Mifepristone Followed by Prostaglandin Vs Prostaglandin alone for induction of Labour in Intrauterine Foetal Death at or more than 28 Weeks of Pregnancy

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INTRODUCTION
Motherhood is a divine gift but in cases of intrauterine foetal death women have to suffer unbearable pain without any gain. Therefore, an effective and safe and reliable method is needed to minimise induction delivery interval. Intrauterine foetal death is defined as death of a foetus of 20 weeks or more and 500 grams weight. But in our scenario foetal survival is difficult in less than 28 weeks or 1000 grams, so in India “ IUFD is defined as death of foetus at or after 28 weeks of gestation and at 1000 grams weight”.1,2 Intrauterine Foetal Death is encountered in about 1% of pregnancies, and it is mainly due to hypertensive disorders of pregnancy, haemoglobinopathies, and other medical disorders in women, foetal causes as infections, Rh iso immunization, and placental dysfunction. If left undelivered, IUFD can lead to serious maternal complications.3 About 1 in 4 women develop consumptive coagulopathy, if dead foetus retained for 4 or more weeks. Since decades, prostaglandins are being used for induction of labour in intrauterine foetal death cases. Misoprostol, a prostaglandindE1 analogue, is a preferred choice because of its ease of administration, cost effectiveness and stability at room temperature. Repeated doses of prostaglandin have its side effects.4,5 Mifepristone (RU 486) is a potent antiprogesterone and anti-glucocorticoid weak anti-androgen. Increases sensitivity of the uterus to prostaglandin was also seen. It leads to decreased induction delivery interval and lesser doses of misoprostol and subsequently lesser side effects. The doses of misoprostol and routes of administration are highly variable.6 Misoprostol is a synthetic analogue of prostaglandin E1. Although only approved by the US Food and Drug Administration (FDA) in 1988 for the prevention of stomach ulcers, misoprostol has many off-label uses applicable to obstetrics and gynaecology. Misoprostol is used for cervical ripening in labour induction, management of postpartum haemorrhage, cervical preparation for trans-cervical procedures, miscarriage management, as well as first and second trimester pregnancy termination.7 Misoprostol is the preferred commercially-available prostaglandin, because it is affordable, widely available, remains stable at room temperature in non-tropical climates, and has no known effects on pulmonary bronchi or blood vessels. Misoprostol can be administered via multiple different routes, including orally, sublingually, buccally, vaginally, and rectally. Each route of administration results

ABSTRACT
Introduction: Intrauterine fetal death (IUFD) is a rare but devastating event for the mother and family. Rapid expulsion of the foetus is usually requested, although there are no medical grounds for it. Labour following IUFD often needs to be induced by medical means. Prostaglandin analogues, such as misoprostol and gemeprost, have been extensively studied and proven to be safe and effective in the induction of abortion in the second trimester of pregnancy. Hence, the aim of the present study was to compare the required dose of prostaglandin and induction delivery interval in Mifepristone with Prostaglandin and Prostaglandin alone in Intrauterine Foetal Death at or more than 28 weeks of pregnancy
Material and methods: The present was a prospective study in which women came with ultrasonography confirmed intrauterine death were counselled and divided into two groups randomly. First group had Tab mifepristone (200mg) orally followed by Dinoprostone gel intracervically after 24 hrs and misoprostol (50mcg) 4 hourly thereafter, whereas second group had a multivitamin tablet orally and after 24 hours dinoprostone gel applied intracervically followed by misoprostol tab (50 mcg) 4 hourly upto maximum 6 doses in both groups.
Results: The induction to delivery interval in hours was found to be higher in Group B than A. This was found to be statistically significant at p value 0.021. Number of dosage of misoprostol was also seen higher in majority of cases in Group B which was also found to be statistically significant.
Conclusion: This study showed that combination of Mifepristone (200 mg) and prostaglandin was found to be more effective than Prostaglandin alone for induction of labour in intrauterine foetal death of 28 weeks or more.
Keywords: Intrauterine Foetal Death, Prostaglandin, Mifepristone, Induction Delivery Interval.

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in a different length of time at which the peak drug level is reached and different overall bioavailability. Mifepristone has been FDA-approved for abortion care and is a derivative of norethindrone and acts directly at the progesterone receptor as a competitive inhibitor. Mifepristone disrupts the progesterone support required during early pregnancy and has multiple effects on the reproductive tract, including increasing uterine contractility, increasing sensitivity to prostaglandin, altering the endometrium causing decidual necrosis, and ripening of the cervix. The medication is administered orally, is easily absorbed, undergoes first-pass metabolism in the liver, and reaches a dose-independent peak concentration within one to two hours when using doses of 100 mg or greater. The WHO, SFP and ACOG recommend 200 mg of oral mifepristone, followed 24-48 hours later by a loading dose of 800 mcg misoprostol vaginally and an additional 400 mcg misoprostol vaginally every 3 hours until expulsion. Many studies have examined the ideal dosing, route of administration and timing of mifepristone and misoprostol regimens for medical abortion for up to 24 weeks of gestation. It was found that misoprostol preceded by a dose of mifepristone is the most effective regimen resulting in shorter times to expulsion. Hence, the aim of the present study was to compare the required dose of prostaglandin and induction delivery interval in mifepristone and prostaglandin and prostaglandin alone in intrauterine foetal death at or more than 28 weeks of pregnancy.

MATERIAL AND METHODS

This present study was a prospective study which was conducted in Department of Obstetrics and Gynaecology, RIMS, a Tertiary Care Institute in Jharkhand. About 100 pregnant women came to Outpatient Department and labour room and were enrolled in this study and detailed history, examination investigation and counselling was done. Two groups of 50 each were randomly selected and one group (A) was given Tab Mifepristone (200 mg) orally 24 hours prior to Dinoprostone gel application intracervical, followed by Misoprostol tab (50 mcg) 4 hourly vaginally maximum 6 doses, whereas second group (B) received one tab of multivitamine (placebo) and after 24 hours followed by Misoprostol (50 mg) maximum 6 doses vaginally. Prostaglandin (misoprostol) was stopped after 6 cms dilatation.

Inclusion criteria
1. Patients with gravidity 4 or less,
2. Patients not in labour,
3. Patients ready to go for medical management

Exclusion criteria
1. Patients with coagulation disorder,
2. Known allergy to prostaglandin and previous exposure to caesarean delivery

Both groups were kept in close supervision and monitoring was done by maternal pulse, B.P. temperature, uterine contractions and progress of labour and induction delivery interval. Vaginal delivery was taken as successful outcome and need for caesarean section was considered to be unsuccessful. All patients were followed up till discharge and side effects and complications were noted e.g. nausea, vomiting, fever, diarrhoea, caesarean deliveries, haemorrhage after delivery, trauma, need for blood transfusion, manual removal of placenta etc. Gestational age was based on menstrual history and confirmation by ultrasonography measurements performed in early pregnancy. Data on maternal and gestational age, parity and previous deliveries, complications of pregnancy and status of the cervix were collected from medical records. Assessment of the cervix was based on Bishop scoring. Information on the method of induction, the dose of misoprostol, progression of labour and the need for oxytocin was recorded. Additional collected data included the need for analgesia, evacuation of retained placenta and complications of delivery.

STATISTICAL ANALYSIS

The data was entered in the excel sheet and was analysed with the help of statistical software SPSS version 21. Descriptive statistics are presented in the form of percentages with the help of graphs and inferential statistics such as independent t-test was performed to find out the difference between the two groups and paired t-test was applied to find out the intra-group difference.

RESULTS

In the present study, Group A which was a combined group of Mifepristone and Prostaglandin, had the majority of the subjects (60%) belonging to age group 18-24 years. Group B, which was a Prostaglandin alone had the maximum number of subjects (68%) belonging to 18-24 years (Graph 1). In Group A, it was observed that maximum number of subjects (56%) were from multigravida whereas in Group B, the majority of the subjects (52%) were from primigravida (Graph 2). The gestation age of 28-34 weeks was seen in majority of the subjects (72%) in Group A also Group B had maximum numbers of subjects (70%) in 28-34 weeks of
gestation age (Graph 3).

In the current study, the mode of delivery was vaginal in all the subjects (100%) of Group A whereas the caesarean was seen only in 4% of the subjects and vaginal in 96% of the subjects in Group B (Graph 4). The dose of misoprostol was 100 mcg followed by 50 mcg in majority of the subjects in Group A whereas in Group B, the maximum number of subjects were treated with 200 mcg followed by 150 mcg and 100 mcg. The majority of the subjects in Group B had side-effects and complications such as vomiting, nausea and fever whereas nearly no subjects presented with complications in Group A (Graph 5 and 6).

The Induction to delivery interval after dinoprostone gel application (in hours) was found to be 8.1 hours to 12 hours in majority of subjects (56%) belonging to Group A. In Group B, maximum number of subjects (32%) took 12.1 to 16 hours after the application of dinoprostone gel and this
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The induction to delivery interval in hours was found to be shorter in Group B i.e., 16.284±3.241 hours than Group A where the mean score was 8.141±3.681 hours. This was found to be statistically significant at p value 0.021. The number of dose of misoprostol was also seen higher in majority of cases in Group B with mean score for age of 5.4±1.54 whereas in Group A where mean score was found to be 4.2±2.16 which was also found to be statistically significant at p value 0.034 (Table 3).

**DISCUSSION**

Intrauterine fetal death is a complicated condition where frequency of intrauterine fetal death with a retained foetus varies, but is estimated to occur in 1% of all pregnancies. This clinical situation is psychologically stressful for the woman and her family members and also for the health professionals providing care. When a foetus dies in the uterus, the options for health care are either to await onset of spontaneous labour or to induce labour. The vast majority of the women will spontaneously labour and deliver within three weeks of the intrauterine death. The World Health Organization (WHO) supports a combination of mifepristone and misoprostol as the recommended regimen for both the first and second trimesters of pregnancy, but doses, routes, and timing of administration vary with gestational age. A systematic review of medical abortions using evidence-based regimens at 63 gestational days or less reported rates of abortion failure requiring surgical completion at 4.8%, on-going pregnancy at 1.1%, hospital admission at 0.3%, and blood transfusion at 0.1%. Wagaarachchi PT et al. revealed that mifepristone in combination with misoprostol is well established in the management of early first trimester termination of pregnancy. Similar regimens have also been used with moderate success in the management of miscarriage. This study has demonstrated an effective combined regimen for induction of labour in late fetal death and these findings are consistent to the results of the present study. Prasai S et al. in their prospective study found that the dose of misoprostol is needed more in misoprostol only group (3.4±1.12) than combined group (1.89±0.96) and the findings were found to be significant and these results are in concordance with the findings of the present study. Also, a single dose of mifepristone plus misoprostol than vaginal misoprostol was more effective.

Furthermore, small number 1(2.85%) of patient needed oxytocin drip in combined group and 5(14.2%) patients needed oxytocin drip in misoprostol only group, about 97.14% patients in combined group and 84.5% patients in misoprostol only group delivered without oxytocin drip. The mean induction to delivery interval time was significantly different in both groups and these finding are similar to results of the present study. For the combined group mean time was found to be 13.97±3.75 hours to delivery in contrast with misoprostol which needed mean time of 24.24±3.19 hours whereas in present study the combined group mean time was 8.141±3.681 years followed by 16.284±3.241 years in prostaglandin given alone. Results from previous series of cases have suggested that pre-treatment with mifepristone prior to misoprostol may be associated with shorter induction-to-delivery times in comparison with use of misoprostol-only regimens. Of the various studies in which both mifepristone and misoprostol have been employed in cases of IUFD, the time to delivery was longest in the present series. The author also used the lowest doses of misoprostol, whereas Fairley et al. employed misoprostol doses of 50-200 mg. In the present study, the doses of 50-300 mg were used in the groups. Another study conducted by Vayrynen W et al found that there were about 65 patients treated with combined regimen and 62 patients with misoprostol tablet only. Combined group was associated with more rapid cervical ripening. Most of the patients successfully delivered vaginally without any complications in both groups in this study. The most common complication among vaginal deliveries was elevated temperature (>100°F) followed by risk of fever, postpartum hemorrhage, and hyperstimulation which did not differ significantly whereas in the present study, the most common complication was vomiting followed by nausea and fever. Shetty A et al reported that about 4% patients needed caesarean section in misoprostol group due to failed induction. Hospital stayed in both groups was almost similar whereas in the present study, the mode of delivery was vaginal in all the subjects of Group 1 whereas the caesarean was seen only in 2 subjects of Group 2. More cases required analgesia in misoprostol group as compared to combination group which can be directly correlated with the length to contraction or duration of labour. Although we preferred to keep all patient admitted in hospital after administration of mifepristone for observation, no adverse event was found.

**CONCLUSION**

In induction of Intrauterine fetal death (IUFD) mifepristone
plus misoprostol is an effective combination found in the present study. It is safe, non-invasive, cost effective, easily tolerable and more effective with less induction to delivery interval than conventional regimen of misoprostol alone.

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