

Misoprostol versus Letrozol with Misoprostol in Management of First Trimesteric Missed Miscarriage

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ABSTRACT

Background: A missed miscarriage represents a form of spontaneous abortion, it occurs in about 26% of all pregnancies and the management may be expectantly, surgical, and medical. Misoprostol and letrozole are medications utilized for medical treatment of miscarriages.

Aim of the work: to match the security and effectiveness of two treatment modalities (Misoprostol versus Letrozol with Misoprostol) in medical treatment of 1st trimesteric missed miscarriages.

Patients and methods: This is an interventional randomized case-control investigation that was performed at the outpatient antenatal care clinic of Luxor General Hospital during the period from February to December 2017. The study included a number of 200 cases who have been randomly classified to 2 equal groups: Group-I "Misoprostol" which included 100 cases received 800-mg of misoprostol vaginally at once of diagnosis and group-II "Letrozol + Misoprostol" which included 100 cases received 10-mg letrozol 2 times a day for 3-days as pretreatment then 800-mg of vaginal misoprostol.

Results: Misoprostol alone group (group-I) has a significantly high duration of vaginal bleeding after the 1st Misoprostol dose and time passed after 1st misoprostol dose till the 1st passage of POC in comparison with group-II, (P-value<0.01 for all). Misoprostol alone group had significantly higher incomplete abortion (P<0.01) and emergency D and C (P=0.03) in comparison with the combined group (group-II). However, induction of abortion interval was significantly high in Letrozol + Misoprostol group in comparison with Misoprostol alone group (99.4 ± 14.3 vs. 61.5 ± 13.2 hrs, P<0.01).

Conclusion: The results revealed that a 3-days course of letrozole (10-mg per day) trailed by misoprostol vaginally (800-mg) was accompanied with a significantly high full abortions rate in women with first-trimester miscarriage compared to misoprostol alone (81.0% vs. 54.0%) without increasing side effects.

Keywords: Misoprostol; Letrozol; Management; First Trimesteric; Missed Miscarriage.

INTRODUCTION

Abortion is the gestation terminations earlier to a fetus can potentially live outside the uterus, it is a mutual complication of gestation occurring either spontaneously (miscarriage) or on purpose (induced abortion).¹ A missed miscarriage happens in 10 to 20% of the clinical recognized gestations.² Between 1990 and 1994, it was estimated that about 50 million induced abortions occurred per year worldwide while, this number increased to 56 million per year during the period from 2010 to 2014.³ Also, it was estimated that about 50% of abortions are not safe and could cause considerable maternal deaths therefore, successful management of abortion is a crucial matter in gynecology.⁴

Vacuum aspiration surgery was the selected method for terminating pregnancy in 1960s, then persuading

abortions using medications is vastly utilized in worldwide levels via mifepristone manufacture.⁵ Persuading abortions via medications is a substitute for surgical treatment, which has economy profits with lower side-effects and its success rate is 60 to 95%.⁶ Several medications can be utilized to persuade abortions and counting limitations in access to mifepristone medications and its high price, it isn't available in the majority of the republics and substitute medications are utilized to persuade abortions.⁷ One of these medications is misoprostol which is prostaglandin E1 analogue.

Misoprostol is a prostaglandin that reasons myometrial cervical softening, contractions, and dilatations and it is utilized to persuade abortions and labour and to manage atonic postpartum hemorrhage and peptic ulcers.⁴ It has the benefit of being economic and steady with a low rate of side-effects, which has result in it has been comprised in the WHO list of important medications.⁶ In addition, misoprostol is could be kept in room temperature, it is affordable and efficient, doesn't need special care

during use and usually used with different routes of administration "vaginally, orally and sublingual".¹ Also, misoprostol is well tolerated by cases and significantly decreases treatments prices in addition, it considerably reduces curettage and the need for surgical intervention.⁵

Letrozole is a key aromatase inhibitor, that is utilized to excite ovulations in non-fertile females suffered from ovulatory dysfunctions, it has a comparatively short 45-h half-life and it is active orally and inhibits aromatase enzymes oppositely.⁸ Letrozole can have a function in abortions therapies by constraining estrogen synthesis that causes rise endogenous gonadotropin and lastly excites the growing of ovaria's follicles.⁹ As well, it has been reported that Letrozole is also used for the treatment of breast cancer related to estrogen and it can replace mifepristone "which is expensive and not available in many countries".¹⁰

Some researchers propose prescriptions of aromatase inhibitors before the usage of major medication "such as misoprostol or mifepristone" for persuading medication abortions rises effectiveness of management regimens and also decreases the necessity for surgery.⁹ A success rate of 86.9% was achieved when letrozole was managed for 3-days trailed by misoprostol.¹¹ In another study, letrozole protocol has been utilized for 7-days and attained 95 % rate of success.⁹ While, letrozole and mifepristone were managed before misoprostol and accomplished a rate of complete abortion 98%.¹⁰ Many studies evaluated the impact of misoprostol with letrozole in management of missed miscarriage, but reaching firm results need further studies. The objective of this work was to match the safety and effectiveness of two treatment modalities (Misoprostol versus Letrozol with Misoprostol) in medical treatment of the 1st trimesteric missed miscarriages.

PATIENTS AND METHODS

This is an interventional randomized case-control research that has been performed at the outpatient antenatal care clinic of Luxor General Hospital during the period from February to December 2017. The study included a number of 200-cases who were randomly classified to 2 equal groups: Group-I "Misoprostol" which included 100 cases received 800-mg of misoprostol at once of diagnosis vaginally and group-II "Letrozol + Misoprostol" which included 100 cases received 10-mg letrozol 2 times a day for 3 days as pretreatment then 800-mg of vaginal misoprostol. All females with 1st trimester missed miscarriages and closed cervix and no conceptions of products in the cervical duct were included in this work. Exclusion criteria were; preceding attempts for termination of pregnancy, IUCD in utero, uterine tumors such as fibroids or malformations in addition to medical disorders such as heart disease, renal, liver disease and hemorrhage or blood disease.

All included cases have been exposed to the following full history taking counting personal history, complaint and present history, menstrual history, family history, history of medical disorders

and full obstetric history. In addition, general, pelvic, abdominal and ultrasonographic examinations were done. Some investigations were done especially, ABO and Rh, sure diagnosis of missed miscarriage and gestational age by ultrasonography if there is a difference between amenorrhea and gestational age by ultrasound gestational age is recorded.

The first group (Misoprostol group) received 800-mg misoprostol (Misotac, Tab. 200 mcg Sigma @, Egypt) vaginally at the first day of enrollment in the study and the second group (Letrozol + Misoprostol group) taken 10-mg letrozole (Femara Tab. 2.5-mg, Novarts @, Egypt) 2 times a day for 3-days then 800-mg vaginal misoprostol. Patients were advised to document the following; date of 1st vagina blood loss, date of 1st passing of tissues parts, occurrence of pains and its strength (mild, moderate or severe) occurrence of bleeding and its strength (mild, moderate or severe) and its period, occurrence of side effects (nausea, vomiting, hyperpyrexia, shivering, colics etc...). Also, they were recommended to come back to the clinic if there were severe pains and blood loss, intolerable side-effect and at 3rd and 7th day after misoprostol dose. At the 3rd day, ultrasound was done for the detection of incomplete abortion complete and second dose of misoprostol was given if missed or incomplete miscarriage. At the 7th day, ultrasound was done and evacuation was done of missed or incomplete miscarriage. The patient was considered to have incomplete abortion if the remnant inside the uterus 2 cm or more. Regarding the taken outcome measures, primary outcome measures include full abortions rate and inductions to abortions period. While, the secondary result measures are duration of bleeding, occurrence of side-effects and the need of emergency evacuation.

Statistical analyzing have been done via SPSS-20 program (IBM, NY, USA).¹² Data are presented as means \pm SD for quantitative data and by No. (%) for qualitative data. Comparison among groups have been done using Student's t testing for parametric data and using Mann Whitney testing for nonparametric data. Chi-Square testing was utilized to examine the significance among studied groups concerning qualitative data or Fisher exact testing when needed. Probability value (P-value) was supposed significant if <0.05 and high significance if it was <0.01 .

RESULTS

The present results showed that nonsignificant changes were found among groups regarding ages (P-value=0.48), BMI (P-value=0.62), gestational age (P=0.32), gravidity (P=0.84) and previous CSs (P=0.83), (Table, 1). Misoprostol alone group (group, I) had significantly higher time passed after 1st misoprostol dose till the start of vaginal spotting compared to group-II (53.9 \pm 14.2 vs. 33.4 \pm 7.4 hrs., P-value <0.01). Also, group-I had a significantly higher duration of vaginal bleeding after the 1st misoprostol dose and time passed after 1st misoprostol dose till the 1st passage of POC in comparison with group-II, (P <0.01 for all), (Table, 2). The results showed that group-I had a significantly higher number of cases needed for

urgent evaluation due to severe pain or bleeding compared to group-II, (22 cases vs. 10 cases) and there was a high statistically significant change among groups as regards following-up (P<0.01), (Table, 3). Nonsignificant change was found among groups in regard to the occurrence of side effects (37 patients in group-I vs. 32 patients in group-II, (P-value=0.46), but nausea and vomiting were significantly prevalent in group-II (P<0.01), (Table, 4 & Figure 1). Also, the results indicated that Letrozol + Misoprostol group (group, II) had a significantly

high rate of success of full abortions as comparison with Misoprostol only group (group, I) (81.0% vs. 54.0%, P<0.01), group-I had a significantly higher incomplete abortion (P<0.01) and emergency D and C (P=0.03), compared to group-II, (Table, 5 & Figure 2). Furthermore, letrozol + Misoprostol group (group-II) had significantly higher induction of abortion into intervals compared to Misoprostol group (group-I), (99.4 ± 14.3 vs. 61.5 ± 13.2 hrs, P<0.01).

Variable	Groups		P. value (Sig.)
	Group-I Misoprostol (n=100)	Group-II Letrozol + Misoprostol (n=100)	
Age (year)	26.3 ± 4.2 (19-40)	25.9 ± 3.8 (19-35)	0.48 ^{NS}
BMI (kg/m ²)	26.1 ± 2.6 (16.7-33.5)	26.3 ± 3.1 (19.1-36.2)	0.62 ^{NS}
Gestational age (days)	55.5 ± 9.3 (45-83)	54.2 ± 8.9 (45-82)	0.32 ^{NS}
Gravidity	PG	25 (25.0%)	29 (29.0%)
	G2	23 (23.0%)	21 (21.0%)
	G3	15 (15.0%)	17 (17.0%)
	G4	10 (10.0%)	12 (12.0%)
	G5	27 (27.0%)	21 (21.0%)
Previous CSs	0	71 (80.0%)	69 (78.0%)
	1	12 (12.0%)	17 (15.0%)
	2	8 (2.0%)	8 (4.0%)
	3	6 (3.0%)	4 (3.0%)
	4	3 (3.0%)	2 (3.0%)

T testing and Chi-square tests have been utilized to compare between groups. NS Not significant.

Table 1: Comparison between groups as regard demographic and baseline data.

Variable	Groups		P. value (Sig.)
	Group-I Misoprostol (n=100)	Group-II Letrozol + Misoprostol (n=100)	
Time passed after 1 st misoprostol dose till the start of vaginal spotting (hrs.)	53.9 ± 14.2	33.4 ± 7.4	<0.01**
Duration of vaginal bleeding after the 1 st misoprostol dose (hrs.)	72.8 ± 21.4	36.2 ± 11.7	<0.01**
Time passed after 1 st misoprostol dose till the 1st passage of POC (hrs.)	72.1 ± 28.4	52.2 ± 15.3	<0.01**

** Significance at (P-value≤0.01)

Table 2: Comparison between groups as regard clinical findings.

Variable	Groups		P. value (Sig.)
	Group-I Misoprostol (n=100)	Group-II Letrozol + Misoprostol (n=100)	
Need for urgent evaluation due to severe pain or bleeding	25 (25.0%)	12 (12.0%)	<0.01**
3 rd day U/S			
No remnant	46 (46.0%)	76 (67.0%)	
Remnant	26 (26.0%)	8 (8.0%)	
7 th day U/S			
No remnant	9 (9.0%)	5 (5.0%)	
Remnant	19 (19.0%)	4 (4.0%)	
Drop out failed to follow	4 (4.0%)	3 (3.0%)	

** Significant (P≤0.01)

Table 3: Comparison between groups as regard follow-up.

Variable	Groups		P. value (Sig.)
	Group-I Misoprostol (n=100)	Group-II Letrozol + Misoprostol (n=100)	
Side effects			0.46 ^{NS}
No	63 (63.0%)	68 (68.0%)	
Yes	37 (37.0%)	32 (32.0%)	
Nausea & Vomiting	4 (10.8%)	18 (56.3%)	<0.01**
Hyperpyrexia	10 (27.0%)	3 (9.3%)	
Severe Pain	7 (18.9%)	5 (15.6%)	
Severe bleeding needing evacuation	16 (43.3%)	6 (18.8%)	

** Significant (P≤0.01)

Table 4: Comparison between groups as regard side effects.

Variable	Groups		P. value (Sig.)
	Group-I Misoprostol (n=100)	Group-II Letrozol + Misoprostol (n=100)	
Outcome			
Complete abortion	54 (54.0%)	81 (81.0%)	<0.01**
Incomplete abortion	20 (20.0%)	4 (4.0%)	<0.01**
Emergency D and C	24 (24.0%)	11 (11.0%)	0.03*
Drop out	2 (2.0%)	4 (4.0%)	0.67 ^{NS}
Induction to abortion interval (hrs)	61.5 ± 13.2	99.4 ± 14.3	<0.01**

Table 5: Comparison between groups as regard outcome and induction to abortion interval.

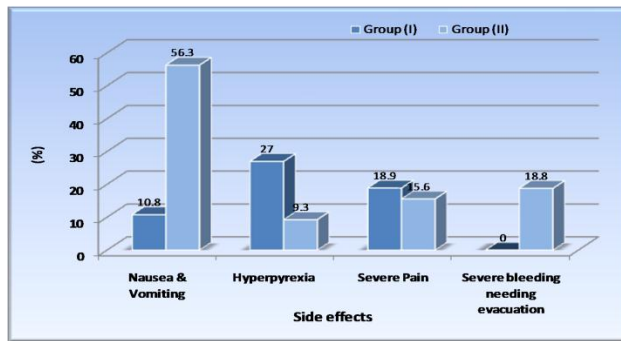


Figure 1: Side effects between groups.

DISCUSSION

A missed miscarriage represents a form of spontaneous abortion, it occurs in about 26% of all pregnancies and it can be managed expectantly, surgically, and medically.² Many medications were used for medical treatment of missed miscarriages, Misoprostol and Letrozole are of these medications. In the current work, we aim to compare the safety and efficacy of 2 treating options in the medical managements of the 1st trimesteric missed miscarriage, the first was Misoprostol alone (800-mg of misoprostol at once of diagnosis vaginally) and the second was Letrozol + Misoprostol (10-mg letrozol 2 times a day for 3 days as pretreatment then 800-mg of vaginal misoprostol).

The present results revealed that there were nonsignificant changes among groups regarding ages (P-value=0.48), BMI (P-value=0.62), gestational age (P=0.32), gravidity (P=0.84) and previous caesarean sections (P=0.83). These non-significant differences between studied groups regarding baseline characteristics are important to ensure the homogenization of the studied groups to get accurate results from the comparison between them. These results are in accordance with Naghshineh et al.⁴, Abbasalizadeh et al.⁵, Torkey et al.¹³.

The current results demonstrated that Misoprostol alone group had significantly higher number of cases needed urgent evaluation "due to severe pain or bleeding" compared to Letrozol + Misoprostol group (22 cases vs. 10 cases). Similar to our findings, Abbasalizadeh et al.⁵ compared the use of misoprostol with or with no Letrozole in inducing abortions. They revealed that 18.8% of cases in Misoprostol alone group needed surgical curettage versus 6.3% in Letrozole + Misoprostol group. Also, similar findings were reported by Lee et al.¹¹, Naghshineh et al.⁴, Javanmanesh et al.¹.

Currently, nonsignificant change was noticed among groups in regard to the occurrence of side effects (37 patients in group-I vs. 32 patients in group-II, P-value=0.46), but nausea and vomiting were significantly prevalent in group-II (P-value<0.01). This is in consistent with Torkey et al.¹³ who found a higher rate of nausea and vomiting in letrozole + Misoprostol group compared to Misoprostol alone group (17.0% vs. 3.0%, p = 0.002). However, they found that the occurrence of other complications

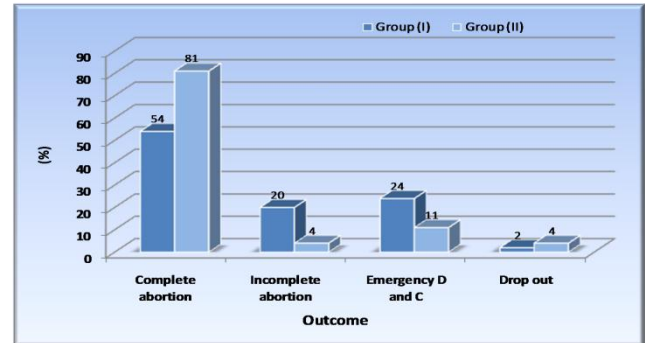


Figure 2: Outcome between groups.

(fever, severe pain and severe bleeding) didn't change significantly among groups. Also, Javanmanesh et al.¹ found that there was nonsignificant change among Letrozole and Misoprostol groups in regard to adverse effects. Furthermore, Naghshineh et al.⁴ found that side-effects occurrence and severity were comparable between Misoprostol alone group and Letrozole + Misoprostol one (P=0.9). Also, Lee et al.¹¹ & Sharami et al.¹⁴ 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^{15,16}. On the other hand, Abbasalizadeh et al.⁵ found that side effects of Letrozole + Misoprostol were significantly low in comparison to that of Misoprostol only (p-value = 0.013).

The present results indicated that the combined group had a significantly high rate of success of full abortions in comparison with Misoprostol only group (81.0% vs. 54.0%, P<0.01). Also, Misoprostol only group had a significantly higher incomplete abortion (P<0.01) and emergency D and C. These results are in agreement with Torkey et al.¹³ 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<0.01). Also, the incomplete miscarriages rate was significantly higher in Misoprostol only group compared to the combined one (61.0% vs. 22.0%, P<0.01). Similarly, Javanmanesh et al.¹ 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). Likewise, Abbasalizadeh et al.⁵ found that the rate of full abortions in combined the group (letrozole + Misoprostol) was 93.75% versus 68.75% in Misoprostol only group (p = 0.001). Also, they found that number of cases who didn't have full abortion in the combined group was significantly lower compared to misoprostol group (6.3% vs. 31.5%, p = 0.001). Additionally, another trial by Behroozi-Lak et al.¹⁷ revealed that using Letrozole before Misoprostol increases the full abortions rate and decreases the induction-abortion interval in women with a gestational age of <14 weeks "which also agreed with our findings". Also, Naghshineh et al.⁴ reported that letrozole + Misoprostol achieved a

complete abortion rate of 76.7% in comparison to 42.6% using Misoprostol alone ($P < 0.001$). Furthermore, Lee et al.¹¹ reported that the administration of Letrozole for 3 days followed by misoprostol achieved a higher rate of success of complete abortions versus Misoprostol alone (86.9% vs. 72.6%).

In a report that tried to find out the mechanism of Letrozole in inducing abortion, Lee et al.¹⁸ reported that Letrozole suppressed the expression of progesterone receptor transcripts, estrogen receptor α and estrogen receptor- α protein in the placentas of cases taking it. Furthermore, Lee et al.¹⁹ 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 have a function in the mechanism of Letrozole action. Also, Lee et al.¹¹ reported that estradiol levels were significantly low afterward Letrozole management in the 1st trimester induction of miscarriage and this proposes that Letrozole can act via suppressing estrogen as well as progesterone receptors. Another explanation, Letrozole was revealed to suppress endothelial growing factor which can have a function in the induction of miscarriage^{20,21}.

Finally, this study has some strengths points and limitations, the relatively high number of included participants are from the strengths points. 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.

CONCLUSION

In conclusion, a 3-days course of letrozole (10-mg per day) trailed by misoprostol vaginally (800-mg) was accompanied with a significantly high full abortions rates in cases with 1st-trimester miscarriages compared to misoprostol alone (81.0% vs. 54.0%) without increasing side effects. Further larger researches 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.

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