INTRODUCTION

Induction of labour is a common intervention, required in situations where continuation of pregnancy may be life-threatening for the mother and/or fetus. In industrialized countries, the induction rate ranges from 10-25%. Such inductions are frequently prolonged and unsuccessful, resulting in a higher cesarean delivery rate of 20%. Several pharmacological agents are being used for labor induction, the commonest being oxytocin and prostaglandins.

Oxytocin alone, especially in unfavorable cervix, frequently leads to induction failure and subsequent caesarean delivery. Misoprostol is a synthetic prostaglandin E1 analogue. It was manufactured for the treatment of peptic ulcer disease. Though unlicensed by the Federal Drug Authority for this purpose, Misoprostol is now increasingly and successfully being used for labour induction, with vaginal as well as oral routes. It is economical, stable at room temperature, has easy handling and storage, rapid absorption and high potency. There is no evidence that oral misoprostol is inferior to the vaginal one and it has lower rates of uterine hyperstimulation because the total systemic bioavailability of orally administered misoprostol is three times lesser than that of vaginally administered misoprostol. In order to avoid uterine hyperstimulation, current suggestions are in favor of oral misoprostol given in small, frequent doses, titrated according to uterine response.

During the last few years, many studies have been carried out with misoprostol on term pregnancies to establish the best dose, administration route and interval between doses for cervical ripening and labor induction and to compare it with oxytocin and dinoprostone. No fetotoxic, teratogenic or carcinogenic effects have been observed in animal studies and no untoward direct effects on neonates have been noted so far in any of the clinical trials.

ABSTRACT

Objective: To determine the effect of oral Misoprostol in labour induction with respect to ease of administration and induction-to-delivery time interval.

Study Design: Observational study.

Place and Duration of Study: Gynaecology/Obstetrics Department, Holy Family Hospital, Rawalpindi, from March to August 2006.

Methodology: Women with live singleton pregnancy of > 37 weeks gestation with cephalic presentation, with an indication for induction of labour were inducted. Oral misoprostol 50 µg to 400 µg was given in divided doses at 4 hours interval up to a maximum of 4 doses, till labour was induced. Fetomaternal outcome and induction to delivering time interval in hours was noted.

Results: In 6 months duration, 250 mothers were recruited for the study. The main indication for labour induction was post date pregnancy (52%) and oxytocin was given in 50% cases. The majority (96%) of mothers went into labour but 4% (9) had failed induction. The majority (73%, n=176/241) of mothers delivered vaginally, 99% being delivered in the first 24 hours. Mean induction-delivery interval was 11±2.7 hours. Sixty five (27%) had to undergo emergency lower segment caesarean section, the major indication being fetal distress (41.5%, n=27) and meconium staining of liquor (40%, n=26). Again, a majority (95%) of the babies were delivered with good Apgar score. However, 10.8% developed meconium aspiration syndrome. Early neonatal deaths occurred in 0.8% (2) cases. Maternal hyper stimulation was seen in 1 case (0.4%).

Conclusion: Oral misoprostol as an agent for labour induction in term pregnancy was easy to administer and the majority of women (99%) delivered in the first 24 hours.

Key words: Oral misoprostol, Term pregnancy, Labour induction, Prostaglandins, Indication-to-delivery time interval.
This study was done to determine the efficacy and side effects of oral misoprostol in labour induction at term by determining the optimal dose with respect to ease of administration and indication-to-delivery time interval.

**METHODOLOGY**

After approval from the hospital Ethical Committee, this study was conducted in the Gynaecology and Obstetrics Department of Holy Family Hospital, Rawalpindi, Pakistan, from March to August 2006. A total sample size of 250 patients was calculated by the World Health Organization (WHO) Sample Size calculator. An informed written consent was obtained. Fetal well being was assured before the start of induction.

All pregnant women (18-40 years) attending the antenatal clinic with a live singleton pregnancy of 37 weeks gestation with cephalic presentation and an indication for induction of labour were selected for this study. All women with a Bishop score > 5, having any contraindication to vaginal birth, having a congenitally anomalous fetus, previous uterine surgery (including caesarean section) and > 5 P (grand multiparas) were excluded from the study.

Induction of labour was done at ≤ 5 Bishop score. < 3 para were given 100 µg per dose and ≥ 3 para were given 50 µg per dose. The dose was repeated at 4 hours interval up to a maximum of 4 doses till labour was induced (3 contractions per 10 minutes). When the Bishop score improved, amniotomy was performed. If necessary, labour was augmented with oxytocin, according to departmental protocol. If labour was not established within 4 hours of the administration of the fourth dose, induction was considered to be failed and such cases were then delivered by caesarean section.

Side effects were noted like uterine hypertonus (a uterine contraction lasting for > 2 minute), fetal distress, fetal tachycardia or bradycardia, non reactive cardiotocograph (CTG) or reduced short term variability (< 5 beats/minute). Fetal heart rate monitoring was done with fetoscope and intermittent cardiotocography. Before each repeat dose, cardiotocography was again done.

Data was collected on carefully designed proforma and analyzed through SPSS software version 10.0. For quantitative variables (age, gestational age, induction to delivery interval in hours), mean values and standard deviation (S.D) were calculated and for qualitative variables (indication for induction of labour, dose requirement of misoprostol, induction to delivery interval, indication for caesarean section, maternal complications) frequency and percentages were presented.

**RESULTS**

Over a period of 6 months, out of the total 2,950 deliveries, 250 cases (8.5%) were recruited for induction of labour. Women were between the ages of 18-40 years, 48% (120) were between 37-40 weeks and 52% (130) were > 40 weeks of gestation. In < 3 para, 47% (118) were primigravida. Para 1 and para 2 were 19% (48) and 14% (35) respectively, while 20% (49) were ≥ 3 para.

The dose requirement for misoprostol according to parity is shown in (Figure 1). Majority of the patients were given upto 200 µg of oral misoprostol and only few mothers required upto 400 µg.

A majority (96%, n=241) of mothers went into labour but 4% (9) had failed induction. Augmentation of labour with oxytocin was done in almost 50% cases.

One hundred and seventy six (73%) mothers achieved successful vaginal delivery; 99% delivered within the first 24 hours while only 1% took > 24 hours (30 hours) for delivery (Figure 2). The mean induction-delivery interval was 11±2.7 hours.

Sixty five (27%) mothers had to undergo emergency lower segment caesarean section, the major indication 1

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**Figure 1**: Dose requirement (of misoprostol) according to parity.

**Figure 2**: Induction to delivery interval.
Imminent eclampsia = Severe uncontrolled pregnancy induced hypertension leading to eclampsia

Failed induction = Failure of the inducing agent to cause induction of labour.

Abruption Placentae = Rupture of placenta

Meconium staining = Decreased amniotic fluid.

DISCUSSION

In this study only a single inducing agent misoprostol was used for all mothers to establish its safety/efficacy, irrespective of any other inducing agent. Past trials have found that a single oral dose of 200 µg or a dose of 50 µg given orally every 4 hours was effective and adverse effects were no different from those in control subjects. This trial was conducted with 50-100 µg of misoprostol per dose depending upon parity and the patients were given maximum 400 µg in ≤ 3P and 200 µg in > 3 P.

With this dosing regimen, failed induction was seen in 4% (9) cases. Out of these, 2 had fetal distress and 1 had meconium staining of liquor as well. These cases were then delivered by caesarean section. Studies which show a failure rate of 0-1% have used a high total dose of oral misoprostol. However, in Abbassi’s study, even with low total dose of oral misoprostol (150 µg), this failure rate was 2.5%. The failure rate remains high with vaginal misoprostol (12-15%).

In the vaginally delivered group (73%), 99% accomplished delivery within the first 24 hours of induction. This percentage is almost double that of Dodd (54%) and Dallen’s result (56%) and could be because of rapid cervical ripening due to higher doses of misoprostol given. This is further strengthened by Nigam’s study where with high doses, vaginal delivery was seen in 91.3% cases and all were delivered within 24 hours.

Oral misoprostol is associated with a shorter induction-delivery interval, with no significant difference in neonatal and maternal outcome. The difference in induction-delivery interval, in different studies, may be due to a different dosing regimen. With low doses, the induction-delivery interval was longer (21 hours), while in recent studies, with high doses (50-75 µg/dose), the induction-delivery interval was shorter (12-14 hours).

In this study, the induction-delivery interval was 11±2.7 hours which is comparable to 15.5 hours, seen in the Khatri study, with 100 µg oral misoprostol per dose, but is longer than Abbassi’s study of 6.7±4.4 hours.

Augmentation of labour with oxytocin was done in almost 50% cases, comparable to other studies where it was (55-60%).

Cochrane review of trials with oral misoprostol has shown a lower risk of caesarean section. In Nigam’s, Dallen’s and Dodd’s studies this rate was 8.3%, 18% and 22.7% respectively. The presently reported caesarean rate of 27% is much higher and can be explained due to the higher dose of misoprostol, which besides expediting vaginal delivery, also led to a higher caesarean rate, mainly due to fetal distress (27%) and meconium staining of liquor with or without fetal distress (26%). This is further strengthened by Dodd results of only 8.8% cases of fetal distress, as a very low dose of misoprostol was used.

Oral misoprostol is associated with a higher incidence of meconium staining of liquor. In this trial, this was seen in 28.4% cases; almost double that of Dodd (16.2%) and Khatri (12%).

As far as fetal outcome is concerned, 95% babies were delivered with a good Apgar score. The 5-minutes Apgar score was < 7 in 4% (10) cases, compared with only 0.6% in the Dodd study. Twenty seven babies required prolonged admission due to the meconium aspiration syndrome, again much more than Dodd’s result (1.4%) and none were seen in the Khatri study. Nevertheless, this rate matches exactly with the 10.8% admissions shown in a large meta analysis of...
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trials, conducting labour induction with inducing agents other than misoprostol.\textsuperscript{13}

When compared with other studies,\textsuperscript{14,20,21} the overall neonatal outcome, including the frequency of meconium aspiration syndrome, incidence of five-minute Apgar scores < 7 and the rate of neonatal admission to a neonatal intensive care unit, showed no significant differences.

Depending upon the dose and frequency of misoprostol administration, the incidence of uterine hyperstimulation varies between 1-10%.\textsuperscript{13} In this study hyperstimulation was seen in only one case (0.4%). This is less than that seen in Dodd (0.8%)\textsuperscript{18} and Abbassi’s trial (2.5%)\textsuperscript{21} and much less than 09% seen in Dallen’s study.\textsuperscript{22}

Multigravidae were given lesser doses than primigravida. Although with such titrated but comparatively high dose, we were able to achieve 99% vaginally deliveries in first 24 hours but this was at the expense of a comparatively higher caesarean section rate (27%) and fetal loss. Trials using low doses of oral misoprostol, show low rate of caesarean section due to fetal distress and other complications but there were also less vaginal deliveries in 24 hours.\textsuperscript{19,21,22} The dosage regimen explains high vaginal delivery rate in first 24 hours but still lacks the more precise dosage regimen so as to lessen the caesarean section and perinatal mortality rate as well.

When compared with pooled data from a control group (induced with any other agent like dinoprostone, oxytocin or placebo),\textsuperscript{13} present results of all outcome measures, except a higher caesarean rate, are better with oral misoprostol. So this drug can be used with confidence for labour induction. Not only women prefer an oral and cheap induction agent, it is also associated with easy storage and perfect stability at room temperature as well. To date, all trials have been conducted with different dosage protocol, exact safety/efficacy and optimal dose of oral misoprostol can not be commented upon. Therefore, all institutes using oral misoprostol for the induction of labour should do regular audit of their clinical protocols and must report any adverse outcome.

**CONCLUSION**

Oral misoprostol as an agent for labour induction in term pregnancy was easy to administer and the majority of women delivered in the first 24 hours.

**REFERENCES**