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Review

ALTERNATIVE APPROACHES TO MEDICAL ABORTION

K. Telbiyska[1,2]*, M. Angelova[2]

[1]Selena University Specialized Hospital for Active Treatment in Obstetrics and Gynecology, Plovdiv, Bulgaria
[2]Department of Obstetrics and Gynecology, Trakia University, Medical Faculty, Stara Zagora, Bulgaria

ABSTRACT
Medical abortion involving various pharmacological agents has demonstrated high levels of complete uterine evacuation. Alternative approaches involving letrozole, mifepristone, methotrexate used synergically with misoprostol are non-invasive elective methods of achieving complete abortion. Abortion induced by mifepristone, letrozole and misoprostol results in complete evacuation in 98% of the cases.The synergic effect of mifepristone and misoprostol achieves 98.2% effectiveness. Medical management of abortion with letrozole and misoprostol has 97.8% complete expulsion. Current reports of surgical termination of pregnancy reveal 97% effectiveness.
Letrozole destabilizes the dominant position of mifepristone but the reports of its non-significant prevalence regarding complete abortion should be verified by a larger number of studies. Medical abortion is non-inferior in its effectiveness to surgical abortion and is unambiguously likely to become in the future the principal recommendation for termination of early pregnancy.

Key words: letrozole, mifepristone, methotrexate, misoprostol, non-invasive, abortion

INTRODUCTION

About 56.3 million abortions performed worldwide have been reported for the period 2010 - 2014 (1). Other topical global reports state 40 abortions per 1000 women, the data being identical in countries with legal and banned abortions (2).

The United States tends to show an affinity to drug-induced abortion. Statistical data from 2020 showed that 54% of all abortions were drug-induced, as compared to 39% in 2017 (3). A prospective study among Bulgarian women found that 80.7% of them preferred medical abortion, with 89.48% in the 18-25 age group, and only 15.35% being in favour of the surgical intervention method (4). Numerous studies have proven the effectiveness of drug-induced abortion <63 days from the last menstrual period (LMP) (5). The combined use of mifepristone and misoprostol is the standard pharmacological approach to early abortion (6).

***Correspondence to:** *Katia Telbiyska, Selena University Specialized Hospital for Active Treatment in Obstetrics and Gynecology, Plovdiv, Peshtersko shosse 80, Bulgaria. E-mail: dr_k.telbiyska@mail.bg*

There is no absolute consensus on the ultrasound verification of complete abortion but it is widely accepted that the lack of gestational sac and endometrial thickness of 15 mm is indicative that no conception products have been retained, whereas thickness of 20 mm or more is considered as incomplete abortion (7, 8).

Misoprostol used individually as vaginal application or in combination with mifepristone is effective in terminating early pregnancy (9). Other pharmacological agents targeting complete uterine evacuation have also been studied. Mifepristone alternatives such as letrozole, when administered before misoprostol, are effective in cases of missed abortion in the first trimester (10). The letrozole/misoprostol regimen has been reported to achieve a higher percentage of complete abortions, as compared to the individual use of misoprostol, without an increase in adverse reactions (11, 12).

DISCUSSION

The letrozole mechanisms of action, which are already known, are contradictory in some aspects. Letrozole is an oral fourth-generation

non-steroidal aromatase inhibitor with a comparatively short half-life of 45 hours. It increases the endogenous gonadotropin FSH released by the hypotalamic-pituitary axis, resulting in a decrease in the serum estradiol, which independently from progesterone plays an important role in maintaining pregnancy. It conjugates competitively and reversibly with the enzyme cytochrome P450 aromatase and inhibits plasma estrogens – estron more than 86% and estradiol 67% - around the 14th day. Cortisol inhibition has also been reported, although it remains within the range of the reference values (13-15).

Letrozole does not affect progesterone levels in spite of the estradiol suppression it induces (16). The reports on its mechanism of action are contradictory. One study found that letrozole suppresses estrogen receptor-α (ERα), estrogen receptor-α protein and progesterone receptor (PR) transcripts in abortion in the second trimester (17). Another study did not confirm suppression of progesterone receptors and induction of apoptosis in decidua and placental tissues after a 7-day administration of letrozole followed by vaginal application of 400 μg misoprostol targeting abortion in the first trimester, and subsequent vacuum aspiration (18). Aromatase inhibitors have no androgenic effect on progesterone and estrogen. Their short-term use in drug-induced abortion does not lead to serious adverse effects (19).

Letrozole significantly decreases the pulsatility index (PI) and the resistance index (RI) of the uterine artery by increasing blood inflow to the uterus in pregnancy up to the 63rd day (20).

Letrozole suppresses vascular endothelial growth factor (VEGF) and angiopoietins, which play a role in remodeling the spiral arteries in normal pregnancy (21).

Letrozole is an abortifacient agent that does not induce uterine contractions and does not affect the tone or increase myometrial sensitivity to misoprostol. Uterine contractility occurs when used synergically with misoprostol (22).

Mifepristone is indicated for termination of pregnancy in combination with misoprostol, as well as for emergency postcoital contraception. It is a synthetic steroid, which binds to progesterone receptors when used in low doses. It is an antiprogesterone drug that induces decidual necrosis. It softens the uterine cervix and sensitizes myometrium to the action of prostaglandins resulting in myometrial contractility. In high doses, it binds to the glucocorticoid receptor and increases cortisol levels by controlling hyperglycemia. Bacterial infection has been reported as an adverse reaction (23).

Misoprostol is used individually or synergically with mifepristone when abortion is targeted. It is effective in inducing uterine contractions, cervical softening and dilation, with low percentage of adverse reactions (24). As a pharmacological agent misoprostol is a prostaglandin E1 analogue that can modulate the expression of prostaglandin receptors in myometrial cells, which results in a diverse response to its application (25).

Misoprostol leads to complications in 0.9% of the cases, as compared to 9.8% resulting from manual vacuum aspiration (26). Its individual use results in 60-80% complete abortion, but studies have reported 92.4% success following 800 μg vaginal misoprostol in early pregnancy failure (27).

Uterine rupture occurs in women with uterine scar. Misoprostol increases the risk, but rupture is a rare complication when it is used for abortion in the first trimester. In inducing labour, a study has found it to increase the risk by up to 18%, even at a very low dose of 25 μg. Reduction of the dose to 100 μg, vaginal application or oral administration of the drug are all protocols, which are not based on evidence proving reduction in the complications caused (10). Misoprostol used for therapeutic abortion in the second trimester in women with previous caesarean section has not been associated with more complications, as compared to its use in women without uterine scar (28).

Previous studies involving the combined use of mifepristone and misoprostol in missed abortion have found complete uterine expulsion in the range of 79%-87%, with individual misoprostol use ranging from 58% to 76% (24). Following drug-induced abortion, prophylactic use of antibiotics and anti-D immunoglobulin have not been recommended in < 12th gestational week; however, other sources have proposed that anti-D Ig should be applied in drug-induced or surgical uterine evacuation (29, 30).

Methotrexate is a chemotherapeutic agent, which is cytotoxic to trophoblasts. It induces increase in trophoblast degeneration by

inhibiting DNA synthesis with a resultant prostaglandin release, which leads to myometrial contraction. In low doses it causes minimal side effects (19, 31).

A study involving intramuscular administration of methotrexate followed by vaginal application of misoprostol 72 h later found 80% complete uterine expulsion against 84% when using misoprostol individually, and concluded that both regimens are safe and effective for missed abortion (32).

Another study compared the effect of methotrexate (50 mg i.m.) and letrozole (tablets 2.5 mg × 3/daily), each of which was used in combination with misoprostol (200 μg/8h) and administered before the latter for 3 days for the purposes of inducing the first trimester missed miscarriage. The complete uterine expulsion in the letrozole group was 91.90%, with an induction/expulsion interval of 2.04 days, against 77.00% in the methotrexate group and an induction/expulsion interval of 2.85 days (19).

Various pharmacological agents have been studied in an attempt to find alternatives to mifepristone; letrozole is likely to find its place among them. A pilot study found unsatisfactory effectiveness of 74% complete abortion - lower than the expected one, at a regimen involving a single dose of 30 mg letrozole followed by buccal administration of 800 μg misoprostol 2 days later in a single fetus pregnancy ≤ 63 days (6). Another study reported complete uterine evacuation of 76.7% in a combined regimen involving letrozole at a dose of 10 mg daily for 3 days, followed by sublingual administration of misoprostol for the purposes of therapeutic abortion <17th week. The control group received sublingual misoprostol only, and the induction/expulsion interval was 5.1 h and 8.9 h in the letrozole and control group, respectively (33).

A study on therapeutic abortions performed < 14 weeks compared the effect of combined use of oral letrozole (10 mg daily for 3 days) and vaginal misoprostol on complete uterine expulsion and found it to be 76.9%, as compared to 41.3 % in the control group where only misoprostol was applied vaginally. The pharmacological approach involving letrozole presents lower curettage levels and higher levels of completeness of abortion (34).

Similar results were reported by a study on the administration of letrozole at a dose of 10 mg, twice daily for 3 days as a synergic agent to misoprostol 800 μg applied vaginally. The placebo group received vaginal misoprostol only. The complete evacuation achieved was 78.0% and 39.0% in the letrozole/ misoprostol group and the vaginal misoprostol group, respectively. The induction/expulsion interval for these groups was 1.42 days and 3.09 days, respectively (10).

Another study compared oral administration of letrozole at a dose of 10 mg per day for 3 days combined with 800 μg sublingual misoprostol, maximum 3 doses in 12 h, in gestation age < 13 g.w. and with 400 μg sublingual misoprostol in gestation age 13-20 g.w. The control group received misoprostol only. The complete abortion observed in the letrozole/ misoprostol group was 78.3%, with an induction/expulsion interval of 22.61h, in contrast to 13.0% complete abortion and 24.09 h induction/expulsion interval in the misoprostol group (35).

An alternative pharmacological approach involving a 3-day course of letrozole at a dose of 10 mg per day, followed by 800 μg misoprostol applied vaginally, resulted in 81.0% complete expulsion in missed miscarriages in the first trimester. In contrast, the individual application of misoprostol achieved 54.0% effectiveness and had a longer duration of vaginal bleeding (8). The combined regimen of letrozole 10 mg daily for 3 days, followed by vaginal application of 800 μg misoprostol resulted in 86.9% complete uterine evacuation when used in pregnancy up to the 63rd day, as compared to 72.6% achieved in the placebo group receiving misoprostol only (12). Two other studies used the above-mentioned letrozole dose followed by a single dose of 600 μg peroral misoprostol and achieved complete abortion of 93.2% and 93.7% in the letrozole/misoprostol group, in contrast to 68,7% completeness achieved in the group receiving misoprostol only (36, 11). The pharmacological approach involving letrozole at a dose of 10 mg daily for 7 days, followed by 800 μg misoprostol applied vaginally on the 7th day resulted in 95% complete abortion in pregnancy up to the 63rd day, which is comparable to the mifepristone/ misoprostol regimen (37).

Drug-induced management of abortion involving letrozole at a daily dose of 10 mg for 3 days, followed by vaginal application of 800 μg misoprostol on the third day, achieved

complete uterine evacuation of 97.8% and a longer induction/expulsion interval of 15.4 h, as compared to the standard regimen with mifepriston at a dose of 200 mg followed by vaginal application of 800 μg misoprostol 24-48 h later achieving 97.2% completeness and 9 h induction/expulsion interval (16). Recent research compared the synergic effects of the three pharmacological agents – a single dose of 200 mg mifepristone and 10 mg letrozole daily for 3 days followed by vaginal application of 800 μg misoprostol – and reported 98 % complete abortion with 5.1 h induction/expulsion interval. The study concluded that the regimen involving mifepristone, letrozole and misoprostol was associated with a higher percentage of complete expulsion up to the 63rd day of pregnancy, with no significant adverse effects (38). Mifepristone combined with misoprostol achieved up to 98.2% complete abortion, as reported in a study on the combined use of 600 mg mifepristone and 400 μg oral misoprostol, with a second dose of 400 μg misoprostol administered in cases when bleeding did not occur (39, 27). Complete abortion of 97% was reported in surgical termination of pregnancy against 95% in drug-induced abortion involving 200 mg mifepristone and 800 μg misoprostol, 24-48 h later (40).

CONCLUSION

Drug-induced abortion is generally not included in abortion statistics on a global scale, because it is not accurately registered, although it is a safe, non-invasive pharmacological approach with a variety of alternatives. Oral aromatase inhibitors, prostaglandins, synthetic steroids such as antiprogesterone drugs and chemotherapeutics cytotoxic to the trophoblast have been investigated, but other pharmacological agents are also likely to be found and used in new regimens targeting complete expulsion after studying their minimum effective dosages and adverse reactions.

The pharmacological approaches to abortion occupy non-contradictory positions and will probably prevail in the future for the purposes of terminating early pregnancy because of their verified effectiveness, making possible the avoidance of cardinal intraoperative and infertility-associated risks of surgical intervention.

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