RESEARCH ARTICLE

Termination of mid-trimester pregnancies: misoprostol versus concurrent weighted Foley catheter and misoprostol [version 1; referees: 2 approved with reservations, 1 not approved]

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The Department of Obstetrics and Gynecology, Faculty of Medicine, Menofyia University, Shibin Elkom, Egypt

Abstract

Objective: To investigate whether the use of a weighted trans-cervical fluid-filled Foley’s catheter would improve the effectiveness of 400µg vaginal misoprostol regimen in terminating mid-trimester pregnancies.

Methods: This study was conducted at the department of Obstetrics and Gynecology, Menofyia University Hospital in Egypt. Fifty eligible primigravidae were allocated into 2 groups. Termination was carried out in group I using vaginal misoprostol while in group II, a weighted fluid-filled intra-uterine Foley’s catheter was inserted and a similar misoprostol regimen was followed as in group I.

Results: The combined group showed shorter induction to termination interval (15.6 ± 4.9 versus 21.9 ± 5.4 hours; P<0.05). There was no significant difference in the occurrence of side effects between the groups.

Conclusion: A combination of a weighted Foley’s catheter and 400µg of vaginal misoprostol every 4 hours is more effective than misoprostol alone in terminating mid-trimester gestations.

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How to cite this article: Shabana A, Salah H, Kandil M et al. Termination of mid-trimester pregnancies: misoprostol versus concurrent weighted Foley catheter and misoprostol [version 1; referees: 2 approved with reservations, 1 not approved] F1000Research 2012, 1:36 (doi: 10.12688/f1000research.1-36.v1)

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Competing interests: The author(s) declared that no grants were involved in supporting this work.

Editorial note:

Please note that the refereeing status of this article was changed from “indexed” to “v1; ref status: not approved 1, approved with reservations 2”.

When this article was first published, F1000Research was still in its beta phase; during this period articles that received any two of “Approved” or “Approved with Reservations” statuses from the reviewers were labelled as “indexed”. When the journal was formally launched in January 2013, the requirements for indexing were tightened, and only articles that are given either two “Approved” or one “Approved” plus two “Approved with Reservations” statuses by the reviewers are labelled “indexed”. The new criteria for “indexing” can still be met in the future if a new revised version receives the necessary approval status from the reviewers.

Introduction

Universal prenatal screening programs have led to an increase in the diagnosis of congenital malformations with subsequent gradual increase in second trimester termination of pregnancy (TOP)\(^1\). This represents 10–15% of total abortions performed worldwide\(^2\).

Termination in the second trimester is more risky than during the first trimester\(^3\) and, therefore, the pharmacologic management seems to be an appealing alternative to surgical evacuation. Misoprostol has been widely used in different dosages and routes for second-trimester pregnancy terminations. Doses ranging from 200 to 800 µg at intervals ranging from 3 to 12 hours have been described\(^4–8\). High doses at short intervals have been linked to a higher percentage of side effects.

Several studies have described the Foley’s catheter as an effective method in ripening the cervix. Obed and Adewole\(^9\) showed that the Foley’s catheter increased the Bishop’s score in women with unripe cervices. Sciscione et al.\(^10\) stated that the Foley’s catheter appears to be of comparable effectiveness as to intravaginal misoprostol for pre-induction cervical ripening. Its use is common in poor countries because it is safe, inexpensive and has a low incidence of contractile abnormalities\(^11\).

This study was designed to investigate whether the insertion of a weighted fluid-filled trans-cervical Foley’s catheter would further improve the effectiveness of 400 µg vaginal misoprostol in terminating mid-trimester pregnancies.

Material and methods

This study was carried out at the department of Obstetrics and Gynecology, Menofiya University Hospital, Egypt. Women were recruited and enrolled in the study from July 2011 until the end of April 2012. The institutional review board approved the protocol of the study and an informed consent was obtained from all participants. (see Supplementary Material).

Women enrolled were primigravidae with a singleton pregnancy at a gestational age ranging between 13 and 23 weeks, with a fetal anomaly that is incompatible with life or a fetal demise within one week. Gestational age was calculated from the date of the first day of last menstrual period and confirmed by a vaginal ultrasound scan. Women with any of the following were excluded from the study: 1) Previous uterine scar; 2) Contraindication to misoprostol; 3) Low-lying placenta; 4) Operation on the cervix; 5) Clinical or laboratory evidence of chorioamnionitis.

Initially we planned to recruit 50 women divided equally between two groups. However, after starting enrollment, we were confronted with the fact that many women preferred to be enrolled in the combined group rather than the misoprostol-only group. When patient number 50 was enrolled, there were 20 women assigned to group I and 30 women to group II.

All participants were subjected to complete history taking and thorough clinical examination. Induction of abortion was carried out in group I by inserting two tablets; each contains 200 microgram misoprostol (Sigma Pharmaceuticals, Egypt), in the posterior vaginal fornix every four hours. In group II, with the patient in the lithotomy position, the cervix was visualized using a Cusco’s speculum and then sterilized with povidone iodine. The anterior lip of the cervix was grasped with a ring forceps and another ring forceps was then used to push the catheter through the cervix under direct visualization. The balloon was then inflated with 30 ml saline (50 ml for those >20 weeks) and the catheter was pulled back snugly against the internal os and taped to the inner aspect of the thigh. A bag filled with saline was applied to the distal end of the catheter to provide moderate traction. Different filling volumes were used at different gestational ages. We used 250 ml at 13–17 weeks, 300 ml with ages at 18–20 weeks and 500 ml at gestational ages more than 20 weeks. The filled bag was approximately equivalent to 250, 300 and 500 g in weight, respectively. A 400 µg misoprostol vaginal dose “two tablets” was then inserted in the posterior vaginal fornix/4 hours as in group I. A maximum of 4 misoprostol doses were used in both groups. Each patient received 1 g ampicillin/6 hours as a prophylactic antibiotic. As soon as the catheter was expelled, re-assessment of the dilatation and effacement of the cervix was carried out. Oxytocin infusion was started 4 hours after the last dose of misoprostol in both groups according to the standard protocol in our department.

The patient was assessed every 4 hours for vital signs, cervical dilation, expulsion of fetus and occurrence of complications such as nausea, vomiting and abdominal pain. All patients received intravenous oxytocin 20 IU after expulsion of the fetus to help placental separation and delivery. Retained placenta was considered if no manifestations for placental separation appeared 30 minutes after fetal expulsion. The patient was anesthetized and manual separation of the placenta was carried out. Surgical evacuation was performed if any remnant of conception such as missed placental lobe or piece of membranes was suspected to be retained inside the uterus.

After placental expulsion, women were observed for the presence of uterine atony and post-abortive bleeding. This was assessed by counting the number and change in the weight of the sanitary pads used by the patient. Bleeding was considered average if less than 200 cc and excessive if more than 200 cc.
The measured primary outcome parameter was the induction to abortion interval. Secondary parameters were: 1) Occurrence of side effects; 2) Need for manual separation of the placenta; 3) The need for surgical evacuation; and 4) Occurrence of post-abortive bleeding.

For the purpose of statistical analysis, women enrolled were categorized into 3 groups according to gestational age (Table 1). Early mid-trimester group between 13 and 17 weeks, mid mid-trimester group 18–20 weeks, and late mid-trimester group 21–23 weeks.

Results were tabulated and analyzed on an IBM personal computer using Epi Info, version 6, a word-processing database and statistics program. Descriptive statistics were expressed as mean and standard deviation. The Student t test was used to evaluate independent variables that are normally distributed. The Chi square test was used to compare 2 rates unless the number in the contingency table was < 6 where Fisher’s exact test was used. A significant statistical level was considered if P was < 0.05.

Results
The age of the participants was not significantly different between both groups (27.93 ± 6.48 years in group I versus 27.19 ± 5.23 years in group II; P > 0.05) There was no significant difference in gestational age at enrollment (18.0 ± 2.41 weeks in group I versus 17.9 ± 2.88 weeks in group II; P > 0.05). Women enrolled in the study were categorized into 3 categories as shown in Table 1.

In the present study, the combined group showed shorter induction to abortion interval at all gestational ages compared to the misoprostol only group. However, this duration increased with increasing gestational age. The mean cumulative evacuation time was 15.6 ± 4.9 hours in the combined group versus 21.9 ± 5.4 hours in the misoprostol-only group (P < 0.01). The evacuation times for different gestational ages is shown in Table 2. In the combined group, 94% of cases (28/30) showed complete evacuation in less than 24 hours from the start of induction compared to only 55% (11/20) in the misoprostol group. At a gestational age of 21–23 weeks, 80% of women had aborted before 24 hours in the combined group but none in the misoprostol group. At a gestational age between 18 and 21 weeks, expulsion of fetus occurred in 100% and 57.1% in the combined and misoprostol groups, respectively. Rates of fetal expulsion were 100% in both groups at a gestational age between 13 and 17 weeks (Table 2).

Table 1. The three categories of patients in the misoprostol group and the combined group according to gestational age.

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Misoprostol group (n=20)</th>
<th>Combined group (n=30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–17 weeks</td>
<td>7 (35%)</td>
<td>11 (36.7%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>18–20 weeks</td>
<td>7 (35%)</td>
<td>9 (30%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>21–23 weeks</td>
<td>6 (30%)</td>
<td>10 (33.3%)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 2. The primary outcome parameter in the misoprostol group and the combined group according to gestational age.

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Misoprostol group</th>
<th>Combined group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–17 weeks</td>
<td>14.6 ± 2.67</td>
<td>10.8 ± 3.91</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>18–20 weeks</td>
<td>22.3 ± 3.76</td>
<td>16.7 ± 3.21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>21–23 weeks</td>
<td>26.15 ± 4.30</td>
<td>19.6 ± 4.11</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 3 shows that the secondary outcome parameters are not statistically different between both groups. Table 4 reports the side effects in both groups.

Discussion
This study showed that the combination of weighted Foley’s catheter and misoprostol resulted in a significantly shorter induction to abortion interval compared to misoprostol alone. Because we used
Table 3. The secondary outcome parameters in the misoprostol group and the combined group according to gestational age.

<table>
<thead>
<tr>
<th>Gestational age</th>
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<th>Combined group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–17 weeks</td>
<td>(n=7)</td>
<td>(n=11)</td>
<td></td>
</tr>
<tr>
<td>Manual separation of placenta</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Surgical evacuation</td>
<td>3/7</td>
<td>2/11</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Blood loss (&lt;200 ml)</td>
<td>6/7</td>
<td>10/11</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Blood loss (&gt;200 ml)</td>
<td>1/7</td>
<td>1/11</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>18–20 weeks</td>
<td>(n=7)</td>
<td>(n=9)</td>
<td></td>
</tr>
<tr>
<td>Manual separation of placenta</td>
<td>2/7</td>
<td>1/9</td>
<td>&gt;0.05</td>
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<td>Surgical evacuation</td>
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<td>(n=6)</td>
<td>(n=10)</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>Blood loss (&lt;200 ml)</td>
<td>4/6</td>
<td>7/10</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Blood loss (&gt;200 ml)</td>
<td>2/6</td>
<td>3/10</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 4. Side effects in the misoprostol group and the combined group.

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Misoprostol group</th>
<th>Combined group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–17 weeks</td>
<td>(n=7)</td>
<td>(n=11)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2/7</td>
<td>4/11</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2/7</td>
<td>2/9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1/7</td>
<td>4/11</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>18–20 weeks</td>
<td>(n=7)</td>
<td>(n=9)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
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<td>Abdominal pain</td>
<td>3/6</td>
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</tr>
</tbody>
</table>

The induction to delivery interval increased with increasing gestational age in both groups. We also had rates of fetal expulsion of 100% in both groups at a gestational age between 13 and 17 weeks, which decreased with advancement of gestational age. This is in agreement with other investigators’ findings. Gómez et al. in 2009 found that the mean induction-to-abortion interval increases by 4 hours after 20 weeks gestation. Ashok et al. (2003) in another study on mid-trimester medical termination of pregnancy concluded that the induction-to-abortion interval was significantly longer in the higher gestational age pregnancies. Similar findings were reported by Dilbaz et al. in pregnancies between 13 and 20 weeks. We used a misoprostol dose of 400 µg administered every 4 hours. Doses of 600 and 800 µg have shown comparable successful abortion rates, but were associated with high rates of side effects. Wong and colleagues compared the efficacy and side effects of 400 µg misoprostol administered every 3 and every 6 hours. They concluded that the three-hour regime was more effective in terms of a significantly shorter drug administration-to-abortion interval at the expense of more side effects. We had no significant difference in the incidence of side effects between both groups. Side effects are less common with the vaginal route compared to other routes of administration.

In the present study, there was no significant difference in the need for post-abortive manual separation of the placenta. Surgical evacuation should only be considered if there is clinical evidence that the abortion is incomplete. In the current study, an incidence of 20% was reported in the misoprostol group while only 10% required surgical evacuation in the combined group. Ashok et al. 2003 studied mid-trimester medical termination of pregnancy using misoprostol and concluded that surgical evacuation of the uterus under general anesthesia was required to complete the abortion in 8.1% of women. In 2005, a report from the Scottish group estimated the rate of surgical evacuation as low as 2.5%. The high incidence of surgical evacuation in this study may reflect the inadequate experience of dealing with second-trimester abortions. Cases of induced abortion in our society are rare because they are considered illegal unless performed to save a maternal life. Our findings showed that the majority of cases who required surgical evacuation in both groups were between 13 and 17 weeks. This is in agreement with the results of other investigators. It is probably wise to inform women undergoing pregnancy termination early in the second trimester of a possible higher chance of incomplete abortion. There was no statistically significant difference in the amount of blood loss between both groups.

To conclude, the use of a weighted trans-cervical Foley’s catheter filled with 30 ml saline improved the effectiveness of 400 µg
vaginal misoprostol in terminating mid-trimester pregnancies, as reflected by a shorter induction-to-delivery interval with no significant increase in the incidence of side effects.

Author contributions
AS, conceived the study and designed it, HS Enrolled participants and collected the scientific material, MK shared the design of the study and wrote the manuscript, ES collected scientific material and performed the statistical analysis and DM enrolled participants.

Competing interests
No competing interests were disclosed.

Grant information
The author(s) declared that no grants were involved in supporting this work.

Supplementary Information – protocol of the study

Introduction
Second trimester or mid-trimester is a period ranging from 14th to 28th weeks of gestation. It is subdivided into an early period between 14th and 20th weeks and a late period between 20th and 28th weeks. There is gradual increase in second trimester terminations of pregnancies because of the availability of prenatal screening programs allowing the diagnosis of congenitally malformed fetuses.

Cervical ripening before surgical termination is an effective method for reducing the complications associated with suction curettage. It is a routine before second-trimester dilation and evacuation. Misoprostol, a prostaglandin E1 analogue, is commonly used for this purpose. It is also useful for elective medical abortion and evacuation of the uterus in cases of embryonic or fetal death. The vaginal route of administration is favored compared to other methods in clinical routine owing to its high clinical efficacy and lack of gastrointestinal side effects.

Several studies have described that the Foley’s catheter as an effective method in ripening the cervix. Obed and Adewole showed that it increased the Bishop’s score in women with unripe cervices in a way comparable to that of prostaglandins.

Objective of the study
This study was designed to investigate whether the insertion of a weighted fluid filled trans-cervical Foley’s catheter would improve the effectiveness of 400 µg vaginal misoprostol in terminating mid trimester pregnancies.

Patients and methods
This comparative study will be carried out at the department of Obstetrics and Gynecology Department, Menofiya University Hospitals. Participants will be women with an indication for second trimester termination. Eligible women will be those with BMI ranging between 20–30 with singleton pregnancies at a gestational age between 14–23 weeks. Pregnancies sonographically diagnosed with a fetal anomaly incompatible with life or a fetal demise within one week will be enrolled.

The procedure will be explained to all women and an informed consent will be obtained from all participants. All women enrolled will have the following routine work up:

1. Complete history taking.
2. Thorough clinical examination with special emphasis on:-
   - Pulse, blood pressure and temperature.
   - Nausea (mild, moderate and severe).
   - Vomiting (mild, moderate and severe).
   - Abdominal pain (mild: less or equal to menstrual cramps, moderate: slightly stronger than menstrual cramps & severe: double strength of menstrual cramps). Women with mild pain will receive no analgesia while those with moderate pain will receive diclofenac sodium & women with severe pain will receive pethidine.
   - Cervical dilatation and consistency by vaginal digital examination (Firm or Soft).
   - Presence or absence of vaginal bleeding.
   - Watery vaginal discharge.
3. Laboratory investigations:
   - Complete blood picture.
   - Prothrombin time, bleeding time, clotting time and INR.
   - Liver enzymes.
   - Kidney function.
   - Random blood sugar.
4. Pelvic ultrasound to detect:
   Number of gestations, viability and gestational age.

Women with any of the following will be excluded from the study:
1. Previous uterine surgery.
2. Contra-indication to misoprostol, E.g. bronchial asthma and coronary heart disease.
3. Law lying placenta.
4. Operation on the cervix.
5. Chorioaminitis (diagnosed by leucocytic count >12000, positive CRP & fever >38).

Fifty women will be recruited and will be divided into 2 equal groups. In group A, termination will be induced by inserting 400 micrograms vaginal misoprostol (2 misotac tablets-sigma pharma- ceuticals) every four hours while in group B. termination will be induced by inserting a 16 F Foley’s catheter trans-cervically then inflating its balloon by (30 ml–50 ml) saline. A bag filled with saline will be applied to the distal end of the catheter to provide moderate traction. Different volumes will be used at different gestational ages; 250 ml. at 13–17 weeks, 300 ml. with ages at 18–20 weeks and 500 ml at gestational ages more than 20 weeks. The filled bag is approximately equivalent to 250, 300 and 500 grams in weight respectively. The same dose of misoprostol as in group A (400 ug/4 hours) will be used as well.

The outcome parameters that will be measured in this study are:-

1. Induction to expulsion interval.
2. Maternal side effects (nausea, vomiting, abdominal pain, rupture of membranes, sepsis, manual separation of the placenta, surgical evacuation and hemorrhage). The amount of vaginal bleeding will be assessed by counting the number and change in the weight of the pads changed by the patient from the start of induction till complete expulsion has occurred. Hemor- rhage will be considered as average if less than 200 cc and excessive if more than 200 cc.

Participants will be assessed every 4 hours for vital signs, cervical dilatation, expulsion of fetus and occurrence of complications.

The steps of the procedure in the Foley’s catheter group:
1. Speculum insertion and exposure to the cervix.
2. Steralization with povidine iodine.
3. Holding the anterior lip of the cervix with ring forceps.
4. Foley’s catheter will be inserted till it passed the internal os (about 5 cm of the catheter was passed through the cervical canal).
5. Inflation of the balloon by 30 ml saline for women at 14–18 weeks and by 50 ml for 19–23 weeks.
6. The ring forceps and the speculum will be removed.
7. 400 ug misoprostol wetted with saline will be inserted in the posterior vaginal fornix.

All patients will receive 20 mIU intravenous oxytocin after expulsion of the fetus. If the placenta does not separate in 30 minutes, the patient will be anaeasthetized and undergo manual separation of the placenta or surgical evacuation.

All women will be observed for the occurrence of side effects during the procedure and for the first 12 hours after termination.

Results will then be tabulated and statistically analyzed. Results will then be compared to those of other investigators.

References


Open Peer Review

This is an interesting study examining the additional benefit of transcervical Foley in second trimester termination of pregnancy with misoprostol. Overall, this study is valuable, but I have a few reservations regarding their methodology.

1. The authors should explain why this was not randomized. It seems like a relatively simple thing to do and it would improve the methods significantly.

2. The authors list more baseline characteristics. Especially considering this was not blinded, how are we to be sure that the groups were equal at baseline?

3. The authors should report the actual p-value, not just whether it was less than or greater than 0.05.

4. How did the authors determine their sample size of 50? There was no power analysis done. A skeptical reader might conclude that the study was stopped only because statistical significance was reached.

5. With so few patients, was the primary outcome normally distributed? If not, the t-test would not be the appropriate statistical test.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.
It is an interesting study adding to the emerging recent evidence on the efficacy of balloon catheters for cervical ripening and induction of labour. However, the above issues need to be addressed in order for the conclusions to be valid:

1. Allocation is by patient choice. Without true randomization the potential for bias exists.
2. How were the sample numbers calculated (power)?
3. Introduction of mechanical devices such as a balloon catheter through cervix into uterine cavity may lead to increased incidence of infection. Although this was an outcome measure in the study protocol, there was no mention of infection rates (whether they were the same or were higher) in the results section – this would have been important if the results are to be useful for general populations in future. Ampicillin was used prophylactically in the combined group – were the authors worried about sepsis too?
4. The age and gestational ages in comparison groups look remarkably similar!
5. Why were only primigravid women chosen?
6. The authors should avoid multiple statistical testing which makes the conclusions invalid.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

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Nathalie Kapp
Department of Reproductive Health and Research, World Health Organization, Geneva 27, CH, Switzerland

The statistical analysis used by the authors is inappropriate as they did multiple testing, and the primary outcome needs a time-to-event analysis (like a survival analysis).

As women chose their treatment group, the conclusions cannot be stated as one may about results from an RCT, given the potential for bias.

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Competing Interests: No competing interests were disclosed.