Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2025, 15(4), 789-805
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

Safety of Misoprostol in Labor Induction for Twin Pregnancies: A Systematic Review

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How to cite this paper: Gueye, M., Hoballah, A., Hage Ali, H., Wade, F.K., Biaye, D., Gning, H.M., Guisse, A. and Mbodji, A. (2025) Safety of Misoprostol in Labor Induction for Twin Pregnancies: A Systematic Review. *Open Journal of Obstetrics and Gynecology*, **15**, 789-805.
https://doi.org/10.4236/ojog.2025.154065

Received: March 25, 2025
Accepted: April 24, 2025
Published: April 27, 2025

Abstract

Objectives: To evaluate the safety of using misoprostol for labor induction in twin pregnancies. **Methodology:** To address the research question regarding the safety and efficacy of misoprostol for labor induction in twin pregnancies, a systematic review was conducted. An extensive search strategy was employed, identifying relevant studies published in English or French between January 1, 1990, and December 12, 2023. Inclusion criteria focused on twin pregnancies with viable fetuses, a gestational age of 34 weeks or more, and the absence of uterine scars. Data extraction was performed using a standardized form, and the results of the selected studies were analyzed and synthesized. **Results:** Five retrospective cohort studies, comprising a total of 1,205 participants, were included in the review. These studies examined the effects of misoprostol for labor induction in twin pregnancies compared to spontaneous labor, oxytocin, dinoprostone, or elective cesarean section. The findings indicated that labor induction in twin pregnancies, particularly with misoprostol, did not significantly increase the risk of adverse maternal or neonatal outcomes. No notable differences were observed in terms of maternal morbidity, cesarean section rates, or neonatal outcomes, such as low Apgar scores at five minutes and umbilical artery pH values. **Conclusion:** This systematic review suggests that the use of misoprostol for labor induction in twin pregnancies may be a safe and effective option. However, the decision to induce labor should be made on a case-by-case basis, considering the individual clinical context and patient preferences. Existing controversies in the literature highlight the need for further research, including multicenter studies and randomized clinical trials, to provide clear guidelines for clinicians.

Keywords

Misoprostol, Twin Pregnancy, Labor Induction, Maternal Outcomes, Neonatal Outcomes, Systematic Review

1. Introduction

Artificial labor induction is defined as a medical intervention aimed at artificially inducing uterine contractions that lead to the progressive effacement and dilation of the uterine cervix, culminating in childbirth [1]. This intervention is intended for women who have not spontaneously entered labor, regardless of membrane status, and who have no contraindications to vaginal delivery.

Twin pregnancy is a reproductive anomaly in humans. Its incidence has risen globally with the advent of medically assisted reproduction techniques [2]. It is considered a high-risk pregnancy, posing significant concerns for obstetrician due to potential complications during gestation and delivery [2]. Labor induction in twin pregnancies may be necessary to minimize morbidity and mortality risks, particularly in cases of medical conditions (e.g., vascular or placental pathologies) or when gestational age reaches 39 weeks of gestation [3].

Multiple methods for labor induction exist. The choice typically depends on cervical status, including length, dilation, effacement, position, and fetal station. For a firm, long, and closed cervix ("unfavorable"), methods to promote cervical ripening ("favorable") may be employed. These include mechanical or pharmacological approaches [4], such as natural or synthetic prostaglandins and oxytocin [4]. Misoprostol, a synthetic prostaglandin E1 (PGE1) analogue, was approved by the U.S. Food and Drug Administration (FDA) in 1988 for preventing and treating gastric ulcers associated with non-steroidal anti-inflammatory drugs (NSAIDs) [5]. However, since the 1990s, its uterotonic effects and role in cervical maturation have garnered increasing interest among obstetricians for off-label obstetric use [5].

Misoprostol offers several advantages over other prostaglandins. It is rapidly absorbed orally and can also be administered sublingually, rectally, or vaginally despite lacking parenteral formulations [5]. It is cost-effective, requires no refrigerated storage, and is widely accessible, making it particularly suitable for use in low-resource settings [5]. Although not formally approved for obstetric indications, its applications continue to expand, including labor induction and intrauterine fetal demise cases, postpartum hemorrhage prevention, and cervical preparation [5].

Twin pregnancies are associated with significantly higher rates of maternal and neonatal complications compared to singleton pregnancies. These include preterm birth in over 50% of cases, postpartum hemorrhage in approximately 10% - 15%, and a threefold increased risk of neonatal intensive care unit (NICU) admission [6] [7]. These elevated risks make the decision to induce labor particularly complex in this population.

Despite its proven efficacy in general labor induction, misoprostol use in twin pregnancies remains controversial. Adverse effects such as uterine hyperstimulation, fetal heart rate abnormalities, and meconium-stained amniotic fluid occur more frequently with misoprostol, though these do not necessarily affect delivery mode or neonatal outcomes [8]. However, severe complications like uterine rupture or

neonatal morbidity raise concerns about its safety in twin pregnancies [8].

Numerous studies have assessed misoprostol's safety, largely concluding that its benefit-risk profile is acceptable. It has demonstrated high efficacy in both second- and third-trimester inductions, shortening labor duration and replacing outdated, poorly tolerated methods [9]. For instance, a 2002 Turkish study reported an increased risk of uterine rupture in women with a scarred uterus [10]. Conversely, some argue that the lack of formal obstetric approval may lead to underreporting of complications [11].

A 2017 study found that prostaglandin use for cervical ripening in twin pregnancies did not increase cesarean rates or complications [12], while another cohort study suggested higher cesarean risks compared to spontaneous labor [13]. Earlier research (2007) supported misoprostol's safety and efficacy in twin gestations [14].

This review specifically aims to assess the safety and effectiveness of misoprostol in twin gestations, given the inconsistent recommendations and exclusion of twin pregnancies in many induction studies.

2. Methodology

2.1. Search Strategy

The search strategy was designed to capture all relevant studies evaluating labor induction with misoprostol in twin pregnancies. Keywords were selected based on MeSH terms and text words identified in prior related reviews, and included: "twin pregnancy", "multiple pregnancy", "labor induction", "misoprostol", "prostaglandin", and "perinatal outcome".

Distinct search strategies were conducted across the following databases: COCHRANE, EMBASE, MEDLINE, and CINAHL, covering the period from January 1, 1990, to December 12, 2023. Only studies published in English or French were included in this literature review. Based on similar searches in the literature and comparable systematic reviews, the following search terms were used: *Twin pregnancies, Twin pregnancy, Twin, Twins, Sibling, Siblings, Reciprocal, Reciprocals, Induced labor, Induction of labor, Induction labor, Inductions labor, Induce labor, Labor induced, Labor induction, Labor inductions, Induction of labour, Inducing labor, Induced labour, Induce labour, Inductions labour, Labour induced, Labour induction, Labour inductions, Inducing labour, Induce Delivery, Misoprostol, Misoprostol induction, Prostaglandin, Gestation pregnancies, Obstetric labor, Expectant, Single pregnancy, Pregnancy, Pregnancies, Ocytocin, Syntocinon, Natural childbirth.*

These keywords, searched in titles and abstracts, were combined using the Boolean operators "AND" and "OR" following the PICOT method. Additional articles were identified from the reference lists of selected studies and relevant systematic reviews. Unpublished randomized controlled trials (RCTs) were also searched on the clinical trials website (http://clinicaltrials.gov) using the keywords *twin*, *multiple pregnancy*, and *labor induction*.

Randomized controlled trials and observational studies (cohort, cross-sectional, and case-control studies) were included if they compared neonatal outcomes based on the mode of labor induction in twin pregnancies. The primary neonatal outcomes were the 5-minute Apgar score and neonatal mortality. Twin pregnancies could be either dichorionic or monochorionic-diamniotic. The gestational age had to be at least 32 weeks, as twins born before this period may present complications unrelated to the mode of delivery. Both Twin A and Twin B had to weigh at least 1.5 kg.

Studies were excluded if they focused exclusively on singleton pregnancies, included non-viable fetuses, had a gestational age below 34 weeks, or involved women with previous uterine surgery or known uterine anomalies. This approach ensured the review focused on the most clinically relevant and comparable studies.

Once the article search was completed, the references were imported into Filemaker Pro 2023 and then EndNote. Duplicates were removed, and the titles and abstracts of the remaining studies were screened to exclude those irrelevant to the research question. The full texts of potentially relevant studies were reviewed to assess their eligibility based on predefined criteria.

2.2. Data Extraction

A specific data extraction form was designed using Filemaker 23 to standardize the collection of information and ensure consistency. The form recorded the study type, authors' names, title, year of publication, study design, country, objectives, results, inclusion and exclusion criteria, number of patients, gestational age of twins, presentation of the second twin, mode of delivery for each twin, birth weight, number of twins with an Apgar score < 7 at 5 minutes, neonatal deaths by twin and delivery mode (vaginal or cesarean), and maternal outcomes.

The extracted data were recorded in customized tables.

2.3. Quality Assessment and Risk of Bias

The selected studies were critically evaluated using the Cochrane Collaboration tool, which assesses the risk of bias as high, low, or unclear across five domains: selection, performance, attrition, reporting, and other biases [15]. Criteria included randomization methods, blinding processes, handling of exclusions, and other potential biases.

Additionally, the included studies were assessed using the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach [16] [17]. The GRADE system assigns a level of evidence (high, moderate, low, or very low) to each outcome based on the following criteria: High: Randomized trials or observational studies with two levels of upgrade; Moderate: Downgraded randomized trials or upgraded observational studies; Low: Randomized trials with two levels of downgrade or observational studies; Very low: Randomized trials with three levels of downgrade, downgraded observational studies, or case series/reports.

Based on these assessments, the GRADE system provides either a strong or

weak recommendation for an intervention.

2.4. Data Analysis

The methodology, interventions, and outcomes of each included study were described and grouped into logical categories. After analyzing and grouping the studies, their results were synthesized to produce a summary, taking into account differences that might influence their conclusions.

A meta-analysis could not be performed due to several limiting factors. First, the collected data were not sufficiently homogeneous to allow a meaningful combined analysis. Second, the reporting methods varied significantly across studies, making direct comparisons and synthesis challenging. Third, the labor induction methods compared to misoprostol were not uniformly represented in the studies. Finally, the small number of available studies (only five) limited the statistical power and generalizability of any conclusions that could have been drawn from a meta-analysis.

3. Results

The search equations using the listed keywords across the four databases retrieved a total of 465 abstracts (Medline: 212, CINAHL: 123, Embase: 120, Cochrane: 10). All references were imported into EndNote X9, and 378 duplicates were removed. Screening the titles and abstracts of the remaining 87 articles identified 30 potentially relevant articles for full-text review. After reading the full texts, five articles met the inclusion criteria and were included in this systematic review. They are listed alphabetically (Figure 1).

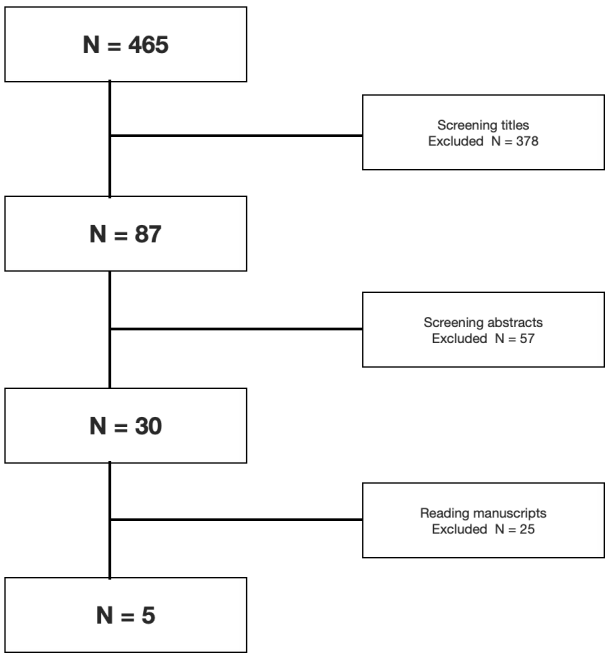

Figure 1. PRISMA flow chart summarizing the study selection process.

- "Is misoprostol safe for labor induction in twin gestations?" by Melissa C. Bush *et al.*
- "Induction of labor in twin pregnancies with oral misoprostol versus vaginal dinoprostone—is it effective and safe?" by Georgine Huber *et al.*
- "Induction of twin pregnancy and the risk of caesarean delivery: a cohort study" by Maria Jonsson.
- "Induction of labor in twin pregnancies—A retrospective cohort study" by Ingrid Mikaelsen *et al.*
- "Induction of labor with oral misoprostol in nulliparous mothers of twins" by Teresinha Simões *et al.*

3.1. Quality Assessment and Risk of Bias

Table 1 summarizes the risk of bias and GRADE assessment for each of the five included studies.

Each study is assigned a risk of bias rating (low, high, or unclear) for each domain. Additionally, the GRADE score (high, moderate, low, or very low) is provided for the overall quality of evidence.

Table 1. Risk of bias and GRADE scores of included studies.

		Bush	Simoes	Huber	Johnson	Mikaelsen
Year		2005	2006	2014	2015	2022
Study Type		RC	RC	RC	RC	RC
Selection Bias	Random Sequence Generation	High	High	High	High	High
Performance Bias	Allocation Concealment	High	High	High	High	High
	Blinding of Participants and Personnel	High	High	High	High	High
Detection Bias	Blinding of Outcome Assessment	High	High	High	High	High
Attrition Bias	Incomplete Data for Apgar Score at 5 min for Twin 1	Low	Low	Low	Unclear	Low
	Incomplete Data for Apgar Score at 5 min for Twin 2	Low	Low	Low	Unclear	Low
	Incomplete Data for Morbidity and Mortality for Twin 1	Low	Low	Low	Low	Low
	Incomplete Data for Morbidity and Mortality for Twin 2	Low	Low	Low	Low	Low
Reporting Bias	Selective Reporting	Low	Low	Low	Low	Low
Total	"High risk of bias" items		4	4	4	4
GRADE		3	3	3	3	3

RC: Restrospective cohort

3.2. Description of Included Studies

3.2.1. Objectives of Included Studies

The five selected studies [13] [14] [18]-[20] aimed to evaluate the efficacy and safety of labor induction in twin pregnancies, as well as neonatal and maternal outcomes. Some studies compared the use of misoprostol for labor induction in twin pregnancies to spontaneous delivery [20], oxytocin [14], or dinoprostone

[18]. One study focused on the association between labor induction and the risk of cesarean delivery [13].

3.2.2. Participant Characteristics

The five studies included a total of 1205 participants. Jonsson *et al.* (2015) [13] had the largest sample size with 462 participants, followed by Mikaelsen *et al.* (2022) [20] with 354 participants. In contrast, Simoes *et al.* (2006) [19] had the smallest sample size with 69 participants.

In all studies, participants had a gestational age of at least 34 weeks, except for Simoes *et al.*, where it was 35 weeks or more. Exclusions included intrauterine fetal death of one or both twins, congenital anomalies incompatible with life, and gestational age below 34 weeks.

Bush *et al.*, Huber *et al.*, and Simoes *et al.* excluded pregnancies where the first twin was non-cephalic. Simoes *et al.* also excluded multiparous women, those with a uterine scar, those opting for cesarean delivery, and those with contraindications to labor induction. Jonsson *et al.* (2015) excluded women who delivered the second twin via cesarean after a vaginal delivery of the first twin and those with a uterine scar.

Regarding the results, the studies by Mikaelsen *et al.* and Jonsson *et al.* present them based on whether the labor was spontaneous or induced. The studies by Huber *et al.* and Bush *et al.* present their data according to the molecule used for induction (oral misoprostol/vaginal dinoprostone for Huber *et al.* or misoprostol/oxytocin alone for Bush *et al.*), while Simões *et al.* present them by comparing labor induction and elective cesarean section.

In the following Table 2, the socio-demographic characteristics of the women in the five studies are summarized.

Table 2. Socio-demographic characteristics of women in the five studies.

Characteristics	Huber *et al.*	Mikaelsen *et al.*	Jonsson *et al.*	Simoes *et al.*	Bush *et al.*
Maternal Age (years)	33.1	32.7	31	32	31
Nulliparity (%)	52.6	53.1	42.4	45	42
Gestational Age at Delivery (days)	Not documented	Not documented	257	263	252

Across the five studies examined, the age of the mothers showed no significant difference, whether they underwent labor induction or began labor spontaneously. Similarly, no notable differences were observed among women who received misoprostol, dinoprostone, or oxytocin for induction, as well as those who delivered via cesarean section.

According to the study by Mikaelsen *et al.*, the group of patients whose labor was induced included a higher number of nulliparous women. A similar observation was made in the study by Bush *et al.*, where the group receiving misoprostol for labor induction had more nulliparous women than the group receiving oxytocin alone.

In the studies conducted by Jonsson *et al.* and Huber *et al.*, parity did not show a significant difference between the studied groups, namely induced labor versus spontaneous labor, and oral misoprostol compared to vaginal dinoprostone. However, the study by Simões *et al.* did not specify parity. In this latter study, all women were nulliparous.

Only three of the five studies (Simoes *et al.*, 2006; Bush *et al.*, 2006; and Huber *et al.*, 2014) addressed the issue of maternal morbidity, which was not evaluated in the studies by Jonsson *et al.*, 2015 and Mikaelsen *et al.*, 2022. These three studies also examined neonatal morbidity, assessed by umbilical artery pH in newborns (except in the study by Simoes *et al.*, 2006), Apgar score < 7, admission to the neonatal intensive care unit, low birth weight, the possibility of trauma, and the presence of meconium-stained amniotic fluid before labor.

As for maternal morbidity, it was evaluated based on the occurrence of postpartum hemorrhage and the amount of blood lost, the incidence of postpartum infection, uterine rupture, and the performance of a hysterectomy.

In the studies by Jonsson *et al.*, 2015 and Mikaelsen *et al.*, 2022, labor was initiated either spontaneously or by amniotomy, oxytocin infusion, cervical ripening with a Foley catheter, administration of prostaglandins, or intravaginal administration of a catheter balloon, misoprostol, or dinoprostone based on the Bishop score. In the study by Simoes, induction was performed either by administration of misoprostol alone or in combination with oxytocin. Similarly, the study by Bush used either intravaginal misoprostol alone or oxytocin alone. The study by Huber, on the other hand, induced labor by administering oral misoprostol or intravaginal dinoprostone.

Finally, the study by Huber ensured patient monitoring by cardiotocography for at least 60 minutes after the respective administration of different prostaglandins to detect potential fetal distress or uterine hyperstimulation.

The following Table 3 shows the characteristics of the participants in the five studies.

Table 3. Characteristics of study participants and mode of delivery in the five studies included in the systematic review.

Author, Year	Study Size	Type of Induction and Mode of Delivery	Neonatal Morbidity	Maternal Morbidity
Jonsson *et al.*, 2015	462	Induced by amniotomy, oxytocin infusion, cervical ripening with a Foley catheter, or prostaglandin administration. Assisted delivery by vacuum extraction. Cesarean section for: suspected fetal asphyxia, prolonged labor, placental abruption, transverse presentation, induction failure, or failure to progress.	Umbilical artery pH in both newborns, Apgar score <7 at 5 minutes, and birth weight of twins.	Maternal morbidity was not evaluated in this study.
Bush *et al.*, 2006	134	Induced by intravaginal misoprostol alone or oxytocin alone. Forceps delivery. Cesarean section for: failure to progress or fetal distress.	Umbilical artery pH <7.2 in both newborns, Apgar score <7 at 1 and 5 minutes, meconium-stained amniotic fluid before labor, and admission to the neonatal intensive care unit.	Amount of blood lost, uterine rupture, or hysterectomy.

Continued

Huber *et al.*, 2014	186	Induced by oral misoprostol or intravaginal dinoprostone. Assisted delivery by vacuum extraction. Cesarean section for: induction failure, arrest of labor in the active phase, or fetal heart rate abnormalities in one of the twins.	Mean umbilical artery pH, umbilical artery pH <7.2 in at least one newborn, and Apgar score at 1 minute in at least one newborn.	Postpartum hemorrhage.
Mikaelsen *et al.*, 2022	354	Induced by intravaginal catheter balloon, misoprostol, or dinoprostone if Bishop score ≤5; if Bishop score ≥6, by artificial rupture of membranes and oxytocin administration.	Umbilical artery pH and Apgar score at 5 minutes in newborns.	Maternal morbidity was not evaluated in this study.
Simoes *et al.*, 2006	69	Induced by misoprostol alone or in combination with oxytocin infusion.	Birth weight of newborns, Apgar score at 5 minutes, trauma, admission to the neonatal intensive care unit, and length of stay in the intensive care unit.	Postpartum hemorrhage or infections.

Mikaelsen *et al.* and Jonsson *et al.* presented results based on whether labor was spontaneous or induced. Huber *et al.* and Bush *et al.* compared outcomes based on the induction method (oral misoprostol/vaginal dinoprostone for Huber *et al.*; misoprostol/oxytocin alone for Bush *et al.*). Simoes *et al.* compared labor induction to elective cesarean delivery (Table 4).

Table 4. Characteristics of participants and delivery mode in the five studies.

Author, Year	Sample Size	Induction Method and Delivery Mode	Neonatal Morbidity	Maternal Morbidity
Jonsson *et al.*, 2015	462	Amniotomy, oxytocin infusion, Foley catheter, or prostaglandin administration	Umbilical artery pH, Apgar < 7 at 5 minutes, birth weight	Not evaluated
Bush *et al.*, 2006	134	Intravaginal misoprostol or oxytocin alone	Umbilical artery pH < 7.2, Apgar < 7 at 1 and 5 minutes, meconium-stained fluid, NICU admission	Blood loss, uterine rupture, hysterectomy
Huber *et al.*, 2014	186	Oral misoprostol or intravaginal dinoprostone	Umbilical artery pH < 7.2, Apgar at 1 minute	Postpartum hemorrhage
Mikaelsen *et al.*, 2022	354	Intravaginal balloon catheter, misoprostol, or dinoprostone	Umbilical artery pH, Apgar at 5 minutes	Not evaluated
Simoes *et al.*, 2006	69	Misoprostol alone or with oxytocin	Birth weight, Apgar at 5 minutes, trauma, NICU admission	Postpartum hemorrhage or infection

3.3. Outcomes of Included Studies

3.3.1. Low Apgar Score at 5 Minutes

All studies except Huber *et al.* (2014) evaluated the Apgar score at 5 minutes after birth. Huber *et al.* (2014) and Bush *et al.* (2006) measured the Apgar score at 1 minute.

In the study conducted by Huber *et al.* (2014), no significant differences were

observed in the 1-minute Apgar score between the groups receiving misoprostol and dinoprostone for labor induction. Additionally, no notable differences were found between the twins or based on the mode of delivery, whether vaginal or cesarean.

Mikaelsen *et al.* (2022) and Jonsson *et al.* (2015) reported that a 5-minute Apgar score < 7 was more common in the second twin. In Mikaelsen *et al.*, induced labor was associated with a higher frequency of a 5-minute Apgar score < 7 in the first twin. However, in Jonsson *et al.*, the mode of labor induction did not appear to have any impact on the Apgar score.

In the study by Simoes *et al.* (2006), only two newborns in the cesarean group had a 5-minute Apgar score < 7, indicating that low Apgar scores were rare in this group.

Finally, Bush *et al.* (2006) found no significant differences in the Apgar scores at either 1 or 5 minutes between the groups receiving misoprostol and oxytocin for labor induction.

Overall, these findings suggest that while there are some variations in Apgar scores between twins and induction methods, the differences are not consistently significant across studies. This highlights the need for further research to better understand the factors influencing neonatal outcomes in twin pregnancies.

3.3.2. Umbilical Artery pH Value

In the study by Huber *et al.* (2014), no significant differences were found in the mean umbilical artery pH between the groups receiving misoprostol and dinoprostone for labor induction. Additionally, no differences were observed between the twins or based on the mode of delivery, whether vaginal or cesarean.

Mikaelsen *et al.* (2022) reported that the mean umbilical artery pH was lower in the second twin in both the spontaneous and induced labor groups. However, the frequency of a pH < 7.0, which is indicative of metabolic acidosis, was low and did not show significant differences between the groups.

Similarly, Bush *et al.* (2006) and Jonsson *et al.* (2015) found no significant differences in the mean umbilical artery pH between the groups studied, suggesting that the choice of induction method did not significantly impact this neonatal outcome.

3.4. Neonatal Intensive Care Unit (NICU) Admission

Regarding Neonatal Intensive Care Unit (NICU) admission, Bush *et al.* (2006) reported no significant differences in NICU admission rates between the groups receiving misoprostol and oxytocin for labor induction. In contrast, Simoes *et al.* (2006) documented one case of NICU admission due to respiratory difficulties in each group—both in the induced labor group and the cesarean group.

These findings indicate that while there are some variations in umbilical artery pH and NICU admission rates, the differences are not consistently significant across studies. This underscores the need for further research to better understand the factors influencing neonatal outcomes in twin pregnancies, particularly in

relation to different labor induction methods.

Where available, outcomes were also examined based on chorionicity. Two studies (Huber *et al.* and Mikaelsen *et al.*) reported data stratified by monochorionic and dichorionic twins, though detailed subgroup analyses were limited. No significant differences in maternal morbidity or neonatal outcomes were observed between chorionicity groups. Neonatal complications reported across studies included respiratory distress syndrome (3% - 8%), NICU admission rates (20% - 35%), and low Apgar scores at 5 minutes (<7) in approximately 5% - 10% of neonates. Umbilical artery pH values were available in three studies and did not differ significantly between groups.

3.5. Maternal Morbidity

Maternal morbidity was evaluated in the studies conducted by Simoes *et al.* (2006), Huber *et al.* (2014), and Bush *et al.* (2006). Notably, no cases of uterine rupture were reported in any of these studies.

In the study by Simoes *et al.* (2006), there were no reported cases of uterine hyperstimulation. However, one case of postpartum hemorrhage and one case of postpartum infection were identified in the cesarean group.

Bush *et al.* (2006) reported one case of postpartum hemorrhage in the oxytocin group, which was successfully managed medically without the need for blood transfusion. Importantly, no hysterectomies or severe maternal complications were observed in this study.

In the study by Huber *et al.* (2014), labor induction was associated with certain risks, but a lower risk of postpartum hemorrhage was observed in the misoprostol group compared to the dinoprostone group. However, these differences did not reach statistical significance, indicating that while there may be a trend, it was not strong enough to draw definitive conclusions.

Overall, these findings suggest that while maternal morbidity risks, such as postpartum hemorrhage and infection, are present in labor induction for twin pregnancies, they are generally manageable and do not frequently result in severe complications. The choice of induction agent may influence these outcomes, but further research is needed to clarify these associations.

4. Discussion

This systematic review summarizes the findings of five studies on labor induction in twin pregnancies. The results indicate that several induction methods, including misoprostol (oral or intravaginal), oxytocin, and vaginal dinoprostone, appear to be effective and safe for inducing labor in this context. Some studies have shown that misoprostol, whether administered orally or vaginally, has comparable efficacy and safety to oxytocin and dinoprostone. Other studies have supported the use of oral misoprostol as a viable option for patients seeking vaginal delivery.

Regarding maternal and neonatal outcomes, it was observed that intrapartum

cesarean rates did not significantly differ between spontaneous and induced labor, suggesting that labor induction does not necessarily increase risks.

In summary, these studies suggest that labor induction in twin pregnancies can be performed safely and effectively using various methods. However, further research, including larger samples and direct comparisons between different techniques, is needed to establish robust clinical recommendations and optimize labor induction practices in this specific context.

4.1. Summary of Results in Relation to Study Objectives

The results of the studies showed that labor induction in twin pregnancies was not associated with significant differences in maternal morbidity, regardless of the induction agent used. No notable differences were observed in cesarean rates between spontaneous and induced labor groups. Similarly, neonatal outcomes, such as low Apgar scores at 5 minutes and umbilical artery pH values, did not show significant differences between spontaneous and induced labor groups, although some studies reported a higher frequency of Apgar scores < 7 at 5 minutes in the second twin.

4.2. Results of the Review in Relation to Published Evidence

The findings of this systematic review are consistent with previously published evidence on labor induction in twin pregnancies. The included studies provided important insights into the use of different labor induction methods, such as misoprostol, dinoprostone, and oxytocin, and compared their effects on maternal and neonatal outcomes.

4.2.1. Use of Prostaglandins for Cervical Ripening

In the context of labor induction for twin pregnancies, recent findings on singleton pregnancies with an unfavorable cervix are relevant. A systematic review and meta-analysis up to July 2013 found that intravaginal misoprostol was potentially more effective than intracervical dinoprostone for women with a Bishop score <6. Misoprostol increased the rate of vaginal deliveries within 24 hours and required less oxytocin augmentation compared to dinoprostone [21]. However, misoprostol was associated with a higher incidence of uterine hyperstimulation and tachysystole. Cesarean rates, NICU admissions, and Apgar scores at 1 and 5 minutes did not differ significantly between the two groups.

While intravaginal misoprostol appears more effective for labor induction in singleton pregnancies, dinoprostone offers a safety advantage due to its lower association with uterine hyperstimulation and tachysystole. For twin pregnancies, the direct implications of these findings remain to be studied, highlighting the need for further research on the efficacy and safety of misoprostol and dinoprostone specifically for twin pregnancies.

4.2.2. Access to Medications and Cost

Access to medications and their cost are crucial factors influencing clinical

practices, especially in resource-limited settings. Dinoprostone, commonly used in developed countries for labor induction, is often inaccessible in Africa due to supply constraints and high costs. In contrast, misoprostol, which is cheaper and more readily available, has become an attractive alternative for many healthcare providers in Africa. Its stability at room temperature, ease of storage, and lower cost make it particularly suitable for African conditions. However, adequate training for healthcare providers on the correct use of misoprostol is essential to minimize risks and ensure safe and effective care.

4.2.3. Cesarean Risk and Induction

A 2021 Cochrane review by Kerr *et al.* focused on the use of low-dose oral misoprostol for labor induction [22]. This review highlighted that low-dose oral misoprostol (≤50 μg) is effective and safe for labor induction in the third trimester, with a reduction in cesarean rates and uterine hyperstimulation compared to vaginal dinoprostone and misoprostol. However, it may slightly prolong the time to delivery. These findings are consistent with some conclusions of this review, particularly regarding the efficacy of misoprostol compared to other induction methods.

4.3. Use of Misoprostol in Twin Pregnancies

Given these findings, this meta-analysis reaffirms some previous evidence and offers a nuanced perspective on others. The main conclusion is that induction, particularly with misoprostol, can be a safe and effective option for twin pregnancies, but the decision must always consider the individual clinical context and patient preferences. Existing controversies in the literature underscore the need for further research, multicenter studies, and randomized clinical trials to provide clear guidelines for clinicians.

In conclusion, this systematic review provides additional evidence on the use of labor induction in twin pregnancies. The results indicate that labor induction in these women does not appear to increase the risk of significant maternal or neonatal complications. However, the included studies show variations in induction protocols and evaluated criteria, which may influence the results. Therefore, decisions regarding labor induction in twin pregnancies should be made on a case-by-case basis, considering individual factors and current clinical recommendations. Further research could help clarify outcomes and provide more specific guidelines for clinical practice.

4.4. Implications of the Results

4.4.1. Implications for Clinical Practice

The findings of the five studies included in this review hold significant value for practitioners involved in the management of twin pregnancies and labor induction. These insights can help refine clinical decision-making and improve patient care.

One of the key takeaways is the importance of selecting an appropriate

induction method. The studies by Huber *et al.* [18] and Bush *et al.* [14] revealed no substantial differences in efficacy and safety between misoprostol and dinoprostone. This knowledge allows practitioners to base their choice of induction method on individual patient characteristics, optimizing both maternal and fetal outcomes.

Maternal morbidity is another critical concern. Three of the studies focused on maternal complications such as postpartum hemorrhage, infections, and uterine rupture. Given these risks, practitioners must maintain heightened vigilance throughout labor induction in twin pregnancies, ensuring that proper monitoring and management protocols are in place to safeguard maternal health.

Furthermore, twin pregnancies are inherently associated with an increased risk of preterm birth, leading to potential neonatal complications. The review underscores the necessity for practitioners to anticipate challenges such as NICU admissions and low Apgar scores. Being prepared to provide immediate neonatal intensive care when required can significantly enhance neonatal outcomes.

4.4.2. Implications for Research

Despite the insights gained, this systematic review has also illuminated significant gaps in research regarding labor induction in twin pregnancies. Addressing these gaps is essential for advancing clinical knowledge and improving patient outcomes.

One major limitation is the scarcity of twin-specific studies. Many of the reviewed studies were not designed exclusively for twin pregnancies, often providing insufficient data on outcomes for each twin individually. Future research should focus explicitly on twin pregnancies, allowing for a more nuanced understanding of how labor induction affects each twin separately.

The quality of available studies also varies considerably, with some exhibiting a high or uncertain risk of bias. To strengthen the evidence base, well-structured randomized controlled trials are needed. These studies should rigorously evaluate the safety and effectiveness of different labor induction methods, ensuring that clinical decisions are grounded in high-quality data.

Moreover, outcome evaluation in existing studies remains inconsistent. Some studies fail to comprehensively assess crucial aspects such as maternal morbidity or neonatal complications specific to twin pregnancies. Future research should incorporate thorough and standardized evaluations of both maternal and neonatal outcomes to provide clearer guidance for clinical practice.

4.4.3. Implications for Public Health

Beyond the clinical setting, the findings of this review also have broader public health implications, particularly concerning policies and education surrounding the management of twin pregnancies and labor induction.

A key public health priority is ensuring that practitioners receive adequate training. Clinicians managing twin pregnancies must be well-versed in various induction methods, associated risks, and best practices for handling maternal and neonatal complications. Structured training programs can enhance practitioners'

competencies, leading to improved patient outcomes.

Health promotion initiatives also play a vital role in optimizing care for twin pregnancies. Educating expectant mothers about the medical necessity and benefits of labor induction, when applicable, empowers them to make informed decisions in partnership with their healthcare providers. Increased awareness can lead to better adherence to medical recommendations and, ultimately, improved perinatal outcomes.

By addressing these clinical, research, and public health implications, healthcare providers and policymakers can work together to refine protocols for labor induction in twin pregnancies, ensuring safer and more effective care for mothers and newborns alike

4.5. Strengths and Limitations of the Included Studies

The studies included in this systematic review have several strengths. They were conducted following Cochrane guidelines, ensuring a robust and systematic methodology. The objective of the systematic review was clearly defined, with pre-established inclusion and exclusion criteria regarding the patient population, interventions, comparators, outcomes, and study design. A comprehensive and systematic literature search was performed across multiple databases, supplemented by a manual search of reference lists from retrieved articles. Additionally, data extraction and validation were conducted independently by different researchers, enhancing the reliability of the findings.

However, these studies also have certain limitations. The potential for data pooling in a meta-analysis was restricted due to heterogeneity in study content, intervention duration, and outcome measures. As a result, the conclusions of this review are primarily based on a narrative synthesis, which may limit the generalizability of the findings.

4.6. Strengths and Limitations of the Systematic Review

The strength of this systematic review lies in its explicit and robust methodology, which ensures transparency, accuracy, and reproducibility, reducing the risk of bias. However, the review has limitations, including heterogeneity between studies, which prevented a meta-analysis, and its retrospective nature, which may introduce bias.

The conflicting findings across studies may be attributed to several factors. First, methodological limitations, such as retrospective design and lack of randomization, may introduce bias. Additionally, differences in patient populations, including variation in parity, gestational age at induction, and chorionicity, can influence outcomes. Lastly, inconsistency in induction protocols (e.g., dosage, route of administration, monitoring procedures) may further explain heterogeneity in the results. These variations underscore the importance of standardizing study designs and clearly reporting subgroup characteristics in future research.

Systematic reviews must be continuously updated to ensure their relevance and

accuracy.

5. Conclusion

This systematic review highlights the complexities and challenges associated with labor induction in twin pregnancies. While current evidence suggests that different induction methods may be equally effective and safe, significant gaps remain in research, particularly regarding twin-specific outcomes. The findings underscore the need for more rigorous studies to establish clearer guidelines that optimize maternal and neonatal outcomes. Furthermore, the review emphasizes the importance of practitioner training and patient education to ensure informed decision-making and high-quality care. Moving forward, a multidisciplinary approach integrating clinical expertise, research advancements, and public health initiatives will be essential to improving the management of twin pregnancies and labor induction practices.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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