Laminaria, induced fetal demise and misoprostol in late abortion

Warren M. Hern*
Director, Boulder Abortion Clinic, 1130 Alpine, Boulder, CO 80304, USA
Assistant Clinical Professor, Department of Obstetrics and Gynecology, University of Colorado Health Sciences Center, Denver, CO, USA

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Abstract

Objectives: To analyze and determine the safety and effectiveness of induced fetal demise as an adjunctive method in outpatient abortion for patients with advanced pregnancies and to evaluate the independent effect of intrauterine misoprostol administered after amniotomy in late abortion. Methods: During a 9-year period, 1677 abortions were performed for patients whose pregnancies ranged from 18 through 34 menstrual weeks in an outpatient facility. Of these, 832 were performed by one physician. Techniques for performing all the abortions included induction of fetal demise by intrauterine fetal injection of digoxin and/or hyperosmolar urea, serial multiple laminaria treatment of the cervix, amniotomy, oxytocin induction of labor, and assisted delivery or surgical evacuation of the fetus and placenta. In the last 411 of the 832 patients whose abortions were performed by one physician, misoprostol was placed in the lower uterine segment following amniotomy in order to enhance labor induction, cervical ripening, and fetal expulsion. Results: Of the entire group of 1677 cases, the median gestational age was 22 menstrual weeks. The median procedure time for all cases was 10 min. Measured median blood loss was 125 ml. Blood loss and procedure time increased with length of gestation, but these were not affected by misoprostol. There were three major complications (0.2%) in the overall series. Among patients seen by one physician (N – 832), amniotomy-to-procedure time was shorter by 26 min for patients receiving misoprostol, and there was 27% more variability in amniotomy-to-procedure time among patients not receiving misoprostol. Complication rates for patients receiving misoprostol were the same as for those not receiving misoprostol. There were no major complications in the 832 patients seen by one physician, no uterine rupture or perforations, and no cervical lacerations. Conclusions: Outpatient abortion may be performed safely from 18 through 34 menstrual weeks using combined surgical and medical procedures. Use of intrauterine post-amniotomy misoprostol was associated with reduced amniotomy-to-procedure time and reduced variability in the amniotomy-to-procedure time. © International Federation of Gynecology and Obstetrics. All rights reserved.

Keywords: Abortion; Misoprostol; Induced fetal demise; Laminaria

1. Introduction

Current techniques in late abortion are eclectic, combining medical and surgical components, hygroscopic dilation of the cervix, pre-operative induced fetal demise, and the use of intraoperative ultrasonographic guidance. Termination of pregnancy in the second trimester and beyond presents formidable obstacles, even when inter-current illness or complications of pregnancy are not present. These challenges are accentuated when a patient has a history of cesarean delivery, cervical scarring, metabolic or cardiovascular illness, or the presence of uterine myomata or multiple gestation. During the past few years, misoprostol has come into wide use in the management of cervical dilation for term labor and for therapeutic abortion. Numerous studies document the use and effects of intravaginal misoprostol in late abortion (defined here as termination of a pregnancy of ≥ 20 menstrual weeks’ gestation) [1 – 12]. Most studies are characterized by a small number of patients with different dosage regimes, but all focus on inpatient abortion achieved by induction of labor. Some studies contain a large proportion of cases in which spontaneous fetal demise had already occurred.
Other reports have described the use of misoprostol in the management of premature rupture of membranes at term, applying misoprostol in several ways [13 – 16].

The induction of fetal demise by intrafetal injection of digoxin or other materials prior to late abortion has become widely practiced during the past 20 years, but only one published report describes this activity [17]. In a more recent study, a randomized clinical trial including 126 patients seeking abortions at 20 – 23.1 weeks found that intra-amniotic digoxin infusion as a means of causing fetal demise resulted in more vomiting but did not increase efficacy in late abortion [18].

This report analyzes the experience with 1677 consecutive patients with gestations ranging from 18 through 34 weeks whose abortions were performed by five different physicians in an ambulatory extramural setting at a single institution. We review techniques, including pre-operative induced fetal demise, used to enhance the safety and efficacy of this procedure, procedure outcome variables, and overall complication rates. Particular attention is given to the independent effects of misoprostol on safety and various outcome variables in these procedures.

2. Materials and methods

All procedures were performed over a period of 9 years ending in May, 1999 in a single private office outpatient facility located across the street from a community hospital. The facility has been specially equipped and staffed to provide assistance for women seeking late abortion. Patients receive individual counseling and personal support throughout their experience at the clinic. Real-time diagnostic ultrasound is performed on all patients during the pre-operative evaluation. Most patients come to the facility by way of referral.

Twenty-six of the patients in the current report were included in a previous monograph which focused on the experience of 124 selected patients ending pregnancies for fetal anomaly or genetic disorder. These pregnancies were terminated by a variety of techniques during a 10-year period which overlapped the current reporting period by approximately 2 years [17].

The routine protocol after ultrasound evaluation and counseling included placement of one or more laminaria in the cervix on day 1, replaced by several laminaria (up to 20, depending on size of the laminaria) in the cervix on day 2 in one sitting or in two sittings 6 h apart, and performance of the abortion on day 3. The serial multiple laminaria pre-operative treatment protocol of 2 days was used for all patients except those who experienced spontaneous labor and fetal expulsion after the first day.

In all patients, induced fetal demise was accomplished by intrafetal injection of digoxin 1.5 – 2 mg on day 1 or 2 under direct ultrasound visualization. In patients with gestations 24 menstrual weeks or greater, 40 g of hyperosmolar urea was injected intrafetally following injection of the digoxin. On the third day of treatment, an intravenous (i.v.) line was placed in order to permit an infusion of Ringer’s lactate solution and the administration of i.v. medications. The most recently inserted laminaria were removed under direct visualization. At that time, the membranes were routinely ruptured under ultrasound visualization using a packing forceps or, if the membranes were visible, with a sharp instrument such as an amniohook or single-tooth tenaculum. Following amniotomy, a 12-mm cannula was inserted into the uterine cavity, and the amniotic fluid was allowed to drain as completely as possible without the use of vacuum. In the second half of the series, amniotic fluid removal was done routinely under direct ultrasound visualization so as to minimize residual amniotic fluid in the uterus, theoretically minimizing the risk of amniotic fluid embolism. An attempt to induce labor was not made until a clear flow of amniotic fluid was established and the risk of amniotic fluid embolism presumably reduced. Amniotic fluid was measured as accurately as possible.

Immediately before the amniotomy, a long-acting paracervical block was placed using 12 ml of bupivacaine (Marcaine) 0.25% (Winthrop Pharmaceuticals, New York, NY). Sixty units of oxytocin were added to 1000 ml of Ringer’s lactate infusion for a 10 units per h infusion to induce labor except in patients with a previous history of cesarean delivery. Due to the known risk of uterine rupture with abortion in someone with a history of previous cesarean delivery, patients with this history received either
no oxytocin stimulation or very light stimulation (2 units/h) for the purpose of maintaining uterine tone [19].

When patients became uncomfortable because of oxytocin-induced labor, they were given meperidine 50-100 mg intramuscularly (i.m.) approximately 30 min before the anticipated expulsion or dilation and evacuation (D & E) procedure. When fetal expulsion was determined by pelvic exam to be imminent, the patient was placed in an operating room where the expulsion was facilitated and controlled by the physician. If expulsion did not begin to occur within a few hours after the artificial rupture of membranes, or if the patient began bleeding heavily, D & E was performed. The D & E procedure was performed under paracervical and/or pudendal block anesthesia using up to 20 ml of 1% lidocaine placed immediately before the procedure.

In the case of assisted fetal expulsion, delivery of the fetus was carefully controlled by the physician so as to minimize the risk of cervical or perineal laceration. This was sometimes accomplished by sharp dissection of presenting fetal parts. For all patients in this series, forceps evacuation of the uterus was routinely accomplished under direct intraoperative ultrasound visualization. The placenta was delivered immediately in most cases by traction on the umbilical cord or forceps removal when it was adherent. Intravenous infusion of oxytocin was increased after delivery of the fetal skull, and 0.2 mg of methylergonovine maleate was given i.m. upon delivery of the placenta.

In the last 411 patients of this overall series, 200-400 µg of misoprostol (Cytotec©; G.D. Searle & Co.) was placed with forceps in the lower uterine segment a few centimeters past the internal os following amniotomy and removal of amniotic fluid. Only the first 12 patients received less that 400 µg of misoprostol, which became the routine dose. All these patients were seen by one physician (W.M.H.).

Procedure time at the time of completion of the abortion was measured from the time the physician actively began assisting with fetal expulsion, when the uterine cavity was entered with instruments or from the beginning of the delivery of the fetus, whichever came first, until completion of the procedure by final curettage and vacuum aspiration. Amniotomy-to-procedure time was measured from the time of the amniotomy to the beginning of the procedure. The effect of misoprostol administration on this variable is reported as well as its apparent effect, if any, on blood loss and procedure time. Blood loss was determined for all patients by directly measuring the blood volume in the collecting basin at the time of the abortion and by removing clots with the gloved hand from the fluid in the basin and measuring the volume of clots.

Post-operative tissue examination included weighing the fetus and placenta separately and carefully measuring fetal parts, including foot length, biparietal diameter, crown-rump length, rump-shoulder length, abdominal diameter, and chest diameter. The method of measurement of fetal parts has been described previously [20]. Diagnosis of actual fetal age according to fetal foot length is based on previously established values [20].

Patients were routinely observed in the recovery room for 1-2 h or more, depending on patient response and the appearance of complications. All patients received routine antibiotic prophylaxis after the intrafetal injection and continuing after the abortion procedure. The standard protocol was 200 mg of doxycycline orally immediately after intrafetal injection followed by 100 mg of doxycycline twice a day for 5 days. Patients allergic to doxycycline were given erythromycin. Cultures for gonorrhea and chlamydia were done only in cases that appeared to be at higher than usual risk for these infections based on history and/or the presence of a mucopurulent cervicitis at the time of the initial exam. Rh-immune globulin was administered to all patients who were Rh-negative.

All patients were strongly encouraged to return for follow-up examination if possible and were given forms to send in when they could not return in person for an examination. Arrangements were made for follow-up with the referring or other local physician when the patient came from a long distance, and for the follow-up physician to return a brief report. Standard follow-up instructions included a recommendation for examination at 4 weeks after the abortion.

We defined major complications using criteria at the Centers for Disease Control: major unintended surgery, hemorrhage requiring transfusion, or pelvic infection with 2 or more days of fever and a peak of at least 40°C or with hospitalization for 11 or more days [21]. A minor complication was defined as any
of the following: an operative or post-operative problem that required uterine aspiration or suture of a cervical laceration, infection (indicated by uterine tenderness at follow-up examination) responding to antibiotic therapy or more than a transitory fever of 38ºC or more on two or more occasions, a total blood loss of more than 500 ml, and documented evidence of coagulopathy not requiring transfusion [21].

In terms of study design, this is a retrospectiv e historical nested case series. The data reported here were generated by a review of consecutive charts for all patients who had an abortion procedure that included induced fetal demise with intrafetal injection of digoxin since 6/1/1990. The data were entered into a computer database. Each chart was individually reviewed, validated and checked by the author and an assistant against the computer entry data to be processed. The Statistical Package for the Social Sciences (SPSS Base 8.0) was used for all statistical analyses, which included general measures of central tendency, comparisons of means, simple linear regression analysis, and Χ²-analysis of two-way tables.

3. Results

Most patients came from throughout the United States and Canada. Several came directly from other foreign countries, principally located in Europe and Central and South America. One-fourth of all patients were from outside Colorado. Patient ages ranged from 12 to 47, with a mean age of 23 and a median age of 21. Fifteen percent of all patients were age 16 or younger, and 35% of the patients were between 17 and 21 years of age. Pre-operative estimates of fetal age ranged from 18 to 34 menstrual weeks. Follow-up contact was obtained with 60.4% of all patients, of whom half (30.2%) received follow-up exams at this office. Ninety-one patients (5.4%) had a history of previous cesarean section, and 11.6% (N=196) of all patients sought assistance because of a diagnosed fetal anomaly or fetal genetic disorder. Abortion procedures were performed by five different physicians, of whom one (W.M.H.) performed half (N=832), another performed one-third (N=565), and another performed 16% (N=266). Forty-seven patients (2.8%) experienced a spontaneous rupture of membranes prior to the final treatment phase and are not included in the amniotomy-to-procedure time analysis. There were nine cases of twins (0.5%), all of which are included in all analyses.

The final estimate of gestational age as defined by measurable fetal foot length [20] was 18-34 menstrual weeks, with a median of 22. The median procedure time for all cases was 10 min, with a mean of 12.5 and a range of 1 to 227. The median blood loss was 125 ml, with a mean of 163 and a range of 5-2500. Procedure time and blood loss increased with length of gestation (Table 1); linear regression analysis showed that gestational length accounted for 10% of blood loss (adjusted $r^2 = 0.102, P <0.001$) and for 27% of procedure time (adjusted $r^2 = 0.274, P<0.001$).

<table>
<thead>
<tr>
<th>Weeks’ gestation</th>
<th>Blood loss (ml)</th>
<th>Procedure time (min)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 19</td>
<td>75</td>
<td>8</td>
<td>211</td>
</tr>
<tr>
<td>20 - 21</td>
<td>125</td>
<td>9</td>
<td>354</td>
</tr>
<tr>
<td>22 - 23</td>
<td>100</td>
<td>10</td>
<td>485</td>
</tr>
<tr>
<td>24 - 25</td>
<td>125</td>
<td>12</td>
<td>349</td>
</tr>
<tr>
<td>26 – 27</td>
<td>150</td>
<td>13.5</td>
<td>214</td>
</tr>
<tr>
<td>28 – 29</td>
<td>138</td>
<td>15.5</td>
<td>42</td>
</tr>
<tr>
<td>30 – 31</td>
<td>125</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>32 – 33</td>
<td>250</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>34 +</td>
<td>635</td>
<td>65.5</td>
<td>2</td>
</tr>
</tbody>
</table>

Blood loss was generally low and within acceptable limits, but 63 patients (3.8%) experienced a blood loss of more than 500 ml. Three patients (0.2%) in the overall series experienced a major complication, blood transfusion, of whom two patients were transfused because of disseminated intravascular
coagulation (DIC) syndrome. The third patient who received a transfusion experienced a cervical laceration, uterine atony, and blood loss of 2500 ml.

Six percent (N = 101) of patients experienced minor complications. Of these, 27 patients (1.6%) required re-aspiration for retained tissue. Five patients (0.3%) experienced sepsis or chorioamnionitis during the treatment, all associated with spontaneous rupture of membranes prior to initiation of the abortion procedure. Three of these patients were referred to us because of spontaneous rupture of membranes of several days’ duration after 20 menstrual weeks in a desired pregnancy. There were two cases of cervical laceration, both sutured primarily, one patient with a prochlorperazine (Compazine) reaction treated with benzotropine mesylate (Cogentin), and one case of suspected amniotic fluid embolism, not proved. In the last case, the patient experienced sudden dyspnea and headache, became cyanotic, and was taken immediately to the hospital emergency room, where her signs and symptoms were already diminishing. No evidence of amniotic fluid embolism could be found by lung scan or change in laboratory values. Disseminated intravascular coagulopathy did not develop.

There were no cases of uterine perforation, uterine rupture, or post-operative infection. Patients with a history of cesarean section did not experience an increased rate of minor complications and experienced none of the major complications.

3.1 Misoprostol use

Because variability among physicians was greater for several outcome variables such as blood loss, procedure times, and amniotomy-to-procedure times than the variation of these observations for patients by whether or not they received misoprostol, comparison of results for patients receiving misoprostol are made only for those patients (N = 832) treated by one physician (W.M.H.).

Misoprostol use was begun for all patients in March, 1997. On the recommendation of colleagues practicing obstetrics, 200-400 µg of misoprostol was placed in the lower uterine segment following amniotomy and release of all amniotic fluid. Since it appeared that 200 µg had little effect for the first 12 patients, the dose was increased to 400 µg, and that became the standard dose for all patients thereafter.

The 411 patients receiving misoprostol were compared with the previous 421 successive patients whose abortions were also performed by the same physician (W.M.H.). The patients in both these groups were similar, with a median age of 22 and a median gestational length of 23 menstrual weeks. Fifty-three percent of these patients had follow-up contact, of whom 22.6% (N = 188) had their follow-up exams at the clinic. Thirteen percent of these patients (N = 108/832) were terminating the pregnancy because of fetal anomaly or genetic disorder. Among the patients with a history of cesarean delivery, 24 received misoprostol and 26 did not.

Patients receiving misoprostol at the time of amniotomy experienced a median blood loss of 175 ml vs. 150 ml for those who did not receive misoprostol (P = 0.082). Median procedure time for patients receiving misoprostol was the same (10 min) as for those not receiving misoprostol. Blood loss and procedure times increased with length of gestation for both treatment and control groups (P<0.001). Length of gestation had no effect on the amniotomy-to-procedure times (P = 0.709). Mean values for these outcome variables are show in Table 2.

Excluding patients who experienced spontaneous rupture of membranes prior to the scheduled amniotomy and procedure (N = 12) and those having amniotomy-to-procedure times of less than 10 min (N = 15) because fetal expulsion was imminent at the time of amniotomy, median amniotomy-to-procedure times were shorter by 26 min for patients receiving misoprostol (162 min vs.136 min; P<0.001), and there was 27% more variability among controls not receiving misoprostol (S.D.=133 vs. S.D.=105).
Table 2  Mean blood loss, procedure times, amniotomy-to-procedure times

<table>
<thead>
<tr>
<th>Weeks gestation</th>
<th>No Cytotec</th>
<th>Cytotec</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Blood Loss (ml)</td>
<td>Procedure time (min)</td>
<td>Amniotomy-to-proc. time (min)</td>
</tr>
<tr>
<td>18 – 19</td>
<td>22 100</td>
<td>6</td>
<td>180</td>
</tr>
<tr>
<td>20 – 21</td>
<td>92 150</td>
<td>8</td>
<td>175.5</td>
</tr>
<tr>
<td>22 – 23</td>
<td>128 125</td>
<td>9</td>
<td>160</td>
</tr>
<tr>
<td>24 – 25</td>
<td>108 150</td>
<td>12</td>
<td>145</td>
</tr>
<tr>
<td>26 – 27</td>
<td>62 175</td>
<td>13.5</td>
<td>172</td>
</tr>
<tr>
<td>28 – 29</td>
<td>5 425</td>
<td>30</td>
<td>190</td>
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<tr>
<td>30 – 31</td>
<td>3 375</td>
<td>22</td>
<td>120</td>
</tr>
<tr>
<td>32 – 33</td>
<td>1 50</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>34</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>421 150</td>
<td>10</td>
<td>161.5</td>
</tr>
</tbody>
</table>

Treatment and control groups by menstrual week of gestation (W.M.H. cases only; N = 832).

In the single-physician (N = 832) series, there were 39 minor complications (4.7%) of which 29 were blood loss of more than 500 ml and five were in patients requiring re-aspiration (0.6%). Three patients (0.4%), previously described in the overall series, presented with long-standing premature rupture of membranes and developed sepsis during treatment. Two other minor complications, previously described, were those of a prochlorperazine (Compazine) reaction and a suspected amniotic fluid embolism that could not be documented.

Including only the minor complications of excessive blood loss and re-aspiration, a X²-test comparing misoprostol vs. control patients showed no difference in complication rates (P = 0.531; Table 3). There were also no differences among patients with a history of previous cesarean delivery (P = 0.500).

Table 3  Minor complications by treatment groupª

<table>
<thead>
<tr>
<th></th>
<th>No misoprostol</th>
<th>Misoprostol</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No minor complications</td>
<td>404</td>
<td>394</td>
<td>798</td>
</tr>
<tr>
<td>Minor complications</td>
<td>17</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>421</td>
<td>411</td>
<td>832</td>
</tr>
</tbody>
</table>

W.M.H. cases only, N = 832, X² = 0.531
ª Includes only minor complications of excessive bleeding (>500 ml) or re-aspiration

In this series by one physician, there were no cases of cervical laceration, uterine rupture or uterine perforation, and there were no major complications.

4. Discussion

Advances in completing late abortion appear to include comprehensive use of both surgical and medical treatments. A fundamental feature of this comprehensive approach is the use of serial multiple laminaria treatment for cervical dilation [22,23].

Another strategy that we feel enhances safety is the pre-operative induction of fetal demise by intrafetal injection performed 24-48 h prior to the abortion. In a previous series, fetal demise and induction of labor was accomplished by the intra-amniotic infusion of hyperosmolar urea on the same day as the abortion procedure [24]. In the current series, the induction of fetal demise as much as 2-3 days before the
induction of labor and/or D & E procedure appeared to produce fetal maceration, cervical softening, dilation, and effacement, and appeared to minimize both blood loss and procedure duration. This was especially true in more advanced pregnancies (26+ menstrual weeks’ duration) and in cases in which a lower uterine segment myoma may have otherwise made successful labor induction or D & E impossible. One such case for the indication of severe fetal hydrocephaly (>10 cm) at 34 menstrual weeks was characterized by an anterior lower uterine intramural myoma 12 cm in diameter. Induced fetal demise, serial multiple laminaria treatment for 3 days prior to the abortion procedure, misoprostol treatment, and percutaneous cephalocentesis with the withdrawal of >200 ml of fetal cerebrospinal fluid permitted a dilation and evacuation procedure to be accomplished without complication.

Careful and complete removal of all amniotic fluid under direct ultrasound visualization may diminish the risk of fatal or sublethal amniotic fluid embolism with an associated disseminated intravascular coagulation (DIC) syndrome. The use of local anesthesia is generally associated with lower risks of morbidity and mortality [25]. Uterine tone is maintained with local anesthesia and the conscious patient can report unusual pain immediately. Assisted fetal expulsion in the operating room or D & E procedure under conditions of fetal maceration, adequate cervical preparation, and placental necrosis was associated in our series in low amounts of measured blood loss.

The protocol combining serial multiple laminaria treatment, pre-operative induced fetal demise, and rupture of membranes with induction of labor backed up by D & E provides satisfactory outcomes in our clinical setting.

In this series, the use of misoprostol was associated with reduced amniotomy-to-procedure times and reduced variability in these times. This is a great advantage in an outpatient setting. Inclusion of misoprostol in the protocol did not increase the complication rates, but it may have enhanced patient comfort by diminishing the total length of time involved in the abortion procedure day. This apparent result remains to be studied by more rigorous means and analysis.

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References


* Tel.: +1-303-447-1361; fax: +1-303-447-0020 E-mail address: bachern@drhern.com (W.M.Hern).

website address: www.drhern.com

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