Misoprostol versus curettage in women with early pregnancy failure: impact on women’s health-related quality of life. A randomized controlled trial

G.C.M.Graziosi1,6, H.W.Bruinse2, P.J.H.Reuwer3, P.H.van Kessel4, P.E.Westerweel2 and B.W.Mol5

1St Antonius Hospital, Koekoekslaan 1, 3435 CM, Nieuwegein, 2University Medical Centre, Heidelberglaan 100, 3584 CX, Utrecht, 3St Elisabeth Hospital, Hilvarenbeeksingeweg 60, 5022 GC, Tilburg, 4Tweesteden Hospital, Dr Deelenlaan 5, 5042 AD, Tilburg and 5Maxima Medical Centre, de Run 4600, 5504 DB, Veldhoven, The Netherlands

6To whom correspondence should be addressed. E-mail: p.graziosi@Antonius.net

BACKGROUND: We aimed to compare patients’ health-related quality of life after a misoprostol strategy to a curettage in women with early pregnancy failure after failed expectant management. METHODS: A multicentre randomized clinical trial was performed in The Netherlands. In all, 154 women with early pregnancy failure confirmed at ultrasonography who had been managed expectantly unsuccessfully for ≥1 week were randomly assigned to undergo either treatment with misoprostol (n = 79) or curettage (n = 75). The main outcome measures were health-related quality of life and satisfaction with treatment. RESULTS: In the misoprostol strategy 47% of the women needed additional curettage, as compared to 4% after curettage. In both groups, health-related quality of life was impaired most severely 2 days after treatment. In the misoprostol group, health-related quality of life was more severely impaired; after 2 days this was due to more pain and after 2 and 6 weeks this was due to a worse general health perception. Health-related quality of life was temporarily significantly more impaired in women in whom misoprostol failed as compared to women in whom misoprostol treatment was successful. In both treatment groups, an equal percentage of women (58%) would choose the same treatment in the future. In women treated with misoprostol, however, this choice depended on the initial success of misoprostol: in cases where misoprostol had caused complete evacuation, 76% of the women would opt for the same treatment, whereas only 38% of women who needed curettage after unsuccessful misoprostol would do so (P < 0.01). CONCLUSION: Our study shows that, although both the misoprostol strategy and the curettage strategy resulted in complete evacuation in the end, women are willing to accept some disadvantages of misoprostol to avoid curettage. A treatment inconvenience using misoprostol is accepted as long as initial evacuation rate is high. This finding should be an integral part of counselling women when deciding upon management of early pregnancy failure.

Key words: curettage/early pregnancy failure/misoprostol.quality of life

Introduction

Curettage is at present the standard therapy in the management of early pregnancy failure. Misoprostol is a non-invasive and inexpensive alternative, easy to perform and available on demand. Misoprostol is reported to be effective in 50–80% of women with early pregnancy failure (Chung et al., 1999; Demetroulis et al., 2001; Sahin et al., 2001; Muffley et al., 2002; Wood and Brain, 2002; Graziosi et al., 2004). In view of these advantages, misoprostol is gaining popularity as a treatment option for early pregnancy failure. Only one study compared psychological well-being, depression, anxiety and satisfaction in women treated with misoprostol as compared to curettage (Lee et al., 2001). No difference in psychological well-being was observed. However, since the study was conducted in China, the authors stated that due to cultural differences these outcomes might not be applicable in Western society.

Recently, we performed a randomized clinical trial comparing misoprostol and curettage in women with early pregnancy failure who had been managed expectantly for ≥1 week after the initial diagnosis (Graziosi et al., 2004). According to our findings, misoprostol treatment is expected to lead to a high percentage (47%) of women who need curettage as well. Moreover, women treated with misoprostol experienced evacuation at home and both severity of bleeding and pain were increased in these women as compared to curettage.

Since, apart from clinical effectiveness, quality of life should be taken into account when deciding for a particular treatment, we assessed health-related quality of life and patients’ satisfaction alongside our randomized clinical trial.
Materials and methods

The study was performed in three teaching hospitals in the Netherlands (St Antonius Hospital Nieuwegein, St Elisabeth Hospital Tilburg and Tweedesten Hospital Tilburg) between November 2001 and June 2003. The institutional review boards of the three hospitals approved the study protocol. The methods of the study have been described previously (Graziosi et al., 2004). In short, women with early pregnancy failure were randomized either to curettage or to a strategy starting with misoprostol. Women with incomplete abortion were not eligible for the study.

Curettage treatment consisted of evacuation of the uterus by suction curettage under general anaesthesia in a day care setting.

Misoprostol treatment (four tablets of 200 mg administered vaginally, repeated after 24 h in cases of incomplete abortion) was given after randomization in an outpatient setting. Participants were allowed to use analgesic medication.

Misoprostol treatment was considered to have failed when curettage was needed. Criteria for the need of curettage were: presence of abnormal bleeding and signs of retained products of conception >3 days following misoprostol administration (i.e. presence of gestational sac or a focal hyperechoic intrauterine mass with an anterior posterior diameter >15 mm at ultrasonography), profuse bleeding or infection.

Similarly, curettage was considered to have failed when intervention was needed because of abnormal bleeding and signs of retained products of conception visible at ultrasonography.

Health-related quality of life was assessed with the use of standard self-administered psychometric measures with established reliability and validity. We used the Short Form 36 (SF36), the State–Trait Anxiety Scale (STAI) and the Self-rating Depression Scale (SDS) (Zung, 1965; Stewart, 1988; de Vries, 1994; van der Ploeg, 2001).

The generic SF36 compromises seven subclasses: physical functioning, role functioning, social functioning, mental health, vitality, pain and health perception. Physical functioning refers to limitations in a variety of physical activities ranging from strenuous to basic (e.g. carrying groceries, climbing stairs and self-care). Role functioning and social functioning refers to limitations in common daily or social activities resulting from health problems (e.g. working, attending school or visiting friends). Mental health was assessed in terms of psychological distress and well-being. Vitality was measured using a scale for energy, and pain was measured using a pain scale. Health perception refers to patients’ overall ratings of their current health in general. The subscales were transformed to a 0–100 scale, with higher scores indicating better quality of life.

Anxiety was measured with the STAI, which measures both state and trait anxiety. State anxiety refers to momentarily experienced anxiety. Trait anxiety refers to the general tendency of an individual to be anxious, and is considered a personality trait. We measured trait anxiety at the start of the study and state anxiety at baseline and at subsequent follow-up. The SDS was used to measure depression. This scale measures the subjective experience of depression as characterized by affective, cognitive, behavioural and psychological symptoms.

Client satisfaction and acceptance of the mode of treatment were assessed 2 weeks after treatment, using a questionnaire derived from the Client Satisfaction Questionnaire (Larsen et al., 1979). Three items were used including overall rating of satisfaction with the medical service, satisfaction with recovery after treatment and whether they would choose the same treatment in the future.

In order to compare treatment effects on health-related quality of life, assessment was made at four points in time. The first set of questionnaires was completed immediately after randomization. Women received a further three sets of questionnaires which were completed after 2 days, 2 weeks and 6 weeks after allocated treatment. All questionnaires were returned in sealed envelopes.

Data analysis

Health-related quality of life was studied on an intention-to-treat basis. Repeated measures analysis of variance were used to establish changes in health-related quality of life over time (time effect), differences in health-related quality of life between both treatment groups (treatment effect) and interaction between changes in health-related quality of life over time and treatment groups (time by treatment effect) (Hays, 1998).

Women with missing measurements were included in the repeated measurement analysis if data were available for at least two different time-points (Zwiderman, 1992). P < 0.05 was considered to indicate statistically significant differences. If statistically significant differences in health-related quality of life between both treatment groups or an interaction between changes in health-related quality of life over time and treatment group was found, Student’s t-test was used to examine differences between treatment groups at specific time-points. As trait anxiety was measured only once, Student’s t-test was used for analysis. In an additional analysis, we compared the health-related quality of life in women in whom misoprostol was successful to women in whom misoprostol did not lead to complete evacuation and curettage was also needed.

The sample size calculation was based on a difference in complete evacuation rate (Graziosi et al., 2004). As only one outcome can be the primary one, and sample size has to be based on this outcome, the number of patients included in the study is based on this power. For the SF-36, in order to detect a 10-point difference in the Physical Component Summary scale and Mental Component Summary scale as relevant, two groups of 65 patients are sufficient to find relevant differences (alpha 0.05; beta 0.80; SD 20).

Results

Of the 241 women who were eligible, 87 (36%) women declined to participate in the trial and were treated with curettage (Figure 1). Of the remaining 154 women, 79 were allocated to the misoprostol strategy, and 75 were allocated to curettage. Forty-two of 79 women (53%) in the misoprostol group had complete evacuation whereas 37 (47%) women needed additional curettage. One woman needed a second curettage. Subsequent curettage after failed misoprostol was needed due to persistent presence of a gestational sac or persistent severe bleeding requiring emergency curettage in 78% (29/37) and ultrasonographic presence of endometrial thickness >15 mm and bleeding in 22% (8/37). In the misoprostol group, there were no surgical complications in women who needed curettage after failed misoprostol.

In the group allocated to curettage, 72 (96%) women had complete evacuation. Three women needed a second curettage. Complications occurred in three women (4%) allocated to curettage.

Emergency curettage was needed in 12 women allocated to misoprostol and two women allocated to curettage.

Seventy-three women allocated to misoprostol (93%), completed at least two questionnaires, as compared to 58 (77%) women allocated to curettage (P = 0.007). Baseline characteristics of women who responded and who did not
respond are shown in Table I. There were no statistically significant differences between responders and non-responders included in the study with respect to baseline characteristics or treatment allocation. The number of women allocated to misoprostol therapy and curettage who completed health-related quality of life measures at separate time-points for misoprostol and curettage were 73 versus 58 after randomization, 71 versus 57 after 2 days, 68 versus 55 after 2 weeks and 61 versus 48 after 6 weeks respectively.

Medical outcomes: Short Form 36

Misoprostol compared to curettage
In both groups, health-related quality of life changed significantly over time for all dimensions. Health-related quality of life was most impaired 2 days after treatment, to improve thereafter (Figure 2, Table II).

Physical functioning, role functioning, social functioning, mental health and vitality were comparable in both treatment groups. Women treated with misoprostol had more pain than women treated with curettage ($P = 0.05$), a difference that was mainly present 2 days after treatment ($P = 0.002$). Pain decreased during follow-up and was comparable in both treatment groups at 6 weeks after randomization. We also found a significant treatment effect for general health perception ($P = 0.02$). Women treated with misoprostol perceived themselves as less healthy than women treated with curettage at 2 weeks and 6 weeks after treatment ($P = 0.01$ and 0.02 respectively).

Failed misoprostol compared to successful misoprostol
Differences in health-related quality of life were more profound and statistically more often significant for more

Figure 1. Flow chart showing the flow of participants through each stage of the randomised trial.
dimensions in women with failed misoprostol as compared to
women in whom misoprostol was successful (Figure 3,
Table III).
Physical function and general health perception were more
impaired after 2 days ($P = 0.04$ and $0.001$ respectively) and 2
weeks ($P = 0.05$ and $0.004$ respectively) in women in whom
misoprostol had failed. Social function and bodily pain were
more impaired after failure of misoprostol at 2 weeks after
the start of treatment ($P = 0.03$ and $0.02$ respectively).

After 6 weeks, physical functioning ($P = 0.05$), social
function ($P = 0.02$), mental health ($P = 0.03$), vitality
($P = 0.006$), bodily pain ($P = 0.02$) and general health
($P = 0.003$) were still impaired in women in whom miso-
prostol had failed as compared to women in whom misopros-
tol caused complete evacuation.

For physical function and mental health, a statistically
significant interaction between changes in health-related
quality of life over time and treatment group was found,
indicating a longer period of recovery in women in whom misoprostol had failed.

State–Trait Anxiety Inventory

There were no statistically significant differences between both treatment groups in trait or state anxiety (Figure 4, Table II).

Similar patterns in anxiety were observed for women with failed misoprostol therapy as compared to successful misoprostol therapy (Table III). A statistically significant interaction between changes in anxiety over time and treatment group was found, mainly due to a slightly higher anxiety level in the curettage group at 2 weeks after treatment.

Depression Scale

Women in both treatment groups were equally depressed at baseline (Figure 4, Table II). Two weeks after treatment, depression had decreased to levels within the normal range in both treatment groups. A statistically significant interaction between changes in health-related quality of life over time and treatment group was found, which was due to a slightly slower recovery in the curettage group.

Client satisfaction and acceptance

The two groups were not significantly different in terms of satisfaction with hospital service (Table IV). Women treated with misoprostol were less satisfied with their recovery after treatment as compared to women allocated to curettage. In terms of satisfaction with recovery and hospital service, participants allocated to the misoprostol strategy were equally satisfied with recovery as compared to women allocated to curettage.

Women were also asked whether they would choose the same mode of treatment if they had to choose again for one of the treatments. In both treatment groups, 58% would choose the allocated treatment again.

Participants who required curettage after a failed misoprostol treatment were equally satisfied with the hospital service and recovery as compared to women in whom misoprostol treatment caused complete evacuation. However, when asked whether they would choose a misoprostol treatment in the future, this choice depended on the initial success of misoprostol: when misoprostol had caused complete evacuation, 58% of women who needed curettage after misoprostol failed would do so (P < 0.05; **P < 0.01), whereas only 38% of women who needed curettage after failed misoprostol would do so (P < 0.01) (Table IV).

Discussion

This study compared women's health-related quality of life after misoprostol therapy to a curettage for early pregnancy failure. Misoprostol resulted in complete evacuation in 53%
of women with early pregnancy failure as compared to 96% in women allocated to curettage. Health-related quality of life was affected most severely 2 days after treatment in both treatment groups. Moreover, it was impaired more severely after misoprostol treatment as compared to treatment with curettage, due to more pain and a worse general health perception.

Only one other study comparing misoprostol to curettage in treatment of early pregnancy failure reported on psychological well-being (Lee et al., 2001). In that study, 218 women were randomly allocated to curettage or misoprostol. Complete evacuation was achieved in 50% of women treated with misoprostol, and the study showed comparable psychological well-being in both groups. This result is in concordance with our findings.

In addition, measurement of health-related quality of life was worthwhile in our trial showing temporarily declined scores for general health and pain in women allocated to misoprostol. This implies that health-related quality of life measurements provide significant supplementary information in assessing psychological dimensions of a treatment intervention.

Many publications confirm the negative psychological impact in terms of anxiety and depression of early pregnancy failure on a significant proportion of women (Thapar and Thapar, 1992; Neugebauer, 2003). This was also observed in our study. The results in our study demonstrate that while there were no obvious differences in anxiety and depression scales, there was a significant interaction mainly due to higher anxiety in the curettage group and slower recovery of depression scales in the curettage group.

Our data on patients’ satisfaction show that a choice for misoprostol treatment in the future depends on the initial success of this treatment, as almost twice as many women (76%) in whom misoprostol treatment succeeded would choose the same mode of treatment in the future. This speaks for the better acceptability of this non-invasive approach to early pregnancy failure, as long as treatment success is high. Equal patterns on satisfaction rates (i.e. willingness to choose the same treatment in the future) were reported in other studies for women in whom misoprostol resulted in complete evacuation (Demetroulis et al., 2001; Wood and Brain, 2002).

Our study has some limitations. Thirty-six per cent of the eligible participants were not recruited into the study. It is important to realize that misoprostol was only available for women in the trial. As a consequence, our findings might be biased in favour of misoprostol, since women who opted for curettage and were not willing to be randomized were treated accordingly. In contrast, women who had a prior preference for misoprostol could only obtain this treatment after randomization.

We had a lower non-response rate in the women allocated to curettage as compared to women allocated to misoprostol.
There were no significant differences in baseline characteristics in non-responders for both treatment allocations. Moreover curettage was almost always successful, and it is unlikely that health-related quality of life in the curettage group differed between responders and non-responders. Furthermore, and more importantly, the response in the misoprostol group was good and there was no difference in response rate between women in whom misoprostol was successful and women who needed additional curettage.

The 53% complete evacuation rate of misoprostol in our study is slightly lower as compared to the 60–88% success rates described in other trials, using comparable misoprostol treatment protocols and criteria for diagnosis of treatment failure (Demetriou et al., 2001; Muffley et al., 2002; Wood...
and Brain, 2002). The preceeding expectant management and criteria for deciding upon failed misoprostol treatment as used in our study protocol might explain the lower evacuation rate in our study. A recent study by Creinin et al. (2004) showed that there is no obvious relationship between increasing endometrial thickness and the need for surgical intervention in women treated with misoprostol for early pregnancy failure. It must be noted, however, that in our study incomplete evacuation in the misoprostol group was due either to profuse bleeding or to persistent presence of a gestational sac in the majority of cases (78%). These women clearly needed additional curettage.

The present study showed an effect on women’s health-related quality of life after both treatments. Misoprostol had a temporarily more negative effect on health-related quality of life, which is explained by the experience of an abortion with pain as well as a high failure rate with the need of additional curettage, whereas high satisfaction was observed in women in whom misoprostol treatment resulted in complete evacuation. The individual weighing of the perceived advantages and disadvantages of both treatments generally should be respected after an open counselling, since some women are willing to trade a treatment burden and possible failure of misoprostol for the benefit of a non-invasive management.

### Table IV. Client satisfaction and acceptance of the treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Curettage</th>
<th>Misoprostol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 68)</td>
<td>(n = 37)</td>
<td>(n = 31)</td>
</tr>
<tr>
<td>Success</td>
<td>4 (2)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Failure</td>
<td>1 (1)</td>
<td>7 (5)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Satisfaction with hospital service, %</td>
<td>47 (26)</td>
<td>49 (33)</td>
<td>46 (17)</td>
</tr>
<tr>
<td>Satisfaction with recovery, %</td>
<td>47 (26)</td>
<td>43 (29)</td>
<td>43 (16)</td>
</tr>
<tr>
<td>Will certainly chose same</td>
<td>4 (2)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>treatment again, %</td>
<td>2 (1)</td>
<td>7 (5)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Might chose same treatment</td>
<td>47 (26)</td>
<td>50 (34)</td>
<td>51 (19)</td>
</tr>
<tr>
<td>again, %</td>
<td>47 (26)</td>
<td>25 (17)</td>
<td>27 (10)</td>
</tr>
<tr>
<td>Will not choose same</td>
<td>2 (1)</td>
<td>12 (8)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>treatment again, %</td>
<td></td>
<td></td>
<td>19 (6)*</td>
</tr>
</tbody>
</table>

*Scores range from 1 to 4; higher scores indicate more satisfaction.

*P < 0.05.

### References


Zung W (1965) A self rating depression scale. Arch Gen Psychiat 12,63–70.


Submitted on December 30, 2004; resubmitted on March 6, 2005; accepted on March 14, 2005.