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Psychological impact of early miscarriage and client satisfaction with treatment: comparison between expectant management and misoprostol treatment in a randomized controlled trial

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KEYWORDS: anxiety; depression; miscarriage; misoprostol; pregnancy complications; psychology; randomized controlled trial; spontaneous abortion

CONTRIBUTION

What are the novel findings of this work?
Symptoms of grief, anxiety and depression after early miscarriage are, in most cases, short-lived, and the duration and amplitude of these symptoms are similar in women treated with vaginal misoprostol and those managed expectantly.

What are the clinical implications of this work?
Women can be reassured that, from a psychological point of view, misoprostol treatment and expectant management are safe and equivalent treatment options for early miscarriage. This information is important when patients are counseled about different treatments for early miscarriage.

ABSTRACT

Objectives *To compare the short- and long-term emotional distress (grief, anxiety and depressive symptoms) after early miscarriage and satisfaction with treatment between women randomized to expectant management* vs *vaginal misoprostol treatment.*

Methods *This was a preplanned analysis of data collected during a randomized controlled trial comparing expectant management with misoprostol treatment in women with early anembryonic or embryonic miscarriage and vaginal bleeding. If the miscarriage was not complete on day 31 after inclusion, surgical evacuation was recommended. The main outcomes were levels of anxiety and grief, depressive symptoms and client satisfaction with the treatment, which were assessed using the following validated psychometric self-assessment instruments: Spielberger State–Trait Anxiety Inventory (STAI, Form Y), Perinatal Grief Scale (PGS), Montgomery–Åsberg Depression Rating Scale (MADRS-S; self-reported version) and Client Satisfaction Questionnaire (CSQ-8). All women were assessed at four timepoints: on the day of randomization, on the day when the miscarriage was judged to be complete, and at 3 months and 14 months after complete miscarriage. The psychometric and client satisfaction scores were compared between the misoprostol group and the expectant-management group at each assessment. Analysis was performed by the intention-to-treat principle.*

Results *Ninety women were randomized to expectant management and 94 to misoprostol treatment. The psychometric and client satisfaction scores were similar in the two treatment groups at all assessment timepoints. At inclusion, 41% (35/86) of the women managed expectantly and 37% (34/92) of those treated with misoprostol had a STAI-state score of* >46 *('high level of anxiety'), and 9% (8/86) and 10% (9/91), respectively, had symptoms of moderate or severe depression (MADRS-S score* ≥ 20*). In both treatment groups, symptom scores for anxiety and depression were significantly higher at inclusion than after treatment and remained low until 14 months after complete miscarriage. Grief reactions were mild in both groups, with a*

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median PGS score of 40.0 at 3 months and 37.0 at 14 months after complete miscarriage in both treatment groups. Four women treated with misoprostol and two women managed expectantly had a PGS score of > 90 (indicating deep grief) 3 months after complete miscarriage, while one woman managed expectantly had a PGS score of > 90 14 months after complete miscarriage. Women in both treatment groups were satisfied with their management, as indicated by a median CSQ-8 score of > 25 at each assessment. More than 85% of participants in each of the two groups reported that they would recommend the treatment they received to a friend.

Conclusions *The psychological response to and recovery after early miscarriage did not differ between women treated with misoprostol and those managed expectantly. Satisfaction with treatment was high in both treatment groups. Our findings support patient involvement when deciding on the management of early miscarriage.* © *2021 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

First-trimester miscarriage affects 12–20% of all pregnancies[1]. Women with early pregnancy loss are at high risk of psychological morbidity[2]. Symptoms of anxiety, grief and depression are common but usually decline over time[3–8].

Early pregnancy loss can be managed surgically, medically (misoprostol or mifepristone combined with misoprostol) or expectantly. Medical treatment is usually associated with more pain than surgery or expectant management[9–11]. Some women request expectant management[12,13], despite a lower success rate than that of misoprostol treatment or surgery[9,14]. The success rates and side effects of various miscarriage treatments have been studied extensively[14]. Less studied is the impact of miscarriage treatment on the emotional response (grief, anxiety, depression) of the women and their satisfaction with treatment. Different treatments may contribute differently to the emotional burden of early miscarriage, for example, because of differences in treatment success.

We recently conducted and published a randomized controlled trial comparing misoprostol treatment with expectant management in early miscarriage with a retained gestational sac in the uterus[9]. The primary aim of the trial was to compare treatment success between the two management strategies[9]. Preplanned secondary aims were to compare emotional response to the miscarriage and fertility and reproductive outcomes after the miscarriage between the two treatment methods.

In this study, we evaluated treatment satisfaction and emotional response to early miscarriage in terms of grief, anxiety and depressive symptoms in women randomized to expectant management or misoprostol treatment.

METHODS

This was a preplanned analysis of data collected prospectively during our randomized controlled trial comparing expectant management with misoprostol treatment (single dose of 800 µg administered vaginally) in women with anembryonic or embryonic miscarriage reporting vaginal bleeding (ClinicalTrials.gov ID: NCT01033903). The trial was approved by the regional ethical review board, Lund University, Sweden (Dnr 83/2008). The trial design is only briefly outlined below, as details have been published previously[9].

Women who attended the emergency unit at the Department of Obstetrics and Gynecology, Skåne University Hospital, Malmö, Sweden, because of vaginal bleeding in early pregnancy, were eligible for inclusion if hemodynamically stable. Women with incomplete miscarriage (no visible gestational sac and heterogeneous tissue in the uterine cavity) or with heavy bleeding needing urgent surgical evacuation of the uterine cavity, as judged clinically, were not eligible. Inclusion criteria were age ≥ 18 years, ability to understand written and spoken Swedish, hemoglobin concentration > 80 g/L, no contraindication to treatment with misoprostol and fulfilling the ultrasound criteria for anembryonic or embryonic miscarriage (fetal crown–rump length ≤ 33 mm)[9]. Women who provided written consent were randomized in an open-label fashion into two parallel groups in a 1:1 ratio to treatment with misoprostol or expectant management. Neither the patient nor the trial physician was blinded to the allocation. All patients were managed as outpatients.

On the day of randomization, the patients were examined clinically and by transvaginal ultrasound. In patients allocated to medical treatment, the study physician applied a single dose of 800 µg misoprostol in the posterior vaginal fornix. The follow-up protocol was the same in both treatment groups. The first follow-up visit was 10 days after randomization. If the miscarriage was judged to be incomplete, follow-up visits were scheduled weekly until the miscarriage was complete. The patient was then discharged and no further follow-up visits were planned. On every follow-up visit, clinical examination and transvaginal ultrasound were performed. All results were entered prospectively into dedicated research forms. If complete evacuation was not achieved on day 31 after randomization, dilatation and evacuation was recommended. However, the participants could ask for dilatation and evacuation at any time, for any reason, during the trial.

The primary outcome of the randomized trial was complete miscarriage within 10 days after randomization[9]. The preplanned secondary outcomes addressed in the current study were levels of anxiety and grief and depressive symptoms after early miscarriage and satisfaction with the treatment, as measured at four timepoints from inclusion until 14 months after complete miscarriage.

Information on demographic and reproductive background data was collected from the patients at inclusion and documented in the research forms. The patients were interviewed, using standardized questions, about their

own and their partner's attitude towards the pregnancy: 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. The answers were entered into the research forms.

Psychometric instruments and satisfaction questionnaire

We used three validated psychometric self-assessment instruments to assess the level of psychological distress of the patients: the Spielberger State–Trait Anxiety Inventory (STAI; Form Y)[15], the Montgomery–Åsberg Depression Rating Scale self-reported version (MADRS-S)[16,17] and the Perinatal Grief Scale (PGS)[18,19]. The Client Satisfaction Questionnaire (CSQ-8)[20] was used to evaluate satisfaction with the allocated treatment.

STAI contains two 20-item scales covering current anxiety (state anxiety) and background anxiety (trait anxiety), respectively. Trait anxiety is a measure of proneness to anxiety of the individual and is considered to be stable over time. State anxiety refers to feelings of anxiety at a defined moment in time that arise in response to a particular situation. Items, formulated as statements, are rated on a four-point Likert scale. The total scores for each scale range from 20 to 80, with higher scores corresponding to higher levels of anxiety. The mean (SD) normative state- and trait-anxiety levels for adult working women are 35 (11) and 35 (9), respectively[15]. We considered state-anxiety levels of > 46 (mean + 1 SD) as representing high levels of state anxiety. The test–retest reliability within 1 month is $r = 0.71$ for the STAI state scale (STAI-state) score and $r = 0.86$ for the STAI trait scale (STAI-trait) score, with Cronbach's alpha (internal consistency) of 0.86 and 0.92, respectively[15].

MADRS-S is a nine-item scale for assessing the severity of core depressive symptoms. It was originally designed to be sensitive to changes in the severity of depressive symptoms[16,17,21]. Each item is rated on a scale from 0 to 6 and the total score ranges from 0 to 54. 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[16]. MADRS-S is well-validated and has a high correlation with expert ratings[17]. It has been found to be equivalent ($r = 0.87$) to the Beck Depression Inventory (BDI), which is the most widely used self-assessment instrument for depression[21]. However, the BDI measures predominantly depressive cognitive symptoms, while somatic symptoms and functional impairment are better measured using MADRS-S[22]. The test–retest reliability of MADRS-S is $r = 0.78$, with a Cronbach's alpha of 0.84[22].

The PGS measures grief after pregnancy loss. The Swedish version contains 33 questions rated on a 10-point Likert scale. The total score is calculated by converting the 10-point scale into a five-point scale, by transforming scores of 1–2 to 1, 3–4 to 2, 5–6 to 3, 7–8 to 4 and 9–10 to 5[23]. The total score ranges from 33 to 165. Answering options range from 'not at all experiencing the symptom' to 'experiencing the symptom to an extreme extent'. Higher scores indicate more grief. A score above 90 indicates possible psychiatric morbidity[24]. The PGS is validated for women who have miscarried[19,23,25,26]. The internal consistency of the PGS is high, with Cronbach's alpha of > 0.90[18].

CSQ-8 is a validated eight-question instrument that assesses satisfaction with the health services[20]. Responses are based on a four-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.

All women were assessed at four timepoints (Figure 1): at inclusion (using STAI-trait, STAI-state and MADRS-S), on the day the miscarriage was judged to be complete (using STAI-state, MADRS-S and CSQ-8), at 3 months after the miscarriage was judged to be complete (using STAI-state, MADRS-S, CSQ-8 and PGS) and at 14 months after the miscarriage was judged to be complete (using STAI-state, MADRS-S, CSQ-8 and PGS). On the first two assessments, the forms were handed out and completed by the women during their visit. The 3-month and 14-month

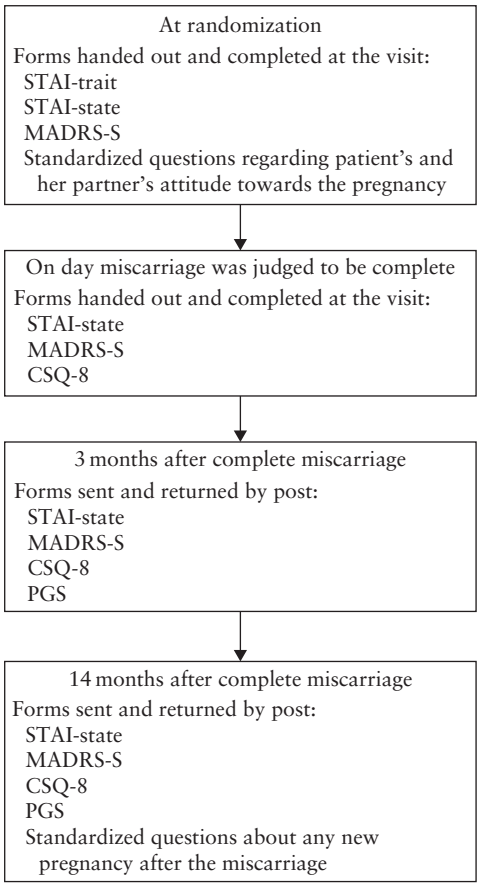

Figure 1 Flowchart showing questionnaires completed by women at each assessment timepoint. CSQ-8, Client Satisfaction Questionnaire; MADRS-S, Montgomery–Åsberg Depression Rating Scale; PGS, Perinatal Grief Scale; STAI-state, State–Trait Anxiety Inventory state scale; STAI-trait, State–Trait Anxiety Inventory trait scale.

sets of questionnaires were sent to the participants by post together with a prestamped envelope for return. At 14 months after the miscarriage, an additional form with questions about any new pregnancy that occurred after the miscarriage was also distributed. Women who did not return their questionnaires were contacted by telephone or by post up to two times after each set of questionnaires had been sent.

Statistical analysis

A sample-size calculation was not performed for this planned secondary analysis, but had been conducted for the primary outcome[9].

Data were collected from the prospectively completed research protocols and from the psychometric questionnaires, and were analyzed according to the intention-to-treat principle (i.e. women were analyzed in the treatment group to which they were randomized).

For the STAI-trait, STAI-state, PGS and CSQ-8 questionnaires, the form was considered to be fully completed if there were no more than two missing answers to the questions. The MADRS-S form was considered to be fully completed if there was no more than one missing answer to the questions. Only fully completed forms were used in the statistical analysis. The total score of included forms with missing answers was obtained by using as a score for the unanswered questions the mean score of the answered questions of the specific instrument (simple mean imputation[27]).

The psychometric scores were compared between the misoprostol group and the expectantly managed group at each assessment timepoint. For this analysis, we included all women with fully completed forms (as defined above) for the particular instrument, even if they had incomplete forms for one or more of the other instruments at that timepoint. The statistical significance of differences in unpaired continuous variables was determined using Student's *t*-test or the Mann–Whitney *U*-test (depending on the distribution of data) and that of differences in unpaired categorical data using the chi-square or Fisher's exact test. We used the Friedman test and Wilcoxon signed-rank test to determine if differences in paired data were statistically significant. $P < 0.05$ was considered to indicate statistical significance.

For each questionnaire, we plotted the scores for each group at each assessment timepoint in order to visualize the trajectory of the scores in the misoprostol group and the expectant-management group. Only women who had completed the respective questionnaire at every assessment timepoint were included in this analysis.

We compared the characteristics of 'respondents' with those of 'non-respondents'. Participants were defined as 'respondents' at a defined assessment timepoint if they completed fully (as defined above) and returned all the relevant forms for that assessment point. Participants who did not return all the forms or returned incompletely filled out forms were defined as 'non-respondents' at that assessment point.

Statistical analysis was performed using SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Between September 2008 and December 2015, 189 women were recruited to the trial, of whom 95 were allocated to expectant management and 94 to treatment with misoprostol. Two patients in the expectantly managed group withdrew their consent shortly after enrolment and three were excluded owing to a revised diagnosis. Therefore, 90 patients in the expectant-management group and 94 in the misoprostol group were included in the analysis[9]. The mean age of women was 31.9 ± 5.5 years in the expectantly managed group and 32.1 ± 5.6 years in the misoprostol group. The proportion of nulliparous women was 52% ($n = 49$) and 37% ($n = 33$) in the misoprostol-treatment and expectant-management groups, respectively.

Complete miscarriage without surgical evacuation (treatment success) was achieved within 31 days in 86% (81/94) of women treated with misoprostol and in 61% (55/90) of those managed expectantly. The number of patients who underwent surgical evacuation was higher in the expectant-management group (31/90 (34%)) than in the misoprostol group (11/94 (12%))[9].

The psychometric scores were similar in the two groups at all assessment timepoints (Table 1). STAI-trait anxiety level at inclusion was representative for gender and age according to the Spielberger validation[15]. More women expressed symptoms of anxiety than symptoms of depression. At inclusion, 35/86 (41%) women managed expectantly and 34/92 (37%) women treated with misoprostol had a STAI-state score of > 46 (corresponding to our definition of 'high levels of anxiety'). On the day when the miscarriage was judged to be complete, substantially fewer women had a STAI-state score of > 46: 12/84 (14%) in the expectant-management group and 10/91 (11%) in the misoprostol group. Levels of anxiety were not affected by the time interval until the miscarriage was judged to be complete (Table S1) or by whether surgical evacuation was performed (Table S2). At inclusion, a similar proportion of women in the expectantly managed group (8/86 (9%)) and in the misoprostol group (9/91 (10%)) had depressive symptoms corresponding to moderate or severe depression (MADRS-S score of ≥ 20). On the day the miscarriage was judged to be complete, the proportion of women with MADRS-S scores corresponding to moderate or severe depression was also similar in the two groups (5/81 (6%) *vs* 5/93 (5%)). Grief reactions were mild in both groups according to the PGS scores. In both treatment groups, the median PGS score was 40.0 at 3 months after complete miscarriage and 37.0 at 14 months after complete miscarriage. Four women in the misoprostol group and two in the expectant-management group had PGS scores of > 90, indicating possible psychiatric morbidity, 3 months after complete miscarriage. At 14 months after complete miscarriage, one woman who

had been managed expectantly had a PGS score of > 90, indicating possible psychiatric morbidity.

Women in both treatment groups were satisfied with their management, as indicated by a median CSQ-8 score of > 25 at all three assessment timepoints (Table 2). A similar proportion of women in the two treatment groups (more than 85% at all assessment timepoints) claimed that they would recommend the treatment they received to a friend. The CSQ-8 scores did not depend on the time it took until the miscarriage was judged to be complete (Table S3) and were similar in women who did and those who did not undergo surgical evacuation (Table S4).

The trajectories of anxiety symptoms, depressive symptoms, grief and satisfaction with treatment are presented in Figures 2–5. In both treatment groups, symptom scores for anxiety and depression were statistically significantly higher at inclusion than after treatment and remained low up to 14 months after complete miscarriage.

In both treatment groups, a substantial number of women did not return all the questionnaires or returned incompletely filled out forms. The number of non-respondents was higher at the later assessment timepoints and in the expectant-management group than in the misoprostol group at all timepoints (Table S5). At 14 months after complete miscarriage, the response rate (defined as fully completed forms for STAI-state, MADRS-S, PGS and CSQ-8) was 61/94 (65%) in the group treated with misoprostol and 44/90 (49%) in the group managed expectantly. Compared with respondents, non-respondents were more often parous and expressed

Table 1 Psychometric scores of women with early miscarriage, according to whether they were managed expectantly or treated with misoprostol, at inclusion, on the day the miscarriage was judged to be complete and at 3 months and 14 months after complete miscarriage

	At inclusion			*At complete miscarriage*			*3 months after complete miscarriage*			*14 months after complete miscarriage*		
Questionnaire	*Expectant management*	*Misoprostol*	P	*Expectant management*	*Misoprostol*	P	*Expectant management*	*Misoprostol*	P	*Expectant management*	*Misoprostol*	P
STAI-trait												
Women who completed form	85	90		NA	NA	NA	NA	NA	NA	NA	NA	NA
Score			0.97	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mean ± SD	34.8 ± 11.2	34.6 ± 10.8										
Median (IQR)	32.0 (27.0–38.0)	32.0 (27.0–41.3)										
Range	21–77	20–71										
STAI-state												
Women who completed form	86	92		84	91		67	78		55	70	
Score			0.78			0.98			0.78			0.38
Mean ± SD	44.3 ± 11.7	43.9 ± 12.8		33.3 ± 9.6	33.5 ± 10.2		34.9 ± 11.1	34.5 ± 11.7		34.3 ± 10.6	33.3 ± 11.6	
Median (IQR)	44.0 (36.0–51.2)	42.0 (34.2–52.8)		31.0 (27.0–39.0)	31.0 (26.0–37.0)		32.0 (25.0–40.0)	33.5 (24.8–41.0)		34.0 (26.0–40.0)	31.5 (23.8–37.2)	
Range	23–76	20–80		20–58	20–76		20–63	20–68		20–69	20–73	
Score > 46	35 (40.7)	34 (37.0)	0.61	12 (14.3)	10 (11.0)	0.51	12 (17.9)	12 (15.4)	0.68	6 (10.9)	9 (12.9)	0.74
MADRS-S												
Women who completed form	86	91		81	93		67	77		47	65	
Score			0.86			0.50			0.29			0.30
Mean ± SD	9.2 ± 8.3	9.0 ± 8.0		6.1 ± 6.8	5.3 ± 6.2		5.7 ± 5.3	5.7 ± 7.0		6.4 ± 7.4	5.4 ± 7.6	
Median (IQR)	7.5 (2.0–12.2)	6.0 (2.0–14.0)		4.0 (0.0–9.0)	3.0 (0.0–7.5)		4.0 (2.0–9.0)	2.0 (0.0–10.0)		4.0 (0.0–10.0)	2.0 (0.0–8.0)	
Range	0–39	0–31		0–29	0–26		0–20	0–28		0–34	0–42	
Level of depression*			0.8†			0.8†			0.2†			0.72†
Mild (score 13–19)	13 (15.1)	19 (20.9)		5 (6.2)	6 (6.5)		7 (10.4)	7 (9.1)		4 (8.5)	4 (6.2)	
Moderate (score 20–34)	5 (5.8)	9 (9.9)		5 (6.2)	5 (5.4)		1 (1.5)	5 (6.5)		4 (8.5)	3 (4.6)	
Severe (score ≥ 35)	3 (3.5)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	1 (1.5)	
PGS												
Women who completed form	NA	NA	NA	NA	NA	NA	67	78		52	69	
Score	NA	NA	NA	NA	NA	NA			0.98			0.45
Mean ± SD							47.3 ± 17.5	48.6 ± 19.1		44.7 ± 15.7	42.1 ± 13.2	
Median (IQR)							40.0 (36.0–53.0)	40.0 (35.0–56.0)		37.0 (35.0–51.5)	37.0 (34.0–44.0)	
Range							33–119	33–112		33–103	33–90	
Score > 90							2 (3.0)	4 (5.1)	0.69	1 (1.9)	0 (0)	0.43

Data are given as *n* or *n* (%), unless indicated otherwise. Patients with completed forms for the particular questionnaire are included (they may have incomplete forms for one or more of the other instruments). *Level of depression according to MADRS-S score. †*P* for comparison of mild *vs* moderate or severe depression. IQR, interquartile range; MADRS-S, Montgomery–Åsberg Depression Rating Scale; NA, not applicable; PGS, Perinatal Grief Scale; STAI-state, State–Trait Anxiety Inventory state scale; STAI-trait, State–Trait Anxiety Inventory trait scale.

more often that the pregnancy was not planned and/or not welcome and/or that they did not wish to become pregnant again and/or that their partner was not positive towards the pregnancy. STAI-trait and STAI-state scores at inclusion did not differ between respondents and non-respondents (Table S5).

Table 2 Client Satisfaction Questionnaire (CSQ-8) scores of women with early miscarriage, according to whether they were managed expectantly or treated with misoprostol, on the day the miscarriage was judged to be complete and at 3 months and 14 months after complete miscarriage

	At complete miscarriage			*3 months after complete miscarriage*			*14 months after complete miscarriage*		
Parameter	*Expectant management*	*Misoprostol*	P	*Expectant management*	*Misoprostol*	P	*Expectant management*	*Misoprostol*	P
Women who completed form	84	93		67	78		54	71	
Overall CSQ-8 score									0.26
Mean ± SD	28.7 ± 4.2	28.2 ± 4.9	0.52	26.5 ± 4.6	27.0 ± 5.1	0.66	25.8 ± 4.6	25.5 ± 5.5	
Median (IQR)	30.0 (27.0–32.0)	30.0 (26.0–32.0)		27.0 (24.0–30.0)	27.5 (24.0–31.2)		26.0 (23.8–30.0)	26.0 (22.0–30.0)	
Range	11–32	0–32		11–32	6–32		9–32	8–32	
Specific items									
'I got the treatment I preferred'			0.48			0.35			0.55
Yes	79 (94.0)	90 (96.8)		60 (89.6)	74 (94.9)		50 (92.6)	63 (88.7)	
No	5 (6.0)	3 (3.2)		7 (10.4)	4 (5.1)		4 (7.4)	8 (11.3)	
'I would recommend the same treatment to a friend'			1.00			0.23			0.60
Yes	80 (95.2)	88 (94.6)		59 (88.1)	74 (94.9)		46 (85.2)	63 (88.7)	
No	4 (4.8)	5 (5.4)		8 (11.9)	4 (5.1)		8 (14.8)	8 (11.3)	
'I would seek care in the same place again'			0.42			0.53			0.27
Yes	80 (95.2)	91 (97.8)		64 (95.5)	76 (97.4)		50 (92.6)	61 (85.9)	
No	4 (4.8)	2 (2.2)		3 (4.5)	2 (2.6)		4 (7.4)	10 (14.1)	

Data are given as *n* or *n* (%), unless indicated otherwise. IQR, interquartile range.

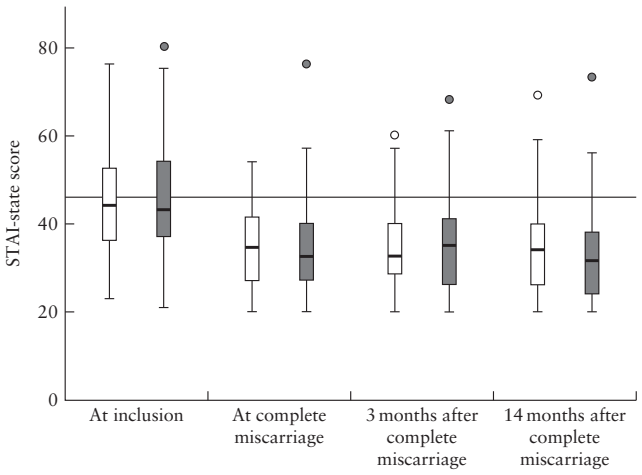

Figure 2 Box-and-whiskers plot showing State–Trait Anxiety Inventory state (STAI-state) scores of women with early miscarriage who were managed expectantly ($n = 48$ (□)) and those treated with misoprostol ($n = 62$ (■)), at inclusion, on the day the miscarriage was judged to be complete and at 3 months and 14 months after complete miscarriage. Only women who completed the questionnaire at all assessment timepoints were included in this analysis. The total STAI-state score ranges from 20 to 80, with higher scores indicating more anxiety. A STAI-state score above 46 (horizontal line, corresponding to mean + 1 SD score for working women in the general population) was considered to indicate high levels of anxiety[15]. Boxes with internal lines are median and interquartile range (IQR), whiskers correspond to values within 1.5 × IQR, and circles are outliers with values between 1.5 and 3.0 × IQR. $P < 0.001$ in both groups by Friedman test.

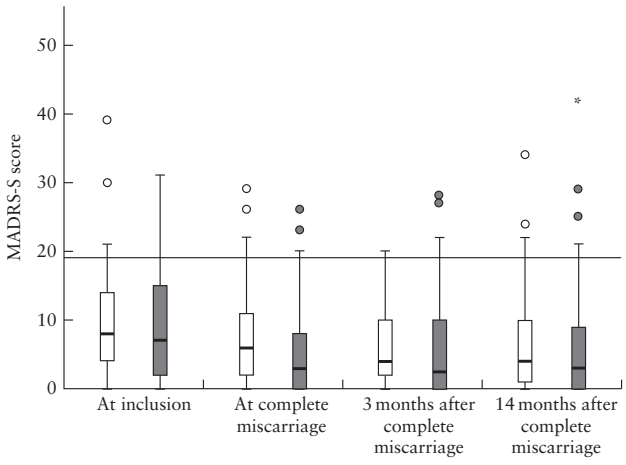

Figure 3 Box-and-whiskers plot showing Montgomery–Åsberg Depression Rating Scale (MADRS-S) scores of women with early miscarriage who were managed expectantly ($n = 41$ (□)) and those treated with misoprostol ($n = 58$ (■)), at inclusion, on the day the miscarriage was judged to be complete and at 3 months and 14 months after complete miscarriage. Only women who completed the questionnaire at all assessment timepoints were included in this analysis. The total MADRS-S score ranges from 0 to 54, with higher scores indicating more depressive symptoms. A MADRS-S score above 19 (horizontal line) indicates symptoms corresponding to at least moderate depression[16,17]. Boxes with internal lines are median and interquartile range (IQR), whiskers correspond to values within 1.5 × IQR, and circles are outliers with values between 1.5 and 3.0 × IQR. The asterisk (*) indicates cases with values more than 3 × IQR. $P = 0.014$ in expectant-management group and $P < 0.001$ in misoprostol group by Friedman test.

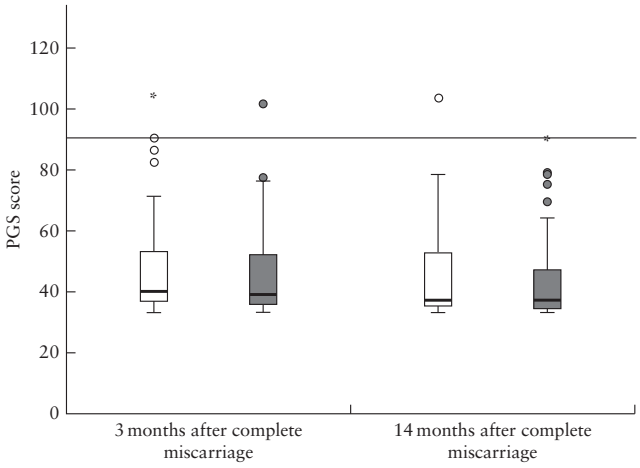

Figure 4 Box-and-whiskers plot showing Perinatal Grief Scale (PGS) scores of women with early miscarriage who were managed expectantly ($n = 48$ (□)) and those treated with misoprostol ($n = 64$ (■)), at 3 months and 14 months after miscarriage was judged to be complete. Only women who completed the questionnaire at both assessment timepoints were included in this analysis. The total PGS score ranges from 33 to 165, with higher scores indicating more intense grief. A PGS score above 90 (horizontal line) indicates deep grief[19]. Boxes with internal lines are median and interquartile range (IQR), whiskers correspond to values within 1.5 × IQR, and circles are outliers with values between 1.5 and 3.0 × IQR. The asterisks (*) indicate cases with values more than 3 × IQR. $P = 0.378$ in expectant-management group and $P = 0.002$ in misoprostol group by Wilcoxon signed-rank test.

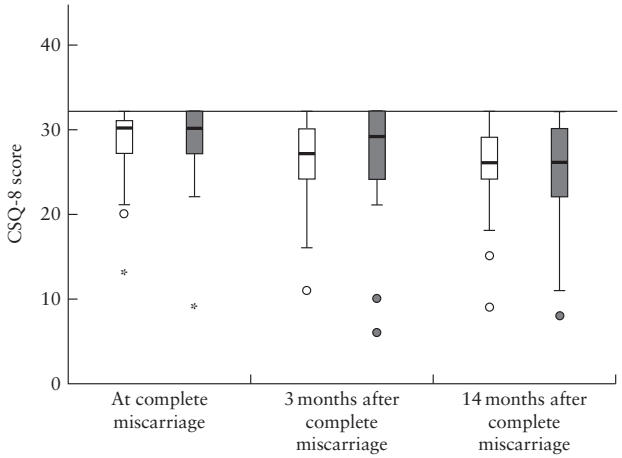

Figure 5 Box-and-whiskers plot showing Client Satisfaction Questionnaire (CSQ-8) scores of women with early miscarriage who were managed expectantly ($n = 49$ (□)) and those treated with misoprostol ($n = 65$ (■)), on the day the miscarriage was judged to be complete and at 3 months and 14 months after complete miscarriage. Only women who completed the questionnaire at all three assessment timepoints were included in this analysis. The total CSQ-8 score ranges from 8 to 32 (horizontal line indicates maximum score of 32) and higher scores indicate higher levels of satisfaction with the treatment[20]. Boxes with internal lines are median and interquartile range (IQR), whiskers correspond to values within 1.5 × IQR, and circles are outliers with values between 1.5 and 3.0 × IQR. The asterisks (*) indicate cases with values more than 3 × IQR. $P < 0.001$ in both groups by Friedman test.

DISCUSSION

The emotional response to early miscarriage did not differ between women managed expectantly and those treated with misoprostol. Anxiety levels were highest on the day when the miscarriage was diagnosed but had decreased when the miscarriage was judged to be complete and then remained at a low level for more than a year. Depression scores and grief scores were low and satisfaction with treatment was high in both treatment groups. The trait-anxiety scores of the study population at inclusion were similar to those of the reference group of adult working women in the study of Spielberger *et al.*[15], indicating that our sample is representative regarding proneness to anxiety.

To our knowledge, this is the first study to compare expectant management with misoprostol treatment of early miscarriage with respect to short- and long-term psychological impact and satisfaction with treatment. A strength of the study is that we used standardized and validated self-reported psychometric instruments. The lack of information on what proportion of invited women declined participation is a limitation of the study, since the psychological state of women who declined to participate may have been different from that of participants; those who declined might have been either more concerned or less concerned about the miscarriage. Understanding written Swedish was an inclusion criterion, which means that our results cannot be generalized to non-Swedish-speaking women in Sweden. Another limitation is the declining response rate from the first to the last assessment point at 14 months after complete miscarriage. Respondents and non-respondents showed some statistically significant differences in their attitude towards the pregnancy they lost, with non-respondents expressing more often ambiguous or negative attitudes towards the pregnancy at inclusion. However, the trait- and state-anxiety levels at inclusion were similar in respondents and non-respondents. Therefore, it is likely that the psychological scores of the respondents were representative of those of the non-respondents.

Other studies have evaluated the psychological status of women after early miscarriage, most often in relation to a control group (e.g. pregnant women, women and partners after live birth, non-pregnant women or women after termination of pregnancy) and rarely in relation to the miscarriage treatment. However, most of these studies were not interventional randomized trials. Comparison between our study and others is also complicated by differences in gestational age at miscarriage, length of follow-up and psychometric instruments used. Nevertheless, the main conclusions of a review article including 21 prospective cohort studies published between 1989 and 2016 are in line with the results of our study. Specifically, the review found that symptoms of anxiety were more common than symptoms of depression after miscarriage, and that the anxiety and depression scores were highest immediately after or within 2 weeks after the miscarriage[2]. Thereafter, the scores declined and returned to normal within 6–12 months in most cases. In

agreement with our experience, the response rate dropped over time in studies with multiple assessment timepoints[2].

We found eight randomized controlled trials that compared the impact of different miscarriage treatments on the emotional response to early miscarriage[4,11,28–33]. In four of them, expectant management was compared with either surgery only or with both medical treatment and surgery[4,30–32]. In all four of these trials, the psychometric instruments partly differed from those used in our study and the follow-up was shorter, not exceeding 12 weeks after inclusion. In agreement with our results, none of the trials found any major differences in psychological wellbeing between the treatment groups. However, in the Chinese trial, women randomized to medical or surgical treatment reported more post-traumatic stress symptoms (as measured using the Chinese Impact of Event Scale – Revised) than did women randomized to expectant management[4]. Specific cultural concepts among Chinese women may be an explanation for this difference[29].

In a recently published study by Farren *et al.*[34], 30% of women experienced post-traumatic stress, suggesting moderate or severe post-traumatic stress disorder (PTSD) at 1 month after miscarriage, while 19% reported post-traumatic stress suggesting moderate or severe PTSD at 3 months after the diagnosis. It is difficult to comment on these findings since our study did not assess post-traumatic stress. Compared with our findings, a slightly higher proportion of women in the study of Farren *et al.*[34] reported moderate-to-severe anxiety and moderate-to-severe depressive symptoms at 3 months after the miscarriage (measured using the Hospital Anxiety and Depression Scale). However, the two studies are not completely comparable since the study design, study populations and psychometric tests used differ. Only first-trimester miscarriages were included in our trial, whereas miscarriages up to 20 gestational weeks were included in the cohort study of Farren *et al.*[34].

Failed treatment had a negative psychological impact on women with early pregnancy failure in two trials in which surgery was compared with expectant management[32] or with misoprostol treatment[28]. In the first trial, women in whom expectant management ended with surgery expressed more anxiety than those with complete spontaneous evacuation after expectant management (evaluated using the Spielberger State Anxiety Inventory Form X)[32]. In the other trial, women felt less healthy and more impaired when misoprostol treatment failed than when it succeeded (evaluated using the Short Form Survey (SF-36) quality of life instrument) but STAI-state scores did not differ between the two groups[28]. In our study, STAI-state scores were not related to the time to complete spontaneous miscarriage and were not higher in women who underwent surgical evacuation than in those who did not.

In two randomized trials, satisfaction with treatment (adapted CSQ) was poorer if the treatment failed and was followed by surgical evacuation[4,29]. In our trial, satisfaction with treatment was not affected by the time from inclusion to spontaneous complete evacuation or by a need for surgical evacuation (Tables S3 and S4). Participants in our trial were not free to choose treatment. Yet, more than 85% of women in both treatment groups claimed that they had received the treatment that they preferred, and that they would recommend the treatment to a friend. This suggests that both treatments were tolerated well. It is likely that women treated in accordance with their own preference would also be satisfied with either treatment. However, the high level of treatment satisfaction may also reflect an unintended therapeutic effect of participating in the trial. The weekly follow-up visits to the same research doctor that formed part of the trial protocol may have contributed to treatment satisfaction.

In conclusion, the findings of this randomized trial show that the impact of early miscarriage in terms of anxiety, depression and grief is similar in women managed expectantly and those managed medically with vaginal misoprostol. We found no support for long-term psychological consequences up to 14 months after the miscarriage. Satisfaction with treatment was high and similar in the two treatment groups, despite substantial differences in treatment success. This information is important when patients are counseled about different treatment options for early miscarriage.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Anxiety level, as measured by State–Trait Anxiety Inventory state (STAI-state) scale, in relation to when the miscarriage, was judged to be complete, in women with early miscarriage, according to whether they were managed expectantly or treated with misoprostol

Table S2 Anxiety level, as measured by the State–Trait Anxiety Inventory trait (STAI-trait) and state (STAI-state) scales, according to whether dilatation and evacuation was performed

Table S3 Satisfaction with the assigned treatment, as measured by the Client Satisfaction Questionnaire (CSQ-8), in women with early miscarriage managed expectantly and those treated with misoprostol, in relation to when the miscarriage was judged to be complete

Table S4 Satisfaction with assigned treatment, as measured by the Client Satisfaction Questionnaire (CSQ-8), in women with early miscarriage managed expectantly and those treated with misoprostol, according to whether surgical evacuation was performed

Table S5 Characteristics of respondents and non-respondents at each assessment timepoint according to age, parity, attitude towards the pregnancy and STAI-state and STAI-trait scores at inclusion