Comparison between letrozole pretreatment with Misoprostol and Misoprostol alone for medical management of missed Abortion

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Abstract

Background: Pregnancy termination methods in the first trimester are widespread but most of these methods are not available in most countries. Therefore, identifying and diagnosing the best available regimen for medical abortion is very important so we need to assess the effect of letrozole with misoprostol versus misoprostol alone in terminating the first trimester missed abortion.

Keywords: letrozole , Misoprostol , missed Abortion

Introduction:

Missed abortion: Is a condition in which a dead immature embryo or fetus is not expelled from the uterus for 2 months or more.The uterus decrease in size, and symptoms of pregnancy abate; maternal infection and blood clotting disorders may follows. The fetus , and placenta may become necrotic; less commonly the fetus becomes calcified, and the rest of the products of conception are resorbed***(1)***.

Incidence:

Spontaneous abortion is the most common complication of early pregnancy **.** The frequency decreases with increasing gestational age. The incidence of abortion almost 15% of all clinically detectable pregnancy, nearly 80%0f spontaneous abortion occur in first trimester, after 12 weak incidence sharply decreased **.** Loss of unrecognized or subclinical pregnancies is even higher, occurring in 13 to 26 percent of all pregnancies **(2)**.

Clinical presentation:

Spontaneous abortion usually presents as vaginal bleeding or pelvic pain or is an incidental finding on a pelvic ultrasound performed in an asymptomatic patient .Some women who present with spontaneous abortion have a previously unrecognized pregnancy. This is particularly likely for women with irregular menses or those who had another recent episode of vaginal bleeding that was interpreted as menses **(3)**,

Any bleeding or pelvic pain in a pregnant woman warrants further evaluation .Decreased fetal movement is only rarely a presentation of spontaneous abortion, since most abortions occur before fetal movements are perceptible to the patient **(4).**

- **Vaginal bleeding:** The bleeding associated with spontaneous abortion ranges from scant brown spotting to heavy vaginal bleeding. The volume or pattern of bleeding does not predict a spontaneous abortion. Vaginal bleeding is common in the first trimester, occurring in 20 to 40 percent of pregnant women. Even heavy, prolonged bleeding can be associated with a normal outcome. In 90 to 96 percent

of pregnancies in which vaginal bleeding occurs between 7 to 11 weeks of gestation and fetal cardiac activity is observed, pregnancy continues; success rates increase with gestational age when bleeding occurs. Vaginal bleeding may be accompanied by passage of fetal tissue, which typically is solid and has the appearance of a white mass covered with blood. Patients may mistake a blood clot for fetal tissue. Passage of fetal tissue is usually accompanied by severe cramping **(5)**.

- **Pelvic pain:** The pain that accompanies a spontaneous abortion is typically crampy or dull in character and may be constant or intermittent **(5)**.

Sonographic parameters:

Miscarriage should be diagnosed only if any of the following criteria are met upon ultrasonography visualization:

- Crown-rump length of at least 7 mm and no heartbeat.
- Mean gestational sac diameter of at least 25 mm and no embryo.
- Absence of embryo with heartbeat at least 2 weeks after an ultrasound scan that showed a gestational sac without a yolk sac.
- Absence of embryo with heartbeat at least 11 days after an ultrasound scan that showed a gestational sac with a yolk sac.
  (6)

Treatment

Expectant management:

Expectant management is often the initial treatment choice for patients experiencing a spontaneous pregnancy loss. However, women who choose this option should be counseled that complete expulsion may take up to 1 month. By day 7 post-diagnosis, approximately 50% of women request surgical management; 70% do so by day 14 **(7)**.

Medical management:

The drug most commonly used is a prostaglandin analogue misoprostol, which can be given in single or divided doses. It is licensed for oral use only, but can also be given vaginally, sublingually, or rectally **(8).**

Many drugs can be used to induce abortions. One of these drugs is misoprostol which is a prostaglandin E1 analogue. This drug can be used both vaginally and orally **(9).**

Misoprostol

It is prostaglandin E1 analogue (15-deoxy-16 hydroxy methyl PGE1) manufactured by (Searle pharmaceutical, Skokie, Illinois, USA), and it was originally developed in the early 1970 for the treatment of peptic ulcer disease and inhibition of gastric acid secretion and was marketed under the trade name of Cytotec and Its safety when used for this indication has been established **Figure (1) (9)**.

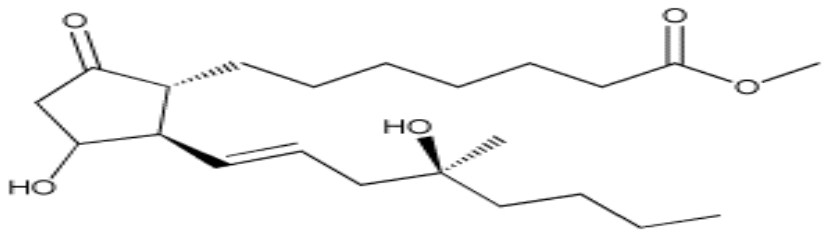

Figure (1): Structure of Misoprostol

Mechanism of action:

Being a prostaglandin E (PGE) analogue, misoprostol acts via interacting with PGE receptors misoprostol, a prostaglandin, binds to myometrial cells by interacting with specific receptors to cause strong myometrial contractions. This interaction results in change in Ca concentration, thereby initiating muscle contraction. Also causes cervical ripening with softening and dilation of the cervix **(10).**

Uterine effects:

Prostaglandin F, PGE and misoprostol have also uterotonic activity. Prostaglandin E is more specific uterotonic agent than PGF, however, and it also has effects on the cervix. Misoprostol seems to have more effects on the cervix than PGE **(11).**

Uses of misoprostol in obstetrics:

A) Induction of abortion:

Misoprostol is used for medical abortions as an alternative to surgical abortion. Medical abortion has the advantage of being cheaper, simpler, less invasive, not requiring anesthesia, and not having the risk of scarring and adhesions associated with surgical abortion **(12).**

B) Cervical ripening and induction of labor at term:

Misoprostol is an effective and economical cervical ripening and labor inducing agent. In a meta-analysis on misoprostol, women who received misoprostol for cervical ripening and labor induction had a significantly lower overall cesarean section rate and a higher incidence of vaginal delivery within 24 hours of misoprostol application **(13).**

C) Primary postpartum hemorrhage:

Misoprostol is also used to prevent and treat postpartum hemorrhage**.** Orally administered misoprostol at a dose of 600 μg was tested versus oxytocin 10 IU in a large randomized, controlled study. The study, involving a substantial number of patients receiving either oral or intravenous oxytocin, showed misoprostol to be marginally less effective for this purpose **(14).**

Misoprostol in management of first trimester abortion:

Misoprostol is widely used off-label in obstetric and gynecologic care and is included in the FDA-approved labeling of mifepristone for medication abortion. Misoprostol promotes increased uterine tone and contractility and causes cervical softening. In abortion care, misoprostol is used alone or in combination with mifepristone or methotrexate for medication abortion and alone or in combination with osmotic dilators to prepare the cervix for surgical abortion **(13)**.

Timing of misoprostol:

Chen and Creinin (2015) published a review of 20 medication abortion studies, including a total of 33,846 women through 70 days gestation. When they compared data from the six studies reporting a 24-h interval between mifepristone and buccal misoprostol and the 13 studies reporting a 24- to 48-h interval, the authors found that success rates were slightly lower with a 24-h interval (94.2% compared with 96.8%). Lower success of the shorter misoprostol interval was found in both the earliest abortions of 49 or less days (96.8% compared with 98.2%, respectively) and in abortions at 50–63 days (92.1% compared with 96.3%, respectively); of note, they found insufficient data to draw conclusions regarding misoprostol interval in the 64–70-day range due to less published data on later medication abortion**.(15)**

Another study of abortions up to 55 days compared misoprostol administration 48 h after mifepristone to 2 h after; 48 h after remained superior. All women in the 48-h

arm completed termination within 48 h while only 76% of women in the 2-h arm achieved completion at 48 h **(16)**.

Contraindications:

Misoprostol should not be taken by pregnant women to reduce the risk of NSAID induced gastric ulcers because it increases uterine tone and contractions in pregnancy which may cause partial or complete abortions, and because its use in pregnancy has been associated with birth defects .Misoprostol should not be administered to nursing mothers because the potential excretion of misoprostol acid could cause significant diarrhea in nursing infants. It is also contraindicated in people with known hypersensitivity to misoprostol or other prostaglandin **(16).**

Adverse effects:

Misoprostol is a safe and well-tolerated drug. Preclinical toxicological studies indicate a safety margin of at least 500-1000 fold between lethal doses in animals and therapeutic doses in human**.** No clinically significant adverse hematological, endocrine, biochemical, immunological, respiratory, ophthalmic, platelet or cardiovascular effects have been found **(17).**

A) Gastrointestinal:

In subjects receiving misoprostol 400 or 800 μg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea, abdominal pain, nausea and vomiting. Diarrhea is considered the major adverse reaction mainly with long term administration of misoprostol, which occurred in about 10% of patients receiving 200 μg twice daily of misoprostol in treatment of peptic ulcer. **(18).**

B) Shivering and pyrexia:

It is probable that high plasma concentrations of misoprostol, besides acting on uterine receptors to produce contractions, also act on thermoreceptors, primed by the pregnancy state, resulting in disturbed thermoregulation. There is probably a threshold plasma concentration of misoprostol at which these side effects are triggered **(18).**

C) Gynecological:

Women who received misoprostol during clinical trials reported the following gynecological disorders: Spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal bleeding may be related to misoprostol administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology **(19)**.

Letrozole

Its Chemical Formula is C17H11N5 (figure 2), and its Molecular Weight is 285.31 g/mol. **(20)**.

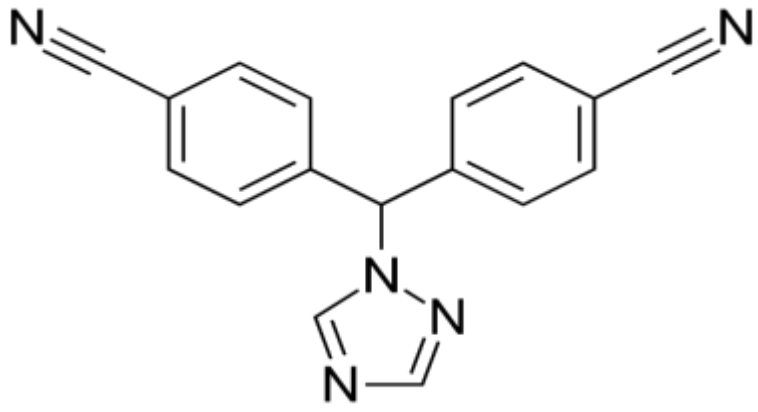

Figure (2): Letrozole structure

Clinical usage:

Letrozole is mainly used in the treatment of advanced or locally advanced breast cancer in postmenopausal women. It is also used for the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer; treatment is generally given for 5 years or until tumor relapse occurs, the usual oral dose is 2.5 mg daily **(20)**.

Mechanism of letrozole in inducing abortion:

Letrozole suppressed the expression of progesterone receptor transcripts, estrogen receptoralpha and estrogen receptor-α protein in the placentas of cases taking it. Furthermore, **it is** evaluated the influence of Letrozole on uterine artery Doppler indices earlier to operative terminations of the 1st trimester pregnancies and they revealed that pulsatility as well as resistances indexes decreased significantly in the Letrozole group, that proposes that blood flowing fluctuations may has a function in the mechanism of Letrozole action. **(21)**

Adverse effects:

The most common side effects are sweating, hot flashes, arthralgia (joint pain), and fatigue. Other adverse effects include nausea, diarrhea, headache, bone loss and fractures, and vision disturbances. Because aromatase inhibitors promote bone loss, these drugs may not be appropriate for women at high risk of bone fractures **(22)**.

Breast-feeding: Licensed product information states that it is unknown whether Letrozole is distributed into human milk; in the UK its use during breast feeding is contra-indicated while in the USAa decision to use may be made based on clinical judgment **(23)**.

Effects on blood lipids: Letrezole cause notable decrease in high-density lipoprotein (HDL) cholesterol. This resulted in an increase in the atherogenic ratio of low-density (LDL) to HDL-cholesterol **(24)**.

Torky et al. (2018) found a higher rate of nausea and vomiting in letrozole + Misoprostol group compared to Misoprostol alone group (17.0% vs. 3.0%). However, they found that the occurrence of other complications (fever, severe pain and severe bleeding) didn't change significantly among groups. **(25)**. Also, **Javanmanesh et al. (2018)** found that there was nonsignificant change among Letrozole and Misoprostol groups in regard to adverse effects. **(26)**.

Furthermore, **Naghshineh et al. (2015)** found that side-effects occurrence and severity were comparable between Misoprostol alone group and Letrozole + Misoprostol one**(27)**.. Also, **Lee et al. (2013) and Sharami and Arjmandi (2014)** found similar results. Currently, the significantly higher rates of nausea and vomiting in the combined group can be clarified by the elevated risk of developing side-effects when utilizing 2 medications**(21&28)**.. On the other hand, **Abbasalizadeh et al. (2018)** found that side effects of Letrozole + Misoprostol were significantly low in comparison to that of Misoprostol only. **(29)**.

Competing interests:

The authors declare that they have no conflict of interest.

References

1. **Cunningham FG, Leveno KJ, Bloom SL, et al. (2019):** Williams Obstetrics, 24rd Edition. New York: McGraw-Hill. 80:852 - 860.
2. **Lohstroh PN, Overstree JW, Stewart et al., (2005).** Secretion and excretion of human chorionic gonadotropin during early pregnancy. Reproductive Endocrinology 2005; 83(4): 1000-1011.

3. **Jurkovic D, Ross JA, Nicolaides KH (2013):** Expectant management of missed miscarriage. Br J Obstet Gynaecol; 105(6): 670.
4. **Yang J, Hartmann KE, Savitz DA, et al. (2016):** Vaginal bleeding during pregnancy and preterm birth. Am J Epidemiol; 160: 118–25.
478-83.
5. **Hasan R, Baird DD, Herring AH, et al. (2010):** Patterns and predictors of vaginal bleeding in the first trimester of pregnancy. Ann Epidemiol; 20: 524.
6. **Rodgers K., Crystal, John T.,(2020)** Normal and Abnormal US Findings in Early First-Trimester Pregnancy: Department of Radiology,; Einstein Medical Center, 5501 Old York Rd, Philadelphia, 16(2), 61-66
7. **Bagratee JS, Khullar V, Regan L, et al. (2004)..** A randomized controlled trial comparing medical and expectant management of first trimester miscarriage. Hum Reprod 2004;19: 266-271.
8. ***Boersma, A. A., Meyboom-de Jong, B., & Kleiverda, G. (2019).*** Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. The European Journal of Contraception & Reproductive Health Care, 16(2), 61-66.
9. **Naguib AH, Morsi HM, Borg TF, et al. (2015):** Vaginal misoprostol for second-trimester pregnancy termination after one previous cesarean delivery. International Journal of Gynecology and Obstetrics; 108: 248 - 251.
10. **Cleary B. (2010):** Misoprostol Pharmacokinetics and Pharmaco dynamics Int. J Obstet Gynacol, 96 (4): 265-72.
11. **Varaklis K, Gumina and Stubblefield PG (1995):** Randomized controlled trial of vaginal misoprostol and intracervical PGE1 gel for induction of labor at term. Obstet Gynecol; 86: 541-4.
12. **Deborah W, Raymond B, Lauren A, et al. (2013):** Misoprostol Vaginal Insert and Timeto Vaginal Delivery: A Randomized Controlled Trial, Obstetrics and Gynecology; 122 (13): 204-6.
13. **Goldberg AB, Allen RH (2016):** Misoprostol before first trimester surgical abortion: a patient-centered approach. Contraception; 94(5): 576–7.
14. . **Villar J(2002).** Misoprostol to treat postpartum hemorrhage (PPH): a randomized controlled trial (Argentina, Egypt, South Africa, Thailand and Viet Nam). Current Controlled Trials (www.controlled-trials.com/mrct) 2002
15. **Chen MJ, Creinin MD (2015):** Mifepristone with buccal misoprostol for medical abortion: a systematic review. Obstet Gynecol; 126(1): 12–21.
16. **Tendler R, Bornstein J, Kais M, et al. (2015):** Early versus late misoprostol administration after mifepristone for medical abortion. Arch Gynecol Obstet; 292(5): 1051–4.
17. . **Aronsson A (2007):** Misoprostol: Pharmacokinetics and effects on uterine contractility and cervival ripening in early pregnancy. Institutionenförkvinnorsoch barns hälsa/Department of Women's and Children's Health. 13: 102-114
18. **Shetty A, Danielian P, Templeton A (2002):** Sublingual misoprostol for the induction of labor at term. American Journal of Obstetrics and Gynecology; 186(1): 72-6.
19. **Karonoff DM, Hao Y, Chung J, et al. (2018):**Misoprostol Impairs Female Reproductive Tract Innate Immunity against Clostridium sordellii. J Immunol.; 180 (12): 822 - 835.
20. **Geisler, P. & Magon, N(2011)**. Hormones in pregnancy. Nigerian medical journal : journal of the Nigeria Medical Asso-ciation, 2011; 53**,** 179-183.

21. **Lee VC, Gao J, Lee KF, et al. (2013):** The effect of letrozole with misoprostol for medical termination of pregnancy on the expression of steroid receptors in the placenta. Hum Reprod; 28: 2912-9.
22. **Haberfeld H (2019):** Austria- Codex (in German) (2019/2020 ed). Vienna: Osterreichischer Apothekerverlag.; ISBN 16(2), 61-66.
23. **Brayfield A (2014):** THE Martindale the Complete Drug Reference 38 Edition. Pharmaceutical Press. 16(2), 61-66.
24. **McCloskey EV, Hannon RA, Lakner G, et al. (2007):** Effects of third generation aromatase inhibitors on bone health and other safety parameters: results of an open, randomised, multicentre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. Eur J Cancer; 43(17): 2523-31.
25. **Torky H. A. , H. Marie, E. ElDesouky, S. et al. (2018)**. Letrozole vs. Placebo Pretreatment in the Medical Management of First Trimester Missed Miscarriage: a Randomized Controlled Trial. *Geburtshilfe Frauenheilkd.* 2018; 78(1): 63–9.
26. **Javanmanesh F, Kashanian M and Mirpangi S (2018):** Comparison of Using Misoprostol with or without Letrozole in Abortion Induction: A Placebo-Controlled Clinical Trial. Journal of Obstetrics, Gynecology and Cancer Research; 3(2): 49-52.
27. **Naghshineh E, Allame Z, Farhat F (2015):** The effectiveness of using misoprostol with and without Letrozole for successful medical abortion: A randomized placebocontrolled clinical trial. J Res Med Sci; 20(6): 585-9.
28. **Sharami F and Arjmandi S (2014):** Comparison of sublingual and vaginal misoprostol for second-trimester pregnancy terminations. J Family Reprod Health; 8: 41–4.
29. **Abbasalizadeh F, Sahhaf F, Sadeghi-Shabestari P, et al. (2018):** Comparison Between Effect of Letrozole Plus Misoprostol and Misoprostol Alone in Terminating Non-Viable First Trimester Pregnancies: A Single Blind Randomized Trial. J Family Reprod Health; 12(1): 27–33.