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Cross Sectional Retrospective Study on Mifepristone and Misoprostol Combination Vs Misoprostol alone for Induction of Labour in Management of IUFD

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ABSTRACT

The scientific term for stillbirth is intrauterine fetal demise, denoting the unfortunate event of fetal death within the uterus. This term is commonly applied to miscarriages occurring during or after the twenty weeks of pregnancy. This study aims to assess the safety and efficacy of using a combination of mifepristone and misoprostol versus misoprostol alone for labor induction in cases of intrauterine fetal death. Conducted at the Muslim Maternity and Children's Hospital in Hyderabad, India, this retrospective study spanned six months. Its objective was to evaluate the safety and efficacy of mifepristone and misoprostol in combination versus misoprostol alone for labor induction in managing intrauterine fetal death. Patients administered the mifepristone and misoprostol combination exhibited a significantly shorter induction-to-delivery interval (5.8 hours) compared to those who received only misoprostol (23.3 hours). These findings suggest that the combination of mifepristone and misoprostol is more effective than misoprostol alone for labor induction in the management of intrauterine fetal death.

Keywords: *intrauterine fetal death, mifepristone, misoprostol, induction of labor*

Introduction

Experiencing fetal death, regardless of gestational age, is profoundly distressing for both parents and healthcare providers. The term "spontaneous abortion" describes fetal demise before the 20th week of pregnancy, while "stillbirth" or "fetal demise" denotes fetal death after the 20th week [1]. After such an event, the mother faces the decision of awaiting spontaneous labor or opting for induction [2]. Within two weeks of fetal death, 80-90 percent of women undergo spontaneous labor. However, the risk of complications such as disseminated intravascular coagulation leading to bleeding, infections like septicemia, and maternal death necessitate labor induction. Surgical interventions like membrane stripping and anatomy are contraindicated due to infection risks, thus requiring a safe and effective method for terminating the pregnancy [3]. In managing intrauterine death, various approaches have been explored. Before prostaglandins, treatments included high doses of estrogens, intra-amniotic hypertonic solutions, hygroscopic tents, bougies, catheters, balloons, and often high-dose oxytocin infusions, which are less effective before term [4-10]. Prostaglandins have transformed the management of intrauterine death, available via oral, sublingual, intravenous, intramuscular, vaginal, or rectal administration. The Royal College of Obstetricians and Gynaecologists (RCOG) recommends combining mifepristone and prostaglandin as a primary intervention for labor induction in intrauterine fetal death, as per green-top guideline number 55. Conversely, the World Health Organization (WHO) advocates for oral or vaginal misoprostol for induction of labor in the third trimester of pregnancy [11].

Subsequently, combining mifepristone and misoprostol for late intrauterine death induction has emerged as a more effective and safer regimen, yielding a shorter induction-to-delivery interval compared to using either drug alone. Mifepristone, an antiprogesterone steroid, augments uterine activity, enhances myometrial responsiveness to prostaglandins, and promotes cervical ripening with minimal side effects. Shortening the termination duration and enhancing patient comfort remain pivotal goals.

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Material and methods

A retrospective cross-sectional study was conducted involving 114 patients admitted with intrauterine fetal death, all with a gestational age exceeding 24 weeks. Data spanning over 12 weeks was collected retrospectively from March to June 2021 at the Muslim Maternity and Children's Hospital in Hyderabad, India. Permission for the study, aimed at evaluating the safety and efficacy of mifepristone and misoprostol combination versus misoprostol alone for labor induction in the management of intrauterine fetal death, was obtained from the hospital's competent authority under protocol number 2702/01.

The inclusion and exclusion criteria

Inclusion Criteria

- Singleton Pregnancy
- Gestational age of at least 24 weeks Women who are not in labor.
- Ultrasound imaging confirming intrauterine fetal death or fetal anomalies.

Exclusion Criteria

1. Women who are currently in active labor.
2. Women for whom vaginal delivery is not recommended due to specific medical conditions or obstetric complications.
3. Women with scarred uteri, such as those with a history of previous cesarean sections.
4. Women with pre-existing medical conditions including epilepsy, asthma, glaucoma, heart disease, or abnormal coagulation profiles that may pose risks during labor induction.
5. Women who have experienced multiple pregnancies and have previously had an intrauterine fetal death.
6. Grand multipara women, defined as those who have had five or more pregnancies resulting in viable fetuses.

Data Collection

The parameters of the study include:

1. Maternal age categorized into three groups: 20 years, 21-30 years, and over 30 years.
2. Parity status of the mothers.
3. Probable causes for intrauterine fetal death (if identified during gross examination or based on preexisting maternal or fetal complications diagnosed during pregnancy).
4. Whether the case was booked or unbooked.
5. Mode of delivery (vaginal delivery, cesarean section, or laparotomy).
6. Maternal complications observed during the study.

Comprehensive information regarding the patient's history, clinical examination, and investigations, such as complete hemogram, liver function test, renal function test, and coagulation profile, was obtained.

Ultrasonography was performed to confirm intrauterine fetal death.

The induction-to-delivery interval was compared among patients receiving different regimens. The analysis was conducted using appropriate statistical methods at a predetermined level of significance to evaluate efficacy. The primary outcome measures included successful induction and the induction-to-delivery interval. Successful induction was defined as the occurrence of vaginal delivery within 36 hours of mifepristone administration or within 24 hours of the first dose of misoprostol administration.

Statistical analysis

Data was analyzed using one-way ANOVA to find out the relationship between variables.

Results

A retrospective study was carried out in women suffering with IUFD from the year 2018-2021.

Descriptive statistics

Table 1. Age Distribution in Patients

Patient age	NUMBER	PERCENTAGE
18-25	56	49.12280702
26-36	58	50.87719
Total	114	100

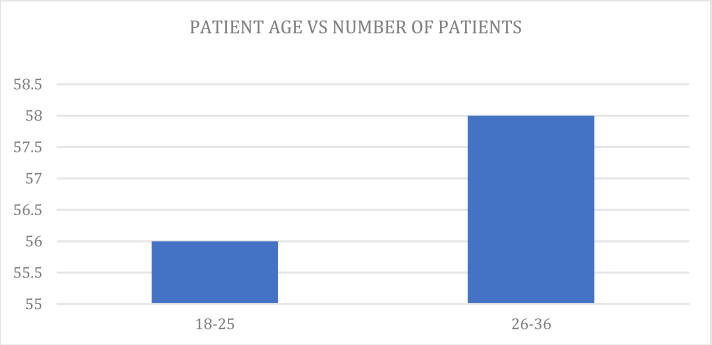

Fig 1. Age Distribution in Patients

The age wise distribution of patients is displayed in fig 1. The maximum number of patients are 58 (50.8%) were in 26-36 age group followed by 56 patients (49.2 %) in age group 18-25.

Table 2. Comorbidities in IUFD Patients

COMORBIDITIES	Samples(N)	Percentage
No Comorbidities	85	74.56140351
preclampsia	12	10.52631579
GDM	3	2.631578947
hypothyroidism	4	3.50877193
cervical fibriod	1	0.877192982
Anemia	1	0.877192982
epilepsy	1	0.877192982
diabetes	1	0.877192982
bicornuate uterus	0	0
preclampsia,GDM	1	0.877192982
preclampsia,Hypothyroidism	1	0.877192982
preclampsia,bicornuate uterus	1	0.877192982
GDM,Hypothyroidism	2	1.754385965
Hypothyroidism,Anemia	1	0.877192982
Total	114	

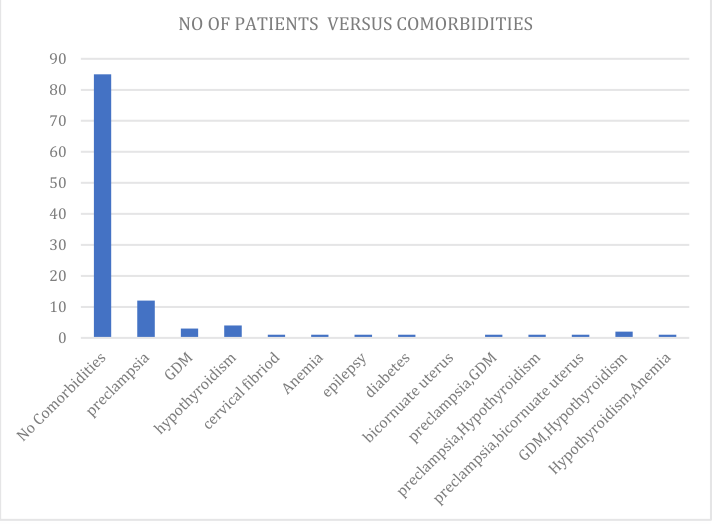

Fig 2. Comorbidities in IUFD Patients

The 74.5% of the patients were not having any comorbidities, 10.5 % were having pre- eclampsia 2.6% were having Gestational Diabetes Mellitus (GDM), 3.5 % were having hypothyroidism and 0.8% were having cervical fibroid, Anemia, epilepsy, diabetes, preeclampsia and GDM, preeclampsia& Hypothyroidism, preclampsia and bicornuate uterus, Hypothyroidism & Anemia respectively and 1.75% were having GDM and Hypothyroidism.

Table 3. Number of patient receiving combination of drug are as follows.

S.No	No of patient	Combination
1	25	0(LSCS)
2	16	Mifepristone+misoprostol
3	4	Mifepristone+misoprostol+oxytocin
4	60	Misoprostol+oxytocin
5	6	misprostol
6	3	oxytocin

Among the patients who received a combination of mifepristone and misoprostol (n=16/114), the mean induction-to-delivery interval was 5.8 hours (S.D. 5.41). Only four out of 114 patients required augmentation with oxytocin, with a mean induction-to-delivery interval of 10.6 hours (S.D. 1.8).

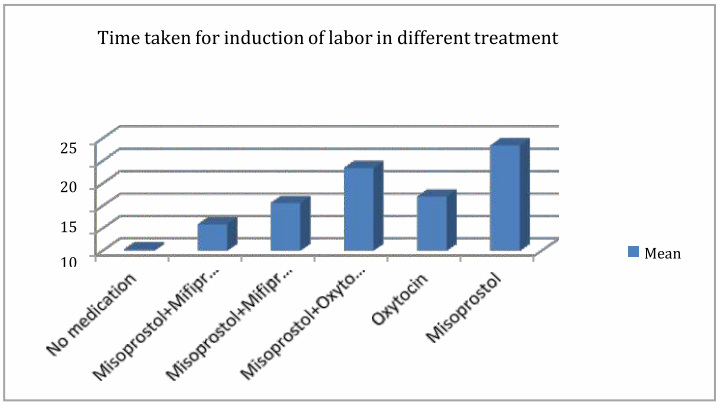

Fig 3. Time vs combination is as follows

Patients who received only misoprostol (n=6/114) had having mean induction to delivery interval of 23.3 hours (S.D .87) and sixty patients (60/114) required augmentation with oxytocin with a mean induction to delivery interval of 18.3 hours (S.D 3.66). Only three patients (n=3/114) were inducted with oxytocin with a mean induction to delivery interval of 12.0 hours (S.D 3.60). 25 patients (n=25/114) were not given any medication and operated for LSCS with a mean of 32 and S.D 1.60.

The comparison of various regimens is as follows

Comparisons	Mean difference	Significant?	P value
Mifepristone+misoprostol vs mifepristone+misoprostol+oxytocin	4.8	no	0.1861
Mifepristone+misoprostol vs misoprostol+oxytocin	12.59	yes	<0.001
Mifepristone+misoprostol vs oxytocin	6.28	No	0.085
Mifepristone+misoprostol+oxytocin vs misoprostol	17.58	Yes	<0.0001
mifepristone+misoprostol+oxytocin vs misoprostol+oxytocin	7.79	Yes	0.0019
Mifepristone+misoproatol+oxytocin vs oxytocin	1.48	No	0.98
Mifepristone+misoproatol+oxytocin vs misoprostol	12.78	Yes	<0.0001
Misoprostol+oxytocin vs oxytocin	6.31	No	0.055
Misoprostol vs oxytocin	4.99	Yes	0.028
Oxytocin vs misoprostol	11.3	yes	0.0008

When comparing the combination of mifepristone and misoprostol with mifepristone and misoprostol alone, the addition of oxytocin did not show statistical significance, with a p-value of 0.18, when mifepristone a misoprostol was compared with misoprostol and oxytocin it was significant with the p value < 0.001. When mifepristone and misoprostol was compared with oxytocin it was not significant with the p value 0.085. When mifepristone + misoprostol + oxytocin was compared with misoprostol it was statistically significant with the p value < 0.0001. When mifepristone + misoprostol + oxytocin was compared with misoprostol + oxytocin was significant with p value 0.0019. When mifepristone and misoprostol+oxytocin was not significant with p value 0.98. When mifepristone and misoprostol+oxytocin was compared with misoprostol was significant with p value< 0.0001.when misoprostol+oxytocin was compared with oxytocin was not significant with p value 0.055. When misoprostol was compared with oxytocin it was significant with p value 0.028. When oxytocin was compared misoprostol it was significant with p value 0.0008.

Discussion

Patients who received the combination of mifepristone and misoprostol (16/114) demonstrated a significantly shorter induction-to-delivery interval of 5.8 hours without reported side effects (p=0.05). Interestingly, only 4 patients required labor augmentation with oxytocin despite receiving the combination regimen. This finding aligns with a study conducted by [12-14] which involved 40 pregnant women with intrauterine fetal death at or beyond 28 weeks of gestation.

In their study, the combination of mifepristone and misoprostol was compared with misoprostol alone. The combination regimen was found to be more effective than misoprostol alone, resulting in a shorter induction-to-delivery interval of 6.72 hours (p=0.05).

Total 66 /114 patient received misoprostol. Patients who were induced only with misoprostol were 6 had induction to delivery interval 23.3 hour. 60 women required augmentation with oxytocin in spite of receiving misoprostol with mean induction to delivery interval 18.3 hours which is in contrast with the study conducted by [15-17]. A Prospective Study included 52 women who were gravid up to their fourth trimester and had IUFD after 28 weeks of pregnancy. Two groups of women were created. The first group of women got a single oral dosage of 200 mg mifepristone, followed by 100 ug intravaginal misoprostol after 24 hours, and then intravaginal 100g misoprostol at four hourly intervals if necessary. The second group of women got 100 g misoprostol per vaginally at four-hour intervals (maximum 600 g in 24 hours). If necessary, oxytocin was administered. The combination regimen group had a shorter induction-to-delivery time.

Conclusion

Intrauterine fetal death, also known as still birth, denotes antepartum death occurring at or beyond 20 weeks of gestation. This study concludes that the combination of mifepristone and misoprostol is notably more effective than misoprostol alone, resulting in a shorter induction-to-delivery interval and fewer side effects, consequently leading to a reduced hospital stay.

Specifically, the induction-to-delivery interval was 5.8 hours for the combination group and 23.3 hours for the misoprostol-only group. These differences were statistically significant, suggesting that the addition of mifepristone to misoprostol for labor induction in intermediate and late intrauterine fetal death cases appeared to be more successful than using misoprostol alone.

Funding: This study was promoted and sponsored by Authors.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration and approved by the Clinical Ethics Committee at the Muslim Maternity Hospital.

Informed Consent Statement: The need for informed consent was waived because this was a clinical audit, in addition to the non-interventional nature of the study, the anonymization of data and the blind evaluation of the clinical performance. This circumstance was clearly explained in the protocol, and the ethics committees approved this procedure.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors thank the ethical committee for carrying out the study.

Conflicts of Interest: No conflict of Interest

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