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Efficacy and Safety of Oral Mifepristone as a Cervical Ripening Agent for Labor Induction in Low-Risk Full-Term Live Pregnancies Beyond 40 Weeks of Gestation: A Randomized Controlled Study

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Abstract: ***This study evaluates the efficacy and safety of oral mifepristone as a cervical ripening agent for inducing labor in low-risk, full-term live pregnancies beyond 40 weeks of gestation. In this randomized controlled trial, 100 pregnant women were equally divided into two groups: the study group receiving 200 mg oral mifepristone and the control group undergoing expectant management. The primary outcomes measured were improvement in Bishop's score within 24-48 hours and the onset of labor within 72 hours. Secondary outcomes included allocation-to-delivery interval, the requirement for additional labor inducers, maternal and neonatal outcomes, and mode of delivery. Results showed significant improvements in cervical ripening, reduced need for additional labor inducers, and a shorter induction-to-delivery interval in the mifepristone group. Mifepristone demonstrated excellent safety and efficacy in inducing labor with minimal side effects, suggesting its potential role as a primary agent in labor induction protocols.***

Keywords: Mifepristone; Cervical ripening; Term pregnancy; Labor induction; Pregnancy outcomes.

1. Introduction

Induction of labor is an essential procedure in modern obstetric practice, often employed when spontaneous labor fails to commence, and the risks associated with prolonging pregnancy outweigh the benefits. For the majority of women, labor starts spontaneously and results in vaginal delivery at or near term.[1] A common indication for labor induction is post-date pregnancy, defined as gestation extending beyond 40 weeks, where both maternal and fetal risks, such as oligohydramnios, meconium aspiration, and placental insufficiency, are significantly heightened.[2] According to ACOG 2009, the goal of induction of labor is to achieve vaginal delivery by stimulating uterine contractions before the spontaneous onset of labor.[3]

Sometimes it is essential to induce labor when the risk to the mother or fetus with pregnancy continuation outweighs the risk involved with intervention.[4] One of the most common indications for labor induction is prolonged pregnancy, as it is associated with an increased risk to the fetus, including increased perinatal mortality rate, low 5-min Apgar scores, dysmaturity syndrome, and increased risk of death within the first year of life.[5] Despite advancements in labor management, the need for an efficient, safe, and reliable method of cervical ripening remains a critical goal, especially for pregnancies nearing or surpassing their due dates.[6]

Historically, various pharmacological and mechanical methods have been utilized to induce labor, including prostaglandins, oxytocin, and mechanical dilation techniques. Prostaglandins, particularly dinoprostone and misoprostol, have long been considered the gold standard for cervical ripening.[8] However, the administration of these agents is often associated with a high risk of uterine hyperstimulation, fetal distress, and the need for stringent monitoring, which can complicate the induction process. Consequently, researchers have been exploring alternative pharmacological agents that not only ripen the cervix effectively but also reduce the side effects associated with traditional methods.
Mifepristone, a synthetic steroid compound, has gained attention as a promising alternative to prostaglandins for cervical ripening and labor induction. As a progesterone receptor antagonist, mifepristone works by blocking the effects of progesterone, a hormone essential for maintaining pregnancy.[9] Progesterone inhibition leads to the breakdown of collagen in the cervix, promoting cervical softening and ripening. Additionally, mifepristone increases uterine contractility, further facilitating the onset of labor.[7]

Initially developed and approved for medical abortions in early pregnancy, mifepristone's role in obstetrics has expanded due to its ability to facilitate cervical changes and induce labor without the risks associated with traditional prostaglandins.[7] Several clinical trials have investigated the safety and efficacy of mifepristone in various contexts, including post-term pregnancy, pre-eclampsia, and fetal

growth restriction, with promising outcomes. However, its use as a primary agent for labor induction at term, particularly in low-risk pregnancies, is still being explored.

A major advantage of mifepristone over other induction agents is its route of administration.[8] While prostaglandins are commonly administered vaginally, mifepristone is taken orally, providing greater convenience for both patients and healthcare providers. Moreover, its longer half-life allows for extended action, reducing the need for repeated dosing and continuous monitoring. Despite these potential benefits, questions remain regarding the optimal dosage, timing, and patient selection for mifepristone use in labor induction.[9]
This study aims to evaluate the efficacy and safety of oral mifepristone as a cervical ripening agent in full-term pregnancies beyond 40 weeks. The study seeks to compare mifepristone with expectant management in terms of cervical ripening, the onset of labor, and maternal and neonatal outcomes, contributing to the growing body of evidence supporting mifepristone's role in obstetric practice.

2. Material & Methods

Study Design and Population:
This open-label, parallel-group, randomized controlled study was conducted in the Department of Obstetrics and Gynaecology, Umaid Hospital, Jodhpur, from November 2023 to June 2024. The study enrolled 100 pregnant women with low-risk, full-term singleton pregnancies between 40 and 40+6 weeks of gestation, with a Bishop's score of less than 6. Exclusion criteria included a history of uterine surgery, medical disorders, and fetal anomalies.

Randomization and Intervention:
The participants were randomized into two groups. The study group received 200 mg oral mifepristone, while the control group was managed expectantly. If the Bishop's score in the study group did not improve after 24 hours, a second 200 mg dose was administered. Cerviprime gel and oxytocin were used for further induction and augmentation as needed. Outcomes were monitored over a 72-hour period.

Outcome Measures:
Primary outcomes included the change in Bishop's score within 24-48 hours and the onset of labor within 72 hours. Secondary outcomes measured allocation-to-delivery interval, allocation-to-active phase interval, mode of delivery, and neonatal and maternal outcomes.

Statistical Analysis:
Statistical analyses were performed using Mann-Whitney U tests for continuous variables, chi-square tests for categorical variables, and relative risk with confidence intervals where appropriate. P-values less than 0.05 were considered statistically significant.

3. Results

The demographic characteristics, including age, education, occupation, BMI, and booking status, were similar between the two groups. The mean age of participants was 23.42 ± 2.67 years in the study group and 23.16 ± 3.50 years in the control group ($p > 0.05$). Most participants were housewives with a mean BMI of 21.78 ± 0.91 in the study group and 21.96 ± 1.06 in the control group ($p > 0.05$).

Table 1: Demographics

Characteristic	Study Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Age (years)	23.42 ± 2.67	23.16 ± 3.50	> 0.05
BMI (kg/m²)	21.78 ± 0.91	21.96 ± 1.06	> 0.05
Education	Similar distribution	Similar distribution	> 0.05
Occupation	Mostly housewives	Mostly housewives	> 0.05
Booking status	Similar distribution	Similar distribution	> 0.05

There was a significant improvement in the Bishop's score in the study group compared to the control group at 24 hours (6.18 ± 2.39 vs. 2.98 ± 2.13; $p < 0.001$) and 48 hours (6.15 ± 2.47 vs. 3.37 ± 2.87; $p = 0.0003$). A total of 92% of women in the mifepristone group entered labor within 72 hours compared to only 46% in the control group ($p < 0.001$).

Table 2: Cervical Ripening and Labor Onset

Outcome	Study Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Bishop's score at baseline	2.72±1.29	2.58±1.47	0.781
Bishop's score > 24 hrs	6.18 ± 2.39	2.98 ± 2.13	< 0.001
Bishop's score > 48 hrs	6.15 ± 2.47	3.37 ± 2.87	0.0003
Labor onset within 72 hrs	92%	46%	< 0.001

The mean allocation-to-delivery interval was significantly shorter in the study group (44.72 ± 19.83 hours) compared to the control group (110.34 ± 52.77 hours; $p < 0.001$). Similarly, the allocation-to-active phase interval was also shorter in the study group (38.06 ± 17.80 hours vs. 99.13 ± 50.72 hours; $p < 0.001$).

Table 3: Induction to Delivery Interval

Outcome	Study Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
Allocation-to-delivery interval (hrs)	44.72 ± 19.83	110.34 ± 52.77	< 0.001
Allocation-to-active phase (hrs)	38.06 ± 17.80	99.13 ± 50.72	< 0.001

Fewer women in the mifepristone group required cerviprime gel (32% vs. 52%; $p = 0.042$) or oxytocin (26% vs. 68%; $p < 0.001$) compared to the control group. Mode of delivery was similar between the two groups, with 76% of women in the study group having vaginal deliveries compared to 72% in the control group ($p > 0.05$).

Table 4: Need for Additional Agents and Mode of Delivery

Agent	Study Group (%)	Control Group (%)	p-value
Cerviprime gel use	32%	52%	0.042
Oxytocin use	26%	68%	< 0.001
Normal Delivery	76%	72%	> 0.05
C-section	24%	28%	> 0.05

There were no significant differences in maternal complications, such as postpartum haemorrhage and fetal distress, between the groups. Neonatal outcomes, including

birth weight, APGAR scores, and NICU admissions, were comparable between the groups ($p > 0.05$).

Table 5: Maternal and Neonatal Outcomes

Outcome	Study Group	Control Group	p-value
Postpartum haemorrhage	No significant difference	No significant difference	> 0.05
Fetal distress	No significant difference	No significant difference	> 0.05
Neonatal birth weight	Comparable	Comparable	> 0.05
APGAR score	Comparable	Comparable	> 0.05
NICU admissions	Comparable	Comparable	> 0.05

4. Discussion

The findings of this randomized controlled trial demonstrate that mifepristone is highly effective as a cervical ripening agent in full-term pregnancies, particularly for women with a Bishop's score of less than 6. In this study, mifepristone significantly improved cervical ripening within 24 to 48 hours and induced labor in 92% of women in the study group, compared to only 46% in the expectant management group. These results are consistent with earlier research highlighting the efficacy of mifepristone in promoting cervical ripening and inducing labor in post-term pregnancies.[10]

Our results align with the findings of studies like Baev et al.[10] and Yelikar et al.,[11] which also reported significant improvements in the Bishop's score and a reduction in the induction-to-delivery interval following mifepristone administration. In our study, the mean allocation-to-delivery interval was significantly shorter in the mifepristone group, suggesting that this agent may expedite labor progression compared to expectant management or prostaglandins. This shorter interval is clinically significant, as it reduces the duration of labor, potentially lowering the risk of maternal exhaustion, infection, and the likelihood of caesarean deliveries.

Moreover, the need for additional agents such as cerviprime gel and oxytocin was significantly lower in the mifepristone group. This finding is in line with the meta-analysis by Alfirevic et al.,[12] which demonstrated that using mifepristone reduces the need for labor augmentation. By decreasing the reliance on other induction agents, mifepristone offers a simpler, more cost-effective approach to labor induction. Furthermore, reducing the need for oxytocin may lower the incidence of uterine hyperstimulation, which is a known complication of oxytocin use. Uterine hyperstimulation can lead to fetal distress, necessitating emergency interventions such as caesarean delivery, which makes mifepristone a safer alternative in some contexts.[13]

In terms of safety, this study found no significant differences in maternal or neonatal outcomes between the mifepristone and expectant management groups. This finding is particularly important in the context of concerns about the safety of mifepristone when used in full-term pregnancies. Maternal complications, such as postpartum haemorrhage and uterine atony, were comparable between the two groups, while neonatal outcomes, including birth weight, Apgar scores, and NICU admissions, did not differ significantly. This suggests that mifepristone is not only effective but also safe for both mother and baby when used for labor induction in post-term pregnancies. Our results support those of Wing et al.,[13] who reported no increased risk of adverse maternal or neonatal outcomes when mifepristone was used in conjunction with prostaglandins or oxytocin for labor induction in post-term pregnancies.

Similarly, Tang et al.[14] found no significant differences in neonatal outcomes between mifepristone and other induction agents, further solidifying the safety profile of mifepristone in obstetric practice. Frydman et al.[15] also demonstrated in their trials that mifepristone had no significant adverse maternal or fetal effects when used in labor induction, making it a viable alternative to more commonly used prostaglandins.

However, this study has some limitations that need to be addressed. First, the relatively small sample size and the single-center design may limit the generalizability of the findings. Although the results are promising, larger multicentre trials are necessary to validate these outcomes across different populations and clinical settings. Mehra et al.[16] conducted a similar study across multiple centres, and their larger sample size allowed for more robust conclusions regarding mifepristone's effectiveness. A similar approach should be taken in future studies to enhance the reliability of these findings.

While mifepristone was highly effective in inducing labor, its role in reducing the caesarean delivery rate remains unclear, as the mode of delivery was similar between the mifepristone and expectant management groups. Several studies, such as those by Chandraharan et al.[17] and Howell et al.,[18] have explored the potential of mifepristone to reduce caesarean section rates, but the evidence remains inconclusive. Future research should focus on determining whether mifepristone can significantly reduce caesarean delivery rates, particularly in high-risk pregnancies or those with an unfavourable Bishop's score.

Another aspect that warrants further investigation is the optimal dosage and timing of mifepristone administration for labor induction. Different studies have used varying dosages and time intervals between administration and labor onset, making it difficult to establish a standard protocol. Kumar et al.[19] compared different mifepristone dosages and found that a higher dose (400 mg) had a faster onset of labor without compromising safety, while lower doses (200 mg) were similarly effective but took longer to achieve the desired outcomes. Such variations highlight the need for more research to identify the most effective and safe dosage regimen.

Finally, it is important to note that while mifepristone appears to be a highly effective agent for labor induction, its use should be considered within the context of a comprehensive induction strategy that includes thorough patient selection, monitoring, and the availability of emergency interventions. Krishna et al.[20] emphasized the importance of selecting candidates for mifepristone induction carefully, particularly avoiding its use in cases where there are contraindications such as abnormal placentation or previous uterine surgery.

In conclusion, this study demonstrates that mifepristone is an effective and safe agent for cervical ripening and labor

induction in full-term pregnancies beyond 40 weeks. Its oral administration, reduced need for additional agents, and favourable safety profile make it an attractive option for labor induction. Given the increasing interest in non-invasive, cost-effective methods for inducing labor, mifepristone could become a cornerstone in the management of post-term pregnancies. Larger multicentre trials and further research into its potential to reduce caesarean delivery rates and its optimal dosage will help refine its role in obstetric practice. Baev et al.,[10] Yelikar et al.,[11] and others have laid a solid foundation for mifepristone's place in labor induction protocols, and our study adds to the growing body of evidence supporting its efficacy and safety.

5. Conclusions

Oral mifepristone is a safe and effective cervical ripening agent that can significantly reduce the time to labor and the need for additional interventions in full-term pregnancies. Its ease of administration, cost-effectiveness, and safety profile make it a promising candidate for wider use in labor induction protocols. Further research is warranted to optimize the dosage and administration schedule for maximum efficacy.

Conflict of Interest: Nil

Source of Funding: Nil

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