difficult to summarize results, as studies are heterogeneous[36, 37, 39, 45-49]. The diversity relates to variability of inclusion criteria (embryonic/anembryonic miscarriage versus incomplete miscarriage, and bleeding at presentation versus no bleeding), interventions (e. g. length of follow-up) and outcomes (definition of complete miscarriage). These factors are likely to influence on the success rate of any treatment. The success rate after medical or expectant management may be underestimated if the follow-up period is very short. The type of miscarriage – incomplete or embryonic/anembryonic – may influence on how well a treatment works. Incomplete miscarriages usually resolve spontaneously within a few weeks and the success rate of expectant management is similar to that after misoprostol treatment[50]. Embryonic or anembryonic miscarriage may be less prone to spontaneous resolution. The presence of vaginal bleeding may reflect the onset of spontaneous expulsion, while no bleeding may signal resistance to expulsion. To individualize treatment, risks and benefits of all treatment options should be discussed with the patient. Evidence-based data is needed. Several trials report difficulties to recruit patients[48, 49, 52, 53], which has been explained by a strong preconceived treatment preference expressed by many women with early miscarriage[43, 54, 55].

Surgical management

Surgical evacuation with dilatation and evacuation (D&E) is efficient with a reported success rate of more than >95%. D&E is usually carried out under general anaesthesia in an operating room, although office manual aspiration is proved to be safe and cost-effective[56, 57]. D&E is the first hand alternative in patients who are hemodynamically unstable or who present with other complicated conditions, i.e. septic shock. Some women may request uterine aspiration for personal reasons, as to avoid pain and cramping or a prolonged and unpredictable waiting for miscarriage resolution. During the last twenty years, the use of surgical procedures for early miscarriage management has decreased significantly and non-surgical management is more common[6]. Only 5.5% of clinicians in an international internet-based survey said that D&E should be the first line of treatment when asked about their views on early miscarriage management[2].

Complications are mainly related to bleeding and infection, but rarely cause long-term effects. Unusual complications associated with general anaesthesia, cervical tears, and uterine perforation may carry serious risks[53, 58]. Bowel damage may result from uterine perforation[58]. Lately, important risks in relation to future fertility have been recognized. Surgical evacuation, especially if repeated, has been identified as the most important risk factor for the formation of intrauterine adhesions, which may cause reduced fertility. In a systematic review, intrauterine adhesions (IUA)were encountered in 19% of women treated for a miscarriage[59]. Although IUAs were mild in more than 50%, with unknown clinical relevance, the risk of impaired future fertility might be less appealing to women. An increased risk of preterm delivery in a subsequent pregnancy has also been associated with surgical evacuation[53].

Expectant management

Expectant management may be perceived as "more natural" than surgical or medical management. A prolonged observation time with no active treatment can minimize the risks related to misdiagnosing, which might otherwise lead to the unintentional termination of a viable pregnancy. Disadvantages include an unpredictable time until resolution of the miscarriage and a substantial risk of failed treatment leading to subsequent surgical evacuation[36, 45, 46, 51].

Expectant management, i.e. awaiting the spontaneous passage of pregnancy products, is preferred by some women[55, 60-62]. In incomplete miscarriage, expectant management may be successful in more than 80% within 14 days [60, 63], which is comparable to medical treatment[50]. In miscarriages with a retained gestational sac,

embryonic or anembryonic – expectant management is less likely to result in complete miscarriage. In randomized trials, evaluating expectant management in relation to other treatments, the success rate varies within a wide range, from 13%-79%[36, 39, 45-47, 64]. This is probably partly explained by methodogical differences between trials. Differences concern inclusion criteria, i.e. what miscarriage subtype was included (incomplete, inevitable, embryonic or anembryonic or a mix), if women had vaginal bleeding or not at inclusion, length of follow-up and definition of treatment success. In the trial with the highest reported success rate, both incomplete and embryonic/anembryonic miscarriages were included[64]. In studies, in which treatment success was evaluated after very a short follow-up (24 h, 48h), a very low rate of success was reported for expectant management or treatment with placebo in embryonic/anembryonic miscarriage[45, 46]. In observational studies with a longer follow-up (4 weeks) expectant management was successful in 50-70% of embryoic and anembryonic losses[43, 62, 66].

Medical treatment

Many women prefer active management as opposed to expectant management[67-70]. Medical treatment let women avoid the risks associated with surgery and anaesthesia and it may be perceived as a more natural process than surgery. In an outpatient setting, medical treatment may allow women to have more control and privacy[35].

Misoprostol
Several different drugs have been used to hasten the expulsion of pregnancy products after miscarriage, but misoprostol is the substance most frequently used. Misoprostol is a synthetic prostaglandin analogue that was first registered for treatment of peptic ulcers. It causes ripening of the cervix and promotes uterine contractions. It has been used off-label for different conditions of pregnancy, e.g. to induce medical abortion, to promote contractions during labour, and to prevent or treat postpartum haemorrhage. The uterus is increasingly sensitive to misoprostol with increasing gestational age.

During the last 25 years misoprostol has been widely introduced for the management of early miscarriage and incomplete abortions. The tablets are cheap and stable at room temperature. Misoprostol is recommended for medical management of early miscarriage by the current World Health Organization (WHO) guideline (Medical management of abortion. Geneva: World Health Organization; 2018) and several national guidelines[30, 31, 33, 34]Administration is usually vaginal or sublingual but oral, buccal or rectal intake is possible.

Randomized trials evaluating misoprostol in early miscarriage management are difficult to summarize due to heterogeneity in study designs. In addition to differences previously described, dose and route of administration are not the same across studies. Reported rates of success vary significantly, from 50%-100%[40, 68, 69, 71-73] Higher failure rates are reported after very short follow-up, 24 or 48 hours[73, 74]. According to a Cochrane review, vaginal misoprostol was more likely to generate complete miscarriage in embryonic or anembryonic miscarriage, compared to expectant management, but it was less effective than surgical management[44]. The most studied regimen was misoprostol 800 micrograms, given as vaginal single dose but great variety of regimens was reported (substance, dose and route of administration). The authors concluded that further research is needed in relation to optimal route and dose of misoprostol, as well as women's views on treatment alternatives and long-term outcomes, notably subsequent fertility[44].

Mifepristone
Mifepristone is a steroid that can act as a primer for prostaglandin activity and it is frequently used (in combination with misoprostol) in legal termination of early pregnancy. Recently a randomized trial reported that pre-treatment with mifepristone prior to misoprostol yielded a significantly higher rate of complete gestational sac expulsion, compared to the use of misoprostol alone. Only embryonic and anembryonic miscarriages were included and the majority of women had no history of vaginal bleeding. The rate of complete miscarriage was 83% in the mifepristone-misoprostol group compared to 67% in the misoprostol-alone group, approximately 2 days (1-4 days) after treatment. The need for subsequent surgical procedures was reduced, from 24% in the misoprostol-alone group to 9% in the mifepristone-misoprostol group[75].

Effects and side effects of misoprostol
Bleeding following misoprostol can be heavy for the first 3-4 days and often lasts for two weeks with additional days of spotting[35, 75-77]. Cramping usually starts within the first two hours after administration but can begin earlier. Other side effects of misoprostol mostly relate to prostaglandin effects and include nausea, vomiting, headache, diarrhoea and fever. The frequency of prostaglandin related side effects seems to vary with route of administration. Fever and diarrhoea are more common after sublingual than after vaginal administration[78].

Chills and gastrointestinal symptoms are common. Chills may be accompanied by fever, but usually wear off within 24 hours after misoprostol intake[76]. Nausea is more common than vomiting. The rates of nausea and diarrhoea are not higher after misoprostol than after placebo[44] and gastrointestinal symptoms after misoprostol usually resolve within 2-6 hours (vomiting and nausea) or 24 hours (diarrhoea) after

intake[76]. Misoprostol should be used with caution in patients with cerebrovascular disease, coronary artery disease, or inflammatory bowel disease.

Serious complications associated with medical management are rare[44, 49, 69]. Severe blood loss or pelvic infection was not more common after treatment with misoprostol than after surgery[44]. A 1% rate of severe haemorrhage leading to blood transfusion or hospitalization has been reported after misoprostol[49, 69]. Pelvic infection (defined as specified clinical findings or as the prescription of antibiotics for a presumed infection) was diagnosed in 2%[49]. A slightly higher rate of bleeding leading to blood transfusion was observed when a regimen of mifepristone-misoprostol was compared to misoprostol-alone, 2% versus 0,7%, but the difference was not statistically significant[75].

Prediction of treatment success

Patient centred counselling is believed to improve patient satisfaction and ideally women's decision should be based on detailed information about treatment alternatives[79]. The chance to achieve complete miscarriage within reasonable time is of main interest to most women choosing between different alternatives[80, 81]. Misoprostol or expectant management are cost-effective and safe alternatives to surgery but show variable and to some degree unpredictable rates of success. Knowledge about factors – clinical or other – that influence on the probability to achieve treatment success after expectant or medical management could help decision making for patients and doctors.

Several studies have explored variables with possible ability to predict the likelihood to achieve complete miscarriage after misoprostol treatment or expectant management[43, 63, 66, 67, 82-93]. Due to heterogeneity, results are difficult to compile. The tested variables partly differed across studies. In addition, studies differed with regard to study population (what types of miscarriage were included and if patients had vaginal bleeding or not) and in how complete miscarriage and treatment success was defined. Success rate after expectant management was higher in incomplete miscarriages compared to embryonic or anembryonic miscarriages [43, 86, 89].

Possible predictive variables
Biochemical variables
β-hCG and progesterone: In early pregnancy, β-hCG is produced by the syncytiotrophoblasts. After pregnancy failure the levels of β-hCG will fall steeply and the level of β-hCG may correspond to the number of viable trophoblasts. The concentration of progesterone correlates to the function of the corpus luteum but also reflects the function of the blastocyst, as β-hCG secreted by the blastocyst promote the continuous production of progesterone. Levels of s-β-hCG and s-progesterone have been related to treatment success of expectant management and the likelihood of success increased with decreasing levels of s-β-hCG and s-progesterone[66, 89, 94, 95].

Clinical and demographic variables
Parity and previous vaginal deliveries: Both the contractility of the myometrium and the duration of cervical ripening differ with parity. Compared to nulliparous women, women with a previous vaginal delivery usually experience shorter latent phase and first stage of labour. Misoprostol for induction of labour is more often successful in parous than in nulliparous women. Parity has been reported to have a negative impact on the chance of treatment success after misoprostol in early miscarriage[83, 88, 96]. Women of lower parity were more likely to achieve complete miscarriage after one dose of misoprostol compared to two doses[93]. It has been suggested that a previous term pregnancy may lead to more successful implantation of the trophoblastic tissue in a subsequent pregnancy[96].

Gestational age: A variable time may have elapsed between embryo demise and the ultrasound examination. More advanced menstrual age may thus correlate to miscarriages less prone to expulsion. In one study, surgical intervention was more often required after medical management in women with advanced menstrual age, compared to those with shorter menstrual age[91]. In another study, mean gestational age was significantly shorter in women with successful expectant management, compared to if the treatment failed[67].

Bleeding and pain: In one study expectant management was more likely to succeed within two weeks if there were bleeding and pain at presentation compared to no symptoms at presentation. However, most included miscarriages were incomplete miscarriage and neither bleeding nor pain could predict treatment success in embryonic or anembryonic miscarriage[87].

Ultrasound variables
Mean diameter of the gestational sac: A smaller gestational sac has been associated with a higher rate of success after expectant management in missed abortions

(embryonic or anembryonic miscarriage)[67] but no correlation was found between gestational sac volume and success after misoprostol treatment[82, 96].

Type of miscarriage: Incomplete miscarriages usually resolve spontaneously within a few weeks without any intervention[50]. Anembryonic miscarriage compared to embryonic miscarriage has been shown to be more resistant to expulsion after expectant management[43].

Presence of blood flow in the intervillous space: To maintain the gradient of oxygen, necessary for early pregnancy development, the blood flow from the mother towards the placenta is blocked during early pregnancy[10]. The maternal blood cells are not supposed to enter the intervillous space until the end of the first trimester when trophoblastic plugs disintegrate[11, 13]. Trophoblastic malfunction has been suggested to cause different pregnancy complications, such as hypertension, intrauterine growth restriction and spontaneous miscarriage[10]. The detection of pulsatile blood flow in the presumed intervillous space was proposed to be a predictor of treatment success after expectant management, in one study[66]. The blood flow in the presumed intervillous space was supposed to reflect the breakdown of the normal embryo–maternal interface, and thus representing the final mechanism causing abortion. An absence of intravillous blood flow would reflect the viability of trophoblasts, making the miscarriage more resistant to spontaneous resolution[66].

Fertility after miscarriage

Most women wish to conceive again, immediately or within a short time after the miscarriage[97, 98]. Previously, women were sometimes asked to delay conception after a miscarriage, but recent studies have found no evidence in support of delaying subsequent conception[99, 100]. When women with a recently diagnosed early miscarriage were asked how they valued different factors when treatment alternatives were considered, the effect on future fertility was the most important factor, besides the probability to achieve complete miscarriage[81].

The assumed cumulative pregnancy rate for one year of unprotected intercourse in normally fertile women is 85-90%[101, 102]. In women with one or two previous miscarriages, the cumulative probability of conception within 12 cycles of follow-up was 85% according to prospective data from a national Danish prospective cohort study[103]. Studies comparing reproductive outcome after miscarriage management are predominantly retrospective. No statistically significant differences between expectant, medical and surgical management have been reported[104-107].

Intrauterine adhesions may be a cause of reduced fertility after early miscarriage. The most important risk factor is pregnancy-related D&Es with increasing risk after repeated D&Es[59, 108]. Retained products of conception leading to infection have also been suggested to cause intrauterine adhesions leading to reduced fertility after miscarriage[59, 108]. In a systematic review, intrauterine adhesions were reported in one fifth of women evaluated by hysteroscopy 1-12 months following miscarriage. In 42% of the women, adhesions were judged to be moderate or severe with a potential of serious reproductive implications. No adhesions were found in women with medical management or with spontaneous miscarriage without intervention, but these represented only 5% of evaluated studies[59].

Psychological impact of miscarriage

Early miscarriage is a distressing life event to most women – and couples. The unexpected loss may challenge the sense of control in life and also the plans of possible parenthood. Several uncertainties may complicate the situation, e.g. the waiting before the diagnose is definitive and an unpredictable waiting time before miscarriage resolution is achieved. Bleeding, sometimes profuse, and pain may also cause stress.

During the last decades management of early miscarriage has changed significantly. Miscarriage is usually diagnosed at an early stage and non-surgical management is most often recommended[2]. The psychological aspects of miscarriage may have changed too, i. e. the general view in society on early miscarriage and accepted ways to express feelings of distress. Several studies investigating psychopathology in relation to early pregnancy loss are of older date. Feelings of grief, anxiety and depression symptoms are commonly described[109-111] but levels tend to return to background rates within one year after miscarriage[112-117]. More recently post-traumatic stress has been explored[118-120].

Miscarriage management may influence on how women cope with early miscarriage and randomized trials evaluating miscarriage management in relation to psychological reactions after miscarriage are requested[110]. However, specific difficulties have been recognized related to strong predefined treatment preferences expressed by many women with early miscarriage[43, 54]. Women may be reluctant to accept randomization and women with certain specific psychological traits may prefer a certain treatment, which could bias results[52].

Grief

Grief is a distinct response to loss, expressed through emotions, thoughts and behaviour separate from depression and anxiety[121, 122] although depression is considered a major component of grief[121]. Miscarriage may be seen as the death of an expected child and the duration and intensity of grief after early miscarriage can be similar to that reported after losses later in pregnancy[123]. The normal, immediate grief reaction after early miscarriage is most intense during the first week and usually abates within a year[112]. Compared to later losses there are some aspects of early pregnancy loss that are clearly unique and may influence on the grief-process after early miscarriage. The loss is "invisible" and other persons, not belonging to the closest family, are usually unaware of the pregnancy. Friends and relatives as well as health care professionals may underestimate the significance of the loss and sometimes act insensitively in relation to the woman. In many cultures, no established traditions or rituals for mourning or burial after early miscarriage exist.

To measure grief

The Perinatal Grief Scale (PGS) is a validated self-assessment instrument that was developed to measure grief after all types of pregnancy loss (spontaneous abortions, ectopic pregnancies, fetal death and neonatal death)[124]. PGS contains 33 statements. The answers are ranked according to a ten-point Likert-scale from "not at all experiencing the symptom" to "experiencing the symptom to an extreme extent". Higher scores indicate more grief. In the Swedish version the total scores are achieved by converting the 10-point scale into a 5-point scale and total score ranges from 33 to 165. A score above 90 indicates possible psychiatric morbidity[125]. The PGS has been validated for women who miscarried[112, 121, 123, 126].

 The PGS may be divided into three subscales measuring different dimensions of grief – "active grief", "difficulty coping" and "despair". According to the initial validation (covering all types of pregnancy losses) the three subscales illustrate different levels of grief. "Active grief" correlates to the normal grief reaction while "difficulty coping" and "despair" are the best predictors of more complicated long-term reactions not present in the majority of women with pregnancy loss. "Despair" is believed to relate to the woman's coping strategy while "difficulty coping" includes more of depression symptoms and correlates to mental health[121]. In older studies, previous mental health symptoms and poor social support has been associated with elevated scores in "difficulty coping", while younger mothers tended to score higher on the "despair" subscale[121]. According to a small Swedish study including women with early miscarriage before 13 weeks' of pregnancy, neither the age of the mother nor the number of previous miscarriages influenced on the intensity of grief[112].

Depression and depressive symptoms

Depressive symptoms are common in the weeks following early miscarriage. Four to six weeks after early pregnancy loss 8-20% of women expressed symptoms above a threshold of moderate depression according to a review article, involving 2500 women with early pregnancy loss. Levels of depressive symptoms returned to background rates within a year[110].

To measure depressive symptoms
MADRS-S is the self-assessment version of the Montgomery-Åsberg Depression Rating Scale (MADRS)[127]. MADRS-S consists of 9 items assessing patients' mood, feelings of unease, sleep, appetite, ability to concentrate, initiative, emotional involvement, pessimism and zest for life. Each item is scored between 0 and 6. The total score is calculated by summing the answers of the nine items, ranging between 0 and 54. Higher scores indicate increased impairment. A score of 0-12 represents "no depression", a score of 13-19 suggests "mild depression", a score of 20-34 "moderate depression" and a score of 35-54 is indicative of "severe depression"[128]. MADRS-S is considered equivalent to the Beck Depression Inventory, BDI[129] but in relation to BDI, which is more concerned with depressive cognitive attitudes, MADRS-S is directed towards core symptoms of depression and assesses somatic symptoms and functional impairment[130]. MADRS-S shows good correlation with expert ratings[131] It is sensitive to change[127, 130] and is recommended to detect differences between treatment regimens in depression care[130].

Anxiety

The feeling of anxiety is usually related to the activation of the autonomic nervous system. The sudden and unexpected nature of a miscarriage, as well as associated bleeding and pain may contribute to anxiety. Worries about possible causes for the miscarriage and about the recurrence risk in future pregnancy are common[132]. 40% of women experience elevated anxiety the first days after a miscarriage was diagnosed[133]. According to a review of 27 studies evaluating the psychological impact of miscarriage, elevated anxiety symptoms were reported by 18-32% of women four to six weeks after early pregnancy loss[110]. Declining anxiety levels were reported during the first six months after the miscarriage and they returned to normal within one year[110, 112, 134].

Some women may experience more elevated levels of anxiety, with symptoms and characteristics consistent with posttraumatic stress disorder, PTSD. The rate of symptoms indicative of PTSD is variable in literature, 0,6% - 19% at three months after miscarriage[118-120, 134, 135].

To measure anxiety

The Spielberger State-Trait Anxiety Inventory (STAI; Form-Y) is a well-documented test for measuring anxiety[136]. It is a self-report inventory composed by two sets of scales evaluating *state* anxiety and *trait* anxiety. *Trait* anxiety intends to relate to the individual trait of character to react with anxiety, i e "anxiety proneness", which is supposed to be a stable personal trait, and varies between different personalities. *State* anxiety refers to the unpleasant emotional state, that can be triggered by an event or another cause and which is supposed to be transitory. The relation between *trait* and *state* anxiety is expressed by the tendency of a person with a certain level of *trait* anxiety to react with *state* anxiety in response to a threatening situation. The stronger the anxiety *trait*, the more probable it will be that the individual will experience a more intense elevation in *state* anxiety. However, both personality and past experiences of the individual will probably determine the extent to which a situation is perceived as threatening[136]. There is a natural overlap between feelings of anxiety and feelings of depression and the original STAI (Form X) has been revised, partly to improve the discriminating ability between feelings of anxiety and depression, resulting in STAI (Form Y)[136].

Each of the two scales includes 20 statements and the respondent is asked to evaluate each statement in relation to how the respondent feels right now (STAI-*state*) and in general (STAI-*trait*). The answer of each statement is graded on a four-step Likert scale. The steps of each scale reflect different levels of *frequency* of anxiety (STAI-*trait*) or *intensity* of anxiety (STAI-*state*).

Frequency of anxiety is graded on STAI-*trait* as:

1. "almost never"   2. "sometimes"   3. "often"   4. "almost always"

Intensity of anxiety is graded on STAI-*state* as:

1. "not at all"   2. "somewhat"   3. "moderately so   4. "very much so"

Total score of each scale ranges from 20 to 80. Higher scores correspond to higher levels of anxiety. Under neutral, nonstressful, conditions the mean STAI-*state* score is usually equal to the mean STAI-*trait* score whereas STAI-*state* total score will be higher if the scale is completed under stressful conditions. STAI-*state* is sensitive to changes in transitory anxiety while STAI-*trait* is not influenced by stress[136]. Normative scores for different subgroups, e.g. working adults, college students, military recruits etc are provided by the manual[136].

Risk factors for elevated psychological distress

Unanimous evidence of specific maternal characteristics predisposing to more elevated levels of anxiety, depressive symptoms and grief in response to miscarriage

has not been recognized[110] A number of factors seem to be related to a higher risk; a past psychiatric history or self-reported poor mental health[114, 115], childlessness[140-142] previous miscarriage[142], poor social support and ambivalence towards the pregnancy[133, 142]. Age is probably not associated with more complicated psychological morbidity after miscarriage[112]. More intense grief has been associated with poor mental health and poor social support[143].

Psychological follow-up after early miscarriage

Psychological follow-up might detect women who are at risk of psychological complications following miscarriage. Unfortunately, evidence to demonstrate that psychological support such as counselling is effective post-miscarriage is insufficient according to a Cochrane review[144]. Any psychological counselling was not proved superior to no counselling. However, conclusions were hampered by heterogeneity of studies. Both the type of intervention and the timing of interventions differed across studies. The report suggests that women's preferences should guide. In a small Swedish study, a partly different approach was applied. Women with early miscarriage were offered more active support, starting from the very onset of any symptom possibly related to miscarriage, e.g. bleeding *before* a miscarriage was diagnosed. Easier access to a gynaecologist during office hours and better understanding, by all professional groups handling women with early miscarriage, that women suffer from grief after a miscarriage were part of the support. Lower grief scores (PGS) four months after miscarriage, higher satisfaction with treatment and a reduction of number of days with sick- leave were reported[145].

Patient satisfaction with treatment

In two randomized trials comparing different management methods for early miscarriage, satisfaction with treatment was poorer if the treatment failed and was followed by surgical evacuation [137, 138].

To measure patient satisfaction with treatment

CSQ-8 is a validated eight-question instrument that assesses satisfaction with health services[139]. Responses are based on a 4-point scale. Total scores range from 8 to 32 with higher values corresponding to higher satisfaction with treatment. Items include satisfaction with the treatment received, satisfaction with recovery after treatment, and a question on whether the respondent would recommend the same treatment to a friend.

Aims

The overall aim of the work described in this thesis was to compare two different management methods - treatment with single-dose vaginal misoprostol and expectant management - in a well-defined group of patients, women with embryonic or anembryonic miscarriage who reported vaginal bleeding.

Specific aims were:

   I.   To compare the rate of complete evacuation of the uterine cavity without dilatation and evacuation, within 10 days, 17 days, 24 days and 31 days.

          To compare complications, side effects and the rate of surgical evacuation.

  II.   To identify variables – biochemical, ultrasonographical or clinical – with ability to predict complete miscarriage after misoprostol treatment or expectant management.

 III.   To compare psychological distress in terms of grief, anxiety and depression symptoms.

          To compare treatment satisfaction.

 IV.   To compare reproductive outcome 14 months after complete miscarriage.

Methods

This was a randomized controlled, open-label trial with individual randomization into two parallel groups (1:1). The open-label design was chosen deliberately to compare the two treatments in clinical practice, in which both patients and doctors know which treatment is given.

The study protocol in brief
Women with early miscarriage were randomized to expectant management or misoprostol treatment and followed up regularly until complete miscarriage was achieved. Maximum length of follow up was 31 days, after which D&E was recommended. Women were contacted by post at 3 months and at 14 months after complete miscarriage and their psychological status and treatment satisfaction were assessed through validated self-assessment scales. New pregnancies achieved within 14 months and the outcome of these were documented. The results are reported in four separate papers.

Subjects

Women with a history of vaginal spotting or bleeding diagnosed with early embryonic or anembryonic miscarriage were recruited from the emergency clinic of the Department of Obstetrics and Gynaecology, Skåne University Hospital, Malmö, Sweden. Hemodynamically unstable women with urgent need of surgical evacuation were not eligible.

Inclusion criteria
Age older than 18 years, ability to understand written and spoken Swedish, haemoglobin concentration (Hb) more than 80 g/L, no contraindications to treatment with misoprostol, meeting the criteria for embryonic or anembryonic miscarriage at ultrasound examination and CRL not exceeding 33 mm.

The ultrasound criteria used in this trial to define a pregnancy as non-viable were changed in 2014 because of revised international recommendations for ultrasound criteria of early pregnancy failure[146-148].

Before April 2014 the criteria for non-viability in this trial were:

1) intrauterine gestational sac with mean diameter > 16 mm with no embryonic or fetal pole[149] *or*

2) a gestational sac with an embryo with CRL ≥5 mm without visible cardiac pulsations[149] *or*

3) if the above criteria were not fulfilled, a gestational sac with or without an embryo or fetus that showed no significant development at a repeat scan after 7 days[149].

After April 2014 the criteria for non-viability in this trial were:

1) intrauterine gestational sac with mean diameter ≥25 mm with no embryonic or fetal pole *or*

2) a gestational sac with an embryo with CRL ≥7 mm without visible cardiac pulsations *or*

3) if the above criteria were not fulfilled, a gestational sac with or without an embryo or fetus that showed no significant development at a repeat scan after 7 days[33, 34, 146, 147].

Twenty-one patients (10 patients in the misoprostol group; 11 patients in the expectantly managed group) were recruited after new ultrasound criteria were adopted.

Study protocol

Randomization
Randomization was computer-generated in blocks of six. An off-site research centre executed the randomization and none of the persons involved in the trial was engaged. Allocation to treatment – expectant management or misoprostol treatment – was hidden in sealed opaque envelopes that were sequentially numbered by staff not involved in the trial. Neither the clinician nor the patient was blinded to treatment.

Inclusion
Written consent was obtained from all participants after the trial procedures had been fully explained. Local Ethical Committee approved of the trial (Dnr 83/2008). **Figure 6** shows the flow of patients through the trial. The day of randomization was Day 1. After clinical examination and ultrasound, patients were randomized to treatment with misoprostol or expectant management. They were interviewed about

demographic and reproductive background data and their attitudes towards the pregnancy were assessed by structured questions, e.g. if the pregnancy was planned, if it was welcome, if the partner was positive towards the pregnancy, and if the patient wished to conceive again after the miscarriage. Blood was drawn for analysis of Hb, β-hCG, progesterone and blood type. hCG + β was measured with a sandwich immunoassay on a Cobas® instrument; Intact hCG + the β-subunit assay (Roche Diagnostics, Mannheim, Germany). Progesterone was measured with a competitive immunoassay on a Cobas® instrument; Progesterone III assay (Roche Diagnostics, Mannheim, Germany).

The trial clinician estimated the level of pain and bleeding on clinical examination. The miscarriage was classified as embryonic or anembryonic on transvaginal ultrasound and if an embryo was present the CRL was measured. The size and shape of the gestational sac was also documented. Doppler ultrasound (greyscale, colour Doppler and arterial Doppler shift) was performed by one of the trial clinicians, to assess the blood-flow in the presumed intravillous space.

Before leaving the hospital, woman assigned to misoprostol, were administrated a single vaginal dose of Cytotec 0,8 mg (four tablets à 0,2 mg), placed in the posterior fornix by the trial clinician. Women randomized to expectant management were discharged without further measures. A structured diary was handed out for each woman to take home for recording bleeding, pain, side effects (nausea, vomiting, diarrhoea, dizziness, headache) and the use of painkillers until the miscarriage was complete (maximum 31 days).
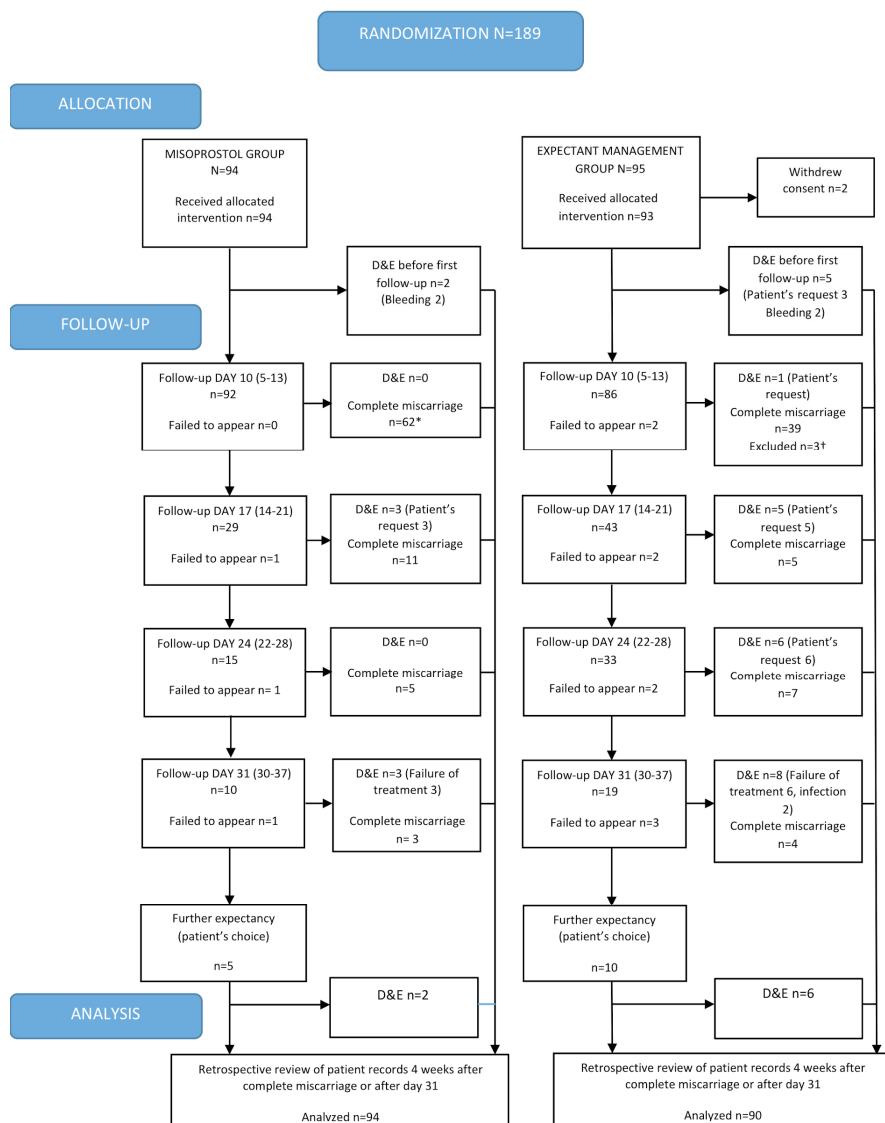
Figure 6. Flow of patients through the trial

Follow-up

The participants were followed up with preplanned intervals (**fig.6**) until the miscarriage was completely expelled (definition of complete miscarriage below) or at maximum 31 days. On every visit, transvaginal ultrasonography and clinical examination was performed. The participants were at any time during the trial

period, free to request D&E, without specifying reasons. If complete miscarriage was not achieved on day 31, D&E was recommended.

As soon as the miscarriage was judged to be complete, the patient was discharged and no further visits were planned.

Four weeks after complete miscarriage or four weeks after day 31, if the pregnancy tissue was not expelled within 31 days, the medical records were searched. The frequency of complications and unplanned out-of protocol visits, the number of days of inpatient care and sick leave was documented in the trial protocol.

Psychological distress and treatment satisfaction were assessed at four different time-points. (**Figure 7**) Three validated psychometric self-assessment instruments were used: the Spielberger State-Trait Anxiety Inventory (STAI; Form-Y)[136], the self-reported version of the Montgomery-Åsberg Depression Rating Scale (MADRS-S)[127, 128] and the Perinatal Grief Scale (PGS)[123, 124]. The patients' satisfaction with the allocated treatment was evaluated by the Client Satisfaction Questionnaire (CSQ-8)[139].

At three months and at 14 months after complete miscarriage questionnaires were sent by post. At 14 months, structured questions about new pregnancies and the outcome of these were included. Women, who did not return the forms, were contacted by telephone or by post up to two times after each set of questionnaires had been sent. At fourteen months, the medical records were also searched for information on any subsequent pregnancies after the miscarriage. All pregnancies, i.e. also pregnancies reported by the patients but not confirmed in the medical records, were included for statistical analysis. Information on the outcome of an ongoing pregnancy at 14 months was obtained from the medical records.

Definitions

C*omplete miscarriage* (treatment success) (Paper I-IV): no intrauterine gestational sac and maximum anterior-posterior diameter of the intracavitary contents < 15 mm on a midsagittal view on transvaginal ultrasound.

Clinical pregnancy (Paper IV): a pregnancy recognized by the woman by clinical signs and a positive pregnancy test or verified by ultrasound.

Miscarriage (Paper IV): the spontaneous loss of a clinical pregnancy before 22 gestational weeks.

Live birth (Paper IV): The birth of a fetus showing any sign of life.

Ongoing pregnancy at 14 months (Paper IV): a clinical pregnancy still ongoing at 14 months, i.e. delivery, miscarriage, a diagnosis of ectopic pregnancy, or legal termination of that pregnancy occurred after 14 months.
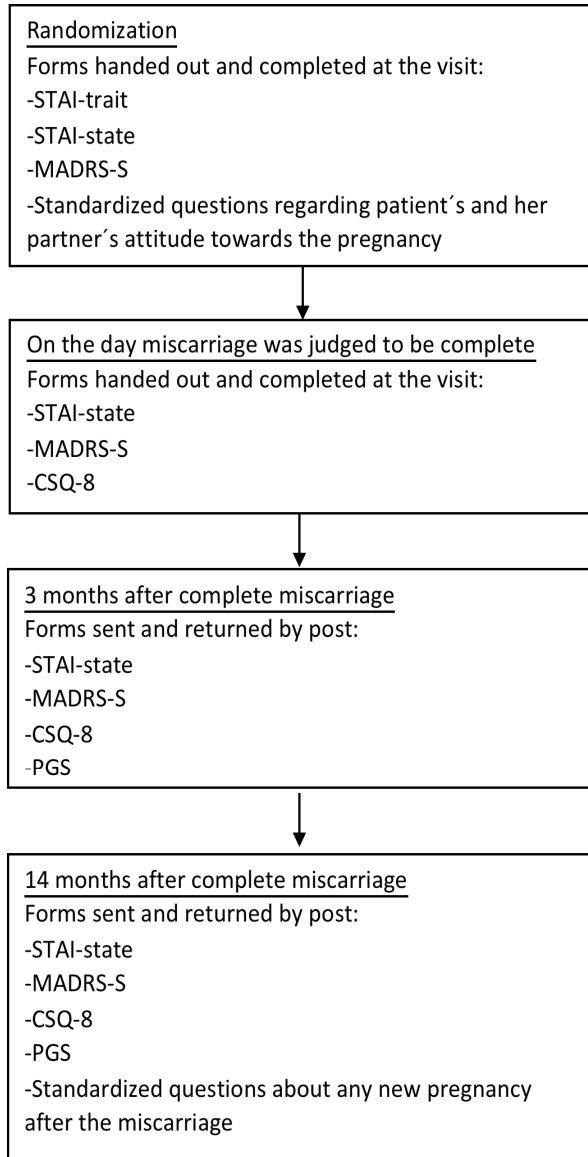
```
┌─────────────────────────────────────────────────────┐
│ Randomization                                        │
│ Forms handed out and completed at the visit:         │
│ -STAI-trait                                          │
│ -STAI-state                                          │
│ -MADRS-S                                             │
│ -Standardized questions regarding patient´s and her  │
│ partner´s attitude towards the pregnancy             │
└─────────────────────────────────────────────────────┘
                         ↓
┌─────────────────────────────────────────────────────┐
│ On the day miscarriage was judged to be complete     │
│ Forms handed out and completed at the visit:         │
│ -STAI-state                                          │
│ -MADRS-S                                             │
│ -CSQ-8                                               │
└─────────────────────────────────────────────────────┘
                         ↓
┌─────────────────────────────────────────────────────┐
│ 3 months after complete miscarriage                  │
│ Forms sent and returned by post:                     │
│ -STAI-state                                          │
│ -MADRS-S                                             │
│ -CSQ-8                                               │
│ -PGS                                                 │
└─────────────────────────────────────────────────────┘
                         ↓
┌─────────────────────────────────────────────────────┐
│ 14 months after complete miscarriage                 │
│ Forms sent and returned by post:                     │
│ -STAI-state                                          │
│ -MADRS-S                                             │
│ -CSQ-8                                               │
│ -PGS                                                 │
│ -Standardized questions about any new pregnancy      │
│ after the miscarriage                                │
└─────────────────────────────────────────────────────┘
```

Figure 7. Schematic figure of distribution of questionnaires

Ultrasound

We used a Sequoia 512 ultrasound machine (Siemens Medical Solutions Inc., Ultrasound Division, Mountain View, CA, USA) with a 4-7.5 MHz transvaginal transducer.

The women were examined at inclusion by AF or LJ. To assess blood flow in the presumed intervillous space flickering areas within the chorion on grey-scale imaging were first looked for. The colour Doppler function was then switched on starting with standardized settings (space–time S2; edge zero; persistence two; colour map V2; gate two; filter three; frequency 7 MHz; colour Doppler gain 50; pulse repetition frequency corresponding to blood flow velocity 2.1 cm/s)which were adjusted to maximize detection of slow velocity blood flow without artifacts. The Doppler gate was placed where colour Doppler signals were seen inside the chorion. By adjusting the position of the probe, arterial Doppler shift signals inside the chorion were looked for as previously described[150, 151]. At follow-up women were examined by AF or LJ. To assess the endometrial thickness during follow-up, the endometrium was measured in the midsagittal plane from one myometrium/endometrium interface to another across the widest part of the cavity.

Manuscript preparation
The manuscript (Paper I) was prepared following the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The aim of the CONSORT guidelines is to encourage complete, clear, and transparent reporting on methodology and findings of randomised controlled trials. The guidelines include a checklist and provide published examples of transparent reporting[156]

Outcome variables
The primary outcome of the randomized trial was complete miscarriage within10 days. All secondary outcomes were pre-planned and defined in the study protocol.

Specific outcomes:

I.   Primary outcome: Complete miscarriage without D&E within 10 days after randomization.

Secondary outcomes: Complete miscarriage without D&E within 17, 24, and 31 days after randomization. Self-reported pain, use of analgesics, duration of vaginal bleeding and side effects (nausea, vomiting, diarrhea, headache, dizziness), from randomization until complete miscarriage or up to 31 days. Complications (infection, D&Es emergency and others, blood transfusion, change in Hb concentration from inclusion until complete miscarriage, prescription of antibiotics, unplanned visits, hospitalisation, sick-leave) from randomization until 4 weeks after the uterine cavity was judged to be empty (with or without D&E), or if expulsion did not occur within 31 days, until 4 weeks after day 31

II. The predictive ability of pre-defined variables in relation to treatment success after misoprostol or expectant management: serum/plasma levels of progesterone and β-hCG, gestational age according to LMP, previous

vaginal delivery, parity, bleeding at inclusion, pain at inclusion, shape of the gestational sac, mean gestational sac diameter, CRL, type of miscarriage (embryonic or anembryonic), visible blood flow in the presumed intervillous space, arterial Doppler shift signals in the presumed intervillous space.

III.   Levels of anxiety, depressive symptoms, grief and satisfaction with treatment as measured at four assessment points from randomization until 14 months after complete miscarriage.

IV.   Reproductive events (live births, miscarriages, terminations of pregnancy, ectopic pregnancies, ongoing pregnancies and outcome of ongoing pregnancies at 14 months) 14 months after complete miscarriage.

Statistics

Power analysis
Sample size analysis was performed for the main outcome – complete miscarriage without D&E within 10 days. We assumed that complete miscarriage would be achieved within 10 days in 70% of women in the misoprostol group versus 50% of women after expectant management. A p-value of <0.05 (two-sided test) was assumed to reject the null hypothesis (type I error) and power was set at 80% (1-type II error). The calculated required sample size was 93 patients in each group. We aimed at recruiting 120 patients to each group to compensate for dropouts, exclusions and missing data.

Comments on power
Power calculation for any of the secondary outcomes was not performed, as post hoc power analysis is strongly advised against by statisticians[152]. Statistical power is the probability of correctly rejecting the null hypothesis under some assumed conditions (distribution of the study outcome, planned sample size and prespecified significance level). A high statistical power means that the test results are likely to be valid. As the power increases the probability of making a type II error (to wrongly accept the null hypothesis when it is actually false) decreases. The statistical power usually aimed at is 80% or 90%, which means that the probability to reject the null hypothesis when it is truly false would be 80% or 90%. (However, there will be a 10% or 20% risk to get results that are not statistically significant even though a difference truly exists.) If the power is too low, the test results will be questionable. To achieve the desired power, sample size is calculated from an estimation of the probable distribution of the outcome. The study must be large enough to reliably conclude that a difference exists, if a meaningful difference truly

exists. Either, one can assume that a difference of a certain size is likely to occur (outcome distribution) or one can design a trial to reliably detect only a difference large enough to carry clinical implications. The problem with using the observed effect size to calculate power after a study is completed is that the observed significance level of a test will also determine the observed power. A test with a small p-value will have high "observed" power and a higher p-value will lead to lower "observed" power.

Statistical methods

Analysis was by intention to treat. Observed differences between the groups were tested for statistical significance. Student's t-test or the Mann-Whitney U-test was used for unpaired continuous data, depending on distribution. For unpaired categorical data the Chi-squared or, in cases with small numbers of an outcome, Fisher's exact test was used. To determine the statistical significance of differences in paired data we used the Friedman test and Wilcoxon signed rank test. P-values < 0.05 were considered statistically significant.

Risk differences and confidence interval

In Paper I and Paper IV, we used absolute risk differences with 95% confidence intervals (CI) as the main effect measure. While the p-value will determine the reliability with which the null hypothesis can be rejected, a confidence interval will assess the precision of the result. The confidence interval provides a range of values within which the true value is situated with a certain level of confidence. If the confidence interval includes a very wide range, it is a sign of imprecision of the results and the results should be interpreted with caution although a strong statistical relation may exist. If zero is included in the confidence interval a statistically significant difference probably does not exist[153].

For calculating differences in proportions with 95% confidence interval, including continuity correction, a calculator derived from www.vassarstats.net (©Richard Lowry) was used. A calculator from the somersd package in Stata version 14 (StataCorp LLC, College Station, TX, USA) was used for calculating differences in continuous variables with 95% confidence interval.

Likelihood ratio tests and odds ratios

In Paper II, odds ratios and their 95% confidence interval were used as the main effect measure to describe the relation between the predefined predictive variables (continuous or categorical) and treatment success. Univariable logistic regression with likelihood ratio test was used to detect differences of statistical significance. A two-sided p-value of <0.05 was considered statistically significant.

The likelihood ratio test is used to test the statistical significance of the difference between the probability of treatment success when a possible predictor is present and the probability of treatment success when the predictor is not present.

For categorical variables, the calculated p-value will only indicate if a difference actually exists in relation to the variable. The direction of the difference (if the probability decreases or increases in presence of the predictor) will not be indicated by the p-value. To understand the effect of a predictor, odds ratios were used. The odds ratio compares the odds of two events. The odds of an event is the probability that the event occurs divided by the probability that the event does not occur. In Paper II, the events of interest are success versus failure when a predefined variable is present and success versus failure when the predefined variable is not present.

For continuous predictors odds ratios greater than 1 indicate that the event is more likely to occur as the predictor increases. Odds ratios less than 1 indicate that the event is less likely to occur as the predictor increases. As an example, β-hCG was found to be a predictor of treatment success after expectant management, with odds ratio <1 (0.956). As the level of beta β-hCG increases the probability of treatment success after expectant management will decrease and, conversely, decreasing levels of β-hCG will lead to a higher probability of treatment success after expectant management.

For categorical predictors the odds ratio compares the odds of the event at two different levels of the predictor, a level when the predictor is *present* versus a level when the predictor is *absent*. Odds ratios greater than 1 indicate that the event is more likely at predictor-present-level. Odds ratios less than 1 indicate that the event is less likely at predictor-absent-level.

The odds ratios are given with 95% confidence interval, i.e. the true value of the odds ratio lies within the boundaries of the confidence interval with 95% probability. The confidence interval for odds ratios should not include 1 to indicate statistical significant difference.

Multivariable regression analysis
To determine which of the variables were independently associated with treatment success multivariable logistic regression analysis was used. Multivariable models for prediction of complete miscarriage after expectant management or misoprostol treatment were built. Different approaches were used for model building. In a first approach, multivariable backward step-wise logistic regression analysis was employed, in which all of the predetermined variables (with a sufficient number of individuals presenting with the variable, i.e. a minimum of five individuals was required in each cell of a contingency - four-field - table displaying the specific variable in relation to failure and success) were included. In another approach, only

variables that had a *P* value of less than 0.20 in the univariable analysis were included from the beginning, after which variables that were believed to be clinically relevant were added.

Area under the receiver-operating curve
In order to evaluate the discriminatory ability of the suggested models, the area under the receiver-operating curve (ROC) was calculated with its 95% confidence interval (CI). For plotting the ROC curves, individual data of each patient was entered into the models to calculate the individual probability of treatment success. In the ROC curve, the sensitivity (true positive rate) is plotted versus 1-specificity (false positive rate) for varying cut-off values. Each point of the ROC-curve represents a sensitivity/specificity pair corresponding to each individual's probability of treatment success according to the model. By calculating the area under the ROC curve (AUC) the model's ability to distinguish between treatment success and treatment failure was estimated. The AUC can be interpreted statistically as the probability of the model to correctly distinguish patients in whom treatment failed and patients in whom treatment was successful. An AUC with a value of 1 represents a perfect test (in which the model can distinguish all patients with treatment success from all patients with treatment failure) while a value of 0.5 represents a useless test with the discriminatory ability equivalent to tossing a coin. The AUC denotes the probability that a randomly selected individual from the success group has a calculated post model probability of treatment success that is higher than that from a randomly selected individual from the failure group.

ROC-curves may be used to define a specific cut-off value for probability of treatment success, for which it is reasonable to opt for expectant management, for example. In that way, multivariable regression models can be used to guide treatment decisions in clinical praxis and for patient counselling. However, predictive modelling can also be used to expose complex relationships and thereby contribute to the building of new explanatory hypotheses[154]. Before predictive models are used, they need to be validated on a new set of patient data.

Psychometric measures and missing data
The psychometric scores were compared between the misoprostol group and the expectantly managed group at each assessment point. Only completed scores were included in the statistical analyses. For each psychometric instrument, only a predefined maximum number of missing items were permitted to count the instrument form as completed. *For STAI-trait, STAI-state, PGS and CSQ-8 the maximum number of missing items permitted were two and for MADRS-S only one missing item was permitted.* To visualize and compare the trajectories of the scores, psychometric scores were plotted against time, separately for the misoprostol group

and the expectantly managed group. Only women, who had completed the questionnaire at every assessment point, were included in these analyses.

Missing data for psychometric measures is commonly reported[119]. There are two types of missing data. In studies with multiple assessments, there may be difficulties to retain participants throughout the study, which leads to *missing scale score* due to the drop out of a participant (the questionnaire is not returned). Missing items *within* a scale result from participants omitting responses for single items of a specific questionnaire. Non-random missing data may induce bias. If missing items are ignored, the total score - the responses of the remaining items are summed - will lead to an underestimate of the participants' score. If participants with missing items are not included in the statistical analysis this will also cause bias and the power of the study will be reduced. In the current work, simple mean imputation, i.e. subject mean was used for missing items within a scale within each patient. The mean score of available items' responses was used to replace the missing item response. In cases where this resulted in fractional values, they were rounded to the next higher number. As different items in psychometric tests are correlated with each other, this method is supposed to be the most unbiased approach in psychometric research[155]. In the STAI manual this is also recommended[136].

Results and Comments

Between September 2008 and December 2015, 189 women were recruited. The targeted sample size of 240 was not reached despite a prolonged recruiting period. The number of participants included for analysis in each paper is shown in **Table 1**.

Table 1. Overview of participants included for analysis in the four papers

	Misoprostol treatment	Expectant management
Randomized	94	95
Withdrawal of consent	-	2
Received allocated treatment	94	93
Revised diagnosis, not included in analysis	-	3
	Included for analysis	
Paper I (Treatment effect)	94	90
Paper II (Prediction)	92 D&E before first follow-up n=2, not included	85 D&E before first follow-up n=5, not included
Paper III (Psychological impact)	94	90
Paper IV (Fertility)	89 Reproductive data not available n = 5	83 Reproductive data not available n = 7

Paper I and II

(Rate of success, side effects, complications and prediction of treatment success)

Treatment success, complications and side effects

Subjects
Paper I: 184 patients were analysed with regard to treatment outcome (expectant management n=90; misoprostol n=94). Paper II: Patients that underwent D&E before first follow-up (Day 10) were excluded for the analysis of predefined variables in relation to treatment success. 177 patients (expectant management n=85; misoprostol n=92) were analysed in relation to treatment success within 10 days. Predefined variables in relation to treatment success within 17 days were analysed for 174 patients (expectant management n=83; misoprostol n=91). Baseline characteristics of the study population are presented in **Table 2**.

Despite the randomized design the groups differed slightly: more women in the misoprostol group than in the expectantly managed group were nulliparous: 49/94 (52%) versus 33/90 (37%) and the median value of β-hCG was slightly higher and CRL slightly smaller in the expectantly managed group. Mean (SD) age was 32.1 (5.6) years in the misoprostol group, and 31.9 (5.5) years in the expectantly managed group. Gestational age according to LMP ranged from 6 to 16 weeks. The distribution of the different types of miscarriage (anembryonic or embryonic) was similar in the two groups. Twenty-four of 94 (26%) women in the misoprostol group and 33/90 (37%) women in the expectantly managed group women had suffered one or more miscarriages before the index miscarriage.

Treatment success
The rate of treatment success, side effects and complications is presented in **Table 3.** More women in the misoprostol group than in the expectant group achieved complete miscarriage within 10 days: 62/94 (66.0%) *vs* 39/90 (43.3%) (risk difference (RD) 22.6%; 95% CI, 7.5–36.5%). The cumulative rate of complete miscarriage (without D&E) was higher in the misoprostol group at all time points – 10, 17, 24 and 31 days. At 31 days, 81/94 (86.2%) of women treated with misoprostol had achieved complete miscarriage *vs* 55/90 (61.1%) of the women in the expectantly managed group (RD 25.1%; 95% CI, 11.6–37.5%). Vaginal bleeding lasted for about two weeks after inclusion.

Table 2 Baseline characteristics of participants

Characteristic	Misoprostol treatment n=94	Expectant management n=90
Age (years)	32.1±5.6	31.9±5.5
Gestational age according to LMP (days)	76.5±14.3	75.5±12.3[a]
Nulliparous	49 (52.1)	33 (36.7)
Previous miscarriage	24 (25.5)	33 (36.7)
Previous legal termination of pregnancy	22 (23.4)	22 (24.4)
Haemoglobin concentration (g/L)	131.2±8.4	129.2±9.3[b]
p- β-hCG (IU/L)[e]	5303.5 (6-77286)[c]	8483.0 (107-80317)
p-progesterone (nmol/L)[e]	18 (1-63)[d]	19 (3-190)[d]
Crown-rump-length (mm)	11.0 (1.9-31.0)	6.4 (3.0-26.0)
Type of miscarriage on ultrasound		
Embryonic	66 (70.2)	56 (62.2)
Anembryonic	28 (29.7)	34 (37.8)
Days from start of bleeding to inclusion	5.0 (1-42)	6.0 (1-60)*

Values are numbers (%), mean±SD, or median (range)
[a] 5 missing values, [b] 4 missing values, [c] 2 missing values, [d] 1 missing value. [e] Before mid May 2013 human chorionic gonadotropin and progesterone were analysed in serum and not in plasma – reference intervals are not affected

Side effects and complications
The frequency of severe pain did not differ between the groups but a significantly higher number of women in the misoprostol group took oral painkillers, 85/91 (93.4%) *vs* 59/77 (76.6%) (RD 16.8%; 95% CI, 5.2–28.7%)(**Table 4**). Other reported side effects did not differ significantly across the groups.

Significantly more women in the expectant management group than in the misoprostol group underwent D&E, at patient's request or because of failed treatment after 31 days: 10/94 (10.6%) *vs* 31/90 (34.4%) (RD −23.8%; 95% CI, −35.8 to −11.1%). The rate of unplanned emergency D&E was similar, 2/94 (2.1%) in the misoprostol group *vs* 4/90 (4.4%) in the expectantly managed group (RD −2.3%; 95% CI, −9.7 to 4.5%), but the number of patients undergoing D&E at their own request was much higher in the group receiving expectant management, 15/90 (16.7%) *vs* 3/94 (3.2%) (RD 13.5%; 95% CI, 4.1–23.4%). Other major complications were rare.

Table 3 Outcome for women treated with vaginal misoprostol or expectant management

Outcome	Misoprostol treatment n=94	Expectant management n=90	Difference (95% CI)
Complete miscarriage without D&E			
≤10 days	62 (66.0)[a]	39 (43.3)	22.6 (7.5 to 36.5)
≤17 days	73 (77.7)	44 (48.9)	28.8 (14.2 to 41.9)
≤24 days	78 (83.0)	51 (56.7)	26.3 (12.4 to 39.1)
≤31 days	81 (86.2)	55 (61.1)	25.1 (11.6 to 37.5)
Total number of patients undergoing D&E	10 (10.6)	31 (34.4)	-23.8 (-35.8 to -11.1)
D&E before first follow-up			
Emergency (bleeding)	2 (2.1)	2 (2.2)	-0.1 (-6.3 to 6.7)
Patient request	0	3 (3.3)	-3.3 (-10.1 to 2.2)
D&E during follow-up	8 (8.5)	26 (28.9)	-20.4 (-32.0 to – 8.4)
Patient request	3 (3.2)	12 (13.3)	-10.1 (-19.6 to -1.3)
Failure of treatment	5 (5.3)	12 (13.3)	-8.0 (-17.8 to -1.4)
Emergency (bleeding)	1 (1.1)[a]	0	1.1 (-4.1 to 6.6)
Emergency (endometritis)	0	2 (2.2)	-2.2 (-8.6 to 3.0)
Endometritis	1 (1.1)	3 (3.3)	-2.3 (-91 to 3.8)
Prescribed antibiotics	3 (3.2)	7 (7.8)	-4.6 (-13.0 to 3.2)
Haemoglobin at last follow-up (g/L)	124.2±12.3[b]	123.5±12.2[c]	0.7 (-3.6 to 5.1)
Received blood transfusion	1 (1.1)	1 (1.1)	0.0 (-5.9 to 5.6)
Out-of protocol visits[d]	27 (28.7)	50 (55.6)	-26.8 (-40.3 to -11.8)
Number of out-of protocol visits	0.5±1.0	1.0±1.2	-0.5 (-0.8 to -0.2)
Hospitalized	3 (3.2)	4 (4.4)	-1.2 (-8.8 to 5.9)
Days of hospitalization	0.0±0.2	0.1±0.4	-0.05 (-0.1 to 0.04)

Values are numbers (%) or mean±SD [a] One patient judged to have had a complete miscarriage at first follow-up returned with vaginal bleeding after 2 months and underwent dilatation and evacuation (D&E); she is not included in total number of patients undergoing D&E, because she could not be classified both as having had a complete miscarriage and as failure of treatment. [b] 17 missing values.[c] 37 missing values.[d] From inclusion until 4 weeks after complete miscarriage or after 31 days if not complete miscarriage on day 31

Table 4. Self-reported bleeding and pain according to returned diaries. Number of patients who completed and returned the diaries n=168

	Misoprostol treatment n=91	Expectant management n=77	Difference (95%)
Vaginal bleeding, number of days after inclusion	12.7±6.6	15.0±8.2	-2.3 (-4.6 to -0.6)
Patients with pain	91 (100.0)	71 (92.2)	7.8 (1.0 to 16.8)
Patients with severe pain	64 (70.3)	47 (61.0)	9.3 (-5.8 to 24.2)
Number of days with severe pain	1.3±1.6	1.3±1.5	0.02 (-0.5 to 0.5)
Patients taking painkillers	85 (93.4)	59 (76.6)	16.8 (5.2 to 28.7)

Values are numbers (%) or mean±SD

Prediction models

None of the examined variables could predict treatment success after misoprostol treatment. In patients managed expectantly the likelihood of spontaneous complete miscarriage was almost twice as high in embryonic as in anembryonic miscarriage. 28/52 (53.8%) versus 11/33 (33.0%) (*P* 0.06) within 10 days; 32/51 (62.7%) versus 12/32 (37.5%) (*P* 0.02) within 17 days. The association (univariable analysis) between the predefined predictors and treatment success within 17 days after expectant management is shown in **Table 5**. In multivariable analysis, the following variables were independently associated with treatment success after expectant management: gestational age according to LMP (the higher the more likely successful treatment), mean gestational sac diameter (the smaller the more likely successful treatment) and CRL (the larger the more likely successful treatment). When type of miscarriage, instead of CRL, was included in the multivariable model, the odds of treatment success were approximately six times higher in embryonic than in anembryonic miscarriages (**Table 6a and 6b**). In another model, either s-β-hCG or s-progesterone (not both) and crown-rump-length or miscarriage type was independently associated with complete miscarriage. The AUCs of the models ranged from 0.71 to 0.77.

In embryonic miscarriage, the success rate ≤ 10 and ≤ 17 days increased with increasing gestational age according to LMP, increasing CRL and decreasing mean gestational sac diameter; or with decreasing s-progesterone or s-β-hCG (not both) and increasing CRL. The AUCs of the models ranged from 0.80 to 0.84. No variable was statistically significantly associated with complete miscarriage of anembryonic miscarriages.

Table 5. Association between predefined possible predictors and success of expectant management of embryonic or anembryonic miscarriage ≤17 days (univariable logistic regression analysis); n=83

Variables tested as possible predictor	Success n=44	Failure n=39	p-value[a]	Odds ratio (95%CI)
s-β-hCG (IU/L)[b]	9530.6±7483.3 8308.0 (107-26,585)	2 missing 18,128.3±21019.9 7990.0 (1006-80,317)	0.01	0.958 (0.922-0.995)[c]
s-Progesterone (nmol/L)[b]	18.5±10.6 18.0 (3-41)	1 missing 34.6±38.2 20.5 (4-190)	0.003	0.965 (0.936-0.995)
Gestational age according to LMP (days)	2 missing 77.8±10.7	3 missing 72.4±12.4	0.04	1.042 (1.000-1.086)
Vaginal delivery			0.843	0.915 (0.382-2.195)
yes	25 (56.8)	23 (59.0)		
no	19 (43.2)	16 (41.0)		
Parity			0.679	1.208 (0.493-2.963)
Parous	29 (65.9)	23 (61.5)		
Nulliparous	15 (34.1)	15 (38.5)		
Bleeding at inclusion, moderate/heavy[d]	10 (22.7)	3 (7.7)	0.053	3.529 (0.894-13.927)[e]
Any pain at inclusion	13 (29.5)	11 (28.2)	0.893	1.067 (0.412-2.765)
Collapsed gestational sac	12 (27.3)	11 (28.2)	0.925	0.955 (0.365-2.499)
Gestational sac diameter (mm)[f]	24.1±9.5	1 missing 24.1±7.9	0.967	0.999 (0.950-1.050)
CRL (mm)	7.5±7.0 5.6 (0.0-26.0)	3.6±4.9 0.0 (0.0-17.0)	0.004	1.119 (1.028-1.218)
Miscarriage type on ultrasound			0.024	2.807 (1.126-6.998)
Embryonic	32 (72.2)	19 (48.7)		
Anembryonic	12 (27.3)	20 (51.3)		
CRL if embryonic miscarriage (mm)	n=32 10.3±6.2 9.5 (3.0-26.0)	n=19 7.4±4.6 5.3 (3.0-17.0)	0.069	1.109 (0.981-1.254)
Blood flow in presumed intervillous space according to				
Grey-scale ultrasound			0.105	0.205 (0.023-1.840)
yes	39 (88.6)	38 (97.4)		
no	5 (11.4)	1 (2.6)		
Colour Doppler ultrasound		1 missing	0.008	0.105 (0.013-0.873)
yes	35 (79.5)	37 (94.9)		
no	9 (20.5)	1 (2.6)		
Spectral Doppler (arterial blood flow)	4 missing	4 missing	0.125	0.468 (0.175-1.252)
yes	23 (57.5)	25 (71.4)		
no	17 (42.5)	10 (28.6)		

Values are numbers (%), mean ± SD or median (range)
CI confidence interval
[a]Likelihood ratio test
[b]After mid May 2013 beta-human chorionic gonadotropin and progesterone were analyzed in plasma and not in serum, reference intervals are not affected

Table 6 a and b. Multivariable regression models for predicting complete miscarriage ≤ 10 and ≤ 17 days in women with embryonic or anembryonic miscarriage managed expectantly

6a. Complete miscarriage ≤10 days	AUC (95%CI) 0.739 (0.628-0.850) Constant -5.058		
Variables in model	Coefficient	Odds ratio	p-value[a]
Gestational age according to LMP (OR for change in days)	0.083	1.087 (1.024-1.153)	0.002
Mean sac diameter (OR for change i mm)	-0.099	0.905 (0.838-0.978)	0.007
Type of miscarriage (embryonic or anembryonic)	1.737	5.682(1.724-18.730)	0.002

6b. Complete miscarriage ≤17 days	AUC (95%CI) 0.754 (0.645-0.863) Constant −4.783		
Variables in model	Coefficient	Odds ratio	p-value[a]
Gestational age according to LMP (OR for change in days)	0.076	1.079 (1.017-1.144)	0.006
Mean sac diameter (OR for change in mm)	-0.076	0.927 (0.858-1.001)	0.046
Type of miscarriage (embryonic or anembryonic)	1.802	6.060 (1.837-19.992)	0.001

The probability of treatment success is calculated as
$[e^z/(1 + e^z)]$ where $e = 2.718$ (base value of natural logarithm) and z is calculated as:
z = constant + (coefficient × gestational age according to last menstrual period in days + coefficient × type of miscarriage where anembryonic gestation is coded as 0 and embryonic gestation as 1 + coefficient × mean sac diameter in mm)
AUC area under receiver-operating characteristic curve, CI confidence interval, OR odds ratio, LMP last menstrual period
[a]Likelihood ratio test

Comments and Conclusions Study I and II

The well-defined study population (only women with embryonic or anembryonic miscarriage and who reported vaginal bleeding) and the generous observation time (31 days) are the major strengths of this trial. The prediction models have not been validated in a new study sample, which is a weakness. A slight imbalance between the treatment groups was noted. More women in the expectantly managed group were parous, had slightly higher β-hCG levels (while progesterone levels were very

similar) and the CRL of their fetuses was smaller. It is uncertain if these imbalances, explained by chance, affect the results.

The rates of treatment success - after misoprostol and after expectant management - in this trial confirm the results of others. Compared to expectant management, misoprostol treatment shortens the time to complete miscarriage in women with embryonic and anembryonic miscarriage[36, 37, 45, 46, 49, 51]. The high success rate associated with misoprostol is likely to explain why no factor could predict treatment success after misoprostol.

In the current trial, approximately 50% of women with embryonic or anembryonic miscarriage who have started to bleed miscarried spontaneously and completely within 2–3 weeks. A longer observation time is safe and it probably reduces the number of women in need of surgical evacuation, compared to a shorter waiting time. It is possible that the number of unplanned visits and D&Es at patient's request was influenced by the fact that women were not free to choose treatment in this trial. If women in accordance with their preference would choose expectant management both unplanned visits and D&E at patient's request may be reduced.

The most important factor for prediction of treatment success after expectant management was the type of miscarriage - if it is embryonic or anembryonic. The other tested variables showed only moderate predictive value. Studies exploring possible predictors of complete miscarriage after expectant management are heterogenous[43, 62, 66-67, 85-89, 94, 95]. This is probably explained by differences in study populations (types of miscarriage, symptomatology), definitions of complete miscarriage and treatment success, and variables tested as predictors. However, more than one study reported that the lower the s-β-hCG and s-progesterone values the higher the likelihood of success of expectant management[66, 89, 94]. Two studies were reasonably similar to the current study with regard to inclusion criteria and definition of treatment success[66, 94]. Schwärtzler et al found that pulsatile flow in the presumed intervillous space was a predictor of successful treatment[66]. This was not confirmed in the current study, but it has been suggested that this may be related to a lack of experience of the trial examiners. Memtsa et al. reported that the older the patient and the lower the s-progesterone level the higher the likelihood of complete miscarriage < 7 days[94]. Maternal age was not tested as a predictor in the current study, because age seemed unlikely to be related to the time to complete evacuation of the uterine cavity.

Comments on the prediction models
The concentrations of s-β-hCG and s-progesterone are supposed to reflect viability of the trophoblast and corpus luteum. Higher concentrations are compatible with earlier stages of miscarriage, which may be less likely to resolve spontaneously

within reasonable time. The relation between gestational age according to LMP, crown-rump-length and gestational sac diameter may reflect the time elapsed since the embryo died. A smaller gestational sac in relation to a large embryo may originate from the apoptotic process being faster for the gestational sac than for the embryo and may be predictive of treatment success. Long time between embryonic death and start of bleeding may indicate a resistance to expulsion. Anembryonic miscarriages were more resistant to spontaneous resolution within the observation time. The absence of an embryo may be explained by the resorption of an embryo that has already been dead for a long time, signalling resistance to expulsion.

Conclusions Study I and II
Misoprostol is more effective than expectant management for treatment of women with early embryonic or anembryonic miscarriage reporting vaginal bleeding. D&E and out-of-protocol visits were more common after expectant management, but more patients experienced pain and took painkillers after misoprostol treatment. Major complications were rare in both groups. The probability to achieve complete miscarriage after expectant management was higher in embryonic than in anembryonic miscarriage. Other factors with possible prognostic value with regard to treatment success after expectant management were gestational age, CRL, size of the gestational sac and levels of progesterone and β-hCG. Prognostic factors may be helpful to provide patients with realistic expectations, but the prediction models need to be prospectively validated.

Paper III

(Psychological reactions)

Psychological reactions and patient satisfaction

Subjects

184 women were analysed (expectant management n=90; misoprostol treatment n=94). A substantial number of women in both groups did not return all of their questionnaires or returned incompletely filled out forms. The number of non-respondents increased with later assessment points and significantly more women in the expectantly managed group than in the misoprostol group dropped out or omitted several questions. The response rate at 14 months was 44/90 (49%) versus 61/94 (65%). When non-respondents were compared to respondents, more of them were parous and said that the pregnancy was unplanned and/or not welcome and/or that they did not wish to become pregnant again and/or that their partner expressed a negative attitude towards the pregnancy. However, anxiety at inclusion, expressed as STAI-trait and STAI-state scores did not differ between respondents and non-respondents.

Anxiety, depression and grief

The psychometric scores of the groups did not differ significantly on any of the assessment points. "Proneness to anxiety" (STAI-trait scores at inclusion) was representative for gender and age in both groups. (Data not shown) Scores of anxiety and depressive symptoms were higher at inclusion than at later assessments. **(Table 7, Figure 8 and 9**). Anxiety was more common than depressive symptoms. Both anxiety and symptoms of depression decreased significantly from inclusion until the miscarriage was judged to be complete. The proportions of women expressing high levels of anxiety or symptoms correlating to moderate or severe depression at inclusion, when the miscarriage was judged to be complete, at three months and at 14 months after miscarriage are shown in **Table 7.**

At inclusion: 35/86 (41%) of the women in the expectantly managed group and 34/92 (37%) in the misoprostol group expressed high levels of anxiety (STAI-state scores >46). Symptoms corresponding to moderate or severe depression (MADRS-S >20) were expressed by 8/86 (9%) in the expectantly managed group versus 9/91 (10%) in the misoprostol group.

At later assessments: When the miscarriage was judged to be complete, 12/84 (14%) in the expectantly managed group and 10/91 (11%) in the misoprostol group reported high levels of anxiety while major depressive symptoms were expressed

by 5/81 (6%) versus 5/93 (5%). The levels remained low until 14 months after the miscarriage. Anxiety levels were not related to how many days it took until complete miscarriage or to if D&E was performed or not. Grief reactions were mild according to PGS. (Data not shown) Three months after complete miscarriage, grief scores compatible with possible psychiatric morbidity were reported by four women treated with misoprostol and two women managed expectantly. At 14 months, one woman in the expectantly managed group reported a similar high score.

Table 7. Psychometric scores for the expectantly managed group and the group treated with misoprostol at the different assessment points

	At inclusion			At complete miscarriage			At 3 months after complete miscarriage			At 14 months after complete miscarriage		
	Misoprostol treatment	Expectant management	p-value	Misoprostol treatment	Expectant management	p-value	Misoprostol treatment	Expectant management	p-value	Misoprostol treatment	Expectant management	p-value
STAI state score >46 (high level of anxiety)	n=92 34 (37.0)	n=86 35 (40.7)	0.61	n=91 10 (11.0)	n=84 12 (14.3)	0.51	n=78 12 (15.4)	n=67 12 (17.9)	0.68	n=70 9 (12.9)	n=55 6 (10.9)	0.74
MADRS-S												
Levels of depression[a]	n=91	n=86	0.89[b]	n=93	n=81	0.82[b]	n=77	n=67	0.22[b]	n=65	n=47	0.72[b]
Mild (13-19)	19 (20.9)	13 (15.1)		6 (6.5)	5 (6.2)		7 (9.1)	7 (10.4)		4 (6.2)	4 (8.5)	
Moderate (20-34)	9 (9.9)	5 (5.8)		5 (5.4)	5 (6.2)		5 (6.5)	1 (1.5)		3 (4.6)	4 (8.5)	
Severe (≥35)	0	3 (3.5)		0	0		0	0		1 (1.5)	0	

Values are numbers (%)
STAI, State Trait Anxiety Inventory; MADRS-S, Montgomery-Åsberg (Self-assessment) Depression Scale; Patients with completed forms for the actual instrument are included (they may have incomplete forms for one or more of the other instruments)

[a] Level of depression according to MADR-S score (score shown in brackets) [b] Mild vs. moderate or severe
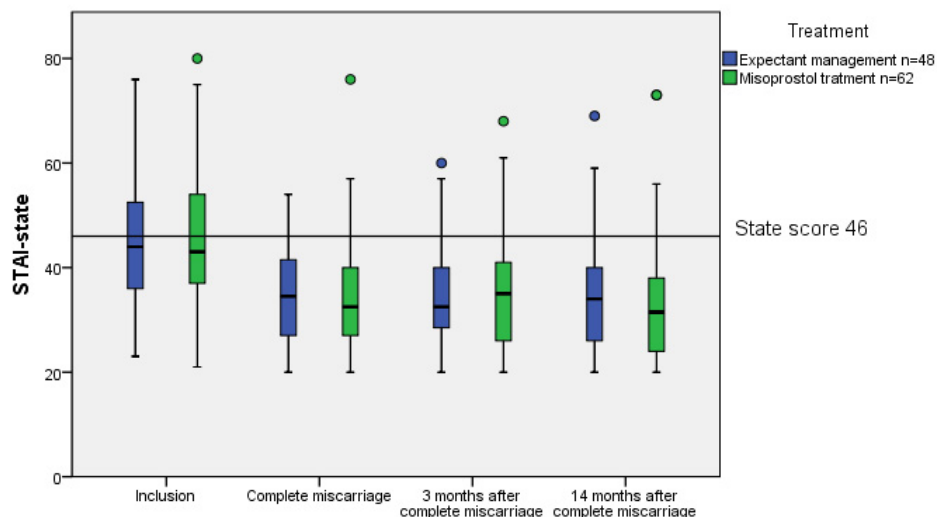
Figure 8. State-Trait Anxiety Inventory (STAI) state scores in the two treatment groups at inclusion, on the day of complete miscarriage, at 3 months and at 14 months after complete miscarriage. Only women who had completed the questionnaire at every assessment point are included in this analysis. The total score can take values from 20 to 80. Higher scores indicate more anxiety. The horizontal line denotes state-anxiety score 46 (corresponding to mean for working women in the general population plus 1 standard deviation)[136]. The box represents the interquartile (IQ) range which contains the middle 50% of the results. The line inside the box is the median. Whiskers correspond to values within 1.5 times of the IQ range. Circles are outliers with values between 1.5 and 3 times the IQ range. The Friedman test showed P < 0.001 in both groups.
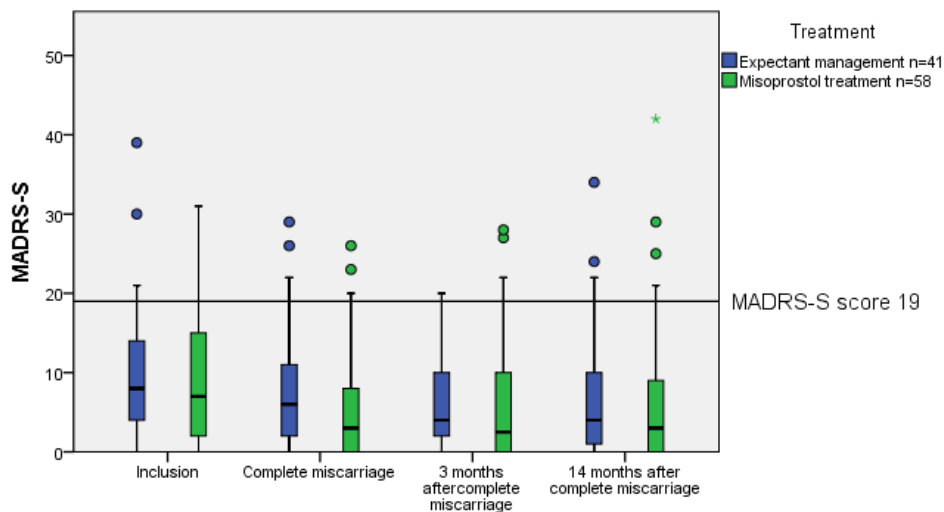
Figure 9. Montgomery Asberg Depression Rating Scale (MADRS-S) scores in the two treatment groups at inclusion, on the day of complete miscarriage, at 3 months and at 14 months after complete miscarriage. Only women who had completed the questionnaire at every assessment point are included in this analysis. Scores can take values from 0 to 54. Higher scores indicate more depression symptoms. Scores above the horizontal line corresponding to MADRS-S score 19 indicate symptoms corresponding to at least moderate depression[127, 128]. The box represents the interquartile (IQ) range which contains the middle 50% of the records. The line inside the box indicates the median. Whiskers correspond to values within 1.5 times of the IQ range. Circles are outliers with values between 1.5 and 3 times the IQ range. Extremes (*) are cases with values more than 3 times the IQ range. The Friedman test yielded P-value 0.014 in the expectantly managed group and P-value < 0.001 in the misoprostol group.

Treatment satisfaction

Women in both groups were satisfied with their management. No relation was found between treatment satisfaction and the length of the waiting time until complete miscarriage or between treatment satisfaction and if D&E was performed or not.
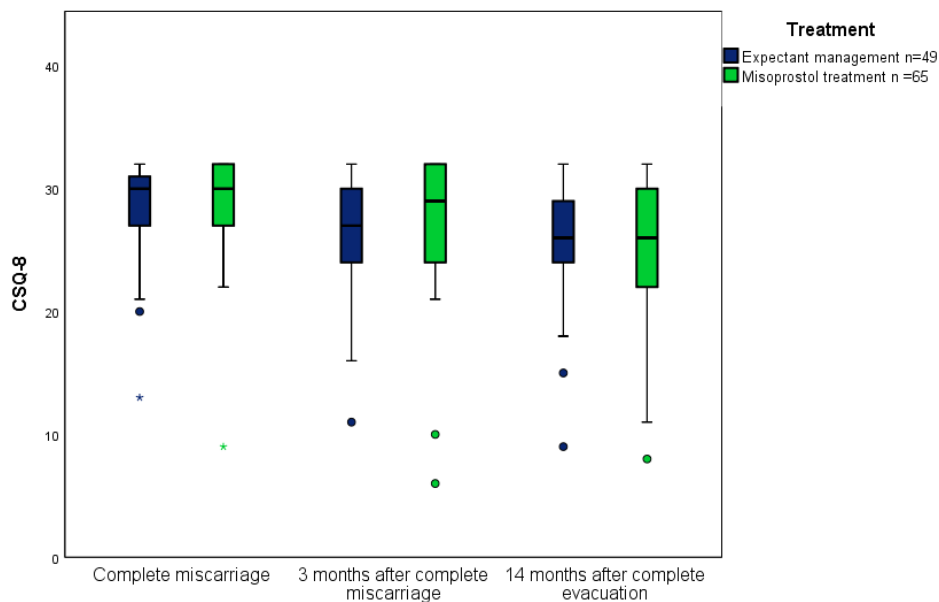
Figure 10. Client Satisfaction Questionnaire-8 (CSQ-8) scores in the two treatment groups at complete miscarriage, at 3 months and at 14 months after complete miscarriage. Only women that had completed the questionnaire at every assessment point are included in this analysis. Total score can take values from 8 to 32. Higher scores indicate higher level of satisfaction[139]. The box represents the interquartile (IQ) range which contains the middle 50% of the records. The line inside the box indicates the median. Whiskers correspond to values within 1.5 times of the IQ range. Circles are outliers with values between 1.5 and 3 times the IQ range. Extremes (*) are cases with values more than 3 times the IQ range. The Friedman test showed P < 0.001 in both groups.

Comments and Conclusions Study III

This is the first study to compare short- and long-term psychological reactions and satisfaction with treatment between women treated with expectant management or with misoprostol. The use of standardized and validated self-report measures is a strength. No information is available on how many of the invited women that declined, which is a weakness, as it cannot be ruled out that women who decline may differ psychologically from study participants. Understanding written Swedish was an inclusion criterion, why the results cannot be generalized to non-Swedish-speaking women in Sweden, which is another limitation. The declining response rate over time is an important weakness, but that was also reported in other similar studies with multiple assessments[110]. Respondents and non- respondents showed some significant differences in relation to the attitude towards the lost pregnancy. As the anxiety levels (STAI-trait and STAI-state) at inclusion did not differ between respondents and non-respondents a clinically important psychological difference was not assumed, however.

The psychological impact of early miscarriage has been explored and the results of 21 prospective cohort studies published between 1989 and 2016 were evaluated in a review article[110]. In similarity with the current sudy, anxiety symptoms seemed to be more common than depression symptoms, and the psychological distress diminished from a high level immediately after, or within two weeks after diagnosis, to resolve within 6 – 12 months in most cases. Randomized trials evaluating emotional distress after early miscarriage in relation to miscarriage management differed from the current study in relation to psychometric instruments used and time of follow-up. The follow-up did not exceed 12 weeks in any of the trials[48, 49, 55, 110, 137, 138, 157]. However, no major differences in psychological reactions between the treatment groups were reported, which is consistent with the current results.

In the current trial women reported a high level of treatment satisfaction, which is reassuring but it cannot be ruled out that it was influenced by an unintended therapeutic effect associated with participation in the trial.

Conclusions Study III
Psychological distress after early miscarriage, expressed as anxiety, depressive symptoms and grief reactions did not differ between women managed expectantly and women treated with misoprostol. When the miscarriage was judged to be complete, the psychological distress had abated in the majority of women. The satisfaction with treatment was high and did not differ between the groups despite a substantial difference in treatment success.

Paper IV

(Reproductive outcome)

Fertility after miscarriage and miscarriage management

Subjects

Fifty-five of 90 (61%) women in the expectantly managed group and 60/94 (64%) in the misoprostol group returned the questionnaire on reproductive history sent at 14 months after the index miscarriage. After searching the medical records, information on reproductive outcome was available for 83/90 (92%) in the expectantly managed group and 89/94 (95%) women in the misoprostol group. Twenty-seven of 81 (33%) women in the expectantly managed group and 21/88 (24%) in the misoprostol group had experienced one or more miscarriages before the index miscarriage. Seventy-four of 82 (90%) women in the expectantly managed group and 84/89 (94%) in the misoprostol group said at trial inclusion that they wanted to conceive again after the miscarriage.

Reproductive outcome

Reproductive outcome at 14 months after complete miscarriage is shown in **Table 8a**. No statistically significant differences were found between the two groups. 75% of the women in both groups reported at least one new clinical pregnancy and 36/89 (40%) women in the misoprostol group and 29/83 (35%) in the expectantly group had delivered a live baby within 14 months (MD 5.5, 95% CI of difference -9.7 to 20.3). At fourteen months, nine women (10%) in the misoprostol group had experienced exclusively failed pregnancies (one or more miscarriages or an ectopic pregnancy) compared to ten women (12%) in the expectantly managed group. Two (2%) women managed expectantly had terminated an early pregnancy. No stillbirths were reported.

The outcomes of all pregnancies reported at 14 months are summarized in **Table 8a and 8b**. 56/89 (63%) in the misoprostol group versus 46/83 (55%) in the expectantly managed group delivered a live baby after a pregnancy conceived within 14 months (MD 7.5%, 95% CI of difference -7.9 to 22.4).

Among women who expressed a wish to conceive again after the index miscarriage, when asked at inclusion, the rate of new pregnancies was similar across the groups: 66/84 (79%) in the misoprostol group versus 58/74 (78%) in the expectantly managed group. (Data not shown)

Table 8a. Reproductive outcome of women treated with misoprostol or with expectant management

Proportion of women	Misoprostol treatment n=89	Expectant management n=83	Difference (95%CI)
Reproductive outcome assessed at 14 months after complete miscarriage			
At least one clinical pregnancy within 14 months	67 (75.3)	62 (74.7)	0.6 (-13.0 to 14.3)
New pregnancy conceived after IVF	1 (1.1)	1 (1.2)	
At least one live birth within 14 months	36 (40.4)	29 (34.9)	5.5 (-9.7 to 20.3)
Reproductive outcome when all clinical pregnancies conceived within 14 months are included			
At least one live-birth after a pregnancy conceived within 14 months	56[a] (62.8)	46 (55.4)	7.5 (-7.9 to 22.4)
Exclusively failed pregnancies (miscarriage or ectopic pregnancies) after a pregnancy conceived within 14 months[b]	10 (11.2)	13 (15.7)	-4.4 (-15.8 to 6.7)

Values are numbers (%) and mean difference with 95% confidence interval (CI)
IVF, in vitro fertilization [a] One woman had a live-birth at 23 weeks and an ongoing pregnancy at 14 months that ended with term live-birth. [b] One woman had both a miscarriage and an ectopic pregnancy

Table 8b. Outcome for all clinical pregnancies conceived within 14 months after miscarriage (with known outcome at 14 months or still ongoing at 14 months)

Outcome of pregnancies	Women treated with misoprostol n=89	Women treated with expectant management n=83
Total number of clinical pregnancies conceived within 14 months	83[a]	71[b]
Pregnancies that ended with miscarriage or ectopic pregnancy	24[a]	22[b]
Pregnancies that ended with live birth	57	46
Pregnancies that ended with legal termination	0	2
Pregnancies with unknown outcome	1	1

[a] Four women reported two or more miscarriages, one woman had both a miscarriage and an ectopic pregnancy, [b] Five women reported two or more miscarriages

Comments and Conclusions Study IV

The reproductive outcome at 14 months after miscarriage did not differ clinically or statistically between the treatment groups. The prospective design is a strength of the current study. The results may not be generalizable for women undergoing assisted reproductive technology treatments or to women with recurrent pregnancy loss as the patients in the current study were relatively young and most of them experienced their first miscarriage.

68

No important differences have been reported when the reproductive outcome subsequent to miscarriage was evaluated in relation to different treatments of early miscarriage in four retrospective studies[104-107]. This is supported by the current results. The reported reproductive outcomes differed between the studies and the time of evaluation also differed from 18 months to 6 years after the index miscarriage. In two studies, the live-birth rate was reported, ranging from 60% within 2 years[106] and 88% within 6 years after the index miscarriage[107]. One study reported the cumulative conception rate (conception rate was not defined but probably means cumulative rate of clinically recognized pregnancies) after one year, which was 75%[104]. This is very similar to the results of the current study. In the fourth study, the cumulative ongoing pregnancy rate at 12 months after child wish was 87% and no difference was reported between women treated with misoprostol or with surgical management.[105] In the current trial, 78% of the women who had expressed a wish conceive again at inclusion had become pregnant at least once within 14 months after the miscarriage.

Intrauterine adhesions, induced by pregnancy-related D&Es[59, 108], may be a cause of reduced fertility after early miscarriage. In the current trial, D&E was more common after expectant management, at patient's request or because of incomplete expulsion of pregnancy products, than after misoprostol treatment. Despite this, the reproductive outcome did not differ between the management groups. Infections caused by retained products of conception have also been suggested to contribute to the formation of intrauterine adhesions resulting in reduced fertility after miscarriage[59, 108]. In this trial, as well as in others, the rate of infection was low and did not differ between the management groups.

Conclusion Study IV
No clinically important differences are found between misoprostol treatment and expectant management, in relation to fertility and reproductive outcome after miscarriage.

Conclusion

Principal findings

Women with embryonic or anembryonic miscarriage and vaginal bleeding are more likely to achieve complete resolution of pregnancy products after treatment with single-dose misoprostol than if spontaneous resolution is awaited. Three quarters of women treated with misoprostol achieved complete miscarriage within 31 days compared to two thirds of the women treated expectantly.

More women need D&E, due to failed treatment, after expectant management than after misoprostol. Both methods are safe. The number of women achieving complete miscarriage increases with a prolonged observation time.

Spontaneous resolution is significantly more likely in embryonic miscarriage than in anembryonic miscarriage.

Treatment with misoprostol and expectant management are equivalent in terms of treatment satisfaction, psychological effects and subsequent fertility.

Clinical implications

Treatment with misoprostol or awaiting spontaneous resolution are safe alternatives for women experiencing early miscarriage. Women can be reassured that future fertility is not significantly affected by any of the treatments.

Women's preferences should guide treatment decisions. When different treatments are discussed with the patient, the time from diagnosis to complete miscarriage as well as treatment-associated discomfort, such as pain and limitations of conduct of life while awaiting complete miscarriage, should be taken into account.

Svensk sammanfattning
(Swedish summary)

Målsättning

Det övergripande målet var att jämföra två olika typer av behandling för att åstadkomma tömning av livmoderhålan vid tidigt missfall - behandling med läkemedlet misoprostol och behandling med expektans, dvs att invänta det naturliga förloppet för utstötning av graviditetsvävnaden. I fyra delstudier gjordes jämförelser mellan hur väl behandlingarna lyckades, dvs andel kvinnor som kunde friskförklaras, förekomst av biverkningar och komplikationer, hur patienterna mådde efter missfallet, hur nöjda de var med behandlingen, samt hur många som blev gravida och fick barn upp till 14 månader efter missfallet.

Bakgrund

Tidigt missfall, före graviditetsvecka 13, är vanligt och c:a en av fem graviditeter går under i den första trimestern. Blödning och buksmärta är typiska symtom vid missfall. Ofta stöts den avstannade graviditeten ut spontant utan någon behandling men olika medicinska metoder kan användas för att påskynda förloppet. Kirurgisk behandling, dvs skrapning, är den metod som säkrast leder till fullständig tömning av livmoderhålan (fullständigt missfall), med en lyckandefrekvens på över 95%. Vid skrapning sugs graviditetsresterna ut med en elektriskt driven vacuumsug och ingreppet utförs oftast i generell narkos, dvs patienten sövs, vilket gör behandlingen resurskrävande. Under de senaste decennierna har risker förknippade med skrapning uppmärksammats alltmer. Sällsynta, men potentiellt allvarliga komplikationer kan härledas till narkos och till risken att skada livmodern och andra bukorgan under ingreppet. Den potentiella risken att påverka framtida fertilitet negativt har också bidragit till att andra, icke-kirurgiska, behandlingsmetoder numera anses mer lämpliga som förstahandsalternativ. Behandling med läkemedel eller behandling med expektans, dvs att invänta det naturliga förloppet, är idag väl beprövade

metoder som gör att kirurgiska såväl som anestesiologiska risker kan undvikas. Misoprostol är det läkemedel som oftast används. Tabletterna kan sväljas eller föras upp i slidan för att framkalla livmodersammandragningar som leder till att den avstannade graviditeten stöts ut.

Flera studier har gjorts för att jämföra olika typer av behandling vid missfall - skrapning, behandling med läkemedel eller expektans (ingen behandling). Eftersom studierna skiljer sig åt i flera avseenden är det svårt att sammanställa studieresultaten för att kunna dra säkra slutsatser. Flera olika läkemedel har använts och även dos och administrationssätt skiljer sig åt mellan studierna. Andra skillnader som gör det svårt att sammanfatta resultaten, rör vilken typ av missfall som studerades, om försökspersonerna hade vaginal blödning eller inte, samt hur lång observationstid som tillämpades. Tidiga missfall kan klassificeras utifrån ultraljudsbilden som missfall med ett synligt embryo (ett foster före graviditetsvecka 10) utan hjärtslag eller som missfall utan något synligt embryo, s k "ofostrigt missfall". Ibland har graviditetsvävnaden delvis stötts ut vid diagnostillfället och endast graviditetsrester (utan någon tydlig fostersäck) syns vid ultraljudsundersökning. Det brukar kallas "ofullständigt missfall". Vid ofullständigt missfall är chansen stor att resterna stöts ut av sig själv inom ett par veckor och att invänta det naturliga förloppet är oftast lika effektivt som behandling med läkemedel. När fostersäcken är kvar i livmoderhålan kan det emellertid dröja länge – veckor eller i vissa fall månader - innan spontan utstötning sker. Därför bör studier som jämför olika typer av behandling redovisa resultaten för ofullständiga missfall och för missfall med kvarvarande fostersäck separat. Ibland kan det ta lång tid innan en kvinna får blödning efter att graviditeten avstannat. Det är rimligt att anta att vaginal blödning är ett led i den naturliga utstötningsprocessen. Av detta skäl är det lämpligt att i studier skilja mellan kvinnor som börjat blöda och kvinnor som inte börjat blöda. Sannolikt stöts de allra flesta missfall ut spontant förr eller senare. Observationsstudier har visat att när man inväntar det naturliga förloppet efter missfall, kommer varje veckas ytterligare väntan innebära att lite fler kvinnor blir friska (uppnår fullständig utstötning av graviditetsvävnaden). Behandlingsresultatet, både efter läkemedelsbehandling och efter behandling med expektans, påverkas således av hur lång tid som förflyter efter behandlingsstart. Vid en mycket kort observationstid kommer färre kvinnor att uppnå fullständigt missfall än vid en längre observationstid.

I praktiken är det förstås önskvärt att veta hur stor chansen är för att en viss behandling ska lyckas. S k predikerande faktorer är faktorer som har betydelse för den sannolikheten. De skulle kunna vara *biokemiska*, dvs nivån på vissa graviditetsrelaterade ämnen i blodet, *demografiska*, t ex om kvinnan har fött barn

tidigare, eller *kliniska*, t ex vilken typ av missfall det rör sig om eller hur stort fostret är. Kunskapsläget vad gäller predikerande faktorer är idag osäkert.

Kvinnor som drabbas av missfall genomgår ofta en krisreaktion och många upplever både sorg och symtom på ångest och nedstämdhet. Hur olika typer av behandling vid missfall påverkar kvinnor psykologiskt är ofullständigt belyst, liksom hur patienterna upplever behandlingen, om de är nöjda eller inte.

Få studier med hög vetenskaplig standard har undersökt hur olika behandlingar påverkar kvinnans framtida förmåga att bli gravid och föda barn.

Syfte och metoder

Kvinnor med tidigt missfall med kvarvarande fostersäck i livmoderhålan, och som rapporterat vaginal blödning, rekryterades från Kvinnokliniken på Skånes Universitetssjukhus, Malmö. Kvinnorna lottades (1:1) till behandling med 800 µg misoprostol (4 tabletter à 200 µg) i vaginal enkel dos eller till behandling med expektans (ingen behandling). De undersöktes kliniskt och med ultraljud. Skattningsskalor användes för att skatta ångest och depressionssymtom. Blodvärde och graviditetsrelaterade hormon i blodet mättes. Deltagarna tilldelades en "dagbok" att använda hemma för att registrera blödning och smärta. Efter det första besöket skedde uppföljning enligt studieprotokollet, ca en gång i veckan, tills missfallet hade stötts ut fullständigt, eller i maximalt 31 dagar. Så fort kvinnorna kunde friskförklaras, eller som längst efter 31 dagar avslutades återbesöken och de ombads att på nytt skatta ångest och depressionssymtom. En särskild skala användes för att skatta hur nöjda deltagarna var med behandlingen. Kvinnorna kontaktades per brev tre månader och 14 månader efter fullständigt missfall. I brevet bifogades skalor för att skatta psykiskt mående och hur man upplevde behandlingen. Kvinnorna ombads rapportera eventuellt nya graviditeter vid 14 månader och de medicinska journalerna kontrollerades också.

Resultat

95 kvinnor lottades till expektans och 94 kvinnor lottades till behandling med misoprostol. Fler kvinnor uppnådde fullständigt missfall efter behandling med misoprostol än efter behandling med expektans och en större andel kunde friskförklaras inom en kortare väntetid. Efter 10 dagar friskförklarades 66% av kvinnorna i misoprostolgruppen (86% efter 31 dagar), jämfört med 43% i

expektansgruppen (61% efter 31 dagar). Fler kvinnor i misoprostolgruppen angav att de använde smärtstillande läkemedel än i expektansgruppen. En större andel av kvinnorna som behandlades med expektans blev skrapade (34%) jämfört med dem som fick misoprostol (11%), både på grund av att behandlingen misslyckades och på grund av att de själva önskade det innan hela observationstiden hade förflutit.

Ingen faktor kunde kopplas till sannolikheten för att uppnå fullständigt missfall efter behandling med misoprostol. Sannolikheten för spontan utstötning av missfallet (= lyckad behandling med expektans) var större ifall det *inte* var ett "ofostrigt missfall", dvs ifall ett embryo var synligt vid diagnostillfället. Vissa andra faktorer – bla relationen mellan fosterstorlek, storleken på fostersäcken och graviditetslängden – förefoll också ha betydelse men det beräknade prognostiska värdet (förmågan att förutspå behandlingsresultat) bedömdes vara måttligt.

Ångest och nedstämdhet skiljde sig inte mellan behandlingsgrupperna. Både ångest och nedstämdhet var vanligare vid första mättillfället, dvs i samband med att diagnosen missfall ställdes, än vid senare tillfällen. 10% av kvinnorna rapporterade nedstämdhetsymtom motsvarande måttlig-svår depression och drygt en tredjedel rapporterade uttalad ångest vid det första besöket. När missfallet stötts ut (friskförklaring) angav 5% av kvinnorna måttlig-svår nedstämdhet och 10% höga ångestnivåer. I båda grupperna var kvinnorna nöjda med behandlingen. Mer än 85% angav att de kunde tänka sig att rekommendera en vän samma behandling. Varken ångest eller nöjdhet med behandlingen påverkades av hur lång tid det dröjde innan missfallet stöttes ut (10-31 dagar).

Ingen skillnad sågs mellan grupperna när nya graviditeter analyserades 14 månader efter missfallet. Tre fjärdedelar av kvinnorna hade blivit gravida minst en gång efter missfallet och drygt en tredjedel hade fött barn inom 14 månader. När alla graviditeter som uppstått inom 14 månader (även de som slutade med förlossning, missfall etc. *efter* 14 månader) sammanställdes, hade 63% av kvinnorna i misoprostolgruppen och 55% av kvinnorna i expektansgruppen fött barn, vilket inte var någon statistiskt säkerställd skillnad.

Slutsatser

Behandling med misoprostol är mer effektivt än att invänta spontan tömning av livmoderhålan. En längre observationstid efter behandlingen, både vid expektans och efter misoprostol, gör att fler kvinnor kommer att kunna friskförklaras. Tre fjärdedelar av kvinnorna som behandlades med misoprostol och två tredjedelar av kvinnorna utan behandling kunde friskförklaras inom 31 dagar. Fler kvinnor (1/3)

behövde skrapas när det naturliga förloppet inväntades än om misoprostol gavs (1/10). Eventuellt medför behandling med misoprostol mer smärta. Sannolikheten för att all graviditetsvävnad ska stötas ut spontant (utan behandling) är avsevärt lägre vid ofostrigt missfall än vid missfall med ett synligt embryo. Inga andra viktiga skillnader mellan behandlingarna påvisades. Behandlingarna bedöms vara likvärdiga vad gäller påverkan på det psykiska måendet efter missfall samt framtida fertilitet.

Tack! (Acknowledgements)

Slutligen – ett särskilt tack till alla kvinnor med tidigt missfall, som i en svår stund tackade ja till att delta i denna studie.

References

1.   Blohm F, Friden B, Milsom I. A prospective longitudinal population-based study of clinical miscarriage in an urban Swedish population. *Bjog* 2008; **115**: 176-182; discussion 183.

2.   Mizrachi Y, Shoham G, Leong M, Sagiv R, Horowitz E, Raziel A, Weissman A. Misoprostol treatment for early pregnancy loss: an international survey. *Reprod Biomed Online* 2021; **42**: 997-1005.

3.   Hemminki E. Treatment of miscarriage: current practice and rationale. *Obstet Gynecol* 1998; **91**: 247-253.

4.   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.

5.   Lidegaard Ø, Mikkelsen AP, Egerup P, Kolte AM, Rasmussen SC, Nielsen HS. Pregnancy loss: A 40-year nationwide assessment. *Acta Obstet Gynecol Scand* 2020; **99**: 1492-1496.

6.   Linnakaari R, Helle N, Mentula M, Bloigu A, Gissler M, Heikinheimo O, Niinimäki M. Trends in the incidence, rate and treatment of miscarriage-nationwide register-study in Finland, 1998-2016. *Hum Reprod* 2019; **34**: 2120-2128.

7.   Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *Bmj* 2000; **320**: 1708-1712.

8.   Kolte AM, Bernardi LA, Christiansen OB, Quenby S, Farquharson RG, Goddijn M, Stephenson MD. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. *Human Reproduction* 2015; **30**: 495-498.

9.   Loughna P, Chitty L, Evans T, Chudleigh T. Fetal Size and Dating: Charts Recommended for Clinical Obstetric Practice. *Ultrasound* 2009; **17**: 160-166.

10.   Weiss G, Sundl M, Glasner A, Huppertz B, Moser G. The trophoblast plug during early pregnancy: a deeper insight. *Histochem Cell Biol* 2016; **146**: 749-756.

11.   Huppertz B, Gauster M, Orendi K, König J, Moser G. Oxygen as modulator of trophoblast invasion. *J Anat* 2009; **215**: 14-20.

12.   Burton GJ, Jauniaux E. Oxidative stress. *Best Pract Res Clin Obstet Gynaecol* 2011; **25**: 287-299.

13. Jauniaux E, Watson AL, Hempstock J, Bao YP, Skepper JN, Burton GJ. Onset of maternal arterial blood flow and placental oxidative stress. A possible factor in human early pregnancy failure. *Am J Pathol* 2000; **157**: 2111-2122.

14. Ross C, Boroviak TE. Origin and function of the yolk sac in primate embryogenesis. *Nat Commun* 2020; **11**: 3760.

15. Feichtinger M, Reiner A, Hartmann B, Philipp T. Embryoscopy and karyotype findings of repeated miscarriages in recurrent pregnancy loss and spontaneous pregnancy loss. *J Assist Reprod Genet* 2018; **35**: 1401-1406.

16. Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. *BMJ : British Medical Journal* 1989; **299**: 541-545.

17. Bottomley C, Bourne T. Diagnosing miscarriage. *Best Pract Res Clin Obstet Gynaecol* 2009; **23**: 463-477.

18. Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. *BMC Med* 2013; **11**: 154.

19. Ogasawara M, Aoki K, Katano K, Aoyama T, Kajiura S, Suzumori K. Prevalence of autoantibodies in patients with recurrent miscarriages. *Am J Reprod Immunol* 1999; **41**: 86-90.

20. Agenor A, Bhattacharya S. Infertility and miscarriage: common pathways in manifestation and management. *Womens Health (Lond)* 2015; **11**: 527-541.

21. Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. *Bmj* 2019; **364**: l869.

22. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril* 2008; **90**: 714-726.

23. Boots C, Stephenson MD. Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review. *Semin Reprod Med* 2011; **29**: 507-513.

24. Chan YY, Jayaprakasan K, Tan A, Thornton JG, Coomarasamy A, Raine-Fenning NJ. Reproductive outcomes in women with congenital uterine anomalies: a systematic review. *Ultrasound Obstet Gynecol* 2011; **38**: 371-382.

25. Murugan V, Murphy B, Dupuis C, Goldstein A, Kim Y. Role of ultrasound in the evaluation of first trimester pregnancies. *Ultrasonography* 2019; **39**.

26. Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, Lau TK, Papageorghiou AT, Raine-Fenning NJ, Stirnemann J, Suresh S, Tabor A, Timor-Tritsch IE, Toi A, Yeo G. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol* 2013; **41**: 102-113.

27. Pexsters A, Luts J, Van Schoubroeck D, Bottomley C, Van Calster B, Van Huffel S, Abdallah Y, D'Hooghe T, Lees C, Timmerman D, Bourne T. 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**: 510-515.

28. Hately W, Case J, Campbell S. Establishing the death of an embryo by ultrasound: report of a public inquiry with recommendations. *Ultrasound Obstet Gynecol* 1995; **5**: 353-357.

29. Ledger WL, Turner MJ. Implementation of the findings of a national enquiry into the misdiagnosis of miscarriage in the Republic of Ireland: impact on quality of clinical care. *Fertil Steril* 2016; **105**: 417-422.

30. Practice Bulletin No. 150: Early Pregnancy Loss. *Obstet Gynaecol* 2015; **125**: 1258-1267.

31. Australasian Society for Ultrasound in Medicine: Guidelines for the performance of first trimester ultrasound. http://www.asum.com.au/files/public/SoP/D11-Guidelines-for-the-Performance-of-First-Trimester-Ultrasound.pdf [22 August 2017].

32. Lane BF, Wong-You-Cheong JJ, Javitt MC, Glanc P, Brown DL, Dubinsky T, Harisinghani MG, Harris RD, Khati NJ, Mitchell DG, Pandharipande PV, Pannu HK, Podrasky AE, Shipp TD, Siegel CL, Simpson L, Wall DJ, Zelop CM. ACR appropriateness Criteria® first trimester bleeding. *Ultrasound Q* 2013; **29**: 91-96.

33. National Guideline C: ACR Appropriateness Criteria® first trimester bleeding. https://www.guideline.gov/summaries/summary/43883 [24 April 2017].

34. National Institute of care and excellence: Ectopic pregnancy and miscarriage: diagnosis and initial management. https://www.nice.org.uk/guidance/cg154 [24 April 2017].

35. Dempsey A, Davis A. Medical management of early pregnancy failure: how to treat and what to expect. *Semin Reprod Med* 2008; **26**: 401-410.

36. 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**: 266-271.

37. Blohm F, Fridén BE, Milsom I, Platz-Christensen JJ, Nielsen S. A randomised double blind trial comparing misoprostol or placebo in the management of early miscarriage. *BJOG* 2005; **112**: 1090-1095.

38. Demetroulis C, Saridogan E, Kunde D, Naftalin AA. A prospective randomized control trial comparing medical and surgical treatment for early pregnancy failure. *Hum Reprod* 2001; **16**: 365-369.

39. Nielsen S, Hahlin M, Platz-Christensen J. Randomised trial comparing expectant with medical management for first trimester miscarriages. *BJOG* 1999; **106**: 804-807.

40. 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**: 367-372.

41. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J. Endometrial thickness after misoprostol use for early pregnancy failure. *Int J Gynaecol Obstet* 2004; **86**: 22-26.

42. Sawyer E, Ofuasia E, Ofili-Yebovi D, Helmy S, Gonzalez J, Jurkovic D. The value of measuring endometrial thickness and volume on transvaginal ultrasound scan for the diagnosis of incomplete miscarriage. *Ultrasound Obstet Gynecol* 2007; **29**: 205-209.

43. 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**: 873-875.

44. Lemmers M, Verschoor MA, Kim BV, Hickey M, Vazquez JC, Mol BWJ, Neilson JP. Medical treatment for early fetal death (less than 24 weeks). *Cochrane Database Syst Rev* 2019; **6**: Cd002253.

45. Kovavisarach E, Sathapanachai U. Intravaginal 400 microg misoprostol for pregnancy termination in cases of blighted ovum: a randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2002; **42**: 161-163.

46. Lister MS, Shaffer LET, Bell JG, Lutter KQ, Moorma KH. Randomized, double-blind, placebo-controlled trial of vaginal misoprostol for management of early pregnancy failures. *Am J Obstet Gynecol* 2005; **193**: 1338-1343.

47. Ngai SW, Chan YM, Tang OS, Ho PC. Vaginal misoprostol as medical treatment for first trimester spontaneous miscarriage. *Hum Reprod* 2001; **16**: 1493-1496.

48. Shelley JM, Healy D, Grover S. A randomised trial of surgical, medical and expectant management of first trimester spontaneous miscarriage. *Aust N Z J Obstet Gynaecol* 2005; **45**: 122-127.

49. 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**: 1235-1240.

50. Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. *Cochrane Database Syst Rev* 2017; **1**: Cd007223.

51. Wood SL, Brain PH. Medical management of missed abortion: a randomized clinical trial. *Obstet Gynecol* 2002; **99**: 563-566.

52. 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**: 2445-2450.

53. Lemmers M, Verschoor MAC, Hooker AB, Opmeer BC, Limpens J, Huirne JAF, Ankum WM, Mol BWM. Dilatation and curettage increases the risk of subsequent preterm birth: a systematic review and meta-analysis. *Hum Reprod* 2016; **31**: 34-45.

54. 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**: 167-173.

55. Wieringa-De Waard M, Hartman EE, Ankum WM, Reitsma JB, Bindels PJ, Bonsel GJ. Expectant management versus surgical evacuation in first trimester miscarriage: health-related quality of life in randomized and non-randomized patients. *Hum Reprod* 2002; **17**: 1638-1642.

56. 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**: 355-360.

57. Tunçalp O, Gülmezoglu AM, Souza JP. Surgical procedures for evacuating incomplete miscarriage. *Cochrane Database Syst Rev* 2010; **2010**: Cd001993.

58. Hooker AB, Aydin H, Brölmann HA, Huirne JA. Long-term complications and reproductive outcome after the management of retained products of conception: a systematic review. *Fertil Steril* 2016; **105**: 156-164.e151-152.

59. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brölmann HA, Mol BW, Huirne JA. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. *Hum Reprod Update* 2014; **20**: 262-278.

60. Blohm F, Fridén B, Platz-Christensen JJ, Milsom I, Nielsen S. Expectant management of first-trimester miscarriage in clinical practice. *Acta Obstet Gynecol Scand* 2003; **82**: 654-658.

61. Nanda K, Lopez LM, Grimes DA, Peloggia A, Nanda G. Expectant care versus surgical treatment for miscarriage. *Cochrane Database Syst Rev* 2012; **2012**: Cd003518.

62. Wieringa-de Waard M, Ankum WM, Bonsel GJ, Vos J, Biewenga P, Bindels PJ. The natural course of spontaneous miscarriage: analysis of signs and symptoms in 188 expectantly managed women. *Brit J Gen Practice* 2003; **53**: 704-708.

63. Luise C, Jermy K, Collins WP, Bourne TH. Expectant management of incomplete, spontaneous first-trimester miscarriage: outcome according to initial ultrasound criteria and value of follow-up visits. *Ultrasound Obstet Gynecol* 2002; **19**: 580-582.

64. Nielsen S, Hahlin M. Expectant management of first-trimester spontaneous abortion. *Lancet* 1995; **345**: 84-86.

65. Acharya G, Morgan H, Paramanantham L, Fernando R. A randomized controlled trial comparing surgical termination of pregnancy with and without continuous ultrasound guidance. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2004; **114**: 69-74.

66. Schwarzler P, Holden D, Nielsen S, Hahlin M, Sladkevicius P, Bourne TH. The conservative management of first trimester miscarriages and the use of colour Doppler sonography for patient selection. *Hum Reprod* 1999; **14**: 1341-1345.

67. Jurkovic D, Ross JA, Nicolaides KH. Expectant management of missed miscarriage. *BJOG* 1998; **105**: 670-671.

68. Robledo C, Zhang J, Troendle J, Barnhart K, Creinin MD, Westhoff C, Huang X, Frederick M. Clinical indicators for success of misoprostol treatment after early pregnancy failure. *Int J Gynaecol Obstet* 2007; **99**: 46-51.

69. 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**: 761-769.

70. Schreiber CA, Chavez V, Whittaker PG, Ratcliffe SJ, Easley E, Barg FK. Treatment Decisions at the Time of Miscarriage Diagnosis. *Obstet Gynecol* 2016; **128**: 1347-1356.

71. Graziosi GC, Mol BW, Ankum WM, Bruinse HW. Management of early pregnancy loss. *Int J Gynaecol Obstet* 2004; **86**: 337-346.

72. 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**: 1060-1065.

73. Chung TK, Lee DT, Cheung LP, Haines CJ, Chang AM. Spontaneous abortion: a randomized, controlled trial comparing surgical evacuation with conservative management using misoprostol. *Fertil Steril* 1999; **71**: 1054-1059.

74. Graziosi GCM, Mol BWJ, Reuwer PJH, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. *Human Reproduction* 2004; **19**: 1894-1899.

75. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. *N Engl J Med* 2018; **378**: 2161-2170.

76. Blum J, Winikoff B, Gemzell-Danielsson K, Ho PC, Schiavon R, Weeks A. Treatment of incomplete abortion and miscarriage with misoprostol. *International Journal of Gynecology & Obstetrics* 2007; **99**: S186-S189.

77. Gemzell-Danielsson K, Ho PC, Gomez Ponce de Leon R, Weeks A, Winikoff B. Misoprostol to treat missed abortion in the first trimester. *Int J Gynaecol Obstet* 2007; **99 Suppl 2**: S182-185.

78. Tang OS, Ong CY, Tse KY, Ng EH, Lee SW, Ho PC. A randomized trial to compare the use of sublingual misoprostol with or without an additional 1 week course for the management of first trimester silent miscarriage. *Hum Reprod* 2006; **21**: 189-192.

79. Shorter JM, Atrio JM, Schreiber CA. Management of early pregnancy loss, with a focus on patient centered care. *Semin Perinatol* 2019; **43**: 84-94.

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**: 2340-2347.

81. Hentzen J, Verschoor MA, Lemmers M, Ankum WM, Mol BWJ, van Wely M. Factors influencing women's preferences for subsequent management in the event of incomplete evacuation of the uterus after misoprostol treatment for miscarriage. *Hum Reprod* 2017; **32**: 1674-1683.

82. Acharya G, Morgan H. Does gestational sac volume predict the outcome of missed miscarriage managed expectantly? *J Clin Ultrasound* 2002; **30**: 526-531.

83. Agostini A, Ronda I, Capelle M, Romain F, Bretelle F, Blanc B. Influence of clinical and ultrasound factors on the efficacy of misoprostol in first trimester pregnancy failure. *Fertil Steril* 2005; **84**: 1030-1032.

84. 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**: 384-386.

85. Casikar I, Lu C, Oates J, Bignardi T, Alhamdan D, Condous G. The use of power Doppler colour scoring to predict successful expectant management in women with an incomplete miscarriage. *Hum Reprod* 2012; **27**: 669-675.

86. Casikar I, Lu C, Reid S, Condous G. Prediction of successful expectant management of first trimester miscarriage: development and validation of a new mathematical model. *Aust N Z J Obstet Gynaecol* 2013; **53**: 58-63.

87. Casikar I, Lu C, Reid S, Condous G. Does symptomatology at presentation correlate with successful expectant management of first trimester miscarriage: a prospective observational study. *Aust N Z J Obstet Gynaecol* 2013; **53**: 178-183.

88. Creinin MD, Huang X, Westhoff C, Barnhart K, Gilles JM, Zhang J. Factors related to successful misoprostol treatment for early pregnancy failure. *Obstet Gynecol* 2006; **107**: 901-907.

89. Elson J, Tailor A, Salim R, Hillaby K, Dew T, Jurkovic D. Expectant management of miscarriage--prediction of outcome using ultrasound and novel biochemical markers. *Hum Reprod* 2005; **20**: 2330-2333.

90. Kim JI, Park IY, Yim JM, Cheon JY, Yun HG, Kwon JY. Serum beta-hCG concentration is a predictive factor for successful early medical abortion with vaginal misoprostol within 24 hours. *Obstet Gynecol Sci* 2017; **60**: 427-432.

91. Lavecchia M, Abenhaim HA. Effect of Menstrual Age on Failure of Medical Management in Women With Early Pregnancy Loss. *J Obstet Gynaecol Can* 2015; **37**: 617-623.

92. 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**: 1705-1710.

93. Schreiber CA, Ratcliffe SJ, Quinley KE, Miller C, Sammel MD. Serum biomarkers may help predict successful misoprostol management of early pregnancy failure. *Reprod Biology* 2015; **15**: 79-85.

94. Memtsa M, Jauniaux E, Gulbis B, Nyrhinen NC, Jurkovic D. Maternal serum markers in predicting successful outcome in expectant management of missed miscarriage. *Reprod Biomed Online* 2017; **34**: 98-103.

95. Nielsen S, Hahlin M, Odén A. Using a logistic model to identify women with first-trimester spontaneous abortion suitable for expectant management. *BJOG* 1996; **103**: 1230-1235.

96. Odeh M, Tendler R, Kais M, Maximovsky O, Ophir E, Bornstein J. Early pregnancy failure: factors affecting successful medical treatment. *Isr Med Assoc J* 2010; **12**: 325-328.

97. Tzur Y, Samueloff O, Raz Y, Bar-On S, Laskov I, Tzur T. Conception rates after medical versus surgical evacuation of early miscarriage. *Fertil Steril* 2021; **115**: 118-124.

98. Flink-Bochacki R, Hamm ME, Borrero S, Chen BA, Achilles SL, Chang JC. Family Planning and Counseling Desires of Women Who Have Experienced Miscarriage. *Obstet Gynecol* 2018; **131**: 625-631.

99. Sundermann AC, Hartmann KE, Jones SH, Torstenson ES, Velez Edwards DR. Interpregnancy Interval After Pregnancy Loss and Risk of Repeat Miscarriage. *Obstet Gynecol* 2017; **130**: 1312-1318.

100. Love ER, Bhattacharya S, Smith NC, Bhattacharya S. Effect of interpregnancy interval on outcomes of pregnancy after miscarriage: retrospective analysis of hospital episode statistics in Scotland. *Bmj* 2010; **341**: c3967.

101. Evers JL. Female subfertility. *Lancet* 2002; **360**: 151-159.

102. Guttmacher AF. Factors affecting normal expectancy of conception. *Journal of the American Medical Association* 1956; **161**: 855-860.

103. Wildenschild C, Riis AH, Ehrenstein V, Hatch EE, Wise LA, Rothman KJ, Sørensen HT, Mikkelsen EM. Fecundability among Danish women with a history of miscarriage: a prospective cohort study. *BMJ Open* 2019; **9**: e023996.

104. Blohm F, Hahlin M, Nielsen S, Milsom I. Fertility after a randomised trial of spontaneous abortion managed by surgical evacuation or expectant treatment. *Lancet* 1997; **349**: 995.

105. Graziosi GC, Bruinse HW, Reuwer PJ, Teteringen O, Mol BW. Fertility outcome after a randomized trial comparing curettage with misoprostol for treatment of early pregnancy failure. *Hum Reprod* 2005; **20**: 1749-1750.

106. Smith LF, Ewings PD, Quinlan C. Incidence of pregnancy after expectant, medical, or surgical management of spontaneous first trimester miscarriage: long term follow-up of miscarriage treatment (MIST) randomised controlled trial. *Bmj* 2009; **339**: b3827.

107. Tam WH, Tsui MH, Lok IH, Yip SK, Yuen PM, Chung TK. Long-term reproductive outcome subsequent to medical versus surgical treatment for miscarriage. *Hum Reprod* 2005; **20**: 3355-3359.

108. Dreisler E, Kjer JJ. Asherman's syndrome: current perspectives on diagnosis and management. *International journal of women's health* 2019; **11**: 191-198.

109. Brier N. Understanding and managing the emotional reactions to a miscarriage. *Obstet Gynecol* 1999; **93**: 151-155.

110. Farren J, Mitchell-Jones N, Verbakel JY, Timmerman D, Jalmbrant M, Bourne T. The psychological impact of early pregnancy loss. *Hum Reprod Update* 2018; **24**: 731-749.

111. Lok IH, Neugebauer R. Psychological morbidity following miscarriage. *Best Pract Res Clin Obstet Gynaecol* 2007; **21**: 229-247.

112. Adolfsson A, Larsson PG. Applicability of general grief theory to Swedish women's experience after early miscarriage, with factor analysis of Bonanno's taxonomy, using the Perinatal Grief Scale. *Ups J Med Sci* 2010; **115**: 201-209.

113. Broen AN, Moum T, Bodtker AS, Ekeberg O. Psychological impact on women of miscarriage versus induced abortion: a 2-year follow-up study. *Psychosom Med* 2004; **66**: 265-271.

114. Broen AN, Moum T, Bodtker AS, Ekeberg O. The course of mental health after miscarriage and induced abortion: a longitudinal, five-year follow-up study. *BMC Med* 2005; **3**: 18.

115. Cumming GP, Klein S, Bolsover D, Lee AJ, Alexander DA, Maclean M, Jurgens JD. The emotional burden of miscarriage for women and their partners: trajectories of anxiety and depression over 13 months. *Bjog* 2007; **114**: 1138-1145.

116. Janssen HJ, Cuisinier MC, Hoogduin KA, de Graauw KP. Controlled prospective study on the mental health of women following pregnancy loss. *Am J Psychiatry* 1996; **153**: 226-230.

117. Lok IH, Yip AS, Lee DT, Sahota D, Chung TK. A 1-year longitudinal study of psychological morbidity after miscarriage. *Fertil Steril* 2010; **93**: 1966-1975.

118. Farren J, Jalmbrant M, Ameye L, Joash K, Mitchell-Jones N, Tapp S, Timmerman D, Bourne T. Post-traumatic stress, anxiety and depression following miscarriage or ectopic pregnancy: a prospective cohort study. *BMJ Open* 2016; **6**: e011864.

119. Farren J, Jalmbrant M, Falconieri N, Mitchell-Jones N, Bobdiwala S, Al-Memar M, Tapp S, Van Calster B, Wynants L, Timmerman D, Bourne T. Posttraumatic stress, anxiety and depression following miscarriage and ectopic pregnancy: a multicenter, prospective, cohort study. *Am J Obstet Gynecol* 2019.

120. Sham A, Yiu M, Ho W. Psychiatric morbidity following miscarriage in Hong Kong. *Gen Hosp Psychiatry* 2010; **32**: 284-293.

121. Potvin L, Lasker J, Toedter L. Measuring grief: A short version of the perinatal grief scale. *Journal of Psychopathology and Behavioral Assessment* 1989; **11**: 29-45.

122. Cullberg J. Kris och utveckling. Stockholm: Natur och kultur; 2006.

123. Toedter LJ, Lasker JN, Janssen HJ. International comparison of studies using the perinatal grief scale: a decade of research on pregnancy loss. *Death Stud* 2001; **25**: 205-228.

124. Toedter LJ, Lasker JN, Alhadeff JM. The Perinatal Grief Scale: development and initial validation. *Am J Orthopsychiatry* 1988; **58**: 435-449.

125. Adolfsson A, Larsson PG. Translation of the short version of the Perinatal Grief Scale into Swedish. *Scand J Caring Sci* 2006; **20**: 269-273.

126. Yan E, Tang CS, Chung T. Validation of the Perinatal Grief Scale for use in Chinese women who have experienced recent reproductive loss. *Death Stud* 2010; **34**: 151-171.

127. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382-389.

128. Svanborg P, Asberg M. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta Psychiatr Scand* 1994; **89**: 21-28.

129. Svanborg P, Asberg M. A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Asberg Depression Rating Scale (MADRS). *J Affect Disord* 2001; **64**: 203-216.

130. Fantino B, Moore N. The self-reported Montgomery-Asberg Depression Rating Scale is a useful evaluative tool in Major Depressive Disorder. *BMC Psychiatry* 2009; **9**: 26.

131. Cunningham JL, Wernroth L, von Knorring L, Berglund L, Ekselius L. Agreement between physicians' and patients' ratings on the Montgomery-Åsberg Depression Rating Scale. *J Affect Disord* 2011; **135**: 148-153.

132. Nikcevic AV, Tunkel SA, Nicolaides KH. Psychological outcomes following missed abortions and provision of follow-up care. *Ultrasound Obstet Gynecol* 1998; **11**: 123-128.

133. Prettyman RJ, Cordle CJ, Cook GD. A three-month follow-up of psychological morbidity after early miscarriage. *Br J Med Psychol* 1993; **66 (Pt 4)**: 363-372.

134. Brier N. Anxiety after miscarriage: a review of the empirical literature and implications for clinical practice. *Birth* 2004; **31**: 138-142.

135. Engelhard IM, van den Hout MA, Arntz A. Posttraumatic stress disorder after pregnancy loss. *Gen Hosp Psychiatry* 2001; **23**: 62-66.

136. Spielberger C, Gorsuch R, Lushene R, Vagg PR, Jacobs G. Manual for the State-Trait Anxiety Inventory (Form Y1 – Y2): Consulting Psychologists Press Inc.; 1983.

137. Kong GW, Lok IH, Yiu AK, Hui AS, Lai BP, Chung TK. Clinical and psychological impact after surgical, medical or expectant management of first-trimester miscarriage--a randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2013; **53**: 170-177.

138. 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**: 953-958.

139. Attkisson CC, Greenfield TK. The UCSF Client Satisfaction Scales: I. The Client Satisfaction Questionnaire-8. The use of psychological testing for treatment planning and outcomes assessment: Instruments for adults, Volume 3, 3rd ed. Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers; 2004. p. 799-811.

140. Janssen HJ, Cuisinier MC, de Graauw KP, Hoogduin KA. A prospective study of risk factors predicting grief intensity following pregnancy loss. *Arch Gen Psychiatry* 1997; **54**: 56-61.

141. Neugebauer R, Kline J, Shrout P, Skodol A, O'Connor P, Geller PA, Stein Z, Susser M. Major depressive disorder in the 6 months after miscarriage. *Jama* 1997; **277**: 383-388.

142. Thapar AK, Thapar A. Psychological sequelae of miscarriage: a controlled study using the general health questionnaire and the hospital anxiety and depression scale. *Br J Gen Pract* 1992; **42**: 94-96.

143. Lasker JN, Toedter LJ. Acute versus chronic grief: the case of pregnancy loss. *Am J Orthopsychiatry* 1991; **61**: 510-522.

144. Murphy FA, Lipp A, Powles DL. Follow-up for improving psychological well being for women after a miscarriage. *Cochrane Database Syst Rev* 2012: Cd008679.

145. Adolfsson A. Women's well-being improves after missed miscarriage with more active support and application of Swanson's Caring Theory. *Psychology research and behavior management* 2011; **4**: 1-9.

146. Abdallah Y, Daemen A, Guha S, Syed S, Naji O, Pexsters A, Kirk E, Stalder C, Gould D, Ahmed S, Bottomley C, Timmerman D, Bourne T. Gestational sac and embryonic growth are not useful as criteria to define miscarriage: a multicenter observational study. *Ultrasound Obstet Gynecol* 2011; **38**: 503-509.

147. Abdallah Y, Daemen A, Kirk E, Pexsters A, Naji O, Stalder C, Gould D, Ahmed S, Guha S, Syed S, Bottomley C, Timmerman D, Bourne T. Limitations of current definitions of miscarriage using mean gestational sac diameter and crown-rump length measurements: a multicenter observational study. *Ultrasound Obstet Gynecol* 2011; **38**: 497-502.

148. 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**: 489-496.

149. Levi CS, Lyons EA, Lindsay DJ. Ultrasound in the first trimester of pregnancy. *Radiol Clin North Am* 1990; **28**: 19-38.

150. Valentin L, Sladkevicius P, Laurini R, Soderberg H, Marsal K. Uteroplacental and luteal circulation in normal first-trimester pregnancies: Doppler ultrasonographic and morphologic study. *Am J Obstet Gynecol* 1996; **174**: 768-775.

151. Valentin L, Sladkevicius P, Laurini R, Soderberg H, Olofsson P, Marsal K. Effect of a prostaglandin E1 analogue (gemeprost) on uterine and luteal circulation in normal first trimester pregnancies. A Doppler velocimetry study. *Eur J Obstet Gynecol Reprod Biol* 1995; **59**: 25-34.

152. Althouse AD. Post Hoc Power: Not Empowering, Just Misleading. *J Surg Res* 2021; **259**: A3-a6.

153. Flechner L, Tseng TY. Understanding results: P-values, confidence intervals, and number need to treat. *Indian J Urol* 2011; **27**: 532-535.

154. Shmueli G. To Explain or to Predict? *Statistical Science* 2010; **25**: 289-310, 222.

155. Siddiqui O. Methods for Computing Missing Item Response in Psychometric Scale Construction. *American Journal of Biostatistics* 2015; **5**: 1-6.

156. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010; **63**: 834-840.

157. Nielsen S, Hahlin M, Moller A, Granberg S. Bereavement, grieving and psychological morbidity after first trimester spontaneous abortion: comparing expectant management with surgical evacuation. *Hum Reprod* 1996; **11**: 1767-1770.

FACULTY OF MEDICINE