Medically induced abortion in second trimester with intravaginal misoprostol

Carmen A. Bulucea, Nikos E. Mastorakis, Mariana F. Paun, and Alina Neatu

Abstract—Prostaglandins are more and more used for second trimester pregnancy termination. Their preferential application is vaginal and because the intracervical variant is laborious and invasive, the posterior vaginal fornix became increasingly used and investigated. Misoprostol is an E₃ prostaglandin synthetic analog with an innocuity equivalent to that of E₂ prostaglandin, but doubled by an increased efficiency and a lower cost. This study is intended to extend the existent experience regarding the intravaginal misoprostol for second trimester therapeutic abortion induction. This prospective clinic study selected 20 pregnant women, with a gestational age of 15 to 27 weeks who have been checked in the Clinic of Obstetrics-Gynecology of the University of Medicine and Pharmacy of Craiova, for therapeutic abortion induction. The 20 pregnant women received in PVF a 200µg misoprostol tablet each 12 hours, respecting strictly the protocol developed by the authors. Our results demonstrate clearly that in the conditions of therapeutic correction/counteraction of the complications associated to pregnancies that must be terminated in the second trimester, the rate of abortion in the first 24 hours from the intravaginal misoprostol application (following the protocol developed by the authors) can become 100%, while the average duration of the abortion induced in the same manner drops to under 12 hours. Our observations indicate a rate of complete abortion of 60%, which reduced significantly the rate of postabortum complications, such as dilation and expulsion as well as oxytocin perfusion (methods that are preferred in modern obstetrics to intraverteine instillations [7]), prostaglandins (PGs) are nowadays more and more used, both for second trimester pregnancy termination [8, 9, 10, 11, 12, 13, 7] as well as for cervix maturation [14, 15, 16, 17, 18, 19] and labor induction [20, 21, 22, 23, 4].

The interest for PGs is not random because in case of humans the normal parturition and the preterm labor can be the consequence of various processes, with actual evidence more and more conclusive to support the central role of amniodecidual PGs increased synthesis among these diverse mechanisms [24], of which the infection, the chorionic prostaglandin dehydrogenase deficit (whose gene is stimulated by the progesterone), corticotropin-releasing the stress induced placental hormone as well as the β-endorphins or nitric oxide are increasingly investigated [25, 26, 27].

The prostaglandins are hormone-like substances, rapidly inactivated in the general circulation, being synthesized and locally released from fat acids precursors and exercising its intracellular effects by means of cAMP (cyclic adenosine monophosphate), thus involved in various events, such as release of calcium ions in the myometrial cells with uterotonic effect, as well as structural alterations of the conjunctive tissue responsible for cervix maturation [28, 29].

The limited success in abortion and the high frequency of systemic side effects, mainly digestive, in case of PG administration in a general (intravenous, intramuscular or oral) or intrauterine (extra/intra amniotic) manner led to a preferential vaginal administration and, because the intracervical variant is laborious and invasive, the posterior vaginal fornix (PVF) became increasingly used and investigated [30].

Recent publications indicate the innocuity equivalent to that of PGE₂ (5 times more active than PGF₂α), doubled by an increased efficiency and the cost that is 200 times smaller in case of the intravaginal misoprostol (synthetic product analogue to PGE₁), in various dosage for cervix maturation, induction of second trimester abortion and third trimester labor [8, 13, 20, 21, 22]. Nonetheless, due to the small dimensions of the groups studied by these publications as well as different regimes of misoprostol administration, the ideal protocol for vaginal administration of this PGE1 analogue to terminate a second trimester pregnancy still lacks [7, 23, 31, 32, 33, 5, 34].

This study is intended to extend (but starting from an
original idea, resulted by combining the literature and the personal observations preliminary to this report) the existent experience regarding the intravaginal misoprostol for second trimester therapeutic abortion induction.

II. MATERIAL AND METHODS

This prospective clinic study selected 20 pregnant women, with a gestational age (confirmed in all cases by means of an ultrasound based on the biparietal fetal diameter) of 15 to 27 weeks (table I) who have been checked in the Clinic of Obstetrics-Gynecology of the University of Medicine and Pharmacy of Craiova, for inducting therapeutic abortion, in accordance with the current legislation.

The criteria for inclusion in this study were:

1. Indication of therapeutic abortion in second trimester, materialized in the analyzed interval by 7 pregnancies with dead fetuses and 13 pregnancies with alive fetuses but complicated: a) 7 cases by spontaneous broken membranes before 28 weeks of gestation (without clinical signs of chorioamnionitis but prophylactically treated with broad spectrum antibiotics); b) 1 case of plurimalformed fetus (anecephaly + spina bifida + omphalocele, situation during which the absolute hypoestrogenism with hyperactive uterus at the first dose of PGE<sub>1</sub> analogue imposed the increase of the vaginal misoprostol by oral administration of 0.6 mg of ethinylestradiol); c) 1 case of Rh isoinmunization (antibodies in 1/64 dynamic); d) 4 cases of psychosis (depressive of schizoid) under chronic treatment with Phenobarbital +- diazepam +- antidepressants.

It is worth noticing that from the group of 7 cases in the latency period (forerunning the spontaneous trigger of painful uterine contractions, according to Artal [35]) of the extremely preterm (between 20 and 27 gestational weeks [36]) spontaneous rupture of fetal membranes, in case of one pregnant woman there was identified by means of an ultrasound the coexistence of a very voluminous, low lying, nonhemosrrhagic placenta whose hyperprogesteronemy inherent to the excessive placental volume and implicitly the excess of chorionic prostaglandin dehydrogenase [24] suggested also by the uterine hypoactivity after the first intravaginal PGE1 doses, imposed the increase of the vaginal misoprostol dose (by increasing the administration frequency to 4 hours and the number of tablets, applied 2 by 2 in PVF) for abortion induction.

2. Pregnancy with one fetus, closed, long cervix due to the lack of painful uterine contractions.

3. The absence of contraindications to administer PGs (glaucoma, asthma, specific hypersensitivity, cardiovascular, renal, hepatic dysfunctions, the last 3 being valid especially in case of general administration of prostaglandin).

4. The lack of contraindications to a vaginal resolution of the abortion.

5. The absence of the typical integral schema of predisposition to uterine rupture [38], including: scarred uterus + multiparity + old age of the mother + pregnancy over 21 weeks + duration of the abortion over 24 hours + continuous oxytocin perfusion of over 12 hours (the absence of the last 3 conditions allowed the inclusion in our study of a scarred uterus with dead fetus in case of an older multiparous woman).

6. The lack of a clinically manifested infection (that allowed recruitment of 2 pregnant women, in whose case only the positive smear for the association Candida and Trichomonas signed the subclinical mixed vaginitis with inherent cervicitis diagnose).

7. The written consent for abortion induction, given both by a department head as well as by the patient.

8. Following strictly the therapeutic protocol developed by the authors [31, 32, 33, 5, 34], described in the following paragraphs.

The 20 pregnant women selected in this manner, comprising a group with alive fetuses and one with dead fetuses, after vagina disinfection (with H<sub>2</sub>O<sub>2</sub>, followed by physiological serum and removal of excess liquid) received in PVF a 200µg misoprostol tablet (Cytotec 200, Searle, Brussels) each 12 hours, in hospitalization conditions and bed rest during the whole period of late abortion induction.

The vital signs have been checked every 4 hours, while any adverse reaction would be registered and treated, like fever (more than 38°C), vomiting, diarrhea, pelvic pain that may or may not require analgesics.

The failure of the therapy has been defined as the lack of conception product expulsion in the first 48 hours from the initial dose of PG or serious signs and systemic symptoms that would justify stopping the Cytotec administration in PVF.

During the expulsion of the conception product there was systematically applied an intravenous perfusion with oxytocin 15IU/500ml glucose serum 5%, doubled by 2 vials of intramuscular Ergomet to prevent uterine atony.

In the first 6 hours from the expulsion of the conception product, as a routine, there was investigated the possibility of an incomplete abortion, both by means of a bimanual pelvic examination as well as by means of an ultrasound, such that a uterine instrumental control (sharp curettage) under paracervical anesthesia (10ml of lidocainum 1%) be practiced only in case of incomplete abortion or scarred uterus, thus reducing the risk of uterine synchiae [39].

A value p<0.05 represented a statistical significance when comparing results by Mann Whitney and square Chi tests, as it was the case of mean values or correlations [40].

III. RESULTS AND DISCUSSIONS

The demographic characteristics (table I) of the 2 groups of pregnant women (7 with dead fetuses and 13 with alive fetuses) studied here are comparable, even if the statistical difference is significant (p<0.05) in case of nulliparous women
number, because there exist analyses that ascertain the fact that there is no association between the rate of success or mean duration of late abortion induced with vaginal misoprostol and demographics [13, 7].

The dominance of fetal indications to terminate second trimester pregnancy, striking in this study (tables I and II), is also encountered in vast statistics [10] but with different structure, that is in the vast analyses in literature the Rh isoimmunisation appears in 0% of cases, the premature membranes rupture in only 30% of cases and the neural tube defects in only 11% of cases, as opposed to the corresponding results obtained by this study, respectively 7.6%, 53.8% and 7.6% of the late abortion induction indications.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>DEMOGRAPHICS OF THE GROUPS TREATED WITH INTRAVAGINAL MISOPROSTOL FOR LATE ABORTION INDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies with alive fetuses (number=13)</td>
<td>Pregnancies with dead fetuses (number=7)</td>
</tr>
<tr>
<td>Average maternal age [years]</td>
<td>20.9 (17 – 28)</td>
</tr>
<tr>
<td>Nulliparous number (%)</td>
<td>11 (84.6%)</td>
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</tbody>
</table>

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<thead>
<tr>
<th>TABLE II</th>
<th>INDICATIONS OF ABORTION INDUCTION IN PREGNANCIES WITH ALIVE FETUSES, IN SECOND TRIMESTER OF PREGNANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous rupture of fetal membranes in second gestational trimester*</td>
<td>7 (53.84%)</td>
</tr>
<tr>
<td>Anencephaly + spina bifida + omphalocele</td>
<td>1 (7.69%)</td>
</tr>
<tr>
<td>Rh isoimmunisation 1/64</td>
<td>1 (7.69%)</td>
</tr>
<tr>
<td>Psychoses (depressive or schizoid) under chronic treatment with neuroleptics (Phenobarbital) + benzodiazepines + antidepressants</td>
<td>4 (30.76%)</td>
</tr>
</tbody>
</table>

From the group of 7 cases in the latency period of the extremely preterm (between 20 and 27 gestational weeks) spontaneous rupture of fetal membranes, in case of one pregnant woman there was identified by means of an ultrasound the coexistence of a very large (“tumoral”), low lying, nonhemorrhagic placenta. After the induced abortion with prostaglandins (at 20-21 gestational weeks), in this case, the placenta represented approximately half the weight of the fetus and because the VDRL and the tolerance to glucose tests have been negative, and the severe erythroblastosis with fetal hydrops or fetal congestive cardiac insufficiency were infirmed, in the absence of the histopathologic, cytogenetic and placental enzymatic autopsy results, the large placenta has been attributed to a twin/multiple pregnancy in which the other fetus or fetuses stopped evolving and was/were resorbed.

Table III compares the intravaginal misoprostol late abortion induction between the pregnancies with dead and alive fetuses, both concerning the success rate at 24 and 48 hours from the start of the therapy as well as the average abortion duration, the average number of tablets necessary to pregnancy termination and the unwanted reactions to the therapy, as follows:

a) Statistically significant difference between the 2 compared groups concerning the abortion rate at 24 hours from the start of the PVF misoprostol therapy, being 85.7% for the pregnancies with dead fetuses compared to 61.5% for those with alive fetuses, but this difference is null at 48 hours from the start of the treatment, when late abortion was done in 100% of cases, in both investigated groups.

b) The significant increase (p<0.05) in the average duration of the abortion in the pregnancies with alive fetuses with respect to those with dead fetuses (21 hours compared to 11 hours) becomes indistinguishable (11 hours for both groups) after excluding the cases with cervicitis (that slow down the prostaglandin maturation of the cervix), absolute hypoestrogenism (corrected very late), hyperprogesteronemia by large placenta and implicitly excess of chorionic prostaglandin dehydrogenase, as well as chronically treated psychoses with Phenobarbital +/- diazepam, being well known the role of hepatic enzymatic inductor and placent (with the increase of the chorionic prostaglandin dehydrogenase level and implicitly the PGs rate of degradation) of the chronic administration of Phenobarbital, while, nowadays, one can only speculate on the possible influence of the chronic psychotrophs therapy on the trophoblastic peptides related to proopiomelanocortin as well as on the system composed of nitric oxide and cyclic guanosine monophosphate controlling the activity of the human pregnant uterus, suppositions that can be verified by later experiments following the Facchinetti and Buhimschi models [26, 27].

c) The significant increase (p<0.05) of the average number of Cytotec tablets necessary for terminating pregnancies with alive fetuses with respect to those with dead fetuses (2.6 tablets compared to 1.2) also becomes imperceptible after excluding the same pathology associated to the pregnancy mentioned in the above paragraph, corresponding in practice to the precedence or association from the beginning of the prostaglandin therapy of the medical correction of cervicitis (vaginitis) and respectively of the absolute hypoestrogenism with synthetic estrogens, while of the prostaglandin dehydrogenase excess by administration of larger doses of intravaginal misoprostol.

d) The rate of the complete abortion, defined as
simultaneous and integral expulsion of both fetus and placenta, while the membranes remain intact, did not differ significantly between the two compared groups, being 53.8% for alive fetuses and 71.4% for dead fetuses.

e) The only side effect of the vaginally administered misoprostol following our protocol was a bearable pelvic pain, affecting approximately 15% of the pregnant women from each group.

The estimated uterine hemorrhage was below 500ml in all cases of therapeutic abortion, induced with misoprostol in PVF, during the course of the present investigation (more abundant after the sudden termination of estrogenization).

The late complications of intravaginal misoprostol, as those described by Goldenberg and team or Hunfeld [41, 42] are still in evaluation.

### TABLE III

**Characteristics of late abortion induced with misoprostol in the posterior vaginal fornix (PVF)**

<table>
<thead>
<tr>
<th>Description (limits)</th>
<th>Average number of Cytotec tablets (n=13)</th>
<th>Significance</th>
<th>Pregnan cies with alive fetuses</th>
<th>Pregnan cies with dead fetuses</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average number of misoprostol tablets necessary to induce</td>
<td>1.66 (1-2)</td>
<td>p**&gt;0.05</td>
<td>1.16 (1-2)</td>
<td>1.41 (1-2)</td>
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</tr>
<tr>
<td>Rate of abortion in the first 24 hours from the misoprostol therapy initiation</td>
<td>8/13 (61.5%)</td>
<td>p**&lt;0.05</td>
<td>2/13 (15.38%)</td>
<td>7/13 (53.8%)</td>
<td>14/20 (70%)</td>
</tr>
<tr>
<td>Rate of abortion in the first 48 hours from the misoprostol therapy initiation</td>
<td>13/13 (100%)</td>
<td></td>
<td>7/7 (100%)</td>
<td>20/20 (100%)</td>
<td></td>
</tr>
<tr>
<td>Complete rate of abortion (simultaneous and complete expulsion of fetus and placenta while fetal membranes remain intact)</td>
<td>7/13 (53.8%)</td>
<td>p**&gt;0.05</td>
<td>5/7 (71.42%)</td>
<td>12/20 (60%)</td>
<td></td>
</tr>
<tr>
<td>Average duration of abortion, hours (limits)</td>
<td>21.46 (7-48)</td>
<td>p**&lt;0.05</td>
<td>11.71 (5-25)</td>
<td>16.58 (5-48)</td>
<td></td>
</tr>
<tr>
<td>Corrected average duration of abortion (after excluding cases of absolute hypoestrogenism, large placenta, cervicitis, chronically treated psychosis), hours (limits)</td>
<td>11.33 (7-16)</td>
<td>p**&gt;0.05</td>
<td>11.4 (5-19)</td>
<td>11.36 (5-19)</td>
<td></td>
</tr>
<tr>
<td>Side effects of misoprostol (bearable pelvic pain)</td>
<td>2/13 (15.38%)</td>
<td>p**&gt;0.05</td>
<td>1/7 (14.28%)</td>
<td>3/20 (14.8%)</td>
<td></td>
</tr>
</tbody>
</table>

* Chi square test; ** Student’s t test

Our results demonstrate clearly that in the conditions of therapeutic correction/counteraction (equivalent of the corrected parameters in table III) of the complications associated to pregnancies that must be terminated in the second trimester, the rate of abortion in the first 24 hours from the intravaginal misoprostol application (following the protocol developed by the authors) can become 100%, while the average duration of the abortion induced in the same manner drops to under 12 hours (with reduction in dosage, cost and risk of adverse effects to PG), indicating on one hand the insignificant influence of the alive fetus presence on the abortive efficiency of the PGE$_2$ analog, and on the other hand the possibility of increasing the success of this therapy with respect to some results published on this subject [8, 13, 7] that already suggested the practical superiority of misoprostol applied in PVF with respect to all other prostaglandin variants, even associated to RU486 [9, 11, 12, 43].

The limitation of this study, with respect to the small number of evaluated cases is cancelled by the similarity of our non corrected results to other publications on misoprostol [8, 13, 7] applied in PVF to induce late abortion (nonetheless after protocols differing in administration rhythm and/or associations).

Unlike the data supplied by [7], our observations indicate a high rate of complete abortion of 60% (the average of the 2 analyzed groups), due to the supplementation of oxytocin in expulsion with ergometrine, compared to the prior protocol [12], and the increased number of “complete eggs” (with decreased risk of amniotic cavity contamination) expelled in this manner reduced significantly the rate of postabortum curettage, in the same time opening new perspectives, on fetal transplant [44] and noninvasive investigation of the amniotic fluid.

The innocuity of the method enhanced by us for therapeutic pregnancy termination in the second trimester, even on the scarred uterus of a large multiparous woman having a certain age, supports previous observations [45, 46, 28, 24, 29, 47] on the key role of PGs in the physiolog of the labor.

### IV. Conclusions

The misoprostol applied in the posterior vaginal fornix in the original manner elaborated by us is a physiological,
practical (cheap, simple, fast, noninvasive, without notable adverse effects and opening new opportunities in research, including preterm labor) and effective method if it adapts to the particularities of the case as dose and timely associated therapy.

REFERENCES


