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"Medical Induction for Intrauterine Fetal Death (IUFD) in a Tertiary Care Hospital"

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Abstract **Original Research Article**

Introduction: Intrauterine fetal death (IUFD) is a sad event for both mothers and medical personnel. In the developing world, IUFD is calculated based on deaths at 28 or more weeks of gestation or weight of 1000 gms or more. Traditionally, early nonviable pregnancies (less than 14 weeks) have been terminated by surgical evacuation and later pregnancies (14 weeks onwards) have been ended by medical induction. In this study, we aimed to evaluate the outcome of medical induction for IUFD in a tertiary care hospital. ***Methods:*** This was a prospective observational study and was conducted in the Department of Obstetrics & Gynecology, Holy Family Red Crescent Medical College Hospital, Dhaka, Bangladesh during the period from January 2019 to December 2020. In our study, we included 20 pregnant women with IUFD who attended the department of obstetrics & gynecology. ***Result:*** The mean age of our patients was 27.25±4.47 years. The majority of patients had 2nd gravida (45%), and most of our patients (45%) were 28-32 weeks pregnant. Among all our diagnosis findings, we found that the majority of patients (50%) had a previous history of IUFD, followed by severe preeclampsia (35%) and pregnancy-induced hypertension (20%). Among all patients, Mifepristone was taken by 100%, followed by Misoprostol was taken by 90%. The majority (40%) of patients were successful in IUFD after the combination of Mifepristone and 2nd dose of Misoprostol. ***Conclusion:*** Our study findings showed that the combination of mifepristone with misoprostol was more effective than misoprostol or mifepristone alone for the induction of labor in IUFD, in terms of a higher rate of successful delivery.

Keywords: Outcome, Intrauterine fetal death (IUFD), Misoprostol, Mifepristone.

INTRODUCTION

Intrauterine fetal death (IUFD) is a sad event for both mothers and medical personnel. The CDC's definition of "IUFD" is based on the definition promulgated by the WHO in 1950 [1]. Intrauterine fetal death is defined as when a fetus dies in utero and does not expel after the period of viability. Different countries have varied definitions for IUFD; some use 16 weeks of gestation, while others use 28 weeks [2-4]. In many countries particularly in the developing world, intrauterine fetal death (IUFD) is calculated based on deaths at 28 or more weeks of gestation or weight of 1000 gms or more [5]. In wealthy nations, IUFD affects roughly three births out of every 1000, whereas in developing nations, the prevalence can reach 45 per 1000 pregnancies. [6,7] According to the first-ever joint UN assessment, Bangladesh recorded roughly 72,508 IUFDs in 2019, or 24.3 per 1,000 births. IUFD is caused by several risk factors, which can be roughly divided into general and particular categories. Specific factors include placental, fetal, maternal, and umbilical cord problems; general factors include sociodemographic aspects including domicile, occupation, and education [8].

Moreover, after the diagnosis of IUFD, the emotional burden and social pressures of delivery are considerable, and the medical consequences of postponing delivery can be life-threatening. Earlier termination of these pregnancies will avoid the risks of disseminated intravascular coagulation and intrauterine infection and may reduce the emotional and mental distress for the patient and her family [9]. Traditionally, early nonviable pregnancies (less than 14 weeks) have

been terminated by surgical evacuation and later pregnancies (14 weeks onwards) have been ended by medical induction [10-12]. For the termination of IUFD, various types of medical treatment are suitable as alternatives to surgical treatment. Two types of drugs are mainly used for the management of IUFD, e.g., Misoprostol and Mifepristone.

Misoprostol is a prostaglandin E1 analogue, marketed for the prevention and treatment of peptic ulcers. Recognized as a potent method for terminating pregnancies, it is inexpensive, stable at room temperature, and has few systemic effects [13]. Misoprostol is an effective myometrial stimulant of the pregnant uterus, selectively binding to EP-2/ EP-3 receptors [14].

Mifepristone (RU 486), a progesterone antagonist that increases the sensitivity of the myometrium to prostaglandins, has been used before misoprostol for the termination of pregnancy (TOP) in a few randomized trials with proven benefits [15-17]. Mifepristone can be used alone or in combination with misoprostol. It is seen that mifepristone alone is also effective for the expulsion of a fetus.

However, the evidence related to the use of such a combination for the induction of labor in second and third-trimester IUFD is deficient in the absence of well-designed randomized controlled trials (RCT) [18]. Therefore, this study aims to evaluate the outcome of medical induction for IUFD in a tertiary care hospital.

METHODOLOGY & MATERIALS

This was a prospective observational study and was conducted in the Department of Obstetrics & Gynecology, Holy Family Red Crescent Medical College Hospital, Dhaka, Bangladesh during the period from January 2019 to December 2020. In our study, we included 20 pregnant women with IUFD who attended the department of obstetrics & gynecology.

These are the following criteria to be eligible for enrollment as our study participants: a) Patients aged more than 18 years; b) Patients with up to 4th gravida; c) Patients with pregnancies of at least 28 weeks of gestation; d) Patients who were willing to participate were included in the study And a) Patients with multiple gestations; b) Patients with known allergy/hypersensitivity to study medicine; c) Patients with any history of acute illness (e.g., renal or pancreatic diseases, ischemic heart disease, asthma, COPD etc.) were excluded from our study.

Mifepristone: All of our patients got the starting dose of 400 micrograms of Mifepristone.

Misoprostol: Among our patients, 14 patients got 200 micrograms of misoprostol every 6 hours until delivery.

Statistical Analysis

All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using SPSS 21 (Statistical Package for Social Sciences) for Windows version 10. The study was approved by the Ethical Review Committee of Holy Family Red Crescent Medical College Hospital.

RESULTS

Table 1: Age distribution of our study patients (N=20)

Age group	N	%
18-25 years	7	35.0
26-30 years	9	45.0
>30 years	4	20.0
Mean age	27.25±4.47	

Table 1 shows that most of our patients (45%) were aged between 26-30 years, followed by 7 (35%) patients were 18-25 years, and 4(20%) patients were more than 30 years old. We found the mean age of our patients was 27.25±4.47 years.

Table 2: Distribution of our study patients by Gravida (N=20)

Gravida	n	%
Primigravida	4	20.0
2nd gravida	9	45.0
3rdgravida	4	20.0
4thgravida	3	15.0

Table 2 shows the gravida of our study patients. The majority of patients had 2nd gravida (45%), both primigravida & 3rd gravida were found in 4(20%) patients, followed by 4th gravida was found in 3(15%) patients.

Table 3: Distribution of our study patients by week of pregnancy (N=20)

Pregnancy (wks)	n	%
28-32 Weeks	9	45.0
33-36 Weeks	7	35.0
>36 Weeks	4	20.0
Mean ±SD	33.15±3.69	

Table 3 shows the distribution of our study patients by week of pregnancy. Most of our patients (45%) were 28-32 weeks pregnant, followed by 35% were 33-36 weeks pregnant and 20% were pregnant more than 36 weeks.

Table 4: Distribution of our study patients by the diagnosis findings (N=20)

Diagnosis finding	n	%
Previous history of IUFD	10	50.0
Severe Pre-eclampsia	9	45.0
Pregnancy-induced hypertension (PIH)	4	20.0
Hypertension (HTN)	3	15.0
COVID +ve	2	10.0
Placenta previa	3	15.0
Abruptio placenta in pregnancy	2	10.0
Breech presentation	1	5.0
SLE	2	10.0
Intrauterine Growth Restriction (IUGR)	1	5.0
Maternal perception of less fetal movement (LFM)	1	5.0
Severe Anemia	2	10.0
Premature rupture of membranes (PROM)	3	15.0
Hypothyroidism	1	5.0
Rh-negative mother	1	5.0
Gestational *diabetes mellitus* (GDM)	1	5.0
Antepartum hemorrhage (APH)	4	20.0

Table 4 shows the diagnosis findings of our study patients. We found the majority of patients (50%) had a previous history of IUFD, followed by severe preeclampsia (45%), pregnancy-induced hypertension (20%), antepartum hemorrhage (20%), 15% had placenta previa, hypertension was present in 15% patients and 10% patients were covid positive.

Table 5: Distribution of our study subjects by medicine tablets prescribed to them (N=20)

Medicine tablet	n	%
Mifepristone	20	100.0
Misoprostol	18	90.0

Table 5 shows that Mifepristone was given to all of our patients, followed by Misoprostol was taken by 90% of our patients.

Table 6: Distribution of our study patients by the dose of medicine (N=20)

Dose medicine	n	%
Dose of Mifepristone		
1st dose	20	100.0
Mean ± SD	1.00±0.00	
Dose of Misoprostol		
1st dose	18	90.0
2nd dose	14	70.0
3rd dose	6	30.0
4th dose	2	10.0
Mean ± SD	2.10±0.99	

Table 6 shows the dosage of medicine in our patients. All patients got the starting dose of Mifepristone and among all the patients, 90% of them got the 1st dose, 70% & 30% got the 2nd & 3rd dose of Misoprostol respectively, and only 10% got the 4th dose.

Table 7: Outcome analysis of IUFD among our study participants

Outcome of IUFD	n	%
Mifepristone single dose	2	10.0
Combination of Mifepristone and 1st dose of Misoprostol	4	20.0
Combination of Mifepristone and 2nd dose of Misoprostol	8	40.0
Combination of Mifepristone and 3rd dose of Misoprostol	4	20.0
Combination of Mifepristone and 4th dose of Misoprostol	0	0.0
Cesarean section	2	10.0
Manual removal of placenta under G/A	1	5.0

Table 7 shows the outcome analysis of IUFD among our study participants. Among all participants, only 2(10%) patients were successful in the expulsion of IUFD after a single dose of mifepristone. The majority (40%) of patients were successful in IUFD after the combination of Mifepristone and 2nd dose of Misoprostol. Among all patients, only 10% patients had a cesarean section, and 1(5%) patient had manual removal of the placenta.

Table 8: Side effects of study medicine

Side effects	n	%
Nausea	2	10.0
Vomiting	2	10.0
Diarrhea	1	5.0
No side effects	16	80.0

Table 8 shows the side effects of our study patients. Most of our study participants (80%) had no side effects. Among all patients, nausea and vomiting were the most common side effects.

DISCUSSION

Intrauterine fetal death results in stress and psychological distress for patients and their families. For a long period, numerous initiatives have been made to reduce its frequency. The incidence of IUFD is still far too high, despite a general decline in the rate of perinatal fatalities. Jamal S. *et al.*, found the incidence of IUFD was higher in emergency admissions, 66% compared to 33.9% in booked cases [19]. Kameshwaram *et al.*, observed a five times higher IUFD rate in emergency cases [20]. Al Kadri *et al.*, found a 70% risk of IUFD in patients not receiving antenatal care [21].

In our study, most of the patients (45%) were aged between 26-30 years. Maximum incidence was found in the age group of 16-20 years (33.9%), indicating that teenagers were the group most commonly affected as reported by Jamal S. *et al.*, [19]. Similarly, as reported by Desai S *et al.*, in her study, the incidence in the teenage group was 30.76% [22]. The majority of adolescent pregnancies are unplanned, and they carry a significant risk of anemia, HDP, and delivery difficulties. In our investigation, a higher maternal age did not significantly contribute to the results. One major element influencing the outcome of a pregnancy is parity. The majority of instances (45%) in the current study included mothers with 2nd gravida. Desai S *et al.*, noted a similar thing in their study (46.15%) [22]. Nonetheless, a study by Raymond E. G. *et al.*, showed that multigravida females had a greater rate of IUFDs [23].

In the current study, most of the fetal mortality (45%) was at gestation of 28-32 weeks. In a maximum of 32.1% of cases, Jamal S. *et al.*, diagnosed fetal mortality at gestation of 20–24 weeks [19]. In terms of gestational age, IUFDs were most common between 28 and 32 weeks (45%), followed by 33 - 36 weeks (20%), which contradicts Mufti *et al.*,'s findings [24]. Hypertensive Disorders of Pregnancy (HDP) were a complicating factor in the majority of these instances. The most common factor in pregnancies with early IUFD was congenital abnormalities. Pregnancy-related hypertension problems made up 20% of the present research. Patel S discovered that HDP was present in 33.7% of the patients in his study [25].

Though, HDP maintains the legacy of being the most common etiological factor in maternal causes, in our study, although there was no maternal mortality, previous history of IUFD was the most common finding among our study participants. Severe preeclampsia (45%), was the second most common finding of our study. While mortality from 20–27 weeks has remained mostly stable, the rate of fetal deaths after 28 weeks has decreased since 1990. This emphasizes how crucial it is to assess the etiology of intermediate IUFD [19]. In the present study, among the fetal causes, placenta previa was in 15% of cases.

Furthermore, our study found hypertension to be a substantial risk factor for IUFD, which is consistent with previous research [26-30]. Hypertensive diseases quadruple the risk of IUFD due to placental insufficiency and an increased frequency of retroplacental hematomas, which impair fetal perfusion. Severe anemia was frequent in our study population, with 5% having hemoglobin levels less than 8 gm/dl. These results are consistent with other research that found varied degrees of anemia [19,31]. In our study, maternal variables like as pre-eclampsia and premature rupture of membranes (PROM) were related to IUFD at a rate of just 45% & 15% respectively, which contradicted findings from Kumari *et al.*, (30%) and Lucy *et al.*, Various research investigations have found that fetal and cord-related variables play a role in IUFD [19, 24, 31].

The rate of successful delivery with the combined regime in our study (85%) was comparable with the results of Wagaarachchi *et al.*, (87.5%) and Stibbe *et al.*, (86%) [32,33]. There were 2 cesarean cases in this study. One of the C/S was done to relieve pain as the patient was psychologically upset about being in too much pain and the other one was done to prevent rupture.

In the current study, nausea and vomiting were the most common side effects and the majority (80%) of them had no side effects. As side effects of misoprostol are dose-related, a marginally higher incidence of such side effects was observed in the misoprostol-only group in a few previous studies [34,35].

Pre-eclampsia, abruption, and fetal development restriction are associated with an increased risk of IUFD among women who have previously experienced an IUFD [19]. Pregnancy-induced

hypertension, congenital abnormalities, protracted membrane rupture, antepartum hemorrhage, poorly managed labor, and underlying medical disorders such as diabetes mellitus and heart illness are among the most common risk factors for fetal death in developing nations [36]. Umbilical cord problems become the most common cause of fetal death in the third trimester. Regretfully, these issues are frequently seen as unanticipated and unpreventable. On the other hand, insertion anomalies including knots, nuchal cords, and velamentous insertions happen quite frequently and aren't always connected to fetal death [37,38].

Even in cases where preventive steps might have been implemented, many undetected cases of IUFD occur in Bangladesh as a result of insufficient prenatal care and low awareness among women. Nonetheless, patient education, recognition of warning signals, routine prenatal visits, and early referrals could prevent a sizable percentage of IUFD cases. Determining the likely and potential cause of fetal death is therefore crucial.

Limitations of the study

Our study was a single-center study. We took a small sample size due to our short study period. After evaluating those patients, we did not follow up with them for the long term and did not know other possible interference that may happen in the long term with these patients.

CONCLUSION AND RECOMMENDATIONS

In this study, our findings showed that the majority of our patients had no side effects and medical induction was successful without any major complications. We also found that a combination of misoprostol with mifepristone was more effective than misoprostol or mifepristone alone for the induction of labor in Intrauterine fetal death, in terms of a higher rate of successful delivery. So further study with a prospective and longitudinal study design including a larger sample size needs to be done to determine the optimum dose and the dosing interval of the two drugs to further improve outcomes.

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