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ORIGINAL RESEARCH

Efficacy of Vaginal Misoprostol for Labor Induction in Intrauterine Fetal Death: A Cohort Study from West Java Largest Hospital

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Purpose: To evaluate the efficacy of vaginal misoprostol for labor induction in intrauterine fetal death (IUFD) at ≥20 weeks' gestation.

Patients and Methods: This retrospective cohort study reviewed medical records of IUFD cases between 2021 and 2023 at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Women with IUFD at ≥20 weeks' gestation who underwent vaginal misoprostol induction were included, and cases with incomplete key data were excluded. Outcomes included induction-to-contraction interval, induction-to-delivery interval, and cumulative misoprostol dose. Comparisons across gestational age groups (21–27, 28–36, and ≥37 weeks) were performed using the Kruskal–Wallis test; categorical variables were analyzed using the chi-square test.

Results: Of 155 IUFD cases, 71 received misoprostol-only induction and were analyzed. Median induction-to-contraction intervals were 12 hours, 6 hours, and 3 hours in the 21–27, 28–36, and ≥37 weeks groups, respectively ($p<0.001$). Median induction-to-delivery intervals were 13 hours, 10 hours, and 6 hours, respectively ($p=0.010$). Median cumulative misoprostol doses decreased significantly with advancing gestational age: 200 µg, 100 µg, and 50 µg, respectively ($p<0.001$). Maternal age and parity did not differ significantly among groups.

Conclusion: Vaginal misoprostol was associated with shorter induction intervals and lower cumulative dose requirements at later gestational ages in IUFD. Prospective multicenter studies are needed to confirm optimal regimens and safety.

Keywords: labor induction interval, gestational age stratification, prostaglandin, induction dosing, stillbirth management

Introduction

Fetal death, according to the American College of Obstetricians and Gynecologists (ACOG), is defined as a fetus that shows no signs of life, including no breathing, no heartbeat, no umbilical cord pulsation, or muscle movement.[1] Currently, there is variability in the definitions of Intrauterine Fetal Death (IUFD) based on gestational age across different sources. According to Williams Obstetrics, IUFD refers to fetal death in the womb at a gestational age of more than 20 weeks. Meanwhile, the Royal College of Obstetricians and Gynaecologists (RCOG) defines IUFD as fetal death occurring after 24 weeks of gestation.[2]

Indonesia ranks as one of the top 10 countries with the highest number of neonatal deaths globally. The perinatal mortality rate in Indonesia is estimated at 21 deaths per 1,000 live births. In West Java province in 2022, the IUFD rate was recorded at 2.6 per 1,000 live births.[3] The management of IUFD presents its own challenges. In cases of IUFD, the decision lies between waiting for spontaneous labor or immediately inducing labor. Waiting for spontaneous labor is associated with increased emotional stress, intrauterine infection, and risks related to consumptive coagulopathy.[4]

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Over the past two decades, prostaglandins (PG) have provided an alternative method for labor induction in women with IUFD. Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is used to promote cervical ripening and labor induction in various conditions and gestational ages, with different administration routes and dosage regimens.[5,6] Misoprostol can be absorbed and administered orally, vaginally, rectally, or intracervically. The vaginal route believes to offer advantages as the peak dose is reached more slowly and lasts longer, resulting in fewer side effects.[7]

In Indonesia, misoprostol remains widely used off-label in obstetric and gynecologic practice, including for labor induction in IUFD cases. Previous Indonesian observational data demonstrated variability in misoprostol indication, dosage, and route of administration across clinical settings, reflecting the absence of standardized institutional practice and the limited availability of local evidence regarding optimal regimens.[8] Furthermore, because misoprostol is primarily licensed for gastrointestinal indications rather than obstetric use, concerns regarding dose selection, administration route, efficacy, and safety continue to be clinically relevant. Therefore, this study was conducted to evaluate the efficacy of vaginal misoprostol for IUFD induction and to compare outcomes across gestational age subgroups.

Materials and Methods

Study Design

This retrospective cohort study was conducted at Hasan Sadikin General Hospital, Bandung, West Java, Indonesia, between 2021 and 2023. The study focused on assessing the influence of vaginally administered misoprostol on labor induction in cases of IUFD and utilized secondary data extracted from patient medical records. The population included pregnant women diagnosed with IUFD at gestational ages exceeding 20 weeks. This study has receive approval by the Ethics Committee of Hasan Sadikin General Hospital.

Inclusion and Exclusion Criteria

Eligible cases were patients with a diagnosis of IUFD who underwent vaginal delivery. Exclusion criteria included missing documentation of gestational age, induction start time, delivery time, or total misoprostol dose administered.

Induction Procedure and Data Collection

During the study period, labor induction for intrauterine fetal death (IUFD) was performed according to the institutional protocol of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, with the regimen determined based on gestational age.

For pregnancies >24–28 weeks of gestation, vaginal misoprostol 100 μg was administered and could be repeated once after 6 hours. For pregnancies >28 weeks of gestation, vaginal misoprostol 50 μg was administered and could also be repeated once after 6 hours.

Adjunctive induction methods, including laminaria insertion, balloon catheter placement, and oxytocin augmentation, were used when clinically indicated according to institutional protocol. Cesarean delivery was performed when vaginal delivery was considered unsuccessful or when maternal indications for abdominal delivery were identified.

For the present analysis, only patients who underwent induction using vaginal misoprostol alone were included.

For each eligible case, demographic characteristics, obstetric history, gestational age, cumulative misoprostol dose, induction-to-contraction interval, and induction-to-delivery interval were retrospectively collected from medical records.

Data Analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. Categorical variables were analyzed using the Chi-square test. Continuous variables were compared across gestational age groups using the Kruskal–Wallis test. A p-value <0.05 was considered statistically significant.

Results

During the study period, a total of 155 IUFD cases were identified. The distribution of management methods is presented in Figure 1, categorized as follows: Misoprostol induction only were 71 cases (46%); Spontaneous expulsion were 59 cases (38%) and other methods were 25 cases (16%). The “other methods” category included: Cesarean section were 10

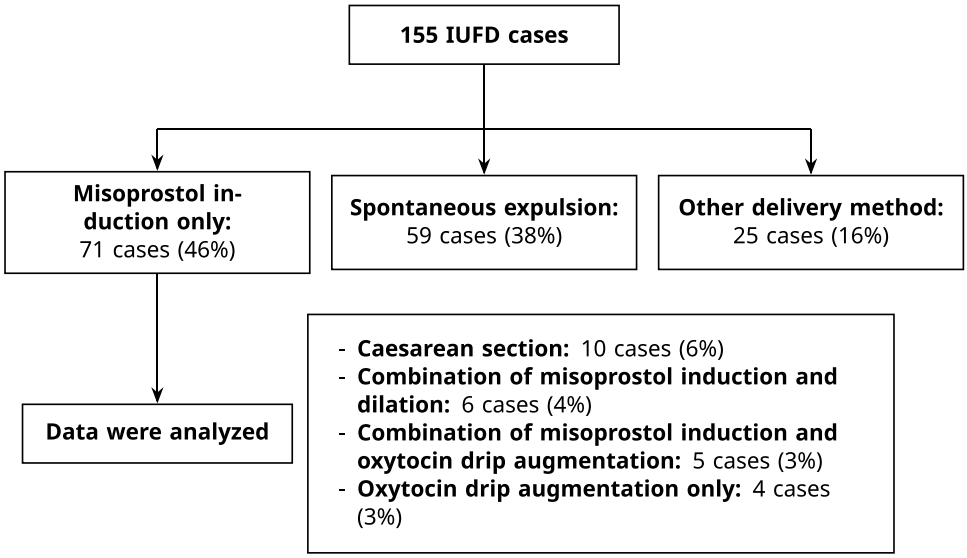

Figure 1 Flowchart of case selection and delivery management methods among patients with intrauterine fetal death (IUFD).

cases (6%); combination of misoprostol induction and dilation were 6 cases (4%).; combination of misoprostol induction and oxytocin drip augmentation: 5 cases (3%). Oxytocin drip augmentation only were 4 cases (3%). Out of these, the 71 cases of misoprostol induction only were analysed further.

The comparison of patient characteristics and clinical outcomes according to gestational age is shown in Table 1. Continuous variables including age, induction-to-contraction interval, induction-to-delivery interval, and total

Table 1 Comparison of Patient Results by Gestational Age

Variables	Gestational Age			P-value
	21–27 weeks (n=15)	28–36 weeks (n=49)	>37 weeks (n=7)	
Age				0.840
Mean±Std	34.60±18.161	32.67±16.861	32.00±8.062	
Median	31.00	28.00	30.00	
Range (min-max)	21.00–95.00	19.00–129.00	22.00–42.00	
Parity				0.646
0	3(20.0%)	19(38.8%)	3(42.9%)	
1–2	8(53.3%)	23(46.9%)	3(42.9%)	
>3	4(26.7%)	7(14.3%)	1(14.3%)	
Induction-to-contraction interval (hours)				0.0001*
Mean±Std	10.47±4.357	5.47±2.073	3.86±1.574	
Median	12.00	6.00	3.00	
Range	4.00–18.00	1.00–9.00	2.00–6.00	
Induction-to-delivery interval (hours)				0.010*
Mean±Std	11.93±5.007	9.41±2.886	6.86±2.268	
Median	13.00	10.00	6.00	
Range (min-max)	4.00–21.00	5.00–14.00	4.00–10.00	
Total dose of misoprostol				0.0001*
Mean±Std	193.33±70.373	89.80±33.819	64.29±24.398	
Median	200.00	100.00	50.00	
Range (min-max)	100.00–300.00	50.00–150.00	50.00–100.00	

Notes: Categorical variables were analyzed using the Chi-square test. Continuous variables were analyzed using the Kruskal–Wallis test. *p <0.05 considered statistically significant.

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Table 2 Characteristics of Risk Factors in Patients with IUFD

Characteristics	Number of Patients (n=155)	Percentage (%)
Maternal Factors		
Hypertension		
Preeclampsia	38	25
Superimposed preeclampsia	14	9
HELLP syndrome	2	1
Chronic hypertension	3	2
Gestational hypertension	3	2
Infection		
Syphilis	5	3
COVID-19	5	3
Asymptomatic bacteriuria	2	1
Dengue fever	2	1
Tuberculosis	2	1
Others		
Systemic Lupus Erythematosus	4	3
Major thalassemia	2	1
Breast cancer	1	1
Fetal factors		
Congenital disorder	21	14
Twin-to-twin transfusion syndrome	3	2
Hydrops fetalis	1	1

misoprostol dose were compared across gestational age groups using the Kruskal–Wallis test. No significant difference was observed in maternal age or parity ($p>0.05$). However, significant differences were found in induction-to-contraction interval, induction-to-delivery interval, and total misoprostol dose ($p<0.05$).

It was found that the median induction-to-contraction intervals were 12 hours at 21–27 weeks, 6 hours at 28–36 weeks, and 3 hours at >37 weeks. The median induction-to-delivery intervals were 13 hours, 10 hours, and 6 hours, respectively. Median total misoprostol doses were 200 µg, 100 µg, and 50 µg respectively.

The characteristics of maternal and fetal risk factors among IUFD cases are summarized in Table 2. Among the 155 patients, 108 (70%) had maternal or fetal comorbidities, while 47 (30%) were idiopathic. The most common maternal conditions were hypertensive disorders and infections, while the most frequent fetal factor was congenital anomaly. These conditions should be interpreted as associated factors recorded in the medical charts rather than proven causes of IUFD. No fetal autopsy was performed; therefore, the exact cause of IUFD could not be confirmed.

Discussion

A number of studies have supported the role of misoprostol as an agent for labor induction in IUFD. A meta-analysis by Zhang et al reported that misoprostol facilitates labor induction and reduces the need for additional oxytocin without compromising safety.[9] Another study also found a shorter mean time from induction to the onset of contractions in gestations beyond 28 weeks, suggesting greater efficacy of misoprostol at later gestational ages, which is consistent with the present study.[10]

Other evidence further reinforces our observations. For instance, the Bugalho et al clinical trial observed a mean induction-to-delivery interval of 12.6 hours in intravaginally administered misoprostol-treated IUFD patients—this is quite comparable to our observation of reducing intervals with increasing gestational age.[11] Similarly, the intervention review by Dodd and Crowther concluded that vaginal misoprostol is efficient and has fewer gastrointestinal side effects compared to other prostaglandin medications. This is similar to our findings, which showed misoprostol is effective in inducing the labor process in the case of IUFD, with special dosing based on gestational age.[12]

Our study found that the required dose of misoprostol decreased with advancing gestational age, as demonstrated by significantly shorter intervals from induction to contraction and from induction to delivery in pregnancies beyond 37 weeks. These findings align with contemporary FIGO recommendations for IUFD management, which recognize that vaginal misoprostol tends to be more effective at earlier gestational ages. For pregnancies beyond 28 weeks, FIGO advises that induction should follow standard obstetric practice and need not rely solely on misoprostol, particularly with caution in women who have prior uterine scars.[1]

The shorter induction-to-contraction interval observed at higher gestational ages likely reflects both increased myometrial responsiveness and the lower cumulative number of misoprostol doses required to achieve effective contractions. Therefore, the association observed in this retrospective study should not be interpreted as gestational age alone causing faster induction, because dose requirement and gestational age are closely linked.

From a biological perspective, this pattern is likely explained by the progressive increase in myometrial responsiveness to prostaglandins as gestation advances. Greater receptor sensitivity and improved cervical readiness in later pregnancy may allow effective uterine stimulation with lower pharmacologic doses, resulting in shorter induction intervals and more efficient labor progression.[13]

Our observations are further supported by prior clinical studies. Sumiya Gul et al reported that increasing gestational age was associated with shorter induction-to-labor intervals and reduced cumulative misoprostol dose requirements.[14] Similarly, cohort data from Berger et al showed that lower prostaglandin doses were associated with a longer time to fetal expulsion, particularly at earlier gestations, whereas higher or medium starting doses shortened induction duration without increasing adverse outcomes.[13] This supports the importance of gestational age–based dosing strategies. Consistent with this, Gómez Ponce de León et al summarized clinical guidance recommending progressive dose reduction with advancing gestation, reflecting increasing uterine sensitivity to prostaglandins.[15]

In our routine practice, a 50 μg dose was approximated by quartering a 200 μg misoprostol tablet according to institutional protocol. However, manual splitting may introduce dose variability and may affect the precision of the delivered dose. This limitation should be considered when interpreting the cumulative dose findings.

In this study, parity did not significantly influence the induction-to-contraction or induction-to-delivery interval across gestational age groups. This finding is consistent with Menticoglou et al, who reported that parity did not affect misoprostol efficacy in IUFD induction.[7] However, conflicting evidence exists. Miller et al found that multiparous women had shorter induction-to-delivery times than nulliparous women, suggesting that parity may influence responsiveness to induction agents in some settings.[16]

This study has several limitations. First, the relatively small sample size may limit the statistical power of the analysis and the robustness of subgroup comparisons across gestational age categories. Second, the retrospective observational design using secondary medical record data introduces the risk of selection bias and limits causal inference. In addition, although incomplete records were excluded, this may have resulted in the loss of potentially relevant clinical information. In addition, indications for cesarean delivery were not consistently documented in all medical records, limiting further evaluation of the clinical factors contributing to failed vaginal induction or the decision for abdominal delivery. Third, because the study was conducted in a single tertiary care center over a two-year period, the findings may not be generalizable to other settings or populations. Fourth, the study relied on a gestational-age–based institutional protocol, and manual tablet splitting may have introduced some dose variability in low-dose regimens.

Conclusion

Vaginal misoprostol was associated with shorter induction-to-delivery intervals and lower cumulative dose requirements at higher gestational ages in IUFD cases. These findings are hypothesis-generating and should be confirmed in prospective multicenter studies before being used to define optimal dosing strategies.

Statement on the Use of Generative Artificial Intelligence (AI)

Generative artificial intelligence (AI) was used solely to assist in language refinement, grammatical editing, and structural improvement of the manuscript. The AI did not contribute to study design, data collection, data analysis, interpretation of

results, or scientific conclusions. All intellectual content, clinical interpretation, and final decisions remain the responsibility of the authors.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval

This study was approved by the Ethics Committee of Hasan Sadikin General Hospital, Bandung, Indonesia (Ethical Approval No: DP.04.03/D.XIV.6.5/218/2024). The study protocol underwent review and received clearance from the institutional ethics review board prior to commencement. As this research involved human participants and clinical data, all procedures were conducted in accordance with the ethical standards of the institutional research committee and in compliance with the principles of the Declaration of Helsinki (1964) and its subsequent amendments.

Patient Consent

Written informed consent for participation and publication of anonymized data was obtained from all patients (or their legal guardians) in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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