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Research Article

A Comparative Study between Methotrexate versus Letrozole Prior to Misoprostol in Induction of First Trimester Missed Miscarriage

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Abstract

Background: Miscarriage is the loss of a pregnancy before the period of viability. In the better resourced parts of the world, fetuses weighing 500 g or more or a gestational age above 24 weeks can survive although they may be handicapped. A missed miscariage is a nonviable intrauterine pregnancy that has been retained within the uterus without spontaneous abortion. Aim is to compare the synergistic effect of methotrexate versus letrozole before misoprostol for induction of first trimester missed miscarriage. **Method:** The study was conducted at Minia University Hospital and Eledwa General Hospital in the period from February 2021 to February 2022. The study included 199 women randomly allocated into two groups: Group (A): 99 women received letrozole (2.5 mg×3 tablets/day) + misoprostol (200 µg)/8h for 3 days], and Group (B): 100 women received [methotrexate (50 mg) im+ misoprostol (200 µg)/8h for 3 days]. **Result:** Both letroazole and methotrexate are effective in increasing the efficiency of misoprostol in inducing first trimester missed with a better side effects profile in the letrozole group. **Conclusion:** Letrozole administration prior to misorostol can be a safe and effective treatment in inducing first trimester missed miscarriage.

Keywords: Methotrexate; Letrozole; Misoprostol; Miscarriage.

Introduction

Miscarriage, spontaneous or induced, is a common complication of pregnancy and exploration of available and safe regimens for medical abortion in developing countries seems crucial. Based on the reports of WHO, 53 million miscarriages occur annually[1]. Inducing miscarriage by drugs is vastly used in global level and its use has increased since 1950[2]. Selected method for terminating pregnancy in 1960s was vacuum aspiration surgery, and then by manufacturing mifepristone in 1980s, usage of pregnancy termination methods by drugs increased [3]. Misoprostol is a cheap drug which could be kept in room temperature and usually used as vaginally and orally [4]. Besides being affordable and efficient, misoprostol has lower side effects and doesn't need special care during use. This drug is well tolerated by patients and reduces treatment costs significantly and also significantly reduces curettage and need for surgical intervention [3].

Misoprostol is a prostaglandin that causes myometrial contractions, cervical softening and dilatation. It is used to induce miscarriage and labor and to treat atonic postpartum hemorrhage and peptic ulcers. It has the advantage of being cost-effective and stable with a low rate of side effects, which has led to it being included in the World Health Organization list of essential medications. Misoprostol is licensed for use to induce miscarriage in Egypt. It has not been licensed to induce labor or

miscarriage in certain countries such as Germany, but it is used off-label to induce labor in the UK and in Germany[5].

Misoprostol by itself is used for the medical management of miscarriage as an alternative to surgery, with a success rate up to 65%. It is more effective in the early stages of pregnancy, where it also has the advantage of being cheaper, less invasive and avoiding surgical complications. For the Increasing failure rate with misoprostol and other side effects as severe bleeding, many combination with other medication is under trial to increase success rate of complete miscarriage [4].

Letrozole is a third-generation aromatase inhibit***or.*** Letrozole followed by prostaglandin has been proposed as a novel method of conducting medical terminations of pregnancy. Its proposed mechanism involves a drop in serum estrogen levels, leading to altered progesterone receptor concentration resulting in a loss of pregnancy [6]. It acts by suppressing the peripheral conversion of androgens to estrogens which is used to stimulate ovulation in infertile women suffering ovulatory dysfunction. This drug is one of the main drugs for inhibiting aromatase, with a relatively short 45-hour half-life, which is active orally and inhibits aromatase enzyme reversibly. By this drug, estrogen synthesis block leads to increase endogenous gonadotropin and finally stimulates growth of ovarian follicles, and also this drug could play a role in abortion therapy via inhibiting estrogen synthesis [7]. It is hypothesized that acute suppression of the serum estradiol concentration by letro-zole in early human pregnancy would increase uterine artery resistance and affect corpus luteum function, thus facilitating termination in early pregnancy [8].

As a third-generation aromatase inhibitor and also non-steroidal inhibitor, letrozole also has benefits including potent reversible and anti-estrogenic effects that prevent morphologic interference of the endometrium and cervical mucosa. In addition, aromatase inhibitors have no androgenic effects on progesterone or estrogen, and therefore raise new opportunities in gynecology and might be considered a significant therapeutic choice. However, further studies are needed to get a more reliable conclusion on the use of these drugs for first-trimester missed abortion [9]. This drug is one of the main drugs for inhibiting aromatase, with a relatively short 45-hour half-life, which is active orally and inhibits aromatase enzyme reversibly. By this drug, estrogen synthesis block leads to increase endogenous gonadotropin and finally stimulates growth of ovarian follicles, and also this drug could play a role in abortion therapy via inhibiting estrogen synthesis [1]. This drug is also used to breast cancer related to estrogen [10]. Short time use of letrozole in inducing miscarriage had no severe consequences and its usual side effects are sweating, arthralgia, and fatigue, but could decrease bleeding resulted from medical miscarriage [11].

Previous studies have reported different results after the vaginal administration of misoprostol alone or in combination with other drugs. Rate of complete abortion of between 68% and 81% was reported for misoprostol alone[12,13]. Previous study compared the effect of letrozole plus misoprostol and misoprostol alone on first trimester missed abortion, using 7.5 mg of letrozole daily for 3 days followed by 800μg of vaginal misoprostol. They reported rates of complete abortion of 80% and 51.8%, respectively, and an induction duration of 6.1 ± 1.6 and 9.4 ± 2.2 hours, respectively ($P<0.05$). Another study reported that the rate of complete abortion was 93.7% in the group taking 10 mg of letrozole daily for 3 days followed by 600 μg of oral misoprostol and 68.7% in the misoprostol only group [10].

Methotrexate is cytotoxic to trophoblast and, in low doses, has minimal side effects [14]. It is used to treat both gestational trophoblastic neoplasia and ectopic pregnancy. The cytotoxic effects of methotrexate on intrauterine trophoblast

should be equivalent [15]. Methotrexate main action in abortion induction is by increasing trophoplast degeneration, increasing PG release and adding to myometrial contractility.

The aim of the current study was to compare the synergistic effect of letroxole versus methotrexate prior to misoprostol in inducing first trimester missed miscarriage.

Patients and methods

This study was interventional controlled randomized clinical trial and had been conducted at Minia university hospital and Eledwa general hospital in the period from February 2021 to February 2022.The study included 199 women randomly allocated into two groups: Group (A): 99 women received [letrozole (2.5 mg×3 tablets/day) + misoprostol (200 μg)/8h for 3 days], and Group (B): 100 women received [methotrexate (50 mg) im + misoprostol (200 μg)/8h for 3 days]. The study was approved by the ethical committee of the Faculty of Medicine, Minia University. Informed written consent was obtained from all participants before recruitment in the study, after explaining the objectives of the work. Confidentiality was guaranteed on handling the data base.

Inclusion criteria in the present study included: gestational age less than 12 weeks, hemoglobin >10 g/dL, BMI between <30 kg/m^2, heamodynamically stable, and missed abortion. While exclusion criteria involved: molar pregnancy, uterine pathology as fibroid, uterine anomalies, previous uterine surgery (e.g., myomectomy), coagulopathy, medical disorder that contraindicates induction of abortion (e.g., heart failure), previous attempts for induction of abortion in the current pregnancy, and allergy to misoprostol or letrozole or methotrxate.

The sample size was calculated with 208 subjects in each arm of the study, using the formula for comparison of proportion with alpha = 0.01, beta = 0.05, and power = 95%, and 15% dropout rate during follow up. Sample size calculation was done using the results of a recent randomized clinical trial designed to compare the efficacy and safety of letrozole with placebo pretreatment in the medical management of first trimester missed miscarriage [16]. We calculated the effect size that was 0.3, alpha error was 0.01 and power of 0.95 was used. Accordingly, sample size was calculated with G*Power (3.1.9.4) software using a priori analysis for difference between two independent means (two groups) independent sample t-test. Patients allocated into the study were randomized into either of two groups using a computer-generated list at a 1:1 ratio. Concealment was achieved using opaque envelopes.

Outcome measures:

- Primary study primary outcome was occurrence of complete miscarriage.
- Secondary study outcomes were: need for surgical intervention, drop in Hb level, significant blood loss, interval to achieve complete miscarriage, and need for repeated doses of misoprostol.

Statistical Analysis

The collected data were coded then entered and analyzed using the SPSS version 25 (Statistical package for social science) for windows 10. The following tests were used: 1. Descriptive analysis of the results in the form of percentage distribution for qualitative data and (minimum, maximum, mean and standard deviation) calculation for quantitative data. 2. Cross tabulation and Chi Square test ($\chi 2$): For comparison between categorical variables and percentage values. 3. Student t- test: For comparison between means of two unrelated groups with a normal distribution. 4. P-values equal to or less than 0.05 were considered statistically significant. 5. Simple graphs were used to illustrate some information.

Results

The current study was a comparative study, conducted on patients with first trimester missed abortion, to compare

between synergistic effect of methotrexate before misoprostol and letrozole before misoprostol in induction of first trimester missed abortion. The study included 199 women randomly allocated into two groups: Group (A): 99 women received [letrozole (7.5mg) + misoprostol (200µg)], and Group (B): 100 women received [methotrexate (50mg) + misoprostol (200µg)].

Outcome measures in the table demonstrated a comparison between the two studied groups regarding their baseline data. Women's age, parity, BMI, gestational age, history of previous abortions and previous C.S. showed non-statistically significant difference between two studied groups, (p-values >0.05). Complete Abortion was significantly higher among Letrozole as compared with Methotrexate groups, (91.90% vs. 77.00%, p=0.003) of the studied women among two groups respectively. According to table (3), surgical intervention was significantly lower among Letrozole as compared with Methotrexate groups, (8.10% vs. 24%, p=0.002) of the studied women among two groups respectively.
Regarding interval from misoprostol administration to abortion (days), days interval was significantly shorter among Letrozole as compared with Methotrexate groups, (2.04±1.38vs. 2.85±1.75, p=0.023) days among two groups respectively. There was more drop in Hb level among Methotrexate as compared with Letrozole groups, (21% vs. 18.20%) of the studied women among two groups respectively, but without a statistically significant difference. Blood loss was lower among Letrozole as compared with Methotrexate groups, (10.20% vs. 18%, p=0.486) of the studied women among two groups respectively. Finally, as regarding dose repetition for misoprostol, it was significantly fewer among Letrozole as compared with Methotrexate groups, (7.10±4.2 vs. 13.64±6.8, p=0.001) tablets among two groups respectively.

Table 1: Basic characteristics between studied groups

Studied Variables		Studied population		*p-value*
		Group (A): Letrozole N= 99	Group (B): Methotrexate N= 100	
Age	**Mean ±SD**	29.3 ±6.8	29.6 ±6.0	0.712
Parity	**Mean ±SD**	3.02 ±1.4	2.83 ±1.3	0.587
BMI	**Mean ±SD**	25.86 ±2.16	25.48 ±2.37	0.234
Gestational age	**Mean ±SD**	6.64 ±1.3	6.39 ±1.9	0.384
History of previous abortion	**No**	47 (47.50)	56 (56.00)	0.314
	Yes	52 (52.50)	44 (44.00)	
Previous CS	**No**	41 (41.40)	49 (49.00)	0.403
	Yes	58 (58.60)	51 (51.00)	
Outcome	**Partial or incomplete abortion**	8 (8.10)	23 (23.00)	**0.003***
	Complete Aborted	91 (91.90)	77 (77.00)	
Interval (days)	**Mean ±SD**	2.04 ±1.38	2.85 ±1.75	**0.023***
Hb level	**No affection**	81 (81.80)	79 (79.00)	0.374
	Affection	18 (18.20)	21 (21.00)	
Surgical intervention	**No**	91 (91.90)	76 (76.00)	**0.002***
	Yes	8 (8.10)	24 (24.00)	
Side effect (bleeding)	**No**	89 (89.80)	82 (82.00)	0.486
	Yes	10 (10.20)	18 (18.00)	
Tablet misoprostol	**Mean ±SD**	7.10 ±4.2	13.64 ±6.8	**<0.001***

Discussion

Miscarriage refers to the termination of pregnancy before the 20 weeks of gestational age or under birth weight of 500 g [2]. It is estimated that around 40 million abortions occur every year, either legal or illegal, resulting in an abortion rate of 3.5%[17]. Medical abortion decreases side effects such as bleeding and infection, and also stress in patients, comparing with surgery [4]. Misoprostol is an analogue of prostaglandin E1 which is prescribed for the prevention and treatment of gastric and duodenal ulcers. It is also used in obstetrics for the induction of labor, cervical preparation, treatment of postpartum hemorrhage (primary and secondary PPH), and induction abortion[4]. Unlike other prostaglandins, Misoprostol selectively affects the uterus and cervix and has no adverse effect on the bronchi and blood vessels [3].

Success rate in the current study was higher than the reported by Torky et al.,[16] who found that Letrozole + Misoprostol achieved a success rate of 78.0% in complete miscarriage versus a success rate of 39.0% that was achieved by Misoprostol alone (P<0.001), and also higher than Javanmanesh et al.,[18] compared the use of Misoprostol with or with no Letrozole in management of miscarriage, they found that the rate of success was significantly high in the group received Letrozole+ Misoprostol than that of the group receiving Misoprostol only (78.3% vs. 13.0%; p=0.001). The variations between findings may explain by different doses and gestational age in studied women, duration of letrozole, and different doses of administration. However, like previous studies letrozole in combination with misoprostol was more effective than misoprostol alone.

On the other side, a study by Rezai et al.,[19] on pregnant women in the first trimester of pregnancy, the effect of combination of misoprostol and letrozole was compared with misoprostol alone on the termination of pregnancy. It was observed that complete miscarriage occurred in 174 women (81.3%), from which 84 women (78.5%) were in the misoprostol alone group and 90 women (84.1%) in the combination group. They eventually conc-luded that misoprostol alone was as effective as the combination of misoprostol and letrozole.

Methotrexate, combined with a prostaglandin, has been used in some studies with an effectiveness of mostly >90% [20], no trial comparing Letrozole /prostaglandin with methotrexate/prostaglandin was identified. In a study conducted to compare the efficacy for two medical abortion regimens using misoprostol alone, or with methotrexate, they found that success rate of the methotrexate regimen was 80% and did not differ significantly from the misoprostol regimen that had success rate of 84% [21].

Misoprostol alone or in combination with methotrexate could be an acceptable method for the first-trimester miscarriage. Since the rate of success is similar in both methods, it is possible to eliminate the administration of methotrexate, which is a cytotoxic drug with many potential side-effects[22]. Adding methotrexate treatment to vaginal misoprostol has not been demonstrated to be advantageous in a clinical trial conducted to compare a group of patients receiving methotrexate intramuscularly on day 1 and vaginal misoprostol on day 5 to terminate pregnancy in 1st trimester [23].

In a study conducted by Rudasari et al.,[24] in Mashhad (2004- 2006) on 100 pregnant women at their first trimester, the effect of Methotrexate and Misoprostol on the success rate of abortion was investigated. It was found that 81 (81%) of the women had successful medical abortion and 19 women underwent suction curettage. In a rando-mized, controlled trial designed to compare the methotrexate/misoprostol vs. a more standard approach for termination of pregnancies, the mean interval to the end point in the methotrexate/misoprostol group was higher (26.4 days vs. 4.5 days, p<0.0001) [24].

To the best of our knowledge, we compared for the first time between synergistic effect of methotrexate before misoprostol and letrozole before misoprostol in induction of first trimester missed abortion The current study included 199 women randomly allocated into two groups, group (A) included 99 women received [letrozole (7.5 mg) + misoprostol (200 μg)] and group (B) included 100 women received [methotrexate (50 mg) + misoprostol (200 μg)]. In the current study we found that prescribing letrozole prior to misoprostol was effective in increasing efficiency of misoprostol for inducing complete abortion of non-viable fetus in the first trimester of pregnancy as compared to methotrexate prior to misoprostol. Also, prescribing letrozole didn't cause side effects in patients and also abdominal pain and time of bleeding in patients was significantly lower. Complete abortion was significantly higher among Letrozole as compared with Methotrexate groups, (91.90% vs. 77.00%, p=0.003) of the studied women among two groups respectively in the current study.

In our study, induction-to-abortion time in Letrozole group was significantly shorter than the Methotrexate group, days interval was (2.04 ±1.38 vs. 2.85 ±1.75, p=0.023) days among two groups respectively. Regarding the side effects, in the current study, both regimens were tolerated by most women, with a few women reporting side effects such as low-grade fever and severe pain in addition to nausea and vomiting; this finding agreed with the results of other previous studies[16,25-27]. Further randomized controlled studies are warranted to confirm our findings in termination of first trimester pregnancies.

Finally, this study has some strengths points and limitations. Points of strength include the study design as a RCT and the relatively high number of participants included. Regarding the limitations, we could not evaluate the effect of different doses of misoprostol with the least effective dose to decrease the adverse effects in addition; we could not evaluate different routes of administration.

In the current study, miscarriage induced by methotrexate followed by misoprostol and those induced by letrozole followed by misoprostol were both highly successful and acceptable to most women, however, prescribing letrozole prior to misoprostol was effective in increasing efficiency of misoprostol for inducing complete miscarriage of non-viable fetus in the first trimester of pregnancy, and also prescribing letrozole didn't cause side effects in patients and also abdominal pain and time of bleeding in patients was significantly lower. Using letrozole prior to misoprostol could increase success rate of inducing complete miscarriage by misoprostol in the first trimester of pregnancy, without increasing side effects.

Based on this data, we believe that clinicians and patients will be likely to choose letrozole unless availability or cost is a factor. Further larger research via various dosages and extended periods can be necessary to find out the best treating protocol to attain the highest rate of success and the lowest side-effects rates.

Conflict of interest: None.

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References

1. WHO Regional Office for the Western Pacific. Maternal Health Care: Policies, Technical Standards and Services Accessibility in Eight Countries in the Western Pacific Region. World Health Organization, 2019.
2. Teimoori, B., Esmaeilpoor, M., Ashkezari, A. K., & Farzaneh, F. Comparison of induction abortion in the first trimester using misoprostol alone and misoprostol with estrogen priming. blood vessels, 2019; 7, 8.
3. Lui, M. W., & Ho, P. C. First trimester termination of pregnancy. Best Practice & Research Clinical Obstetrics & Gynaecology, 2020; 63, 13-23.

4. Chen, Y., Jiang, W., Zhao, Y., Sun, D., Zhang, X., Wu, F., & Zheng, C. (2021). Prostaglandins for Postpartum Hemorrhage: Pharmacology, Application, and Current Opinion. Pharmacology.2021; 106(9-10),477-487.
5. Raymond, E. G., Harrison, M. S. & Weaver, M. A. Efficacy of Misoprostol Alone for First-Trimester Medical Abortion: A Systematic Review. Obstetrics and gynecology, 2019; 133**,** 137-147.
6. Kumar, P. & Magon, N. Hormones in pregnancy. Nigerian medical journal : journal of the Nigeria Medical Association, 2012; 53**,** 179-183.
7. Haynes, B. P., Dowsett, M., Miller, W. R., Dixon, J. M. & Bhatnagar, A. S. The pharmacology of letrozole. J Steroid Biochem Mol Biol,2003; 87, 35-45.
8. MAI, Q., HU, X., YANG, G., LUO, Y., HUANG, K., YUAN, Y. & ZHOU, C. Effect of letrozole on moderate and severe early-onset ovarian hypersti-mulation syndrome in high-risk women: a prospective randomized trial. Am J Obstet Gynecol, 2017; 216**,** 42.e1-42.e10.
9. Allen, R. & O'brien, B. M. Uses of misoprostol in obstetrics and gynecology. Reviews in obstetrics & gynecology,2009; 2**,** 159-168.
10. Allameh, Z., Goharian, M., & Eslamian, M. Effect of misoprostol with and without letrozole on the induction of abortion for women with first- trimester missed abortion. Interna-tional Journal of Gynecology & Obstetrics, 2020; 151(2), 214-218.
11. Harris, L. H., & Grossman, D. Complications of unsafe and self-managed abortion. New England Journal of Medicine, 2020; 382(11), 1029-1040.
12. Behnamfar, F., Mahdian, M., Rahimi, F., & Samimi, M. Misoprostol Abortion: Ultrasonography versus BetahCG testing for verification of effectiveness. Pakistan Journal of Medical Sciences, 2013; 29(6), 1367.
13. Zhao, R., Wu, Y., Zhao, F., Lv, Y., Huang, D., Wei, J., ... & Qiu, X. The risk of missed abortion associated with the levels of tobacco, heavy metals and phthalate in hair of pregnant woman: a case control study in Chinese women. Medicine, 2017; 96(51).
14. Dickinson, J. E. & Doherty, D. A. Optimization of third-stage management after second-trimester medical pregnancy termination. Am J Obstet Gynecol, 2009; 201**,** 303.e1-7.
15. Parker, B. M., Gupta, A. K., Lymperopoulos, A., & Parker, J. Methotrexate for cornual ectopic pregnancy. Cureus, 2020; 12(8).
16. Torky, H. A., Marie, H., ElDesouky, E., Gebreel, S., Raslan, O., Moussa, A. A., ... & Mohsen, M. N. Letrozole vs. placebo pretreatment in the medical management of first trimester missed miscarriage: a randomized controlled trial. Geburtshilfe und Frauenheil kunde, 2018; 78(01), 63-69.
17. Bankole, A., Remez, L., Owolabi, O., Philbin, J., & Williams, P. From unsafe to safe abortion in Sub-Saharan Africa: Slow but steady progress, 2020.
18. Javanmanesh, F., Kashanian, M., & Mirpang, S. Comparison of Using Misoprostol with or without Letrozole in Abortion Induction: A Placebo-Controlled Clinical Trial. Journal of Obstetrics, Gynecology and Cancer Research (JOGCR), 2018; 3(2), 49-52.
19. Rezai, Z., Heydari Bazardehi, S. S., Ghasemi Nezhad, A., Saeid Sadeghi, A., & Ghorbani Yekta, B. Letrozole and misoprostol versus misoprostol alone for termination of pregnancy: a randomized clinical trial. Tehran University Medical Journal, 2014; 71(11).
20. Siyaya, T. N. Q. Cost-analysis of Misoprostol and Mifepristone versus Misoprostol and Methotrexate when used for medical termination of pregnancy in women of gestational age of 7 weeks and less at Embhuleni Hospital in Elukwatini, Mpumalanga (Doctoral dissertation), 2019.

21. Taher, E., Swelam, M., Mansy, A., & Elgammal, M. Methotrexate and Misoprostol against Misoprostol Alone for Early Medical Abortion: Compa-rative Study. Journal of High Institute of Public Health, 2014; 44(1), 21-24.
22. Verberne, E. A., Manshande, M. E., Wagner-Buitenweg, N. F., Elhage, W., Holtsema, H., & van Haelst, M. M. (2020). Limb anomalies, microce-phaly, dysmorphic facial features and fibroma of the tongue after failed abortion with methotrexate and misop-rostol. Clinical Dysmorphology, 29(4), 182-185.
23. Moran, T., & Deutsch, R. (2005). Methotrexate/misoprostol vs. a more standard approach for termination of pregnancies of undetermined location: a randomized, controlled trial. The Journal of Reproductive Medicine, 50(10), 784-792.
24. Forghani F, Mehdizadeh Kashi A, Sadegi K, Kaveh M, Ghaffari M. Uterine Leiomyosarcoma: A Case Report. Int J Womens Health Reprod Sci. 2018;6(2):223-225.
25. Von Hertzen, H., Piaggio, G., Wojdyla, D., Huong, N. T. M., Marions, L., Okoev, G.,... & Peregoudov, A. (2009). Comparison of vaginal and sublingual misoprostol for second trimester abortion: randomized controlled equivalence trial. Human Reproduction, 24(1), 106-112.
26. Lee, V. C., Tang, O. S., Ng, E. H., Yeung, W. S. & Ho, P. C. A pilot study on the use of letrozole with either misoprostol or mifepristone for termi-nation of pregnancy up to 63 days. Contraception, 2011; 83**,** 62-7.
27. Naghshineh, E., Allame, Z., & Farhat, F. (2015). The effectiveness of using misoprostol with and without letrozole for successful medical abortion: A randomized placebo-controlled clinical trial. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences, 20(6), 585-589.