Medical management of early fetal demise using a combination of mifepristone and misoprostol

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BACKGROUND: This study aims to assess the efficacy of a combination of mifepristone and misoprostol in the management of missed miscarriage and anembryonic pregnancy. METHODS: Data of 220 consecutive women with miscarriage, undergoing medical evacuation of the uterus were collected prospectively at an early pregnancy assessment unit in a tertiary referral hospital. Each woman received a single oral dose of mifepristone 200 mg and 36–48 h later vaginal misoprostol 800 µg. Three hours following the first dose, two further doses of misoprostol, 400 µg each, were administered vaginally or orally at 3 h intervals. Women who failed to pass products of conception were offered repeat medical regime with misoprostol. Success was defined as complete uterine evacuation within 3 days, without the need for surgical evacuation. RESULTS: The overall success rate of medical management was 84.1%. Mifepristone alone induced natural expulsion of products of conception in 18.1% of women. The median dose of misoprostol required was 1600 µg and the median induction miscarriage interval after first prostaglandin administration was 8.04 h (range: 0.58–50.54 h). Of the 142 women who were symptomatic at presentation the medical regime failed in 30 (21.1%), compared with five (6.4%) failures of the 78 who were asymptomatic (P = 0.007). Of the 35 women who had surgical evacuation, eight required an emergency curettage for bleeding. CONCLUSIONS: The combination of oral mifepristone 200 mg with vaginal or oral misoprostol is an alternative to surgical management of early fetal demise, although it is not as effective as surgery.

Key words: anembryonic pregnancy/fetal demise/mifepristone/misoprostol/missed miscarriage

Introduction

The terms ‘delayed miscarriage or early fetal demise’ denote missed miscarriage (presence of a non-viable embryo/fetus) and blighted ovum (anembryonic pregnancy with absent embryonic echo) (RCOG Study Group, 1997). The two conditions are felt to represent different aspects of the same clinical process. A blighted ovum results from an early disturbance of normal embryonic development. In missed miscarriage, an intrauterine sac is seen with an embryo without cardiac activity. Apart from the distinction made at the time of vaginal scan, no clinically significant differences are observed between the two conditions. The diagnosis of early fetal demise has become more common since the introduction of transvaginal ultrasound, and accounts for ~21% of all miscarriages seen in our early pregnancy assessment unit (EPAU) in Aberdeen.

The clinical management of miscarriage has changed little over the years and up to 88% of women undergo surgical uterine evacuation (Hemminki, 1998). There are well-documented risks associated with surgical uterine evacuation (Farell et al., 1982; Heisterberg et al., 1986) and potential cost savings (Hughes et al., 1996) can be generated by promoting alternative strategies of management. The success of expectant management of missed miscarriage appears too low to justify its routine use in clinical practice (Jurkovic et al., 1998), although it may be an acceptable approach in individual patients. Various medical regimens with or without the anti-progesterone, mifepristone, and a prostaglandin analogue have been described to treat early fetal demise. Their efficacy vary widely from 25–92%, depending on the type of miscarriage, outcome measures used, the dose, duration and route of prostaglandin administration (El-Refaey et al., 1992; Creinin et al., 1997).

Based on our experience of first trimester abortion (El-Refaey and Templeton, 1994; El-Refaey et al., 1995; Ashok et al., 1998), we developed a regimen comprising mifepristone 200 mg followed by a combination of the vaginal or oral administration of misoprostol (800–1600 µg) for the management of early fetal demise. We now report our experience of this regimen in 220 consecutive cases.

Materials and methods

A consecutive series of 220 women with ‘delayed miscarriage’ (missed miscarriage and anembryonic pregnancy) between 6 and 13 weeks, during the period 1998–1999, were studied. All women had chosen to undergo medical rather than surgical treatment. The study was performed in the EPAU at Aberdeen Maternity Hospital. The
and associations were tested using the Fisher
and ranges. Categorical variables are given as numbers (percentage)
continuous variables are presented as means with standard deviations
Package (Kinnear and Gray, 1994). In presenting the results,
evaluation undertaken if indicated.
time. The women were followed up in the hospital with ultrasound
products of conception on the ward were given an emergency
midwife). Those women who were allowed home without passing
of treatment, at the hospital or in the community (referring doctor or
ultrasound scan was performed. In the event of uncertainty
of misoprostol (two tablets each) 400
administration pulse, blood pressure, temperature and systemic
products of conception were passed on the ward, the women were
– 3 h. If bleeding was heavy misoprostol was administered orally. If
of misoprostol were inserted into the posterior vaginal fornix by a
nurse. Following administration of the first dose, a further two doses
of misoprostol (two tablets each) 400 µg were given vaginally every
3 h. If bleeding was heavy misoprostol was administered orally. If
products of conception were observed on the ward, the women were
observed for 4 h before being allowed home. Following misoprostol
administration pulse, blood pressure, temperature and systemic
symptoms were monitored hourly. Oral (paracetamol 500 mg plus
dihydrocodeine 10 mg) or parenteral analgesia (morphine 10 mg)
was administered every 4–6 h as required. Patients who failed to pass
products of conception overnight were offered a choice of either
repeat medical regimen (misoprostol 800, 400, 400 µg at 3 h
intervals, orally or vaginally) or surgical evacuation. Complete uterine
evacuation was confirmed clinically by observing expelled products
of conception and speculum examination. In the event of uncertainty
ultrasound scan was performed.
All women were offered a follow-up appointment within 2 weeks
of treatment, at the hospital or in the community (referring doctor or
midwife). Those women who were allowed home without passing
products of conception on the ward were given an emergency
telephone number for contacting staff if they were concerned at
any time. The women were followed up in the hospital with ultrasound
assessment undertaken if indicated.
Data were analysed using the SPSS for Windows Statistical
Package (Kinnear and Gray, 1994). In presenting the results,
continuous variables are presented as means with standard deviations
and ranges. Categorical variables are given as numbers (percentage)
and associations were tested using the Fisher’s exact or χ² tests as
appropriate. Kaplan–Meier survival analysis was used to compare
(by means of the Log Rank test) the cumulative miscarriage rates in
relation to parity. Differences were regarded as statistically significant
if P < 0.05.

Results
Of the 220 women with early fetal demise, 139 (63.1%) had
a missed miscarriage and 81 (36.8%) had an anembryonic
pregnancy. A comparison of patient characteristics, presenta-
tion, treatment outcome, induction–miscarriage interval and
complications between the two groups is shown in Table I.
There were no significant differences.
The mean ± SD age of the 220 women was 31.6 ± 6.1
years (range 16–44). Of the 220 women, 67 (30.4%) were
primiparous and 153 (69.5%) had one or more previous
pregnancies. The mean gestation, by best estimate at the time
of mifepristone administration, was 10.1 ± 1.84 weeks of
amenorrhoea (range 6–13). At presentation to the EPAU, 84
(38.2%) had vaginal bleeding, five (2.3%) had pain and 53
(24.1%) had both pain and bleeding. Seventy-seven (35%)
women were asymptomatic and the diagnosis was made at the
routine first visit scans.
Of the 220 women, 44 complained of heavy bleeding within
48 h of mifepristone administration alone and in 40 complete
miscarriage was confirmed on ultrasound scan. Four had
emergency curettage for heavy bleeding. The treatment out-
come is summarized in Figure 1. Among the 176 women who
went on to receive misoprostol, complete miscarriage occurred
in 145 (without the need for surgical intervention). Thus, the
overall success rate was 185/220 (84.1%). The indications for
surgical intervention are shown in Table II. Eight women had
emergency curettage for bleeding, four before and four after
misoprostol administration. A total of seven women had a
blood loss >500 ml but none required a blood transfusion.
Of the 142 women who were symptomatic at presentation
(pain/bleeding) the medical regime failed in 30 (21.1%) who
required surgical evacuation of the uterus, while five (6.4%)
women of the 78 who were asymptomatic (diagnosis of non-
viable pregnancy on routine ultrasound) required surgical
intervention—a statistically significant difference (P = 0.007).
Of the 185 patients who had a successful outcome, complete

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**Table I. Comparison of details of women with missed miscarriage and blighted ovum**

<table>
<thead>
<tr>
<th></th>
<th>Missed miscarriage (n = 139)</th>
<th>Anembryonic pregnancy (n = 81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>31.67 ± 6.39</td>
<td>31.61 ± 5.61</td>
<td>NS</td>
</tr>
<tr>
<td>Multiparity</td>
<td>97 (69.7%)</td>
<td>53 (65.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous miscarriages</td>
<td>47 (33.8%)</td>
<td>20 (24.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Symptomatic at presentation</td>
<td>89 (64.0%)</td>
<td>53 (65.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Medical evacuation on mifepristone alone</td>
<td>30 (21.5%)</td>
<td>10 (12.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Medical evacuation on full regimen</td>
<td>87/109 (79.8%)</td>
<td>58/71 (81.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Surgical evacuation</td>
<td>23 (16.5%)</td>
<td>12 (14.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>No analgesia</td>
<td>55 (39.5%)</td>
<td>23 (28.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Parenteral analgesia</td>
<td>22 (15.8%)</td>
<td>16 (19.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Readmission</td>
<td>8 (5.7%)</td>
<td>6 (7.4%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.
Medical management of early fetal demise

Figure 1. Outcome of medical treatment in 220 consecutive women with early fetal demise. E indicates women who had emergency curettage.

Table II. Indications and time interval for surgical intervention

<table>
<thead>
<tr>
<th>Indications</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency curettage for bleeding</td>
<td>8 (22.8)</td>
</tr>
<tr>
<td>Incomplete miscarriage</td>
<td>14 (40.0)</td>
</tr>
<tr>
<td>No products passed</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td>Patient choice</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td>Molar pregnancy</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (15.9)</td>
</tr>
<tr>
<td>Misoprostol to surgical intervention interval</td>
<td></td>
</tr>
<tr>
<td>Before misoprostol</td>
<td>4</td>
</tr>
<tr>
<td>Up to 3 days</td>
<td>22</td>
</tr>
<tr>
<td>4–14 days</td>
<td>5</td>
</tr>
<tr>
<td>&gt;15 days</td>
<td>0</td>
</tr>
</tbody>
</table>

Uterine evacuation was confirmed clinically in 130 (70.3%) and ultrasonically in 51 (27.6%).

The median number of misoprostol doses required was three (800 + 400 + 400 µg). Of the 54 women who did not miscarry following overnight stay (three doses of misoprostol), 28 (51.9%) opted for surgical evacuation. The medical regimen was repeated in the remaining 26 patients, of whom 23 (88.5%) had a complete miscarriage. Of the 176 women who received the full mifepristone/misoprostol regimen, the induction-miscarriage interval could be accurately determined in 148 (84%) and of these, 74 (50.0%) miscarried within 6 h of receiving first dose of misoprostol. The median induction—miscarriage interval was 8.04 h (range among those observed: 0.58–50.54). The median (range) induction—miscarriage interval was 8.16 h (2.0–50.54) and 8.0 h (0.58–30.92) in primigravid and multigravid patients respectively. The two groups were compared by Kaplan–Meier survival analysis and no significant difference was found between the two groups (Log Rank test). The cumulative frequency of induction—miscarriage interval is shown in Figure 2.

Data on analgesic use were recorded in 219 women in the study. Of these, 78 (35.6%) required no analgesia (including 40 women who miscarried following mifepristone alone), 101 (46.1%) required oral analgesia only, two received diclofenac suppositories and 38 (17.4%) required parenteral opiate analgesia.

Fourteen (6.3%) women who had had medical treatment for miscarriage required readmission. Of these, four (1.8%) had presumed pelvic infection, five (2.2%) required surgical curettage for prolonged bleeding, four (1.8%) had problems unrelated to the miscarriage and one (0.5%) had a molar pregnancy. One hundred (45.5%) women were given follow-up appointments in hospital, of which 82 (82%) attended. Sixty-three (28.6%) women declined an appointment and the remaining 57 (25.9%) were followed up in the community (referring doctor or midwife).

Discussion

To our knowledge, this study of 220 women represents the largest reported series of the medical regimen for early pregnancy demise. Although incomplete miscarriage may be managed with misoprostol alone (Henshaw et al., 1993; Chung et al., 1997), in the presence of an intact sac and closed cervix (early fetal demise), priming with the antiprogestrone mifepristone makes the regimen more effective (El-Refaey et al., 1992; Hinshaw, 1997). The overall success rate of our regimen was 84.1%, but the true efficacy—by excluding women who had surgical evacuation by choice—was 86.4%.

Nielsen et al. reported a success rate of 52% using a combination of 400 mg of mifepristone and 400 µg of
misoprostol, both taken orally with 13% of women requiring emergency curettage (Nielsen et al., 1997). In our series, emergency surgical intervention was necessary in only 3.6%. Medical treatment may have been less successful in the Nielsen study because of the smaller dose (400 µg) of misoprostol administered by the oral route rather than the vaginal route. Vaginal administration of misoprostol has been shown to be more effective in comparison with the oral route in the context of medical management of miscarriage and first trimester termination of pregnancy (El-Refaey et al., 1995; Creinin et al., 1997). Plasma concentrations and bio-availability of misoprostol tend to be greater and prolonged when administered vaginally compared with the oral route (Zieman et al., 1997). In our study, split analysis showed that the medical regimen was more effective in women who were asymptomatic at presentation (93.5%) with a non-viable pregnancy being diagnosed on routine scanning as opposed to women who presented with pain and/or bleeding (78.8%). In comparison Nielsen et al. only included women who were asymptomatic at presentation and had an efficacy rate of only 52% (Nielsen et al., 1997).

In our study we used clinical parameters for defining success of the method. Once products of conception were passed and bleeding ceased, we did not perform an ultrasound scan to confirm an empty uterus unless indicated. However studies suggesting a lower efficacy with the medical regimen made ultrasound scan assessment of all women following treatment to confirm an empty uterus unnecessary. Only five of the women in this series required subsequent surgical evacuation following discharge from hospital for prolonged bleeding. Our work confirms no real advantage in scanning all women following treatment. In addition to increasing surgical evacuation rates this would also increase the use of resources.

The natural expulsion of products of conception with 200 mg of mifepristone alone occurred in 18.1% of women, while Lelaidier et al. reported 82% expulsion rates using a dose of 600 mg of mifepristone alone (Lelaidier et al., 1993). It has been shown that for termination of early pregnancy a single dose of 200 mg mifepristone is as effective as 600 mg, when used in combination with a prostaglandin analogue (WHO Task Force, 1993). However a higher dose of mifepristone may be required for medical treatment of miscarriage, probably due to a change in progesterone receptor sensitivity, and this is reflected in the higher success rate (96%) from our early study using 600 mg (El-Refaey et al., 1992). This needs to be confirmed in the context of future studies. Mifepristone is relatively expensive and a reasonable success rate (80%) can be achieved by using a combination of 200 mg mifepristone with misoprostol. Misoprostol is cheap, effective and does not require special storage facilities, hence is a promising alternative in the developing world. Most published studies using misoprostol alone for medical management of delayed miscarriage have a success rate of 13–83% (de Jonge et al., 1995; Herabutya and O-Prasertsawat, 1997). Should mifepristone be unavailable, regimens using misoprostol alone may have a place in clinical practice. Table III summarizes published data with respect to medical regimens and success rates.

Demetroulis et al. showed that a single dose of misoprostol 800 µg administered vaginally was successful in 82.5% of women with early pregnancy failure, which included women with incomplete miscarriage, missed miscarriage and anembryonic pregnancy (Demetroulis et al., 2001). If women with an incomplete miscarriage were excluded the failure rate of misoprostol alone for medical management of missed miscarriage and anembryonic pregnancy would have been 23.1% in the above study. This confirms the results from our

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandian et al., 2001a</td>
<td>Misoprostol 600 µg, 400 µg, 400 µg–2 hourly (PO)</td>
<td>84.8</td>
</tr>
<tr>
<td>Demetroulis et al., 2001b</td>
<td>Misoprostol 400 µg (PV)</td>
<td>82.5</td>
</tr>
<tr>
<td>Nielsen et al., 1999b</td>
<td>Mifepristone 400 mg</td>
<td>82.0</td>
</tr>
<tr>
<td>Nielsen et al., 1997c</td>
<td>Mifepristone 400 µg (PO)</td>
<td>52</td>
</tr>
<tr>
<td>Creinin et al., 1997c</td>
<td>Mifepristone 400 µg (PO)</td>
<td>25</td>
</tr>
<tr>
<td>Herabutya and O-Prasertsawat, 1997c</td>
<td>Mifepristone 800 µg (PV)</td>
<td>88</td>
</tr>
<tr>
<td>Hughes et al., 1996c</td>
<td>Misoprostol 200 µg (PV)</td>
<td>83.3</td>
</tr>
<tr>
<td>Chung et al., 1997b</td>
<td>Mifepristone 200 mg</td>
<td>89.1</td>
</tr>
<tr>
<td>Egarter et al., 1995c</td>
<td>Misoprostol 400 µg, 400 µg, 400 µg-over 48 h (PO)</td>
<td>70.6</td>
</tr>
<tr>
<td>de Jonge et al., 1995a</td>
<td>Misoprostol 400 µg (PO)</td>
<td>76.7</td>
</tr>
<tr>
<td>Chung et al., 1994b</td>
<td>Gemeprost 1 mg</td>
<td>45.4</td>
</tr>
<tr>
<td>Henshaw et al., 1993c</td>
<td>Sulprostone 0.5 mg (i.m.) or Misoprostol 400 µg (PO)</td>
<td>96</td>
</tr>
<tr>
<td>Lelaidier et al., 1993c</td>
<td>Mifepristone 600 mg</td>
<td>82</td>
</tr>
<tr>
<td>El-Rafay et al., 1992c</td>
<td>Mifepristone 600 mg</td>
<td>82</td>
</tr>
<tr>
<td>Misoprostol 400 µg, 200 µg 2 h apart (PO)</td>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

aIncomplete miscarriage.
bIncomplete miscarriage, missed miscarriage and anembryonic pregnancy.
cMissed miscarriage and anembryonic pregnancy.
PO = per oral; PV = per vagina; i.m. = intramuscular.
series and previous studies that primaling with the anti-progesterone mifepristone makes the regimen more effective (El-Refaey et al., 1992; Hinshaw, 1997). Demetroulis et al. (2001) also showed that 82.5% of women who underwent the medical regimen for early pregnancy failure were satisfied with treatment compared with 58% of those who underwent surgical treatment.

Medical termination of pregnancy up to 9 weeks, using a combination of mifepristone and misoprostol, had an efficacy of 97.5% (El-Refaey et al., 1994). More recently the feasibility of medical abortion has been shown at gestations between 9 and 13 weeks to have an efficacy of 95% (Ashok et al., 1998). However medical management of early non-viable pregnancy has a much lower efficacy, probably attributable to low progesterone concentrations following fetal demise. The lower failure rate of the medical regime in asymptomatic women compared with symptomatic may also be explained by the same hypothesis. The side effects of misoprostol have not been assessed in this study. However it is well known in the context of medical abortion that the commonest side effects experienced by women are gastro-intestinal (El-Refaey et al., 1995).

Patient acceptability has been shown to be similar between surgical and medical evacuation for incomplete miscarriage and early fetal demise (RCOG, 2000). Acceptability tends to decrease with increasing symptoms and gestation. The uptake of the medical regimen for early fetal demise at our EPAU was 45%. It may be possible to introduce medical management without admission to the EPAU, particularly at early gestations. Out of 54 who did not miscarry following overnight stay, 26 women (48.1%) opted for repeat regimen; 23 (88.5%) were successful. This emphasises the value of offering repeat medical treatment if the standard regimen fails.

Eighteen women did not attend hospital follow-up and 28.6% of women declined an appointment. The Grampian Region is unusual in terms of its catchment population, and there is only one main hospital within a radius of 50 miles. While acknowledging that an unknown number of women may have consulted their General Practitioner with symptoms and minor complications, it can be assumed that any women with a significant complication would have been referred to hospital for further treatment.

In conclusion, medical treatment with 200 mg of oral mifepristone in combination with 800, 400 and 400 µg of vaginal misoprostol given sequentially at 3 h intervals is an effective and safe alternative to surgical and expectant management of early fetal demise. Therefore extending the availability of medical management of early fetal demise at EPAU would reduce the need for surgery and associated complications. Finally, medical management increases women’s choice of methods.

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References


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