The Outcome of Misoprostol in Missed Miscarriage

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ABSTRACT :

The objective of this paper is to evaluate the outcome and efficiency of Misoprostol in the termination of pregnancy regarding gestational age, parity, total numbers of doses used, associated active bleeding and subsequent need for the use of other medication or surgical intervention, srum fibrinogen and presence or absence of symptoms of threatened abortion. Design: descriptive observational study. This study is carried out in the: Obstetrics and gyaenecology department, Surman general hospital. Study population consists of 200 women diagnosed as missed miscarriage. The patients were selected over a period of 1 year from 1/11/2008 to 30/10/2009. The data collected are parity, gestational age, any complain, previous deliveries and serum fibrinogen level. To conclude, misoprostol alone may be more effective in earlier gestation and low parity where the total dose of the drug needed is obviously decreased.

KEY WORDS:
Misoprostol, missed miscarriage, active vaginal bleeding, curettage and blood transfusion.

INTRODUCTION:

Misoprostol is a synthetic prostaglandin E1 analogue. Misoprostol has been on the pharmacy since 1985 under the brand name of cytotec, it is now available in over 80 countries worldwide for the treatment of gastric ulcer after treatment with non-steroidal anti- inflammatory drugs, however, more than 300 scientific articles have been published in peer-reviewed journals showing the usefulness of misoprostol in obstetrics and gynecology. Despite this, the company which held the patent rights for misoprostol never applied for approval for obstetrics or gynecology and it therefore remains unlicensed for use in these indications. The patent rights ran out in 2004 and there are now other brands coming onto the pharmacy that are licensed for use in pregnancy e.g. misoprostol tablets from IVAX, Gymiso and Vagiprost. This will broaden the choice and improve access. Another brand name is Arthrotec containing 200 microgram of misoprostol and 50 to 75mg of diclofenac in one tablet as prophylactic pain. Misoprostol has short been used for termination of missed miscarriage of it[(1)].

Misoprostol belongs to a group of hormones called prostaglandins which can cause uterine contractions and ripening the cervix, although prostaglandins are highly effective, their efficacy depends on the number of prostaglandin receptors in the uterus and this varies according to gestational age. In early pregnancy there are few receptors and large doses of misoprostol may need to be given repeatedly in order to have an effect, no problems have been reported in the first trimester of pregnancy with women who have had previous caesarean sections. Misoprostol is more effective in earlier gestation and with low parity [2]. Failed Misoprostol miscarriages are associated with birth defects in some cases [3,4,5,6,7]. Misoprostol can be given orally, sublingual, vaginal or rectally. As the bioavailability varies with each route, the correct dose must be used for the

route chosen – do not change routes without checking the dose. The route of administration will be decided in accordance with the preference of the patient and the clinical situation. Vaginal loss may have a negative effect on absorption through the vagina. Oral or sublingual route is preferable in these cases provided the patient has no nausea or vomiting.Also most women prefer the oral route to vaginal application. Absorption of misoprostol is fast in all routes of administrations, but the most rapid action occurs when misoprostol is given orally (peak concentration after 12 min, half –life 20-30 min). Misoprostol given vaginally or sublingual takes longer to start working, has a lower peak (peak concentration after 60 min), but a more sustained effect. Thus, smaller doses are needed when misoprostol is used vaginally. In contrast to other prostaglandins, misoprostol has no significant effect on the lungs or blood vessels (and so can be used in asthmatics). With doses over 400 mcg, diarrhea can occur and some women experience a brief increase in temperature with shivering [8]. Both effects are dose dependent and settle rapidly without treatment. It is common to get lower abdominal pain due to the uterine contractions induced by misoprostol, paracetamol or non-steroidal anti-inflamatory drugs (NSAIDs) like ibuprofen or diclofenac are good treatment options. There is no evidence that NSAIDs reduce the efficacy of misoprostol treatment.

PATIENTS AND METHOD:

Descriptive observational study of 200 pregnant women who admitted to department of obstetrics and Gynecology in Surman general hospital. The patients were selected over a period of 1 year from 1/11/2008 to 30/10/2009. The inclusive criteria were those patients diagnosed as missed miscarriage with or without vaginal spotting, any parity, single gestation, gestational age by date range from 11 up to 28 weeks. Exclusive criteria were multiple pregnancy, any medical disorders and any uterine or adnexal pathology. Seum fibrinogen is measured routinely for all the patients. Other data like past obstetrics history, number of misopristol

doses and duration in hours that ended in expulsion of the product of concept. The recommended dosages used in our study as the following:

- < 13 week 600 Mg sublingual in 3 hours apart with maximum doses 1×2.
- 13-17 week 200 Mg vaginally 6 hours apart with maximum doses 1×4.
- > 17 week 100 Mg vaginally 6 hours apart with maximum doses 1×4

RESULTS :

The data collected are presented show that maternal age range from 20 to 45 years with a mean age of 31 years (95% Confidence interval 30-32), table 1.

Table 1: relationship to maternal age

Maternal age	No. Of Cases	Percent %
20 – 25 yr	20	10 %
26 – 30 yr	50	25 %
31 – 35 yr	60	30 %
36 – 40 yr	60	30%
41-45 yr	10	5%
Total	200	

The highest Parity was between I – II which are around 45 %, only 20% of the Patients were primigravida, table 2.

Table 2: relation to parity

Parity	No. Of Cases	Percent %
P0	40	20 %
P_1 - P_2	90	45 %
P_3 - P_4	40	20 %
P_5 - P_6	30	15%
$\geq P_7$	0	0

90% of Patients had a normal vaginal delivery while other 10% with Previous history of caesarean section, table 3, figure 1.

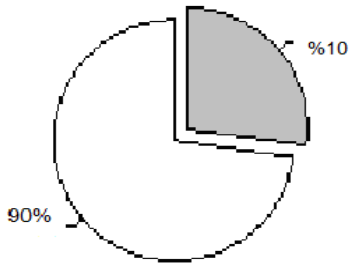

Figure1, relation to past deliveries

Table 3: relation to past obstetrics history

Mode of delivery	**No. Of Cases**	**Percent %**
Normal	180	90 %
Previous C/S	20	10%

The gestational age ranged between 11 to 28 weeks, 45% of cases lying within 15-18 week, table 4.

Table 4: *the distribution of gestational age*

Gestational age	**No. Of Cases**	**Percent %**
11 – 14 wk	40	20 %
15-18 wk	90	45 %
19 – 22 wk	30	15 %
23 – 26 wk	20	10 %
27 – 30wk	20	10 %

Duration of expulsion of product of concept vary, in 45% of cases the abortion happen within 3 to 6 hours from administration of the drug, table 5.

Table 5: total duration by hours that ended in expulsion of fetus

Time / Hours	No. Of Cases	Percent %
3 – 6 hr	90	45 %
7 – 10 hr	20	10 %
11 – 14 hr	60	30 %
15 – 18 hr	20	10%
19 – 22 hr	0	0
23 – 26 hr	10	5%

30% of cases were aborted after 3 doses of misoprostol with gestational age range from 11 to 14wk, while another 30% of cases were aborted after 2 doses of misoprostol with gestation age range from 15 to 18wk, figure 2.

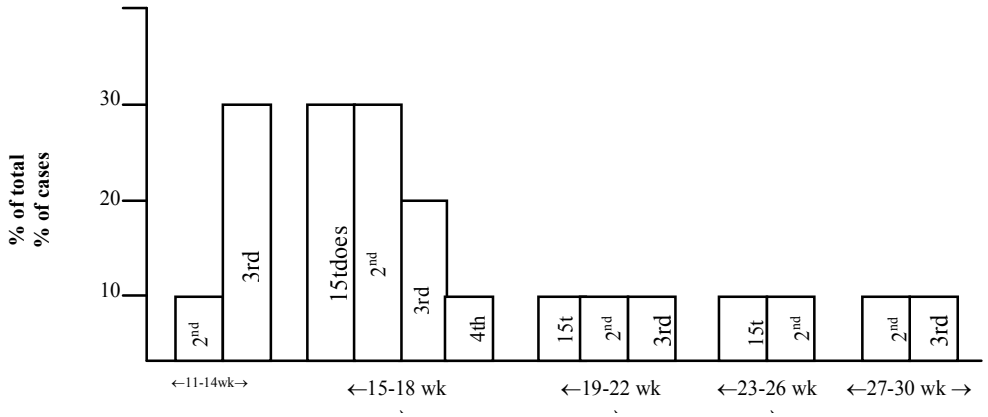

Figure 2: relationship between gestational age and number of doses of misoprostol

50% of cases diagnosed accidentally during routine ultrasound scan without any pain or spots, while another 50% of cases were symptomatic either with mild lower abdominal pain or vaginal spotting or both, figure 3.

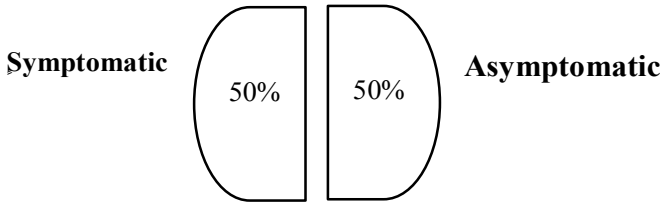

Table 3: relationship to the Presence or absence of mild lower abdominal Pain and vaginal spotting.

Regarding the complain, only 25% of cases were preceded by lower abdominal pain, table 6.

Table 6: relationship to the Presence of Pain or not

symptom	**No .of cases**	**Percent %**
No lower abdominal Pain	150	75 %
Presence of lower abdominal Pain	50	25 %

50% of cases were preceded by vaginal spots antenatty, while other 50% of cases were not, table 7.

Table 7: relation to the presence or absence of vaginal spotting

symptom	**No. of cases**	**Percent %**
Presence of vaginal spotting	100	50 %
Absent vaginal spotting	100	50 %

Only 25% of cases were preceded by both lower abdominal pain and vaginal spots antenatal, table 8.

Table 8: relationship to the Presence of spots and Pain together:

symptom	No. of cases	Percent %
Presence of Pain and spots antenatal	50	25 %
Not present	150	75 %

55% of cases were presented with active bleeding followed the expulsion of fetus, while other 45% of cases were not, table 9.

Table 9: % of active vaginal bleeding following expulsion of fetus

Symptom	No .of cases	Percent %
Presence of active bleeding following expulsion of fetus	110	55 %
Not	90	45 %

All the cases (55%) which complicated with active vaginal bleeding following the expulsion of the product of concept (110 p) ended with urgent evacuation and curettage irrespective to administer oxytocin and methergin. 40% of cases with show no differences between pre and post curettage Haemoglobin concentration, while other 60% of cases with some degree of difference. 40% of cases with actual differences in Haemoglobin concentration result by 1g/dl. No cases register for blood transfusion even in the presence of active vaginal bleeding, table 10, 11.

Table 10 : differences in pre and post Curettage Hemoglobin

Hb result	No. of cases	Percent %
Actual Hb differences	120	60 %
Same Hb result	80	40 %

Table 11: Haemoglobin difference

Pre and Post curettage Hb result differences	No. of cases	Percent %
0.5 g/dl	20	10 %
1 g/dl	80	40 %
2 g/dl	20	10%

Comment:
- 40% of cases with actual differences in Hb result by 1g/dl.

The lowest level of fibrinogen was 190 mg and highest level was 250 mg and there is no relationship between serum fibrinogen level and presence of the active vaginal bleeding, table 12.

Table 12: distribution of fibrinogen level and its relationship to cases which complicate by active vaginal bleeding following expulsion of fetus.

fibrinogen Level	No .of cases	Percent %
491 – 520	10	5
461 – 490	0	0
431 – 460	20	10
401 – 430	30	15
371 – 400	30	15
341 – 370	10	5
311 – 340	30	15
281 – 310	20	10
251 – 280	20	10
221 – 250	0	0
190 - 220	30	15

Discusion :

The age of Patients in our study ranged from 20-45 years with a mean age of 32.5, only 80% of them deliver normally, other 20% were with previous 2 caeserean section. In our study, 45% of the patients were

aborted within 3-6 hours after insertion of misoprostol. This was almost the same result found by *Neilson GP 2006*, where the expulsion happen with average time of 4.8 hours. Minimum number of misopristol doses used was required in the gestational age group ranged from 11 to 14. This result was differ in the study carried out by Barbosa RM 1993 where the minimal dose noted in gestational age of 9 13 weeks. The efficiency of Misoprostol in termination missed miscarriage was highest when the parity is I-II with gestational age range from 15 to 18weeks, results go with that of Rocha J et al, 1994. There seems to be no clear relationship between the efficiency of Misoprostol and presence of pain or vaginal spotting antenatal and not also with the level of serum fibrinogen, results which we cannot be found in the literature to compare.

The side effect of Misoprostol in our study is mostly the continous mild vaginal bleeding presented in around 55% where the curettage was necessary to stop the bleeding and to assure the patients. Minimum number of bleeding and curettage were needed in the study by *Weeks AD 2005*. Only 60% of the these patients complain of hemoglobin drop after curettage, 40% of them lost 1g, 10% lost 0.5g and other 10% lost 2g. Blood transfusion was not necessary in all these patients.

In our study, we observe that one hour after the administration of misoprostol, the patients complain of painless vaginal bleeding which increasing in amount, two hours later the patients start complain of increase frequency of passing stool up to watery diarrhea, almost one hour after, the expulsion was happened. After the expulsion, the patients complain of painful active vaginal bleeding persisting for one to two hours, thing was not accepted psychologically by all of these patients. In two follow up, all of them give the same history of mild vaginal bleeding persist for one week, then start decreasing in amount in the second week till it disappearing completely.

Conclusion:

Although the the usage of Misoprostol in missed miscarriage can avoid the patients other methods of termination, but the active vaginal

bleeding which precede and follow the expulsion was not accepted psychologically by all the patients. Curettage is indicated only in a few patients because of sustained mild vaginal bleeding. Misoprostol is more effective in earlier gestation and with low parity.

Recomendation :

Misopristol has been short used for termination of missed abortion, however, and because of insufficient researches, further researches are needed to establish the efficacy of the drug.

- Failed Misoprostol miscarriages are associated with birth defects in some cases **(3,4,5,6,7)**
- No relationship to outcome of Misoprostol if Patient is symptomatic or not or to the level of serum fibrinogen antenatal.
- The side effects of Misoprostol is active P/V bleeding, which precede and follow the expulsion and AL mostly did not accepted by the patients and insist for curettage, although the hemoglobin drop is mild and no need for subsequent blood transfusion because of iron deficiency anemia which developed is mild in severity, so no serious side effects are reported **(8)**, other side effect was watery diarrhea.

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