EFFECT OF LETROZOLE PRETREATMENT WITH MISOPROSTOL FOR INDUCTION OF MEDICAL ABORTION (RCT)

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Abstract

Background: The most widely used regimen for induction of medical abortion involves the use of oral or vaginal misoprostol. Indeed, the use of mifepristone (antiprogesterone drug) combined with prostaglandins has resulted in increased success in induction of abortion. The next logical step would be to explore the use of anti-estrogenic agents combined with misoprostol.

Aim: This trial was performed to evaluate the effect of letrozole combined with misoprostol on induction of abortion compared with usage of misoprostol alone.

Methods: The subject population was randomly divided into 2 groups: Group A: 99 women (underwent induction of abortion by letrozole 7.5 mg (Femara) once daily for 3 days, followed by misoprostol 400 mcg vaginally every 4h up to a maximum of five doses per day) Group B: 99 women (underwent induction of abortion by misoprostol 400 (Misotac) mcg vaginally every 4h up to five doses per day).

Results: The results of the study demonstrated no clinical significant difference between complete abortion rate of 78% within 24h in women diagnosed as missed abortion less than 13 weeks gestational age with the sequential regimen of letrozole and misoprostol, compared to 74% complete abortions using misoprostol alone. There was no significant difference in the induction to abortion interval (M: 8.2h & 9.4h respectively), also there was no difference concerning the side effects.

Conclusions: These results indicate that letrozole didn't show a significant improvement in the efficacy of misoprostol in induction of first trimester abortion.

Keywords: Letrozole pretreatment; Misoprostol; Medical abortion.

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INTRODUCTION

Medical abortion is the induction of abortion by using special drugs and a successful abortion is achieved when there is no need for any surgical intervention. Medical

management has become an effective and safe alternative to surgical management with better patient satisfaction. (1)

The most popular drugs used for medical abortion are Prostaglandins and their analogs. Owing to its simple and easy administration and less side effects; Misoprostol gained popularity over other prostaglandins. Misoprostol successes rate in inducing abortion successfully has been reported to range from 37% to 86% in many studies and depending on the route of administration, the regimen and dosage used. The combination of misoprostol with other drugs to augment its effect is confirmed to have higher effectivity [2].

It is well known that pregnancy estrogen and progesterone hormones are important hormones in maintaining healthy pregnancy. Indeed, the use of anti-progestogenic agents like mifepristone combined with prostaglandins has resulted in improved success in termination of early pregnancy. The next logical step would be to explore the use of anti-estrogenic agents. (3)

Letrozole is a third-generation aromatase inhibitor which causes suppression of estrogen production. When combined with misoprostol, there is an improvement in rate of abortion and decreased induction-of abortion time .(4)

In this study, we used letrozole (a third-generation selective aromatase inhibitor) as an effective adjunct to misoprostol for termination of first trimester missed abortion; its action is suppressing estrogen production by the corpus luteum which may assist in induction of abortion.

Research question and aim of study

The study involved women with first trimester missed abortion; we used a combination of letrozole and misoprostol to compare between this combination and the usage of misoprostol alone. Would letrozole-misoprostol regimen induce complete abortion during the first 24 h better than misoprostol alone? Methods.

Patients and Methods :

This study was a Randomized control trial WITH allocation 1:1.No important changes have occurred to methods after trial commencement (such as eligibility criteria), Women were considered eligible to participate in the study if they were pregnant with gestational age of 13 weeks or less of missed abortion as confirmed by ultrasound scanning on day 1 of the study, in good general medical condition, and their age is between 20 – 40 years old were accepted, The study excluded women having living fetus, smokers, who gave history of bronchial asthma, IHD, liver or kidney diseases, and those who were receiving regular drug intake before admission to the study except medications for DM, HTN, SLE were accepted.

This study was conducted at Ain Shams University maternity hospital during the period from September2014 to September 2015

The subjects under the study underwent: history taking (Personal history, Complaint and present history, Obstetric history, Past history: Of Diabetes Mellitus (DM), Hypertension, Cardiac Problems, Renal Troubles, Bleeding Tendency, Blood Disease, Bronchial Asthma, Glaucoma, Allergy or Previous Operations (especially Previous Uterine Scar). Full physical examination was performed including General examination included: Abdominal examination, Vaginal examination, Ultrasound examination was performed on women who were eligible for participation in this study in order to confirm missed abortion and the gestational age. Lab was drawn from the patients including CBC, Renal and liver function (urea and creatinine and liver enzymes), Serum E2 concentrations was checked before and after the induction of abortion. Women then were sent home

for 3 days. In the letrozole group patients received 7.5 mg letrozole (Femara, Novartis) on Day 1 to Day 3. A designated research nurse supervised the subjects to take the first dose of letrozole on Day 1, and the subjects took the second dose themselves on Day 2. The third dose of letrozole was given on admission to our hospital on Day 3 then the patients were sent to another research nurse -who received subjects from both groups- to give them 400 mcg vaginal misoprostol soaked with saline every 4 hours up to a maximum of five doses. Administration of misoprostol was withheld if the woman had strong painful uterine contractions. Side effects, uterine contractions, blood pressure and pulse rate were recorded every 4 hours. Pelvic examination was performed every 4 hours to assess dilatation and effacement of the cervix before the next dose of misoprostol. The patient was reassessed if abortion has not occurred after 24 h. If there were no symptoms or signs suggestive of imminent abortion, the second dose of vaginal misoprostol was given (for a maximum of five doses). If abortion still failed to occur, the pregnancy was terminated by D&C.

After abortion, Pelvic ultrasound was done to confirm whether the abortion was complete or not. If necessary, Transvaginal evacuation and curettage of the uterus was performed under general anaesthesia if abortion was incomplete. The women were discharged 24 h after the abortion if there were no complications. Blood sample was taken for complete blood profile and estrogen level as stated above before administration of letrozole and after abortion before discharge.

The Primary outcome of this study was the rate complete abortion during the first 24 h, while the secondary outcomes were : Induction-to- abortion time interval (hours), No. of incomplete abortion, failure of induction of abortion, Doses of vaginal misoprostol (400mg tabs), side effects of drugs, estrogen levels in letrozole and non-letrozole groups.

NO changes occurred to trial outcome from the beginning till end of trial

Sample size calculation: The required sample size has been estimated using G*Power version 3.1.7 (Institute für Experimentelle Psychologie, Heinrich Heine Universität, Düsseldorf, German). The primary outcome measure is the difference between the letrozole-misoprostol protocol and the misoprostol-only group as regards the rate of complete abortion by 24 hours from the induction of abortion. It was estimated that a sample of 198 subjects equally randomized into either of the study groups (n=99 per group) would achieve a power of 80% (type II error = 0.2) to detect a small-to-medium effect size (w) of 0.2 between the two study groups as regards the outcome measures. The effect size (w) is calculated as follows: where $\chi 2$ is the chi square statistic and N is the total sample size. This effect size is chosen as it may be regarded as a clinically relevant difference to seek in this type of research.

The test statistic used for sample size calculation is the two-sided chi square test with one degree of freedom and significance is targeted at the 95% confidence level (type I error = 0.05)

No interim analyses and stopping guidelines: Randomization was done using a computer generated randomization table using Research Randomizer Version 4.0 software in a 1:1 ratio, using a case code written in a piece of paper and put in an opaque concealed envelope which carried the case number. The letter L referred to women randomized to Letrozole group; M refer to control group. Allocation concealment was ensured as the service nurse did not release the randomization code till the patient was recruited into the trial.

RESULTS

Fig 1 shows the flow chart of the patients for each group. For each group, the numbers of

participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome, no statistically significant difference among 2 groups as regard demographic data (Table 1). No Statistically significant difference between 2 groups as regard primary outcome and secondary outcomes as shown in table 2. Table 3 showed statistically significant difference among 2 groups as regard complication and side effects of drugs. Table 4 shows Comparison between estrogen levels in letrozole and non-letrozole groups. There was a high statistically significant difference between serum estradiol concentration in the letrozole group and that of the non-letrozole group on Day 3 and after abortion.

DISCUSSION

In this study, we used letrozole (a third-generation selective aromatase inhibitor) as an effective adjunct to misoprostol for termination of first trimester missed abortion; our Primary outcome in this study was the rate complete abortion during the first 24 h, while the secondary outcomes were : Induction-to- abortion time interval (hours), number of incomplete abortion, failure of induction of abortion, Doses of vaginal misoprostol (400mg tabs), side effects of drugs, estrogen levels in letrozole and non-letrozole groups.

Our results interpretation and its comparison to other studies

In the RCT study of lee et al., 2011; 168 were randomized into two groups. The patients in letrozole group were given letrozole 10 mg daily for 3 days then they received 800 micrograms vaginal misoprostol, while the patients in the placebo group were given placebo for 3 days followed by 800 micrograms vaginal misoprostol. The abortion rate of the studied letrozole group was significantly higher than that of the placebo group in gestations up to 49 days was significantly higher in the letrozole group than in the placebo group which apparently disagrees with our study but our study mean gestational age was about 8.6 weeks and 9.1 weeks in placebo group. In the study of Lee et al., 2011; the corresponding rates for gestation between 50 and 63 days were not significantly different between the two groups which agrees with our study. (5)

In another study of Lee et al. (2011), in accordance with our study they made a randomized placebo-controlled, double-blinded trial with 130 women between 12 and 20 weeks. Letrozole 7.5 mg vs placebo were given for 3 days, followed by misoprostol 400 microgram vaginally every 3 hours (up to a maximum of five doses on the third day). The abortion rate in 24 and 48 hours were similar either for the letrozole and placebo groups. The interval of induction-to-abortion was similar for both groups. Drug side effects were comparable between the both groups. They agreed with our results that the use of letrozole as an adjuvant to misoprostol in abortion does not significantly improve the abortion rate over the misoprostol-only group. (6)

In a RCT by Lee et al., 2012 ; 30 were randomized into two groups: in the letrozole group, the patients received 10 mg of letrozole daily for 3 days, and in the control group, the patients received a placebo for 3 days. Serum estradiol were measured before letrozole intake and then once daily for 6 days. Similar to our results the estradiol levels were significantly lower in the letrozole patients' group than in the control group. (7) In another RCT by Behroozi et al., 2018, they randomized 78 patients into two groups. First group received daily 10mg letrozole for 3 days followed by vaginal misoprostol. In second group the patients received the vaginal misoprostol only. Their results showed a higher complete abortion rate in favor of letrozole group over misoprostol only group. The main limitation of that study compared to our study is their small sample size. (8)

In their randomized controlled trail Naghshineh et al., 2015 randomized 130 patients eligible for legal abortions into two groups. Letrozole group received daily 10 mg letrozole for 3 days followed by misoprostol sublingually. Placebo group received daily oral placebo followed by misoprostol sublingually. The mean induction-to-abortion interval was 5.1 hours in letrozole group and 8.9 hours in placebo ($P < 0.0001$). These results differ from our study which may be explained by the different route used for misoprostol sublingually rather than oral. (9)

In a recent systematic review and meta-analysis, Zhou et al., 2021 analyzed 6 RCTs involving 555 patients (the studies previously mentioned in our discussion). They found that letrozole supplementation showed significantly increased complete abortion (in contrary to our study) and decreased estradiol and no significant effect on induction-abortion time (in accordance with our study.(10) From the point of view of Zhou et al., 2021 their meta-analysis have several limitations. First limitation is that their analysis is based on 6 RCTs, and 3 of them have a relatively small number of patients (number of patients <100) which could lead to overestimation of the letrozole effect. They concluded that more RCTs should be conducted with large sample size to investigate the letrozole effect. Another limitation were different doses and duration of letrozole supplementation which may have affected the pooling results. Last limitation was the different gestational age in all studied RCT which may have a role in judging the letrozole effect. (10).

Strengths and limitation of our study

Strength of our study in relation to other studies was adequate number of patients in both randomized groups while the main limitation of the trial is that it conducted in one hospital which may attribute to statistical bias.

Clinical implication of our study

From our study and in comparison, to other studies; we don't encourage the use of letrozole in clinical practice as adjuvant to misoprostol till more systematic review and meta-analysis study standardize its use.

Recommendations for Future research

Further studies using different regimens of aromatase inhibitors may be warranted

CONCLUSION

The regimen of letrozole pretreatment (7.5 mg daily for 3 days) does not improve the first trimestric abortion rate when compared with that of the misoprostol-only.

Consent for publication

NOT APPLICABLE

Availability of data and materials

All Data and ethical committee documents are available upon request

Competing interests

The authors report there are no competing interests to declare

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Authors' contributions

All authors jointly contributed to conception and design of the study.

Ahmed Sherif Abdel hamid: Design of the study, helped in review of literature, revision of results and data analysis, writing the manuscript and submission to journal

Yaser Abu-Taleb; design of the study, revision of review of literature and revision of manuscript

Moustafa Ibrahim design of the study, revision of review of literature and revision of manuscript

Mohamed Omar Dakrory: registration of trial, obtaining ethical committee approval, reviewed the literature, shared in collection of Data, active participation in process of induction and labor.

AMR Sobhy: helped in review of literature, revision of results and data analysis and contributed in writing the manuscript

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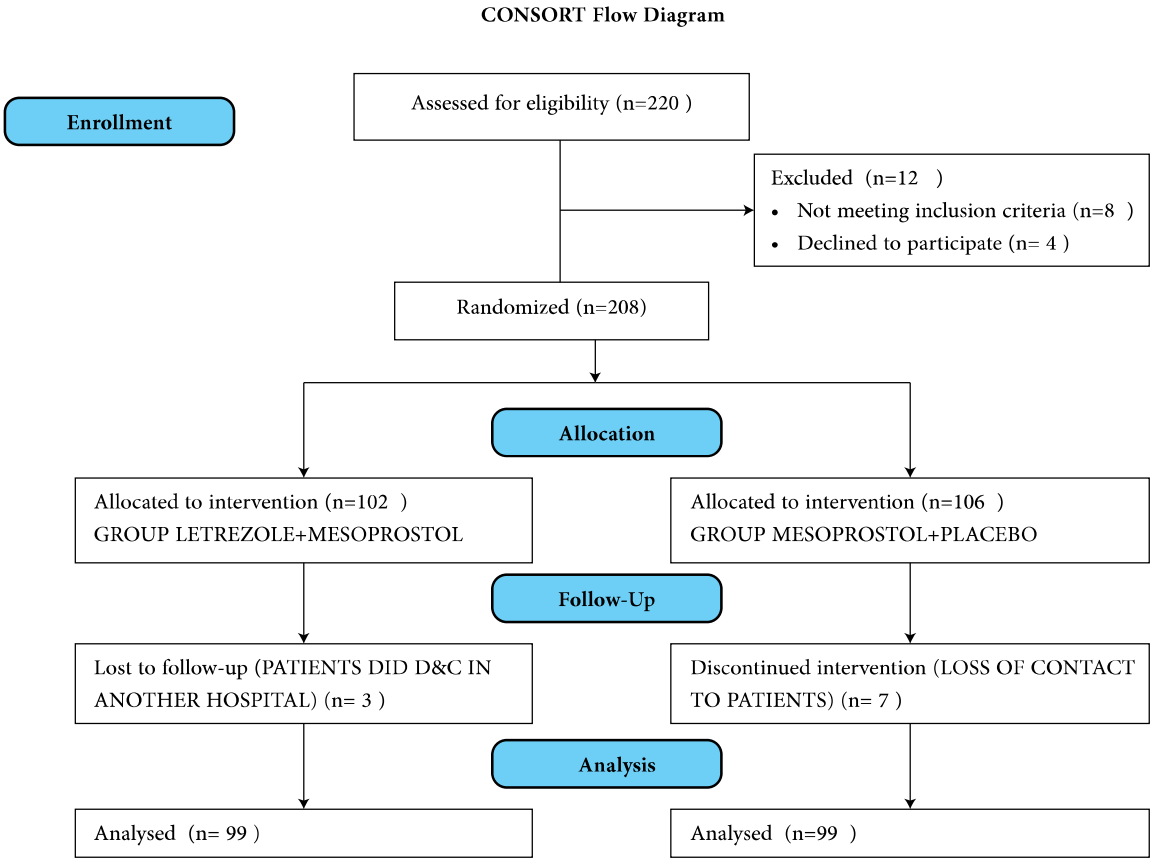

Table 1: Demographic data between the letrozole and non letrozole groups

	Group A (Letrozole) (n=99)		Group B (non Letrozole) (n=99)		p value
	mean	SD	mean	SD	
Age (years)	29.2	5.5	26.04	6.4	0.167
Age (years)	67.7	8.5	70.2	9.4	0.30
Height (cm)	167.6	5.5	165.0	5.1	0.179

Table (2): Comparison between both groups as regard the outcomes of study

	Group A (Letrozole)(n=99)	**Group B (non Letrozole)(n=99)**			**p value**
	mean	SD	mean	SD	
Gestational age by ultrasonography (weeks)	8.6	1.9	9.1	1.5	0.288
No. of subjects with previous pregnancy	number	percentage	Number	percentage	
	78	78.80%	75	75.70%	0.808
No. of subjects with previous abortion	29	29.30%	24	24.20%	0.49
Complete abortion rate in 24 h	78	78.80%	74	74.70%	0.746

	Median	range	Median	range	
Induction-to- abortion time interval (hours)	8.2	3–32	9.4	3.6–48	0.775
No. of incomplete abortion	7		11		0.491
	Range	mean	Range	mean	
Failure of induction of abortion	0		2		0.083
Doses of vaginal misoprostol (400mg tabs)	1-8 tablets	3.8	1-10 tablets	4.6	0.783

Table (3): Comparison between both groups as regard the appearance of side effects

	Group A (Letrozole)(n =99)	**Group B (non letrozole) (n =99)**	**p value**
Nausea	23	18	0.435
Vomiting	17	14	0.632
Fever (>38°C)	8	12	0.371
Dizziness	20	24	0.547
Fatigue	17	23	0.343
Breast tenderness	12	7	0.251
Headache	16	13	0.577
Diarrhea	15	22	0.249
Post abortive bleeding	7	14	0.126

Table (4): Comparison between estrogen levels in letrozole and non letrozole groups

Estradiol level (pg/ml)	Group A (Letrozole)(n =99)		Group B (non letrozole)(n =99)		p value
	mean	SD	mean	SD	
Before treatment	1324.5	456.3	1402.8	418.6	0.131
After three doses of letrozole	211.6	39.4	1347	387.6	0.0001
After abortion	85.8	14.5	148.1	26.2	0.0001