Misoprostol versus High Dose Oxytocin and Laminaria in Termination of Pregnancy in Second Trimester Pregnancies

Azin Alavi[1], Minoo Rajaei[2], Malihe Amirian[1], Lili Nikuee Ghazvini[3]

[1.] Assistant Professor, Hormozgan Fertility & Infertility Research Center, Bandar Abbas, Iran
[2.] Associate Professor, Hormozgan Fertility & Infertility Research Center, Bandar Abbas, Iran
[3.] Obstetrics & Gynecology Resident, Hormozgan Fertility & Infertility Research Center, Bandar Abbas, Iran

Corresponding Author:
Lili Nikuee Ghazvini, Obstetrics & Gynecology Resident, Hormozgan Fertility & Infertility Research Center, Hormozgan University of Medical Sciences (HUMS), Bandar Abbas, Iran, Tel: +989111214130, Email: ali_gandomi@yahoo.com

Abstract:
Background: In 2 recent decades, found drug regimen to induce abortion that are more effective than surgery. Prostaglandins especially misoprostol, oxytocin and osmotic dilators such as laminaria use for termination but the best method is unknown. Therefore we aimed to assess the comparison between the Misoprostol regimen and the highly concentrated oxytocin with laminaria regimen in second trimester of pregnancy termination.
Methods: In this randomized clinical trial, 100 women with gestational age 14 to 24 week coming to hospital due to termination of pregnancy in the absence of uterine contractions and items of exclusion criteria enrolled to study and randomly assign to 2 groups and received misoprostol (group 1) or oxytocin (group 2). Data collected with use of observation, examination and demographic checklist. In group 1, in admission time and then every 6 hour patients received 200 µgr misoprostol until start the pain or vaginal bleeding or abortion in 48 hr. in group 2, patients first received laminaria in cervix with duration of 6 hr and then oxytocin 50 unit in 500 cc normal saline in 3 hr. after 1 hr rest, oxytocin dosage elevated as multiple into 2 and continue until termination or maximum dose of 300 u in 500 cc normal saline. Data entered to SPSS software version 16 and analyzed with use of descriptive methods and also Chi-square and T-test.
Results: In each group enrolled 50 women that approximately no different in baseline characteristic. Number of abortion in misoprostol group was more than oxytocin group ($P<0.001$) and duration of abortion also was shorter than oxytocin in misoprostol group ($P<0.001$). Side effects in 23 (46%) women in misoprostol group were seen but no side effect seen in oxytocin group. Complementally interventions was seen in 31 women (60%) in misoprostol group versus 32 women (62%) in oxytocin group but this difference was not significant ($P>0.05$).
Conclusion: This study demonstrated that misoprostol is effective than oxytocin in termination of pregnancy but with attention to limitation of this study include of limited abortion causes due to legal laws, additional studies on different doses of misoprostol and oxytocin due to achieve to suitable regimen with lower side effects recommended.

Keywords: Misoprostol; Laminaria, Oxytocin; Pregnancy termination

Additional Information for citing this article:
Title of Journal: Electronic physician; Abbreviated title of journal: Electron. Physician
doi: 10.14661/2013.713-718

Editorial information:
Type of article: Original
Published: November.01.2013

1. Introduction

A large number of pregnant women need for termination of pregnancy (TOP) which is due to fetal anomalies, fetal death, or maternal diseases. Surgical interventions and medical treatments are used to achieve this aim. Medical treatment is more favorable treatment and is commonly used for TOP. Misoprostol, mifeprostol, and oxytocin are common drugs used alone or in combination for TOP. Misoprostol is a synthetic prostaglandin E1 analog which is used for TOP in various gestational ages (GA). Nausea and vomiting, diarrhea, and abdominal cramping are

common side effects. Also its use in scarred uteruses is limited (1). Also oxytocin is effectively used in combination with misoprostol in TOP (2).

Second trimester TOP is associated with more complications in comparison to first trimester TOP. The rate of infection and the need for surgical intervention is higher in second trimester TOP (3). Also a large number of curettage is reported after second trimester TOP (4). Uterine rupture is less common but is reported in scarred and unscarred uteruses (5, 6). Also Morotti et al reported Defective Placental Adhesion as complication for TOP in second trimester (7). The rate of complications of TOP in second trimester is reported to be 6% (8). Higher gestational age fetal indication and history of curettage are important risk factors for complication (8-10). Several studies are done in order to obtain the most effective and safe regimen for medical treatment in TOP in second trimester. Misoprostol is reported to be a safe, effective, and acceptable treatment for second trimester TOP (11). Also Ozerkan et al have reported higher effectiveness with no increase in side effects by using high dose of misoprostol (12). Misoprostol is usually used vaginally but similar efficacy is reported for sublingual dosages (13, 14). Although adequate studies are available for comparison of different misoprostol regimens (15-18) and its combination with other treatments (2, 19-22) but still studies are continuing to obtain the most effective regimen with less side effects and complications. Additional misoprostol dosages and oxytocin infusion or rarely hysterotomy is used for treatment of patients when TOP fails (23). The aim of current study is to compare the efficacy of vaginal misoprostol versus oxytocin in second trimester TOP.

2. Materials and Methods

This randomized single–blind controlled trial was conducted at the Shariati hospital, university of Hormozgan in Iran, from December 2010 to January 2012. Total of 120 women 18 to 40 years old with gestational age between 14 to 24 weeks were recruited to the study. Inclusion criteria were pregnant women in second trimester according to LMP or first trimester ultrasonography, who were referred to Shariati hospital for pregnancy termination due to missed abortion, intrauterine fetal death (IUFD), fetal abnormalities or genetic disorders such as major thalassemia, and maternal indication such as cardiac disease with closed cervix in the absence of uterine contractions.

The study was approved by ethics committee of Hormozgan University of Medical Sciences (HUMS) and patients were included in the study after obtaining written informed consent. The exclusion criteria were: chorioamniotitis, incomplete abortion, sever polyhydraminus, diabetes mellitus or hypertention, cerclage or previous cervix injuries, unsuccessful treatment for current pregnancy, placenta previa, and contraindications of prostaglandin use (cardiovascular diseases or hypersensitivity). Finally 100 patients were randomly assigned into two equal groups using random digit table either to receive high dose oxytocin and laminaria or misoprostol. For Patients in first group inserted laminaria intra cervical for 6 hours, then laminaria was removed and the patient received 50 unite oxytocin in 500cc normal saline for 3 hours. After one hour rest oxytocin dosage will be doubled. This increase will be continued up to 300 unite oxytocin in 500cc normal saline.Patients in second group received an initial dosage of 200 micrograms misoprostol intravaginal followed by the same dosage every 6 hours up to 48 hours. Treatment failure was defined as unsuccessful termination after 48 hour after laminaria insertion or misoprostol initial dose. Patients were treated using curettage, hysterectomy or additional misoprostol dosage in a case of incomplete fetal termination (residual placenta).

The primary outcome was treatment success rate; the secondary outcomes were duration of termination from treatment start to termination, complete or incomplete or no termination, need for supplementary methods (hysterectomy, courtage, or additional misoprostol dosage), and drug side effects (Fever, nausea and vomiting, diarrhea, and abdominal cramping). Data was analyzed using SPSS 20 software and descriptive statistics, Chi-Square, and independent samples t-test. A P value less than 0.05 was defined as statistically significant level for differences.

3. Results

One hundred patients were assigned into two equal groups with similar baseline characteristics. Table 1 summarized baseline characteristics of the patients in two groups. As shown in Table 2 rate of pregnancy termination was higher in misoprostol group (98%) in comparison to oxytocin group (56%) and percentage of incomplete termination was higher in misoprostol group than oxytocin group (60% vs. 20%) ($P<0.001$). Mean duration of termination was 14.35±4.71 hours for misoprostol group and 21.85±4.96 for oxytocin group which shows a statistically significant shorter duration for in misoprostol group ($P<0.001$). Drug side effects were reported in 23 patients (46%) in misoprostol group and no patient in oxytocin group. Table 3 compares drug side effects in two study groups. As

shown in Table 3 the rate of nausea and vomiting is higher in misoprostol group. Additional procedures and actions were needed in 31 patients (62%) in misoprostol group and 32 patients (64%) in oxytocin group. This difference wasn't statistically significant (P=0.5). Table 4 compares the need for additional procedures and actions in two study groups.

Table 1. Baseline characteristics

Baseline characteristics		Misoprostol	Oxytocin
Age		22.68 ± 6.6	26.50 ± 5.15
Gestational age		18.94 ± 4.27	17.48 ± 2.63
Fetal life situation	Alive	26 (52%)	27 (54%)
	Dead	24 (48%)	23 (46%)
Cause of termination	Fetal death	24 (48%)	23 (46%)
	Fetal anomalies	26 (52%)	21 (42%)
	Maternal problems	0 (0%)	6 (12%)

Table 2. Situation of pregnancy termination in two groups

Pregnancy termination	Misoprostol	Oxytocin	P value
No termination	1 (2%)	22 (44%)	<0.001
Complete termination	19 (38%)	18 (36%)	<0.001
Incomplete termination	30 (60%)	10 (20%)	<0.001

Table 3. Comparison of drug side effects in two study groups

Side effects	Misoprostol	Oxytocin	P value
Nausea	13 (26%)	0 (0%)	<0.001
Vomiting	7 (14%)	0 (0%)	0.006
Diarrhea	4 (8%)	0 (0%)	0.059
Abdominal cramping	0 (0%)	0 (0%)	0.121
Vaginal bleeding	0 (0%)	0 (0%)	-
Tachycystol	0 (0%)	0 (0%)	-

Table 4. Additional procedures and actions in two study groups

Additional procedures	Misoprostol	Oxytocin	P value
Curettage	18 (36%)	7 (14%)	0.01
Additional misoprostol dosage	13 (26%)	25 (50%)	0.011
Hysterotomy	0 (0%)	0 (0%)	-

4. Discussion

This study compares misoprostol with oxytocin in 2nd trimester pregnancy termination. As shown in this study misoprostol is more effective in 2nd trimester pregnancy termination in comparison to oxytocin. Higher rates of unsuccessful treatment were reported in oxytocin group. Also in patients with successful pregnancy termination, the mean duration of the termination was shorter in misoprostol group in comparison to oxytocin group. Several studies have confirmed the effectiveness of misoprostol (1, 13, 15, 24, and 25). Also studies on misoprostol dosage and different treatment regimens are conducting (12). Few studies have compared the effectiveness of misoprostol and oxytocin and oxytocin is usually used in combination with misoprostol. Despite this, one study has compared concentrated oxytocin with prostaglandin E2 in pregnancy termination have reported lower rates of fever and gastrointestinal side effects in oxytocin group. The most important side effects of misoprostol are gastrointestinal side effects such as nausea, vomiting, abdominal cramp, and diarrhea (1). Our study confirms this finding and the rate of nausea and vomiting was higher in misoprostol group in our study.

Ramin et al. have reported similar findings. They have reported the superiority of high dose of misoprostol in comparison to oxytocin in 2nd trimester (26). This effectiveness was shown in lowering the duration of pregnancy termination and increasing the rate of the patients' delivery within 24 hours after treatment. Previous studies have shown that the combination of misoprostol and oxytocin is more effective in comparison to misoprostol alone in pregnancy termination. Owen et al have reported the success rate of 67% for vaginal 200mcg misoprostol every 12 hours. The researchers in this study have used the similar dose of the misoprostol but have reported the higher rate

of treatment success in comparison to our study. The lower sample size in this study caused statistically insignificant differences despite the higher difference of the treatment success rates. Thirty patients were studied by Owen et al. they have used low dose vaginal prostaglandin E2 in combination to oxytocin. The authors concluded that no treatment is satisfactory for the patients in these two groups (27).

Higher dosages of misoprostol in combination with oxytocin were associated with higher success rate. A success rate of 96.7% is reported for both groups in the study of the comparison of 600mcg initial misoprostol dosage followed by 400mcg every 6 hours and combination of misoprostol and oxytocin after 24 hours follow up in 120 patients (28). There was no statistically significant difference between two groups in need for additional actions and procedures. Further analysis showed higher rate of need for additional misoprostol dosage in oxytocin group, but lower rate of curettage.

In summary, our findings support misoprostol usage for 2nd trimester pregnancy termination. Although misoprostol is associated with higher rate of side effects, but is more effective for treatment of these patients. Also it should be noted that misoprostol side effects in our study and similar studies are mild and self limited gastrointestinal and nausea and vomiting with isn't life threatening. A large percentage of the patients in oxytocin group needed for additional misoprostol dosage, but if they received the additional dosage they had lower rates of need for curettage. This finding supports the possibility of better response to treatment in combination of misoprostol and oxytocin. More studies is still needed to answer the questions about effectiveness of combination therapies and also rout of administration of misoprostol is needed (2, 22, and 29). Sample size and no long follow up of the patients for side effects were main limitations of the study. Pregnancy termination in Iran is limited to medical indications or IUFD. Also there is limitation in access to misoprostol in Iran.

5. Conclusion

Although misoprostol is more effective than oxytocin in 2nd trimester pregnancy termination, but it is associated with higher rate of drug side effects. Therefore more studies on the combination of misoprostol and oxytocin treatment are needed.

Acknowledgements:
This paper is prepared from the results of a residency thesis in Hormozgan University of Medical Sciences (HUMS).

Conflict of Interest:
There is no conflict of interest to be declared.

Authors' contributions:
All of authors contributed to this project and article equally. All authors read and approved the final manuscript.

References

1. Lin CJ, Chien SC, Chen CP. The use of misoprostol in termination of second-trimester pregnancy. Taiwanese journal of obstetrics & gynecology. 2011;50(3):275-82. Epub 2011/10/28.
2. Zangeneh M, Malek-Khosravi S, Veisi F, Rezavand N, Rezaee M, Rajatee M .Multiple-dose vaginal misoprostol and single-dose misoprostol plus oxytocin for termination of second-trimester pregnancy. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2012;117(1):78-80. Epub 2012/01/21.
3. Mentula MJ, Niinimaki M, Suhonen S, Hemminki E, Gissler M, Heikinheimo O. Immediate adverse events after second trimester medical termination of pregnancy: results of a nationwide registry study. Hum Reprod. 2011;26(4):927-32 .Epub 2011/02/15.
4. van der Knoop BJ, Vandenberghe G, Bolte AC, Go AT. Placental retention in late first and second trimester pregnancy termination using misoprostol: a retrospective analysis. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2012;25(8):1287-91. Epub 2011/10/18.
5. Syed S, Noreen H, Kahloon LE, Chaudhri R. Uterine rupture associated with the use of intra-vaginal misoprostol during second-trimester pregnancy termination. JPMA The Journal of the Pakistan Medical Association. 2011;61(4):399-401. Epub 2011/04/07.

6. Cuellar Torriente M. Silent uterine rupture with the use of misoprostol for second trimester termination of pregnancy : a case report. Obstetrics and gynecology international. 2011;2011:584652. Epub 2011/07/19.
7. Morotti M, Podesta S, Musizzano Y, Venturini PL, Bentivoglio G, Fulcheri E, et al. Defective placental adhesion in voluntary termination of second-trimester pregnancy and risk of recurrence in subsequent pregnancies. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2012;25(4):339-42. Epub 2011/05/26.
8. Murphy LA, Thornburg LL, Glantz JC, Wasserman EC, Stanwood NL, Betstadt SJ. Complications of surgical termination of second-trimester pregnancy in obese versus nonobese women. Contraception. 2012. Epub 2012/03/27.
9. Mentula M, Heikinheimo O. Risk factors of surgical evacuation following second-trimester medical termination of pregnancy. Contraception. 2012;86(2):141-6 .Epub 2012/01/14.
10. Wagner N, Abele H, Hoopmann M, Grischke EM, Blumenstock G, Wallwiener D, et al. Factors influencing the duration of late first and second-trimester termination of pregnancy with prostaglandin derivates. European journal of obstetrics, gynecology, and reproductive biology. 2011;155(1):75-8. Epub 2010/11/30.
11. Kunwar S, Saha PK, Goel P, Huria A, Tandon R, Sehgal A. Second trimester pregnancy termination with 400 mug vaginal misoprostol: efficacy and safety. Bioscience trends. 2010;4(6):351-4. Epub 2011/01/21.
12. Ozerkan K, Ocakoglu G, Rehimli S, Uncu G, Develioglu O. A comparison of low-dose and high-dose protocols of vaginal misoprostol for second trimester termination of pregnancy. Clinical and experimental obstetrics & gynecology. 2009;36(4):245-7. Epub 2010/01/28.
13. Tanha FD, Golgachi T, Niroomand N, Ghajarzadeh M, Nasr R. Sublingual versus vaginal misoprostol for second trimester termination: a randomized clinical trial. Archives of gynecology and obstetrics. 2012 . Epub 2012/08/21.
14. Cabrera Y, Fernandez-Guisasola J, Lobo P, Gamir S, Alvarez J. Comparison of sublingual versus vaginal misoprostol for second-trimester pregnancy termination: a meta-analysis. The Australian & New Zealand journal of obstetrics & gynaecology. 2011;51(2):158-65. Epub 2011/04/07.
15. Pongsatha S, Tongsong T. Randomized controlled study comparing misoprostol moistened with normal saline and with acetic acid for second-trimester pregnancy termination. Is it different? The journal of obstetrics and gynaecology research. 2011;37(7):882-6. Epub 2011/03/18.
16. Chaudhuri S, Banerjee PK, Mundle M, Mitra SN. A comparison of two regimens of misoprostol for second trimester medical termination of pregnancy: a randomized trial. Tropical doctor. 2010;40(3):144-8 .Epub 2010/06/18.
17. Brouns JF, van Wely M, Burger MP, van Wijngaarden WJ. Comparison of two dose regimens of misoprostol for second-trimester pregnancy termination. Contraception. 2010;82(3):266-75. Epub 2010/08/14.
18. Pongsatha S, Tongsong T. Randomized comparison of dry tablet insertion versus gel form of vaginal misoprostol for second trimester pregnancy termination. The journal of obstetrics and gynaecology research. 2008;34(2):199-203. Epub 2008/04/17.
19. Zhuang Y, Chen X, Huang L .Mifepristone may shorten the induction-to-abortion time for termination of second-trimester pregnancies by ethacridine lactate. Contraception. 2012;85(2):211-4. Epub 2011/11/10.
20. Hou SP, Fang AH, Chen QF, Huang YM, Chen OJ, Cheng LN. Termination of second-trimester pregnancy by mifepristone combined with misoprostol versus intra-amniotic injection of ethacridine lactate (Rivanol(R)): a systematic review of Chinese trials. Contraception. 2011;84(3):214-23. Epub 2011/08/17.
21. Hou S, Chen Q, Zhang L, Fang A, Cheng L. Mifepristone combined with misoprostol versus intra-amniotic injection of ethacridine lactate for the termination of second trimester pregnancy: a prospective, open-label, randomized clinical trial. European journal of obstetrics, gynecology, and reproductive biology. 2010;151(2):149-53. Epub 2010/05/04.
22. Kelekci S, Erdemoglu E, Inan I. Randomized study on the effect of adding oxytocin to ethacridine lactate or misoprostol for second-trimester termination of pregnancy. Acta obstetricia et gynecologica Scandinavica. 2006;85(7):825-9. Epub 2006/07/04.
23. Pongsatha S, Tongsong T. How to manage unresponsiveness to misoprostol in failed second trimester pregnancy termination. The journal of obstetrics and gynaecology research. 2012. Epub 2012/06/14.
24. Kent A. Second trimester termination of pregnancy. Reviews in obstetrics and gynecology. 2011;4(2):95. Epub 2011/11/22.

25. Naguib AH, Morsi HM, Borg TF, Fayed ST, Hemeda HM. Vaginal misoprostol for second-trimester pregnancy termination after one previous cesarean delivery. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2010;108(1):48-51. Epub 2009/09/29.
26. Ramin KD, Ogburn PL, Danilenko DR, Ramsey PS .High-Dose Oral Misoprostol for Mid-Trimester Pregnancy Interruption. Obstet Invest 2002;54(3):176–179.
27. Owen, J. and J. C. Hauth. "Vaginal misoprostol vs. concentrated oxytocin plus low-dose prostaglandin E2 for second trimester pregnancy termination ".J Matern Fetal Med. 1999; 8 (2): 48-50.
28. Zangeneh, M., S. Malek-Khosravi, et al. "Multiple-dose vaginal misoprostol and single-dose misoprostol plus oxytocin for termination of second-trimester pregnancy." Int J Gynaecol Obstet 2012; 117 (1): 78-80.
29. Almog B, Levin I, Winkler N, Fainaru O, Pauzner D, Lessing JB, et al. The contribution of laminaria placement for cervical ripening in second trimester termination of pregnancy induced by intra-amniotic injection of prostaglandin F(2)alpha followed by concentrated oxytocin infusion. European journal of obstetrics, gynecology, and reproductive biology. 2005;118(1):32-5. Epub 2004/12/15.