Oral versus Vaginal Misoprostol for Termination of Second Trimester Missed Abortion

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ABSTRACT

Background and Objectives: Misoprostol is a synthetic analogue of prostaglandin E1. It became an important drug in obstetric practice because of its uterotonic and cervical ripening effects. This study was done to compare the effectiveness of it in oral versus vaginal route for termination of second trimester missed abortion.
Methods: From 1st of October 2008 to the end of June 2009 at maternity teaching hospital in Erbil, a clinical comparative study was done on 90 patients who had second trimester missed abortion, They were randomly assigned to receive either oral misoprostol tablets (45 patients) in dose of 200 microgram every 4 hours or vaginal misoprostol tablets (45 patients) in dose of 200 microgram every 4 hours. The patients were followed for 48 hours.
Results: The mean induction to abortion interval was significantly shorter for vaginal group (9.98±4.56hours versus 13.30±6.24hours, P=0.005). More patients in vaginal group aborted within 24 hours (95.6% versus 82.22%, P-value=0.045) .The vaginal group required less number of doses than the oral group (2.09±0.90 versus 2.84±1.24, P=0.001). Gastrointestinal side effects of misoprostol were significantly more in the oral group.
Conclusions: Misoprostol was effective drug for termination of second trimester abortion. Vaginal misoprostol resulted in shorter induction to abortion interval, less doses required and fewer side effects than oral misoprostol.
Key words: Misoprostol, missed abortion, uterine hyper stimulation.

INTRODUCTION:

Second trimester miscarriage occurs between 13 and 24 weeks of gestation and complicates approximately 1% o f pregnancies [1]. Missed abortion is defined as a gestational sac containing dead embryo or fetus before 24 weeks of gestation without clinical symptom of expulsion [2,3]. Various management protocols have been used for second trimester pregnancy termination, these includes: surgical technique (dilatation and evacuation) and medical approaches such as intra-amniotic prostaglandin F2alpha instillation, prostaglandin E2 vaginal suppositories, Prostaglandin E1 and high dose oxytocin. [4,5]. The introduction of Prostaglandin analogues in the late 1970 of termination of pregnancy in the second trimester. [6] Different doses, routes and regimens of misoprostol for medical termination of pregnancy during second trimester have been studied with the aim to develop the optimum dose and route of administration for effective termination i.e. acceptable success rate, short induction – termination interval and minimum side effects [7- 9] . Misoprostol has the advantages of being cheap, widely available, stable at room temperature and having few side effects, it has been administered orally , buccally sublingually ,rectaly and vaginally [10].

The aims of the study were:

1. To compare the effectiveness of equivalent doses of oral misoprostol versus vaginal misoprostol in terms of the time

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second trimester missed abortion.
2. to compare the effectiveness of each route to induce complete or incomplete abortion.
3. To compare the number of doses required for each route.
4. To determine the severity of side effects of each route.
5. To compare the rate of satisfaction of patient with each route.

PATIENTS AND METHODS:

This study was conducted as a clinical comparative study from first October, 2008 to the first of June, 2009 at Maternity Teaching Hospitals in Erbil city / Kurdistan region /North of Iraq. Among patients who attended the Hospital, one hundred and ten cases of second trimester missed abortion were interviewed. Ninety pregnant women were included in the study.

Exclusion criteria:-

1. Para5 and more.
2. History of previous 2 or more Caesarean sections.
3. Medical diseases like congenital and acquired heart disease, liver disease and asthma.
4. Known hypersensitivity to misoprostol.
5. Any evidence of infection.
6. Patients with abnormal results of investigations.
7. Patients with cervical changes (dilated internal os) and vaginal bleeding on examination (inevitable abortion).

All patients were cases of second trimester missed abortion with gestational age of (13 -24) weeks .They were diagnosed by ultrasound and were admitted to hospital for termination of their pregnancy.

All patients had detailed history with full medical and obstetrical examination and investigations were done for all including ultrasound

The patients were randomized in two groups (45 patients for each):

First group was arranged to receive oral protocol of Misoprostol (misotac) (Sigma pharmaceutical Industries, SAE, Egypt, each tablet contains 200mc) 200microgram every 4hours up to 5 doses per day, if there was no response the regime repeated in the next day.

Second group was arranged to receive vaginal protocol, which consist of 200 microgram (one tablet) vaginally every 4 hours up to 5 doses per day, if there was no response the regime repeated in the next day.

The misoprostol tablet was placed in the posterior fornix of the vagina; the tablet was moistened with few drops of normal saline as lubricant at the time of insertion. At time of placement of subsequent doses, any remaining undissolved tablets were removed before next tablet was inserted.

All patients were followed in the ward every four hours with observation of pulse rate, blood pressure, temperature and occurrence of side effects, before next dose given uterine contractions and cervical status were assessed by abdominal and vaginal examination, no additional misoprostol dose was repeated if abortion is immenant (patient had at least 70% cervical effacement with 2cm opening). The induction considered to be started when the patient received the first dose of misoprostol and abortion defined as the time when the fetus was expelled (incomplete abortion) although in some cases placenta delivered at the same time (complete abortion) After abortion ultrasonographic examination was done to confirm that the products of gestation (fetus and placenta) had been successfully removed to establish that the abortion was complete. Any retained products of the placenta (not delivered spontaneously one hour after delivery of the fetus) were removed by soft sponging. In this study, failure of induction is considered if the patient did not abort within 48hours. Following the procedure women were kept in hospital for eight hours, and advised for follow up visit after 7 days.

Statistical package for social sciences (SPSS version 17) was used for data entry and analysis. Chi square test of association was used to compare proportions and

frequencies. T-test was used to associate the difference between 2 means of variables. Contingency Coefficient used for nominal variable. P-value of less than 0.05 was considered statistically significant

RESULT:

The mean maternal age for the oral group was (29.04 ± 5.28 years) compared with the vaginal group (29.0 ± 5.90 years), with no statistical significant difference between them (p value 0.970).The mean gestational age(in weeks) according to last menstrual period and gestational age according to the new ultrasound assessment in the oral group were(17.95±2.64and 16.57±2.34 respectively) compared with (18.42±2.72and16.64±2.28 respectively) for vaginal group with no statistical significant difference between them (p value 0.41and 0.89 respectively). Regarding the mean induction to abortion interval (in hours) in the vaginal group was significantly less than in the oral group (9.98±4.56hours versus 13.30±6.24hours, P=0.005), as shown in (Table 1). Regarding the number of successful abortions within 24 hours after the initial drug administration was higher in the vaginal group(95.6% versus 82.22%,P-value=0.045) which is statistically significant .However, all abortions happened within 48 hours after the initial in (Table 2). In regard to the type of abortion ,Within the vaginal group 73.33% of women aborted completely ,compared with 53.33% of women in the oral group (P=0.049) which is statistically significant, as shown in (Table 3). Regarding the mean number of doses of misoprostol required for termination of pregnancy ,we found that vaginal group required significantly less number of doses than that required for orally treated group (2.09±0.90 dose versus 2.84±1.24,P=0.001) which is statistically significant, Regarding the frequency of side effects after misoprostol administration, orally treated group reported more gastrointestinal side effects than vaginally treated group, as shown in (Table 4). Other
reported side effects show no statistical difference between the two groups as abdominal pain requiring analgesia, fever, shivering and headache as shown in (Table 4). In regard to the rate of satisfaction 36 women (80 %) with oral group showed complete satisfaction to the treatment compared with 15 women (33.3%) women in the vaginal misoprostol group, with highly statistical significant difference (p value=0.0001). While 9 women (20 %) of oral misoprostol group were not satisfied to the treatment compared with 30 women (66.7 %) they reported that they will choose oral

Table 1: Comparison in mean induction to abortion interval, in oral and vaginal groups

Parameter	Oral group N=45	Vaginal group N=45	P – Value
Mean induction to abortion interval (hours)	13.30±6.24	9.98±4.56	0.005

P value of less than 0.05 is of statistical significance

Table 2: Comparison of successful abortion within 24 Hours, in oral and vaginal groups

Time	Oral group N=45 (No. and %)	Vaginal group N=45 (No. and %)	P – Value
Successful abortion within 24 hours	37 (82.22%)	43 (95.6%)	0.045
abortion more than 24 hours	8 (17.78%)	2 (4.4%)	0.045

P value of less than 0.05 is of statistical significance

Table 3: Comparison of type of abortion, in oral and vaginal groups

Type of Abortion	Oral group (No. and %)	Vaginal group (No. and %)	P – Value
Complete (no. and %)	24 (53.33%)	33 (73.33%)	0.049
Incomplete (no. and %)	21 (46.67%)	12 (26.67%)	0.049

P value of less than 0.05 is of statistical significance

Table 4: *The frequency of side effects, in oral and vaginal groups*

Side effect	Oral Method (No. and %)	Vaginal Method (No. and %)	Total (No. and %)	P – Value
Nausea	6(13.33%)	2(4.44%)	8(8.89%)	0.026
Vomiting	6(13.33%)	0(0%)	6(6.67%)	0.011
Diarrhea	5(11.11%)	0(0%)	5(5.56%)	0.021
Abdominal Pain	4(8.89%)	2(4.44%)	6(6.67%)	0.404
Shivering	2(4.44%)	1(2.22%)	3(3.33%)	0.562
Headache	2(4.44%)	4(8.89%)	6(6.67%)	0.404
Fever(temp ≥38C)	2(4.44%)	4(8.89%)	6(6.67%)	0.404

P value of less than 0.05 is of statistical significance

DISCUSSION :

The development of safe and effective technique for second trimester missed abortion and intrauterine fetal death termination become a major clinical challenge. Different management protocols are continuously revised to achieve improved success rate and reduced discomfort for the patients. The practice of obstetrics and gynecology has over the revolutionized by the use of prostaglandins .Being highly active organic chemical compounds; they not only affect myometrial contractility, but also accelerate physiological ripening of the cervix [11] There was no significant difference between both groups regarding maternal age and the mean gestational age. This result was in agreement with a study done by Gilbert and Reid, 2001 [12], because these factors do not affect the route of administration.

Regarding the mean induction to abortion interval, it was slightly shorter in our study than a study done by Fadalla et al, 2004 [13]. This is may be due to the dosage we used in our study which was double the dosage used by Fadalla et al, 2004. Our findings disagree with a study done by Feldman et al, 2003 which Showed that induction to abortion interval and hospital stay were slightly shorter for the oral group than vaginal group [9], because Feldman et al, 2003 have not used pure oral misoprostol, he added vaginal tablet with the oral group; therefore it is difficult to conclude that oral administration of misoprostol was more efficacious than vaginal route. Aronsson et al, (2004) studied the effect of misoprostol on the uterine contractility following different routes of administration (Oral, vaginal and sublingual), they found that the first effect observed was an increase in uterine tone which occur significantly in a shorter time following oral (7.8 min) and sublingual (10.7 min) than after vaginal (19.4 min). Regular uterine contraction developed in all subjects following sublingual and vaginal but not with oral administration. The increase in uterine activity was significantly higher after two hours and thereafter for sublingual and vaginal treatment than oral misoprostol [14]. This may explain the more effectiveness of vaginal and sublingual misoprostol than oral misoprostol. Regarding the number of successful abortions within 24 hours, it was in agreement with the study of Dickinson and Evans, 2003 [15], Behrashi and Mahadian, 2008 [16]. Our finding disagree with study done by Saha *et al*,2006, because they have not used pure oral misoprostol ;therefore it is difficult to conclude that oral administration of misoprostol was more efficacious than vaginal route [17]. In regarding to frequency of maternal misoprostol side effects as in (Table4), our results were in agreement with Dickinson and Evans, 2003 results [15]. Regarding the side effects of misoprostol, Bebbington et al ,(2002) found that there case in the current study[8]. No uterine ruptures were observed in the current study even in women with previous one caesarean section. This result was in agreement with study done by Dickinson, (2005) [18]. In the current study, we noticed that the satisfaction rate was more in the oral group. As there is less invasiveness, self administration, and may result in the same effects as vaginal approach. On the contrary, 20 % from the oral group preferred vaginal application if they need such in the future. As patients did not accept the higher incidence of nausea and those patients thought the drug near the uterus, the better it works. Our finding disagrees with Dickinson and Evans, 2003 results, in which they found similar route acceptability between vaginal and oral route [15].

CONCLUSION:

1-Misoprostol alone is very effective agent for termination of second trimester missed abortion.
2-Vaginal administration of misoprostol is more effective than oral administration in termination of second trimester missed abortion
3-Oral preparation of misoprostol can be used vaginally, by this way the effect of misoprostol on the reproductive tract increase and gastrointestinal adverse effects are decreased.
4-Adverse effects of misoprostol are minimum and self limiting.

RECOMMENDATIONS:

1-Further studies are required to asses the long term effect of misoprostol on women s health.
2-Trials needed to optimize the dose and dosage intervals of misoprostol in the second trimester termination of pregnancy.
3-Since oral preparations do not dissolve completely when used vaginally, development of preparations that dissolve more completely, such gel or suppositories are recommended.

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