Therapeutic abortion in the second trimester of pregnancy

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***Abstract*—**Late therapeutic abortion represents termination of pregnancy in the second trimester, before the moment of reaching fetal viability, with the purpose of protecting the mother's health. The techniques for terminating a pregnancy in the second trimester can be classified as surgical ones (cervical dilation followed by uterine evacuation and laparotomy with hysterotomy or hysterectomy) and medical ones (intravenous oxytocin solution, intraamniotic hyperosmotic solution, prostaglandins and intraamniotic, extra-ovular, parenteral, oral and vaginal analogues of prostaglandins, just as sensitizers of the myometrium before applying prostaglandins and various combinations of the above mentioned). Prostaglandins are preferentially used nowadays to terminate second trimester pregnancy because of the drawbacks presented by the other surgical and medical methods (used in this purpose), such as limited efficiency and/or their severe complications. 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 curettage, in the same time opening new perspectives to fetal transplantation and noninvasive investigation of the amniotic fluid.

***Keywords*—**induced abortion, intravaginal misoprostol, second trimester abortion.

I. Introduction

LATE therapeutic abortion represents termination of pregnancy in the second trimester, before the moment of reaching fetal viability, with the purpose of protecting the mother's health [1, 2].

Therapeutic abortion is indicated in the following situations:

- when continuing the pregnancy could jeopardize the woman's life or affect her health [3, 2, 4];
- when the fetus presents severe physical anomalies or risk of mental retard (eugenic abortion) [3, 2] or according to M. Delcroix and C. Gomez when there is a high probability at birth the child to have an affection of a particular gravity incurable at the moment of diagnosis [4];
- when the pregnancy is the result of a rape or incest (ethical abortion) [3, 2].

Recent advances in prenatal screening technology increased the need for safe methods for terminating second trimester pregnancy, when the principle of necessity of ensuring the uterine cavity vacuity (to avoid hemorrhagic and infectious consequences) is unanimously accepted [1]. The optimal universal protocol in terms of security, efficiency, simplicity and reduced cost to solve late abortion is not yet established [5, 6, 7, 8, 9].

In general, all methods of inducing abortive labor in the second trimester of pregnancy have the following common consequences: failure in producing abortion, incomplete abortion, placenta retention, hemorrhage, infection and embolic phenomena [2].

The techniques used for interrupting a second trimester pregnancy are schematized in table I (adaptation for middle trimester after Williams Obstetrics [1]), being classified as surgical and/or medical methods for therapeutic induction of late abortion.

More and more authors indicate nowadays, before inducing late abortion (as in case of the early one as well), the therapy of the bacterial vaginosis, being demonstrated that administration of metronidazol with this purpose reduces the rate of abortive post-intervention infection [10].

On the other hand, in case of D-negative women it is recommended after second trimester abortion prophylaxis with anti-D immunoglobulin, because approximately 5% of Rh negative pregnant women get immunized after abortion [1].

I. The surgical techniques for therapeutic interruption of late pregnancy are: A. cervical dilation and uterine evacuation (D&E) and B. laparotomy with hysterotomy or hysterectomy [11, 12, 13].

A. Dilation and evacuation (D&E), indicated for therapeutic abortion after 14-16 gestational weeks, usually consists of a

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large cervical dilation, followed by a mechanical destruction and evacuation of fetal parts, and after completely removing the fetus, the placenta and the rest of the conception product are extracted by curettage, preferably by suction aspiration, with a large brim probe, and in the end, possibly, controlling the uterine vacuity and integrity with a sharp curette [1].

In the absence of systemic maternal illnesses, termination of pregnancy in the second trimester by D&E does not necessitate further hospitalization [1].

To minimize the trauma of the mechanic dilation of the long and closed uterine cervix there can be used natural hygroscopic dilators (Laminaria japonica) or synthetic ones (for instance polymer hydrogel) believed to absorb water from the complexes of proteoglycans, that dissociate, thus enabling the cervix to soften and dilate [12, 14].

TABLE I
TECHNIQUES FOR INDUCING LATE ABORTION [1]

I. Surgical techniques
A. Cervical dilation followed by uterine evacuation (D&E)
B. Laparotomy with:
1. Histerotomy
2. Hysterectomy
II. Medical techniques
A. Intravenous oxytocin solution
B. Intraamniotic hyperosmotic solution (sodium chloride20% or urea 30%)
C. E_2, $F_{2\alpha}$ prostaglandins and analogues of prostaglandins (in the chronological order of the appearance of the administration method):
1. Intraamniotic injection
2. Extra-ovular injection
3. Parenteral injection
4. Oral ingestion
5. Vaginal insertion
D. Antiprogesterone: RU486 (mifepristone) and epostane, just as sensitizers of the myometrium before applying prostaglandins
E. Various combinations of the above mentioned

Application of a hygroscopic dilator implies: clamping the cervix, previously sterilized, with a cervix forceps, and after carefully measuring the cervical canal with a hysterometer, in order not to break the membranes, the laminaria having adequate dimensions, such that its tip barely overpasses the cervical internal orifice, is inserted with a clamp. After approximately 4 hours, once the laminaria distends, the cervix is opened enough to allow an easier mechanical dilation with the Hegar probes, followed by the evacuation of the uterine cavity, while the possible cramps induced by the laminaria are dealt with by oral administration of codeine 60mg every 4 hours [12].

The alternative to laminaria for cervix maturation is constituted by applications of prostaglandin (or analogue like misoprostol) in the posterior vaginal fornix, adjacent to the cervix, approximately 3 hours before the dilation [14].

After the potential preparation of the cervix with laminaria, for instance, induction of abortion by D&E is preceded by the extraction of the laminaria with a forceps pulling from the wire attached to the hygroscopic dilator, followed by a grooming of the vulva, vagina and cervix. Next, Jacot and team [11] recommend reevaluating the dimension and position of the uterus, and after clamping the anterior cervical lip to the cervix, one performs paracervical anesthesia with lidocaine 1% with aspiration and exclusion of hypersensitivity. Subsequently, by hysterometry, following the same authors, it is identified the status of the internal orifice of the cervix and it is confirmed the dimension and position of the uterus. Then the progressive dilation of the cervix follows (possibly previously prepared) by means of Hegar dilators (using the technique protecting from perforation suggested by the Williams Obstetrics [1]) up to a sufficient dimension, allowing the integral extraction of the fetus, previously fragmented, with Sopher or Schultze forceps, in the conditions of a voluminous fetus and thinner uterine walls in the second trimester of pregnancy.

The rate of immediate (connected to anesthesia but also uterine perforation, cervical laceration, hemorrhage, incomplete evacuation of the conception product, infection, coagulopathy, even fatal [15, 12, 13]) and late complications (cervical incompetence, uterine synechia, infertility, psychic disturbances [16, 17, 18, 19]) can be kept to a minimum, compared to the incidence of post-dilation morbidity and aspiration curettage in the first trimester of pregnancy if: (1) the cervix is sufficiently non-traumatically dilated before attempting to remove the conception product, (2) the conception product is evacuated skillfully, without perforating the uterus and (3) if the entire conception product, but not the basal decidua are extracted [11].

Although the D&E represents the fastest method to terminate late pregnancy, it requires a lot of training (skill) and even if the complications rate is small when performed by a skilled and experimented doctor the morbidity associated to this technique can be very serious, characteristics that nonetheless keep it today in the arsenal of second trimester therapeutic abortion, but not as first choice [14].

B. The laparotomy with hysterotomy or hysterectomy as means of terminating middle trimester pregnancy is rarely preferred to D&E or medical induction, namely when: 1. there coexists a severe uterine suffering (hysterectomy) or 2. sterilization must be associated (hysterotomy and interruption of tubal continuity or hysterectomy, sometimes, are preferable to D&E, followed by tubal sterilization) or 3. in case of failure of medical induction of late abortion [1].

The techniques used for hysterotomy are similar to those from a caesarian section excepting the reduced dimension of the abdominal and uterine incisions, and if the reproductive potential is intended to be kept, the smallest incision that allows extraction of the fetus must be applied on the inferior

segment, and the wound is thoroughly repaired [20, 1].

The increased risk of uterine rupture during subsequent pregnancies (especially in labor) in case of women who have therapeutically aborted by means of hysterotomy often imposes birth by caesarian section to terminate future pregnancies.

Other frequent complications of abdominal hysterotomy and high hysterectomy are poor scars (in almost 50% of cases), hemorrhages necessitating transfusions, venous thromboembolic disease, mechanic intestinal occlusion, necessitating re-intervention, incomplete abortion, necessitating curettage [1].

II. Medical induction of late abortion is based mainly on the techniques using concentrated oxytocin solutions, intravenously administrated, but especially on prostaglandins (PGs) administration, preferably intravaginal, associated, when needed, to antiprogesterone substances (sensitizing the endometrium to the PGs action) or associated even to oxytocin stimulation (in case of slow effect of the arachidonic acid derivatives), while, due to excessive risk of severe complications, the intraamniotic hypertonic solutions are sporadically used [21, 22, 23, 20, 24, 25, 26, 6, 14, 27].

A. Oxytocin. The term oxytocin signifies rapid birth, and the oxytocin has been the first uterotonic involved in initiation of parturition, following Sir Henry Dale's discovery, in 1906, of uterotonic bioactivity in the posterior pituitary gland extracts. These extracts were used in clinical obstetrics, and in 1950 Pierce and Du Vigneaud determined the structure of oxytocin, the uterotonic agent of the posterior pituitary gland (for pioneering in solving this peptidic structure, Du Vigneaud received the Nobel prize [1]).

Oxytocin is a nonapeptide, synthesized in the magnocellular neurons of the supraoptic and paraventricular nuclei, from where, the oxytocin prohormone is transported by the neurophysin protein inside vesicles along the axons towards the neural lobe of the posterior pituitary, where it is stored, to be later released; the oxytocin prohormone is converted by enzymatic cleavage into oxytocin during transportation [1].

Alessandrescu and team [28], Challis and Mitchell [29], Raca and collaborators [6] as well as Keirse [7] show that the role of oxytocin in labor at term and premature is unquestionable and can be synthesized in the following manner: (a) the concentrations of the oxytocin receptors increase in an advanced pregnancy and the expression of the ribonucleic acid, oxytocin messenger, increases during spontaneous labor; (b) the oxytocin stimulates the myometrial contractility and production of prostaglandins by the decidua and for these roles it intervenes not only the oxytocin released in pulses (whose duration and frequency increase during spontaneous labor) but also the oxytocin produced by the decidua, that activates locally, para and autocrine.

To induce late abortion within 24 hours, with an average rate of success of 71%, Jaschevatzky and collaborators [21], in accordance with Williams Obstetrics [1], recommends large doses of oxytocin in small volumes of intravenous solution. Such a regime [1] would be: after dilution of 100UI of oxytocin in 1000 ml of lactate Ringer solution it is started an intravenous perfusion from this solution with 100mU oxytocin/ml concentration, with a rhythm of 0,5 ml/min (50mU/min). The perfusion rate is increased at intervals of 30-40 minutes up to a maximal rate of 2 ml/min (200mU/min). If no efficient uterine contractions were obtained at this rhythm of the perfusion, the solution's concentration is increased, as follows: first the excess at 500ml from the solution of 100mU/ml of oxytocin used up to that point is evacuated. In the 500ml of oxytocin solution with concentration of 100mU/ml, 50 UI oxytocin are added, resulting a solution of 200mU/ml, and the perfusion is resumed with a rhythm of 1ml/min (200mU/min) to be progressively increased every 30-40 minutes with 0,5 ml of solution up to a rhythm of 2ml/min (400mU/min) and this rhythm is kept another 4-5 hours or until the fetus is expelled. After each increase in the perfusion's rhythm one must watch very carefully the frequency and intensity of uterine contractions, given the high concentration of the solution.

In case of failure of inducing late abortion in the first 24 hours following the start of intravenous oxytocin administration in concentrated solution, using the described protocol, this induction can be repeated daily, for 2 to 3 days, ensuring an almost maximal success rate.

The success chance of intravenous concentrated oxytocin perfusion to induce late abortion increases if the cervix is previously prepared with hygroscopic dilators or intravaginal prostaglandins [30, 31, 32].

Comparing the efficiency and safety of concentrated oxytocin perfusion (administered after a protocol similar to the one described) to induce late abortion for dead fetus retention, with that of extraamniotic perfusion of $PGF_{2\alpha}$ used in the same purpose, the Jaschevatzky group [21] remarks that: (a) the success rate in inducing late abortion with concentrated oxytocin was just 70% compared to 100% in case of prostaglandin, that, nonetheless associated oxytocin stimulation in 25% of cases; (b) the average induction-abortion interval has been nonetheless significantly shorter for the group treated with concentrated oxytocin (approximately 6 hours) with respect to the group treated to $PGF_{2\alpha}$ perfusion (circa 12 hours) and (c) the complications associated to these therapies were: uterine atony with hemorrhage or consumption coagulopathy (reactive to immediate therapy) in 3% of cases pertaining to the group treated with oxytocin and nausea, hot flashes, arterial hypotension in 28% of cases with extraamniotic $PGF_{2\alpha}$ perfusion, while for 7% of patients belonging to the same group there was observed uterine hypertonia, treated by temporarily suspending the perfusion.

Among the complications reported in literature and synthesized by Williams Obstetrics [1] associated to oxytocin perfusion, used for therapeutic induction of second trimester abortion, in case of not respecting strictly the protocol and contraindications one remarks: (a) water intoxication, possible when the oxytocin is transported by appreciable volumes of

non-electrolytic solution; (b) uterine rupture, rare, but described in case of grand multipara in the first half of the pregnancy interrupted with concentrated oxytocin; (c) cervical or isthmic rupture in case of concentrated oxytocin perfusion, applied after intraamniotic $F_{2\alpha}$ prostaglandin administration; (d) severe hypotension results in case of intravenous administration in bolus of non diluted oxytocin.

B. Hyperosmotic solutions for intraamniotic administration in order to perform late abortion either contain sodium chloride 20-25% or urea 30-40% and represent techniques rarely used nowadays, being reported only 2% late abortions dealt with by intrauterine instillations maneuvers that seem to be, ever more, replaced by D&E, for advantages in terms of speed, cost but also reduced pain and psychic trauma [14].

The action mechanism of the hyperosmotic agents injected in the amniotic sac is not clear, but seems to be prostaglandin mediated, in the sense that hypertonic solutions, damaging the fetal membranes, release phospholipase, that cleaves the arachidonic acid stored in the fetal membranes; the arachidonic acid released in this manner is then converted in prostaglandins [33, 34, 28, 6].

The possible complications of intraamniotic injection of hypertone solution (described by Watteville [33], Blum & Grunbaum [35], Baudet & Daffos [36], Chevrant-Breton & Roch [34], Alessandrescu et al [28], Cabrol et al [37]) can be systematized as follows: (a) the hypertonic saline solution injected in the amniotic sac can generate severe complications and even death; among these complications there are: (1) hyperosmolar crisis, consecutive to the penetration of the hypertonic saline solution in the maternal circulation, (2) cardiac insufficiency, (3) septic shock, (4) peritonitis, (5) hemorrhage, (6) disseminated intravascular coagulation, (7) water intoxication, (8) myometrial necrosis, following the injection of the hypertonic solution in the myometrium and (9) cervical or isthmic fistulas or lacerations; (b) hyperosmotic urea (30-40%) diluted in 5% glucose solution is injected in the amniotic sac, after which the 400mU/min oxytocin intravenous perfusion starts; urea plus oxytocin have an abortive efficiency similar to the hypertonic saline solution, but this association is less toxic; urea plus $F_{2\alpha}$ prostaglandin injected in the amniotic sac represents an abortive as efficient as the other hyperosmotic variants, combined or not.

Extraamniotic instillation of physiologic serum, used to interrupt second trimester pregnancy (with the rare risk of breaking the fetal membranes and infection) can be applied to perform late therapeutic abortion, under certain circumstances (Falfonel et al [38]): (1) when the amniotic puncture risks to be difficult (beginning of 4th month); (2) when there is an increased risk of hemorrhage by coagulation disorders (macerated fetus or systemic diseases); (3) when there are contraindications for utilization of hypertone chloride serum or prostaglandins (kidney, cardiac or respiratory diseases); (4) when a fetus in a relatively good condition is desired, to perform embryologic, histological or genetic studies.

C. Prostaglandins (PGs). Due to the limited efficiency and/or seriousness of the complications (rare nonetheless, by recently operated amendments [39, 11, 12, 13]) of dilation and evacuation as well as oxytocin perfusion (methods that survive preferentially in modern obstetrics to uterine instillations [14]), prostaglandins (PGs) are used nowadays ever more, both for second trimester pregnancy termination [40, 41, 42, 23, 22, 20, 43, 21, 25, 14, 27] as well as for cervix maturation before mechanic dilation in the first or second gestational trimester [44, 45, 46, 47, 48, 49] and labor induction [30, 31, 32, 50, 51].

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 [29], 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 [52, 53, 54].

Independent immune and infectiously induced disturbances are frequently incriminated in the etiology of the abortion, especially in case of the recurrent one [55, 56, 57, 1, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67].

Repeated measurement of serum concentration of C-reactive protein (CRP) could prove to be a valuable and practical predictive marker of intrauterine infection, both in the late postabortum period as well as in the latency phase of extremely premature rupture of membranes and even when the fetal membranes are intact in the second trimester of pregnancy [68].

Numerous morphopathological observations of the conception product systematically detect, but in different proportions, both in late abortion as well as preterm birth (overlapping in the 20-28 weeks of gestation period [69, 70]) placental ischemia and/or acute amniochoriodecidual inflammation as the most frequently implicated pathological processes from the multifactorial, not so well understood, etiology of preterm labor [71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85].

In a succinct presentation of basic labor mechanisms, Keirse [69] insisted not only on the role of proteases in breaking membranes and on the role of cytokines in uterine cervix maturation, that associates the neutrophilic local infiltrate (among the multiple mechanisms described for these events [86, 87, 88, 45, 48, 46, 47, 49]) but also on the PGs property of strong stimulus of uterine contractility with respect to other uterotonics, such as oxytocin, corticotropin releasing placental hormone, platelet activating factor and endothelins.

The production of PGE_2 and $PGF_{2\alpha}$ by the amnion and decidua and their destruction by the chorion are balanced during most part of the pregnancy, and the loss of the chorionic prostaglandin dehydrogenase can be significant in initiating labor, especially the premature one [29, 70, 89, 90].

The release of amniodecidual PGs is stimulated by the

platelet activating factor and various cytokines, including interleukin 1, interleukin 6 and tumor necrosis factor and there is a mutual stimulation of these activities in the course of the cytokine cascade [91].

The cytokines also stimulate the expression of the oxytocin gene as well as the production of the corticotropin releasing factor by the decidua [29].

The prostaglandins are hormone-like substances, rapidly inactivated and metabolized in the general circulation, being synthesized and locally released on demand from fat acids precursors [92, 93] 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 [94], as well as structural alterations of the conjunctive tissue responsible for cervix maturation [89, 90].

Of the natural PGs (at least 14 related compounds) only PGE_2 and $PGF_{2\alpha}$ are clinically important in reproduction (prostacyclin and thromboxane being catalogued as intermediate products); the PGs activity can be modified by substitution with artificial groups in the molecule, thus generating analogues of prostaglandins resilient to degradation and more specific in action, that have already been used clinically (especially 15-methylprostaglandin $F_{2\alpha}$ methyl ester, diniprostone – analogue of PGE_2 and very recently, misoprostol – analogue of PGE_1 [30]).

Prostaglandins have been clinically used for the first time in intravenous perfusion to trigger labor in 1968 and for abortion induction in 1970 [95, 92, 96].

The high frequency of systemic adverse effects, predominantly digestive and/or limited abortive success in case of PGs administration in a general (intravenous, intramuscular or oral [97, 20, 41, 42]) or intrauterine manner (extra or intra amniotic [98, 99, 100, 101, 102, 43, 21]) led to their preferential vaginal application and because its intra-cervical variant is laborious and invasive [40, 20, 42] the posterior vaginal fornix became increasingly used and investigated [96, 103, 104, 23, 105, 26].

The specialty literature remarks the innoquity equivalent to that of PGE_2 and $PGF_{2\alpha}$ analogues, but doubled by an increased efficiency and a 200 times smaller cost of the PGE_1 analogue, the misoprostol, that applied in the posterior vaginal fornix is evermore used in various doses and schemes for cervix maturation, second trimester abortion induction and third trimester labor [25, 26, 30, 31, 32, 14, 50, 27, 51].

Salamalekis and collaborators [22], with $PGF_{2\alpha}$ extraamniotically administered (20mg) for second trimester dead fetus, remark an average induction-abortion interval of 6 hours, in just 77% of cases, and the failure in inducing late abortion in 23% of patients with dead fetus was corrected in the subsequent 12-48 hours, either with intravenous $PGF_{2\alpha}$ and/or oxytocin perfusion, which in term increased the rate of adverse reactions, mostly digestive, but also the risk of uterine atony, often consecutive to myometrial hyperstimulation, fever, etc. The side effects were not rare, especially the digestive ones, also in case of 25-40mg intraamniotic $PGF_{2\alpha}$ application, by amniocentesis, by the same team, to induce late abortion for alive malformed fetus and various maternal indications, situation when the average induction-expulsion interval was 10 hours.

Side effects similar to those reported by Salamalekis [22] are also encountered in the studies of the Jaschevatzky group [43, 21] on $PGF_{2\alpha}$ administered intra and extra amniotic for therapeutic termination of second trimester pregnancy, but the average induction-abortion interval obtained by Jaschevatzky and collaborators [43, 21] was 12 hours for the extraamniotic way and 6 hours for the intraamniotic one, while the rate of the abortive success in case of extraamniotic application of $PGF_{2\alpha}$ with oxytocin augmentation in 75% of cases reached 100%.

A similar range of non negligible side effects and abortive efficiency in the second trimester comparable to that from the reports of Salamalekis and team [22] and Jaschevatzky and co-researchers [43, 21] is found in the observations on analogues of PGE_2 and $PGF_{2\alpha}$ administered parenteral [106, 97, 96, 104, 87, 101, 41], intrauterine [97, 40, 107, 100, 104, 102] and intracervical [99, 40, 107, 108].

On the other hand, studies on misoprostol (analogue of PGE_1) applied in the posterior vaginal fornix, to terminate second trimester pregnancy with a therapeutic purpose, indicate, when it comes to: (a) the Frunzzetti group [23] an average duration of the induction-abortion interval of 12 hours and a success rate in the first 48 hours of 86%, and (b) the Bugalho group [25] an average duration of the abortion of 14 hours and a success rate of 91% in the first 24 hours following the application of the PG analogue and after a different protocol, while in case of (c) Jain and Mishell [14] (who evaluate with their own scheme the abortive efficiency in the second trimester of intravaginal misoprostol, alone or associated with laminaria) the average interval from the therapy initiation to abortion, of approximately 16 hours, did not differ substantially between groups with and without associated laminaria, the abortion rate at 48 hours after the start of the therapy was 84% and respectively 91% without and with laminaria to complement the misoprostol, the rate of complete abortion, also similar between the two groups reached almost 38%, and the fever, vomiting, diarrhea and pelvic pain were occasional in both groups.

Nonetheless, due to the reduced dimensions of the groups studied by these publications, as well as different regimes of intravaginal misoprostol administration, the limits and ideal protocol to administer intravaginal misoprostol to induce late therapeutic abortion and not only that are not clear [14, 50, 27].

D. Antiprogesterone substances like RU486 (mifepristone) and epostane (acting as competitive inhibitor of progesteronic receptors and respectively as blocker of the endogen synthesis of progesteron) have been used, per os, to induce abortion in the first 6 weeks and respectively 4 weeks of amenorrhea, with a success rate of 85%, reaching 95% after association with prostaglandins [109, 110, 111, 37, 112].

Given the extremely limited abortive efficiency of antiprogesteronics after 6 and respectively 4 weeks of amenorrhea, with the purpose of inducing late therapeutic abortion, antiprogesteronics are applied only as uterine sensitizers, prior to application of the main agent provoking the abortion, usually prostaglandins [113, 114, 115, 24, 116].

Our own preliminary observations (Bulucea et al [27]) show that the RU486 – prostaglandins association, in the manner reported by the Pons group [24], systematically applied to terminate second trimester pregnancy, can be surpassed as efficiency, moreover, with significant economical and security related advantages, by an improved protocol, adapted to the late therapeutic abortion, of intravaginal misoprostol.

The adverse effects of RU486, as well as epostane, are nausea, vomiting, gastro-intestinal cramps, but especially hemorrhage by incomplete abortion or unsuspected ectopic pregnancy [115, 112, 1].

E. Diverse associations among various techniques of inducing late abortion have been reported by older studies, already presented, and the purpose of these combinations, such as RU486 + PG [116], PG + oxytocin augmentation [111, 117, 21], PG + laminaria or Foley catheters [42, 14, 51], PG + intraamniotic hypertonic urea instillation [1], extraamniotic perfusion with physiological serum + oxytocin augmentation [118], was the increase in efficiency of the various current methods of terminating middle trimester pregnancy, with the risk of summing the side effects.

The tendency of associating various therapeutic methods emphasizes their imperfection and implicitly the need to improve them by continuing the research in the area of techniques to therapeutically interrupt second trimester pregnancy, focusing especially on vaginal misoprostol, which seems to currently offer the best guarantees.

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 II) 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 (anencephaly + spina bifida + omphalocele, situation during which the absolute hypoestrogenism with hyperactive uterus at the first dose of PGE_1 analogue imposed a second tablet of misoprostol by oral administration of 0.6 mg of ethinylestradiol); c) 1 case of Rh isoimmunization (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 [119]) of the extremely preterm (between 20 and 27 gestational weeks [69, 70]) 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, nonhemorrhagic placenta whose hyperprogesteronemy inherent to the excessive placental volume and implicitly the excess of chorionic prostaglandin dehydrogenase [29] suggested also by the uterine hypoactivity after the first intravaginal PGE_1 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 [39], 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 [27], 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_2O_2, followed by physiological serum and removal of excess liquid) received

in PVF a 200µg misoprostol tablet (Cytotec 200, Searle, Brussel) 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 synechiae [16].

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 [120].

III. Results and Discussions

The demographic characteristics (table II) 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 [25, 14] 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.

The dominance of fetal indications to terminate second trimester pregnancy, striking in this study (tables II and III), is also encountered in vast statistics [20] 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 II
DEMOGRAPHICS OF THE GROUPS TREATED WITH INTRAVAGINAL MISOPROSTOL FOR LATE ABORTION INDUCTION

	Pregnancies with alive fetuses (number=13)	Pregnancies with dead fetuses (number=7)
Average maternal age [years] (limits)	20.9 (17 – 28)	25.4 (20 – 36)
Nulliparous number (%)	11 (84.6%)	1 (14.2%)
Average gestational [weeks] age (limits)	21.23 (16 – 27)	20.57 (15 – 27)

TABLE III
INDICATIONS OF ABORTION INDUCTION IN PREGNANCIES WITH ALIVE FETUSES, IN SECOND TRIMESTER OF PREGNANCY

	Number of cases (%)
Spontaneous rupture of fetal membranes in second gestational trimester*	7 (53.84%)
Anencephaly + spina bifida + omphalocele	1 (7.69%)
Rh isoimmunisation [1/64]	1 (7.69%)
Psychoses (depressive or schizoid) under chronic treatment with neuroleptics (Phenobarbital) + benzodiazepines +- antidepressants	4 (30.76%)

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 IV 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 prostaglandinic maturation of the cervix), absolute hypoestrogenism (corrected very late), hyperprogesteronemy 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 placental (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 psychrotrophs 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 [53, 54].

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 [121] or Hunfeld and collaborators [9] are still in evaluation.

TABLE IV
CHARACTERISTICS OF LATE ABORTION INDUCED WITH MISOPROSTOL IN THE POSTERIOR VAGINAL FORNIX (PVF)

	Pregnancies with alive fetuses (n=13)	Significance	Pregnancies with dead fetuses (n=7)	Total
Rate of abortion in the first 24 hours from the misoprostol therapy initiation	8/13 (61.5%)	p*<0.05	6/7 (85.7%)	14/20 (70%)
Rate of abortion in the first 48 hours from the misoprostol therapy initiation	13/13 (100%)		7/7 (100%)	20/20 (100 %)
Complete rate of abortion (simultaneous and complete expulsion of fetus and placenta while fetal membranes remain intact)	7/13 (53.8%)	p*>0.05	5/7 (71.42 %)	12/20 (60%)
Average duration of abortion, hours (limits)	21.46 (7-48)	p**<0.05	11.71 (5-25)	16.58 (5-48)
Corrected average duration of abortion (after excluding cases of absolute hypoestrogenism, large placenta, cervicitis, chronically treated psychosis), hours (limits)	11.33 (7-16)	p**>0.05	11.4 (5-19)	11.36 (5-19)
Average number of misoprostol tablets necessary to induce abortion (limits)	2.69 (1-8)	p**<0.05	1.28 (1-2)	1.98 (1-8)
Average number of Cytotec tablets corrected using the same criteria as in case of the average duration of abortion (limits)	1.66 (1-2)	p**>0.05	1.16 (1-2)	1.41 (1-2)
Side effects of misoprostol (bearable pelvic pain)	2/13 (15.38%)	p**>0.05	1/7 (14.28 %)	3/20 (14.83%)

* 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 IV) 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_1 analog, and on the other hand the possibility of increasing the success of this therapy with respect to some results published on this subject [23, 25, 14] that already suggested the practical superiority of misoprostol applied in PVF with respect to all other prostaglandin variants, even associated to RU486 [22, 43, 21, 24].

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 [23, 25, 14] applied in PVF to induce late abortion (nonetheless after protocols differing in administration rhythm and/or associations).

Unlike the data supplied by Jain and Mishell [14], 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 [26], and the increased number of "complete eggs" (with decreased risk of amniotic cavity contamination) expulsed in this manner reduced significantly the rate of postabortum curettage, in the same time opening new perspectives, on fetal transplant [122] 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 [70, 94, 89, 29, 90, 91] on the key role of PGs in the physiology 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.

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