Aus der Klinik und Poliklinik für Frauenheilkunde und Gynäkologische Onkologie
der Universität zu Köln
Direktor: Universitätsprofessor Dr. Florin-Andrei Taran

Sequential Use of Osmotic Dilators and Oral Misoprostol Versus Misoprostol Alone on Unfavorable Cervix

Inaugural-Dissertation zur Erlangung der Doktorwürde
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von
Ruth Sanny Malemna Bangun
aus Kupang, Republik Indonesien

promoviert am 11. März 2026

Gedruckt mit Genehmigung der Medizinischen Fakultät der Universität zu Köln

Druckjahr 2026

Dekan: Universitätsprofessor Dr. med. G. R. Fink
1. Gutachter: Privatdozent Dr. med. Y. Garnier
2. Gutachterin: Privatdozentin Dr. med. E. Weber

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Acknowledgements

I would like to express my deepest gratitude to all individuals and institutions whose support and contributions have been invaluable for the completion of this research.

First and foremost, I would like to extend my deepest gratitude to my primary advisor, Privatdozent Dr. med. Yves Garnier, for his invaluable guidance, rigorous insights, and continuous encouragement throughout the entire research process.

I am also indebted to Dr. med. Götz G. Menke, the Chief of the Obstetrics and Gynecology Department at Marienhospital Osnabrück, for his support in permitting me to conduct the research in his department and for providing the necessary resources and instruments for the study. Additionally, I would like to acknowledge the crucial contribution of all my recruiting colleagues and midwives in the successful completion of this research. They were indispensable, and I would not have been able to reach the study's objectives without their dedication and expertise.

Furthermore, I would like to express my sincere gratitude to my family, closest friends, and my partner, Stephan, for their unwavering encouragement and unshakable belief in me. Their love and support have been instrumental in my perseverance through the highs and lows of this research endeavor.

Lastly, I thank God for granting me knowledge and strength throughout this research journey, from the very start to the end. Nothing would have been possible without Him.

To my father, for always gently encouraging me
to venture beyond the boundaries of my comfort zone.
And to my mother, for her unshakeable faith
and unceasing prayers.

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Abbreviations

AC	- Abdominal circumference
ARED	- Absent or reverse end diastolic flow
cCTG	- Computerized cardiotocography
CPR	- Cerebroplacental ratio
CRL	- Crown-to-rump-length
CTG	- Cardiotocography
DV	- Ductus venosus
EFW	- Estimated fetal weight
FGR	- Fetal growth restriction
HDP	- Hypertensive disorders of pregnancy
HPL	- human placental lactose
ICP	- Intrahepatic cholestasis of pregnancy
IUFD	- Intrauterine fetal demise
LMP	- Last menstrual period
MCA	- Median cerebral artery
MSAF	- Meconium-stained amniotic fluid
PG	- Prostaglandins
PGDH	- Prostaglandin dehydrogenase
PGE1	- Prostaglandin E1
PGE2	- Prostaglandin E2
PGHS	- Prostaglandin H synthase
PI	- Pulsatility index
PROM	- Pre-labor rupture of membranes
SGA	- Small-for-gestational-age
STV	- Short-term variation
Triple I	- Infection, Inflammation, or both
UA	- Umbilical artery
UCDA	- Ursodeoxycholic acid

1. Executive Summary

1.1. Executive Summary

Background and objectives: Although multiple induction methods are available for cervical ripening in cases of an unfavorable cervix, no international consensus exists for an optimal approach. Osmotic dilators are non-inferior to pharmacological agents, based on a pre-specified non-inferiority margin, with favorable safety profiles and the advantage of outpatient applicability. This prospective study aims to assess whether a sequential combination of osmotic dilators followed by misoprostol improves induction outcomes compared to pharmacological induction alone. Given the increasing rates of labor induction and the growing need for efficient use of hospital resources, the study primarily examines whether this approach could reduce the induction-to-delivery interval without adverse or undesired effects on maternal or neonatal outcomes.

Methods: This single-center prospective randomized controlled trial was conducted at Marienhospital Osnabrück, Germany, between July 2023 and February 2025. A total of 130 pregnant women with an unfavorable cervix (Bishop Score < 6) at term were randomized to receive either oral misoprostol (Angusta) alone (control group) or a sequence of osmotic dilators (Dilapan-S) followed by misoprostol (study group). Eligible participants were informed about the study during their prenatal visits and provided written consent. Women in the study group were administered osmotic dilators for a period of 18 to 24 hours, primarily through outpatient procedures. Oral misoprostol was provided subsequently if there were no indications of labor progression. The control group received oral misoprostol alone only under inpatient care. Both groups followed the same misoprostol dosing protocol, with standard obstetric care resuming after 48 hours of induction.

Results and observations: The study demonstrated that a sequential regimen of osmotic dilators followed by misoprostol was as effective as misoprostol alone for labor induction in women with an unfavorable cervix, especially for nulliparous women. Among nulliparous participants, induction-to-delivery intervals were comparable between groups (study group, 38.0 hours; control group, 39.3 hours; $p = 1.000$), despite the clinical challenges this population typically faces. Moreover, the rates of vaginal births within 36 and 48 hours as well as overall spontaneous vaginal delivery were nearly identical in both trial arms. The combined method also allowed for a reduced total dose of misoprostol (median: study group, 100 µg vs. control group, 200 µg; $p < 0.001$) and enabled outpatient cervical ripening in most cases. Although not statistically significant, lower caesarean section rates (25% vs 36.4%; $p = 0.186$) and higher operative vaginal delivery (12.5% vs 3%; $p = 0.053$) in the combination group suggest a potential shift away from surgical delivery. Among multiparous women, misoprostol alone was

associated with a shorter induction-to-delivery interval. Neonatal complications remained low and comparable across both groups. These findings support the combined approach as a safe, efficient, and outpatient-compatible alternative for labor induction.

Conclusions: The combined use of cervical osmotic dilators and misoprostol demonstrates comparable efficacy to misoprostol alone for labor induction, including in nulliparous women. While induction-to-delivery intervals and vaginal birth rates were similar, the combined method required significantly less misoprostol whilst enabling outpatient cervical ripening.

1.2. Zusammenfassung

Hintergrund und Zielsetzung: Trotz zahlreicher verfügbarer Methoden zur Geburtseinleitung besteht bislang kein internationaler Konsens über das optimale Vorgehen bei unreifer Zervix. Osmotische Dilatatoren haben sich unter Berücksichtigung einer vordefinierten Nichtunterlegenheitsmarge als nicht unterlegen gegenüber medikamentösen Methoden erwiesen, besitzen ein günstiges Sicherheitsprofil und ermöglichen ein ambulantes Verfahren. In dieser prospektiven Studie wurde untersucht, ob eine sequentielle Kombination aus osmotischen Dilatatoren und der Gabe von Misoprostol im Vergleich zur alleinigen medikamentösen Einleitung zu verbesserten Outcomes der Geburtseinleitungen führt. Die steigende Einleitungsrate und der zunehmende Fokus auf effizienten Ressourceneinsatz im klinischen Alltag dienten als Hintergrund dieser Studie. Es ist von großem Interesse, ob die kombinierte Methode aus osmotischen Dilatatoren und Misoprostol das Einleitungs-Entbindungs-Intervall verkürzen kann, ohne dabei maternale oder neonatale Risiken zu erhöhen.

Methoden: Die monozentrische, prospektive, randomisierte und kontrollierte Studie wurde zwischen Juli 2023 und Februar 2025 am Marienhospital Osnabrück durchgeführt. Insgesamt wurden 130 schwangere Frauen mit unreifer Zervix (Bishop-Score < 6) am Termin randomisiert und entweder der alleinigen oralen Misoprostol-Gabe (Angusta; Kontrollgruppe) oder einer sequentiellen Kombination aus osmotischen Dilatatoren (Dilapan-S) gefolgt von Misoprostol (Studiengruppe) zugeteilt. Die Aufklärung erfolgte im Rahmen der regulären Schwangerschaftsbetreuung. Ein schriftliches Einverständnis von den Studienteilnehmerinnen lag vor. In der Studiengruppe erfolgte die Einlage von osmotischen Dilatatoren für 18 bis 24 Stunden. Der Großteil der Patientinnen konnte zur Zervixreifung nach Hause entlassen werden. Im Anschluss wurde diesen Patientinnen – bei ausbleibendem Geburtsbeginn – Misoprostol verabreicht. Die Kontrollgruppe erhielt Misoprostol unter stationären Bedingungen. Die Dosierung von Misoprostol erfolgte in beiden Gruppen nach einem einheitlichen Schema; nach 48 Stunden wurde die weitere Betreuung gemäß klinischem Standard fortgeführt.

Ergebnisse und Beobachtungen: Die Kombination aus osmotischen Dilatatoren und Misoprostol zur Geburtseinleitung bei unreifer Zervix erwies sich als gleich wirksam wie die alleinige Gabe von Misoprostol. Dies gilt insbesondere bei Nulliparen: In dieser Subgruppe zeigten sich vergleichbare Intervalle von Einleitung bis Geburt (Studiengruppe: 38,0 Stunden; Kontrollgruppe: 39,3 Stunden; $p = 1{,}000$), trotz der bekannten klinischen Herausforderungen bei Erstgebärenden. Die Raten vaginaler Geburten innerhalb von 36 bzw. 48 Stunden sowie die Gesamtanzahl spontaner vaginaler Geburten waren in beiden Gruppen nahezu identisch. In der Studiengruppe konnte die Gesamtmenge des verabreichten Misoprostols signifikant reduziert werden (Median: 100 µg vs. 200 µg; $p < 0{,}001$), zudem erfolgte die Zervixreifung in den meisten Fällen ambulant. Obwohl nicht statistisch signifikant, war die Sectiorate in der Kombinationstherapie niedriger (25 % vs. 36,4 %; $p = 0{,}186$), während die Rate an vaginal-operativen Entbindungen höher lag (12,5 % vs. 3,3 %; $p = 0{,}053$) – ein Hinweis auf eine mögliche Tendenz zur Vermeidung des Kaiserschnittes. Bei Multiparen zeigte sich hingegen ein kürzeres Einleitungs-Entbindungs-Intervall in der Kontrollgruppe. Die neonatalen Komplikationen waren in beiden Gruppen niedrig und vergleichbar.

Schlussfolgerung: Die sequentielle Anwendung von osmotischen Dilatatoren und Misoprostol zeigte eine vergleichbare Wirksamkeit wie die alleinige medikamentöse Einleitung – auch bei Nulliparen. Während die Geburtsintervalle und vaginalen Geburtenraten ähnlich ausfielen, konnte mit der kombinierten Methode die Misoprostol-Dosis signifikant reduziert und eine ambulante Zervixreifung ermöglicht werden.

2. Introduction

To date, the parturition process is one of the most complex processes in the human body, and its entire course has not been fully understood. This physiological process involves a sequential, integrated series of changes in the myometrium, decidua, and cervix that act gradually and synergistically over the period of days or weeks toward the end of pregnancy, resulting in the expulsion of the fetus and placenta. Ideally, the onset of parturition occurs naturally without any need for human intervention at maturity.

However, daily obstetrical practice reveals a different reality. In addition to post-term pregnancies, which heterogeneously vary between 5 and 15% of all pregnancies [1, 2], some conditions require an early termination of pregnancy. Therefore, induction of labor is used to achieve a better outcome for the mother and the newborn when compared to expectant management.

Yet, inducing labor in an unfavorable cervix, defined by Bishop-Score < 6, is associated with a longer induction-to-labor interval [3, 4], which often leads to lower patient compliance due to frustration and contraction pain. Additionally, a longer interval results in higher costs and an increased workload for already understaffed maternity units. A strategy is therefore needed to induce labor effectively and safely without compromising patient safety or hospital resources.

2.1. Indications for induction of labor

Induction of labor is a common obstetric intervention, applied for a range of maternal and fetal indications that often coexist. Moreover, maternal preference for an induction is becoming increasingly common in clinical practice and should be considered as part of individualized care. Ultimately, the primary aim remains to achieve better maternal and neonatal outcomes compared to expectant management.

2.1.1. Maternal indications

2.1.1.1. Post-term pregnancy

According to the American College of Obstetricians and Gynecologists, post-term pregnancy is defined as a pregnancy that has reached or extended beyond 42 weeks of gestation (294 days) from the first day of the last menstrual period (LMP). Late-term pregnancy refers to a pregnancy that has reached 41+0 and 42+0 weeks of gestation. [5] In Germany, around 37.6% of children were born after 40+0 weeks of gestation in 2017, and 33.3% of these pregnancies underwent induction of labor. [6] Post-term births are associated with an increased risk of maternal complications, such as postpartum hemorrhage, operative vaginal deliveries, and caesarean deliveries. There is also a risk of increased fetal mortality and morbidity, such as

fetal asphyxia, meconium aspiration syndrome, shoulder dystocia, and stillbirths. [7, 8, 9] A comprehensive meta-analysis study was conducted, which evaluated 34 randomized controlled trials (RCTs) that compared the induction of labor after 41 weeks of gestation (>287 days) with expectant management. The study demonstrated a significant reduction in perinatal deaths and caesarean rates in the induction of labor group, without increasing rates of operative vaginal births or admissions to the Neonatal Intensive Care Unit (NICU). [10]

2.1.1.2. Hypertensive disorders of pregnancy (HDP)

Hypertensive disorders of pregnancy are considered one of the leading causes of maternal and neonatal morbidity and mortality worldwide, with increasing prevalence. HDP includes a group of diseases classified as preeclampsia, eclampsia, gestational hypertension, and chronic hypertension.

HDP complicates 5.2-8.2% of all pregnancies [11] and is the third leading cause of maternal deaths globally (16%) [12]. In addition, women with a history of HDP have a higher risk of developing cardiovascular disease later in life, as the hemodynamic alterations in these women during their pregnancies can persist for years. Numerous studies have shown that HDP increases the risk of developing acute myocardial infarction, hypertension, coronary artery disease, heart failure, and stroke within six months to 20 years following birth. [13,14]

To ensure a better maternal and neonatal outcome in pregnancy with HDP, early termination is necessary, and induction of labor is inevitable. Although the induction-to-labor interval was longer on nulliparous and multiparous women with preeclampsia, [15] induction of labor was not associated with an increase in neonatal mortality or morbidity rate. [16] Maternal outcome is not compromised by vaginal birth after induction of labor either. Rather, caesarean delivery is associated with significant postpartum maternal morbidity. [17]

2.1.1.3. Gestational diabetes/preexisting type 1 and type 2 diabetes

Gestational diabetes is defined as a disorder of glucose intolerance occurring for the first time during pregnancy without reaching the diagnostic criteria for manifest diabetes. [18] In Germany, prevalence estimates for gestational diabetes vary widely, ranging between 5.1% and 13.2%. This is due to differences in data sources, study regions, and diagnostic criteria used. [19]

Gestational diabetes can be harmful to both the mother and the newborn. Maternal complications include an increase in pre-eclampsia and a long-term increase in diabetes mellitus. Newborns of mothers with gestational diabetes have a higher risk of excessive birth weight, which can lead to high-grade perineal tears and neonatal injuries related to shoulder

dystocia. A preexisting diabetes mellitus contributes significantly to poorer pregnancy outcomes, including a three- to fourfold higher rate of perinatal mortality. [20, 21]

2.1.1.4. Prelabor rupture of membranes (PROM)

PROM is defined as a rupture of membranes before the onset of labor after 37+0 weeks of gestation and has an incidence of approximately 5-15%. The pathogenesis of PROM may be related to the dissolution of collagen in the extracellular matrix and the apoptosis of membrane cells promoted by biochemical processes. Since collagen is responsible for the strength and elasticity of fetal membranes, its degradation can lead to membrane rupture. In the third trimester, the synthesis, maintenance, and degradation of collagen become imbalanced, and these changes are thought to be responsible for the decreasing resilience of fetal membranes. [22, 23]

Prelabor rupture of membranes requires immediate attention. In such a case, the patient should be admitted to the obstetric unit immediately, followed by close monitoring of maternal and fetal status. Expectant management is feasible in low-risk women with term singleton fetuses in cephalic presentation and with no evidence of non-reassuring fetal heart rates and clear amniotic fluid. Acceptable time frames include up to 24 hours for women with negative group B strep cultures and up to 12 hours for those with positive cultures. [24] If women reach the time limit without signs of labor, induction of labor is required to reduce the risk of Triple I.

2.1.1.5. Intrahepatic cholestasis of pregnancy (ICP)

The etiology of ICP remains poorly understood, as it is complicated and multifactorial. ICP is diagnosed based on pruritus as the main symptom and elevated total serum bile acids after excluding other diagnoses that may cause similar symptoms and laboratory abnormalities. The cut-off for total serum bile acids varies, ranging from 19-100 µmol/l according to the Royal College of Obstetricians and Gynaecologists. [25] Predominantly, nocturnal pruritus causes psychological distress and may be exacerbated by insomnia and fatigue. [26] Although the severity of pruritus does not correlate with maternal serum bile acid levels or prognosis, severe pruritus is usually the reason for the induction of labor.

The most feared complication of ICP is intrauterine fetal demise. The most comprehensive review to date included 5269 patients and found that the rate of IUFD due to ICP with bile acid >100 µmol/l increased significantly to 3.44% after 34 weeks' gestation, about 30 times higher than those with bile acid below 40 µmol/l. [27] Therapy with UCDA could alleviate the maternal symptoms but doesn't necessarily improve the prognosis. The pre-therapeutic or highest ever diagnosed bile acid level should guide obstetric management. An induction of labor between

34+0 and 36+6 weeks of gestation can be taken into consideration in a pregnancy with a bile acid level >100 μmol/l to avoid intrauterine fetal demise. [28]

2.1.2. Fetal Indications

2.1.2.1. SGA and FGR

Both small-for-gestational-age and fetal growth restriction are major issues in obstetrics, and there are still ongoing studies attempting to provide guidelines for their diagnosis and management. [29]

A fetus with SGA grows below the predefined growth curve for its gestational age. The ISUOG criterion for SGA is EFW or AC below the 10th percentile at any given week of gestation. The diagnosis of SGA is usually not made based on a single examination, as the fetal growth should be compared over several serial ultrasound scans. The fetus with SGA exhibits steady growth throughout the ultrasound scan but does not reach its full growth potential. [30] The SGA fetuses, although small, are not at risk of adverse perinatal outcomes. Therefore, termination of pregnancy at early weeks is often not necessary. Vaginal delivery may be attempted in an SGA pregnancy and labor may be induced at 38+0 weeks if there are no signs of labor by that time. However, post-term pregnancy should be avoided.

FGR, on the other hand, shows a higher degree of placental involvement, as reflected by a strong association with pre-eclampsia and a high proportion of abnormal umbilical artery Doppler. [31] FGR has two phenotypes, early-onset and late-onset, which differ remarkably in almost all aspects, and even more so when it comes to its management.

The TRUFFLE study is the largest randomized trial on timing of delivery in early FGR (below 31+6 weeks of gestation). It compared three criteria of delivery: early ductus venosus Doppler changes (PI >95th percentile), late ductus venosus Doppler changes (a-wave at or below baseline), and reduced fetal heart rate STV on cCTG (3.5 ms before 29 weeks and 4.0 ms thereafter). In this study, both DV groups showed a significantly better outcome compared with the CTG-STV group. [32]

The late FGR is defined by a growth restriction that appears after 31+6 weeks of gestation. Fetuses with late FGR are more prone to neonatal death, [33] higher risk of caesarean section for fetal distress, [34] reduction of grey matter volume and weakened brain cells connectivity, [35] and neurobehavioral disorder at 6 years of age, especially in motor and communication skills. [36] The type of delivery on both early and late onset of FGR requires consideration of several factors: gestational age, parity, cervical maturation, Doppler and cCTG findings, and other fetal or maternal conditions. In the case of FGR without non-reassuring Doppler findings

or merely an elevated UA-PI (95th percentile), vaginal delivery is possible, and induction of labor may be attempted. However, the increased risk of complications should be taken into account, and continuous intrapartum observation is essential. In the case of a late FGR with non-reassuring Doppler findings, e.g. low CPR (cut-off of 1.0), induction of labor and vaginal delivery may still be attempted with close intrapartum monitoring of the fetal status. The situation would be different in pregnancies with pathological cCTG, abnormal ductus venosus and/or ARED flow, and in very early weeks of pregnancy: caesarean section is usually the method of choice. [37]

2.1.2.2. Twin pregnancy

The phenomenon of twin pregnancies has reached its peak in recent decades. In Germany alone, twin pregnancies increased from 9.2 to 18.4 per 1,000 deliveries between 1975 and 2015, in France from 9.3 to 17.5, in Denmark from 9.6 to 16.7, and in Japan from 5.9 to 9.9. [38] Twin pregnancies are associated with 2 to 3.5 times higher maternal and neonatal risks. Maternal risks include, for example, insulin resistance due to an increase of chorioplacental lactogen (HPL), and gestational diabetes as a result of excessive weight gain, body mass index, and maternal age, amongst other risks. In addition, the larger uterine size can lead to preterm delivery, placental abruption, PROM, and postpartum atonic hemorrhage. [39]

The fetuses of twin pregnancies, in addition to the aforementioned risk of preterm delivery, bear a higher risk of SGA or FGR and therefore low birth weight, lower APGAR score at 5th minute (<7), stillbirth, and death during the first year of life. [40]

The debate about the safest method of delivery in twin pregnancy has been extensive in the last few decades, and there is generally no straightforward way to determine the best timing and mode of delivery. The current evidence supports an attempt of vaginal birth in dichorionic-diamniotic or monochorionic-diamniotic twin pregnancies where the first twin is in cephalic presentation beyond 32 weeks of gestation. [41] However, a retrospective study in a German hospital that included 540 dichorionic-diamniotic twin births and 98 monochorionic-diamniotic twin pregnancies showed that more than half of planned vaginal births ended with caesarean delivery, further increasing adverse maternal outcomes. [42] So far, most guidelines do not support a trial of vaginal birth in monochorionic-monoamniotic pregnancies due to a high concern of cord complications. [43, 44]

Just as the method of delivery in a twin pregnancy has to be made individually, so is the decision to induce labor. Several studies have shown conflicting results as to whether or not twin pregnancy is an independent risk factor for caesarean delivery after induction of labor. [45, 46]

2.2. Induction of labor on an unfavorable cervix

The rates of induction of labor have increased globally, reflecting changes in obstetric practices and guidelines, as well as an increase in pregnancies involving medical obstetric complications. Key statistics present the following trend: the rate of induction of labor reached 31.9% in 2022 in the USA [47], induction of labor rates increased from 22% in 2012 to 33% in the UK by 2019 [48], and a rate of 21.4% was reported in 2022 in Germany [49]. The rising number of inductions of labor has introduced another challenge to healthcare systems, particularly in managing the clinical resource demands.

When an induction of labor is performed on an unfavorable cervix, it poses additional complexities compared to cases with a favorable cervix, with one of them being an extended induction process. Research has demonstrated that a low Bishop score below six is associated with a significantly longer interval between induction of labor and birth. Another study looking specifically at the length of the cervix prior to induction has shown that shorter cervical length is associated with successful induction of labor. [50] Moreover, it is evident that an extended interval engenders an elevated risk of maternal and neonatal complications, such as operative delivery, chorioamnionitis, postpartum hemorrhage, and neonatal intensive care unit (NICU) admission due to neonatal infection. [51] The inclination towards caesarean section, driven by heightened patient dissatisfaction during a more extended period of induction of labor, is a phenomenon that is observed with alarming frequency in the maternity units, giving rise to a range of short- and long-term complications. Furthermore, it is imperative to acknowledge the augmented workload for understaffed maternity units during the period of induction of labor.

The quest to identify the best method of induction of labor on an unfavorable cervix remains an ongoing endeavor and, therefore, yields a lack of consensus on the optimal approach. Pregnant women must become active participants in determining the most suitable approach to the induction of labor for them in order to increase their willingness to cooperate and cope throughout the process.

2.2.1. Methods of induction of labor

Over decades of practical obstetrics and its attendant advances, the range of methods available for inducing labor has increased considerably. A number of these methods target the uterine cervix, while others increase uterine activity, whilst others affect both the cervix and uterine contractility.

2.2.1.1. Mechanical methods

Mechanical methods for induction of labor were the first developed during the early days of obstetrics and have recently experienced a resurgence in interest. Numerous studies have

confirmed the safety and efficacy of mechanical methods, including the following: equal rates of deliveries with caesarean section compared to induction with PGEs [52], reduced risk of uterine hyperstimulation and non-reassuring fetal heart rate [53], reduced risk of caesarean deliveries compared to the induction with oxytocin [45], and last but not least, lower cost compared to the pharmacological method [54].

Osmotic dilatators are medical devices used to induce cervical dilatation by placing dehydrated material in the cervical canal. There are two types of these osmotic dilatators, Laminaria and Dilapan-S. Laminaria are highly hygroscopic rods made from seaweed (*Laminaria digitata* or *Laminaria japonica*) and have the ability to absorb water from the cervical stroma, thereby swelling to multiple times their original diameter. Despite their effectiveness, Laminaria have fallen out of favor in modern obstetrics due to concerns regarding infection [55], hypersensitivity reactions, and anaphylaxis [56], as bacterial spores can persist on the sticks despite sterilization. Dilapan-S is a synthetic hydrogel composed of Aquacryl, which gradually absorbs moisture from the cervix and causes an expansion of its diameter over several hours. Visualization of the cervix is to be achieved using a sterile speculum, and the Dilapan-S rods are to be inserted through the external cervix gradually and gently, without exerting force. Furthermore, it is crucial that the tip of the rods passes through the internal cervix to ensure dilatation of the entire length of the cervix. The Dilapan-S employs three distinct mechanisms to induce cervical ripening: biophysical, mechanical, and physiological. The osmotic properties of Dilapan-S draw the moisture from the cervix, thereby softening and altering the consistency of the cervical tissue. The expanding dilatators exert radial pressure on the cervical canal, resulting in dilatation and the release of endogenous prostaglandins, which contribute to the effacement of the cervix. [57] The 4 mm dilator, when utilized, has been observed to expand up to 15 mm over a 12-24-hour period. The number of dilatators used depends on the Bishop Score, with 4-5 rods generally recommended by the manufacturer for sufficient cervical ripening.

A further mechanical method for inducing labor is the use of Foley and double-balloon catheters. The dilatation of the cervix and the release of endogenous prostaglandins are the pathways that are targeted by inflating the balloons either in the cervix with the Foley catheter, on the internal and external cervix, or with the double-balloon catheter.

Membrane stripping or sweeping was first documented in literature around the 1800s. [58] This technique, employed by obstetricians or midwives, involves the sweeping of a finger across the membranes that connect the amniotic sac to the uterus wall. The purpose of this action is to separate the amniotic membranes from the uterus, thereby facilitating the release of prostaglandins. A significant proportion of pregnant women have described varying degrees

of discomfort when experiencing membrane sweeping. Yet despite this, a considerable percentage of these women were willing to recommend the procedure to a friend or acquaintance. Furthermore, despite the pain experienced, a substantial percentage of women would opt for membrane sweeping again in subsequent pregnancies. [59]

Finally, a method of induction pioneered by the Persians in the 11th century involved the artificial rupture of the fetal membrane, known as amniotomy. [60] This method has been shown to stimulate oxytocin release from the pituitary gland, leading to the subsequent release of prostaglandins locally in the cervix. [61] Amniotomy has been extensively used in cases of a favorable cervix alone or as an adjunct in the induction of labor. A meta-analysis including 1273 patients revealed that women who received an early amniotomy following successful cervical ripening (e.g., after expulsion of a Foley catheter or ≥3 cm cervical dilation or a Bishop score of ≥5) showed no elevated incidence of caesarean section when compared to those who received a late amniotomy, and the induction-to-delivery interval was approximately 5 hours shorter. [62]

2.2.1.2. Pharmacologic methods

2.2.1.2.1. Prostaglandins (PG)

Prostaglandins have a major function in human parturition at term by promoting uterine contractions, cervical ripening, and fetal membrane rupture. They are synthesized from arachidonic acid via prostaglandin H synthase (PGHS) and are metabolized primarily by prostaglandin dehydrogenase (PGDH), which regulates their activity. The balance between PG synthesis and metabolism is regulated by hormones such as progesterone and cortisol, where local progesterone withdrawal and increased glucocorticoid activity heighten PG action. PG exert their effects through specific receptors in the uterus, which leads to increased intracellular calcium and myometrial contractions. The shift in PG production and metabolism at term pregnancy is a key trigger for the onset of labor. [63]

Despite its great importance in a complex cascade of human parturition, the development of synthetic prostaglandin proved to be a formidable undertaking. Natural prostaglandins are rapidly metabolized and, therefore, orally ineffective. Moreover, a shortened half-life when administered parenterally compromises their efficacy. Over the years, these limitations of prostaglandins in labor induction have been addressed through molecular modifications. The two primary prostaglandin formulations used for cervical ripening and labor induction are dinoprostone (PGE2) and misoprostol (PGE1 analog). Dinoprostone, chemically identical to PGE2, is administered via cervical gel or vaginal insert to enhance cervical ripening locally. Misoprostol, a methyl ester analog of PGE1, was initially developed for gastric ulcer treatment

but is now widely used in obstetrics. [64] Misoprostol is rapidly absorbed after oral administration, reaching peak plasma concentration within approximately 14 minutes, falls steeply by 60 minutes, and remains at low plasma levels for the next 4 hours. [65] It undergoes de-esterification into its active metabolite, misoprostol acid, which has less than 90% plasma protein binding and is partially excreted in breast milk. This drug is primarily eliminated via the urine as an inactive metabolite. The uterotonic effects occur when misoprostol binds to smooth muscle cells in the uterus, leading to increased contractility and collagen degradation in the cervical stroma, resulting in cervical dilation as well as a reduction in cervical tone, which is promoted by increased contraction amplitude and frequency. [66] In Germany, misoprostol (Angusta) has been approved for the induction of labor since September 2020 [67] and is available in the form of 25-µg.

The safety and efficacy of misoprostol have been studied extensively. A substantial body of meta-analysis encompassing 20,026 parturitions suggested that low-dose oral misoprostol is likely to result in a reduced incidence of caesarean sections when compared with vaginal dinoprostone, along with lower rates of hyperstimulation and fetal heart rate changes. Nevertheless, it has been observed that the time to birth may be prolonged. [68] Another extensive meta-analysis study, involving 611 studies, demonstrated that induction of labor with oral misoprostol achieves the lowest odds of caesarean section. [69] A further multicenter prospective cohort study involving 322 pregnant women yielded a comparable outcome, suggesting that oral administration of misoprostol exhibited the highest level of efficacy while maintaining a favorable safety profile when compared to vaginal misoprostol or vaginal dinoprostone. [70]

2.2.1.2.2. Oxytocin

Oxytocin, derived from the Greek term for "rapid birth", is a peptide hormone synthesized in the hypothalamus that expedites uterine contractions during labor and breast milk production during lactation. Oxytocin achieves this by binding to specific G-protein-coupled receptors, leading to increased intracellular calcium concentrations and activation of myosin light-chain kinase. The half-life of oxytocin is approximately 3 to 5 minutes after its release into the bloodstream. Primary metabolic processes occur in the liver and kidneys, with excretion via the urine. Basal oxytocin levels undergo a gradual increase, reaching up to fourfold during pregnancy. As gestation progresses, oxytocin pulses emerge in the circulation, accompanied by a substantial increase in the number of oxytocin receptors in the uterus, reaching their maximal levels. [71] A 100-fold increase in the number of oxytocin receptors has been identified in the human myometrium at the onset of labor. [72]

Synthetic oxytocin must be administered with caution during the induction or augmentation of labor, as elevated levels of the hormone may result in the hyperstimulation of the myometrium. This may lead to compromised placental and fetal blood flow and result in fetal hypoxia. [73, 74] Oxytocin's delayed onset and extended time to reach a steady state may lead to overdosing during labor induction, so Clark et al. Additionally, its therapeutic response is unpredictable due to individual variations in oxytocin receptor sensitivity, increasing the risk of adverse effects. [75]

2.3. Rationale for comparing Misoprostol with Dilapan-S plus Misoprostol

Despite the progress made in achieving effective labor induction on an unfavorable cervix, a successful outcome is still not guaranteed. Given the wide range of options available for cervical ripening, it is natural to question whether combining a mechanical and pharmacologic agent could produce a synergistic effect that would enhance outcomes. Previous studies have indicated several advantages of Dilapan-S compared to the Foley catheter, including no protrusion from the introitus and no need to keep under tension [76], non-inferiority compared to misoprostol, and higher patient satisfaction [77]. Additionally, similar high vaginal delivery rates have been observed with Dilapan-S compared to dinoprostone in outpatient elective induction. [78]

Initiation of mechanical induction with Dilapan-S allows for outpatient management. Due to its high safety profile, CTG monitoring is not required during labor induction. It is expected that labor will be induced gradually in the patient's natural environment, reducing the psychological burden on the patient, and without overburdening the inpatient team. When patients arrive at the hospital, they can proceed to pharmacologic induction, in this trial with misoprostol (Angusta), if necessary, rather than waiting for cervical ripening to take place.

To the best of the author's knowledge, this is the first trial to compare osmotic dilators with sequential misoprostol administration.

The ongoing changes in the German healthcare system drive the need to examine whether this combined approach represents a sustainable model that balances quality of care with effective resource management.

3. Material and Methods

The following is a prospective, randomized, controlled, single-center trial conducted at an academic hospital, the Marienhospital Osnabrück in Germany. Study participants' enrolment occurred between July 2023 and February 2025. The trial was conducted after consulting with the Ethics Committee of the Medical Association of Lower Saxony.

The initial information about the trial was provided before the induction of labor, during the women's prenatal visit by the midwife at our institution (*Geburtsanmeldung*) or during outpatient clinic visits. Flyers were also provided in three different languages (German, English, and Arabic), and posters were displayed in the waiting and examination rooms.

The obstetrician and the midwives responsible for the labor ward were in charge of screening the eligible women for the study. To be eligible to participate in this study, a patient had to be at least 18 years old, be able to provide signed and dated informed consent, and meet the inclusion criteria listed below.

a) Singleton, live fetus
b) Cephalic presentation
c) Term gestation (≥ 37 + 0 weeks of pregnancy), gestational age was based on the initial dating scan between 7 and 14 weeks, which confirms gestational age by CRL.
d) Intact membranes
e) Unfavorable cervix with Bishop score <6
f) No contraindication for a spontaneous labor

Patients who fell into any of the following criteria were excluded from participating in the trial:

a) Active labor
b) Active genital herpes
c) Chorioamnionitis
d) Women with previous caesarean section or cervical surgery
e) Abnormal placental localization or adherence (placenta praevia or unresolved low-lying placenta)
f) Active vaginal bleeding
g) Non-reassuring fetal status
h) Multiple gestation
i) Known fetal anomaly
j) Difficulty understanding the study protocol (e.g., language barrier or not having an interpreter) or not willing to comply with the study procedures

Randomization was performed using a computer-generated random list of numbers, assigning patients to one of the two trial groups. Randomization assignments were kept concealed in

opaque envelopes. Due to the nature of the interventions, blinding of participants and health care professionals was not possible. A total of one hundred thirty eligible pregnant women were allocated to the two trial groups: one that was administered misoprostol (Angusta, Norgine GmbH, Germany) as the sole cervical ripening agent (the control group) and the other, which was administered osmotic dilators (Dilapan-S, MEDICEM, Czech Republic) combined with subsequent administration of misoprostol (the study group).

A CTG was performed for at least 30 minutes to monitor fetal condition and uterine activity before the vaginal examination, performed either by a midwife or an obstetrician in the maternity unit.

Patients randomized to the Dilapan-S and misoprostol group (study group) were administered the synthetic osmotic dilator (minimal 3, maximal 5 rods), placed in the cervix by trained obstetrician colleagues under visualization with a sterile speculum. The Dilapan-S rods were left *in situ* for 18-24 hours, unless removal was clinically indicated before this time (e.g., labor started before the scheduled removal). Patients in this group were permitted to go home provided they did not have any contraindications and provided they adhered to the scheduled return date or an earlier date if rupture of membranes, excessive bleeding, or contractions occurred. A negligible number of patients in this group elected to be admitted to the maternity ward. Upon returning to the clinic as scheduled, the Dilapan-S rods were removed, and the cervix was re-evaluated. Patients without signs of active labor were administered oral misoprostol. The pharmacological induction of labor was always performed in an inpatient setting. Medical induction started with an initial dose of 25-50 µg of misoprostol, followed by either 25 µg after 2 hours or 50 µg after 4 hours. The maximum dose was 200 µg in a 24-hour period.

Patients randomized to the control group were admitted to the maternal ward and received oral misoprostol in an identical dosage scheme as the study group without prior insertion of Dilapan-S. The Bishop score was reassessed after 24 hours. The induction of labor with misoprostol was carried out for a minimum of 48 hours.

After the completion of the 48-hour period, clinical care for both groups was left to the attending healthcare professional’s discretion in accordance with the standard of care at the institution.

3.1. Primary and secondary endpoints

Induction-Delivery-Interval

The primary endpoint of this trial was the interval between induction and spontaneous vaginal delivery (hours).

Interval of induction and active phase of labor

More often than not, labor fails to progress after reaching the active phase (e.g., due to cephalopelvic disproportion). The active phase of labor is defined by the cervical opening > 6 cm.

Gain of Bishop score

The change in the Bishop score after 24 hours of study intervention was assessed whenever possible by the same midwife or obstetrician to reduce interpersonal variability.

Vaginal births in 36 and 48 hours

To ensure the quality of the trial, the rate of vaginal births in 36 and 48 hours were assessed. The 36-hour threshold was selected to more effectively show the impact of the combination method and compare it with the control group.

Mode of delivery

All three modes of delivery: spontaneous vaginal, operative vaginal delivery, and caesarean section, were evaluated as part of the secondary endpoints.

Failed induction of labor

The condition “failed induction” remains less specific to diagnose. For the purpose of the trial, failed induction of labor was defined as the failure to achieve any sign of labor beyond 72 hours after the start of the study intervention and, consequently, requiring a caesarean section.

Dosage of misoprostol (mg)

The total dosage of misoprostol administered to each participant of the trial was documented and evaluated.

Uterine tachysystole

Induction of labor using PGs bears a risk (albeit low) of uterine tachysystole. A tachysystole is defined as more than five contractions per 10-minute period that last over 30 minutes.

Intervention with oxytocin

None of the groups in the trial received oxytocin as part of the induction of labor. The oxytocin was reserved for labor augmentation, e.g., in cases of hypotonic labor, which often resulted in protracted or arrested labor.

Triple I (intrauterine infection, inflammation, or both)

The insertion of a foreign body into the cervix could raise concerns about the occurrence of Triple I, which could result in harm to the mother and fetus. As such, the rate of Triple I was also evaluated in the trial. The diagnosis of suspected Triple I is based on the presence of maternal fever in conjunction with either the presence of baseline fetal tachycardia, a maternal white blood cell counts greater than 15,000/mm3 in the absence of corticosteroids, or the presence of definite purulent fluid from the cervical os. A confirmed diagnosis of Triple I can only be made through amniotic fluid culture or placental pathology.

Meconium-stained amniotic fluid

To monitor fetal well-being during labor, meconium-stained amniotic fluid (MSAF) was also evaluated in the trial. MSAF is demonstrated to be associated with fetal hypoxia, intraamniotic infection or inflammation, and post-term pregnancies.

Non-reassuring fetal heart rate

The most effective tool to date for monitoring fetal well-being is the CTG. At any stage of labor, obstetricians and midwives must be prepared to take action if there is any abnormality in the fetal heart rate. Numerous parameters determine whether to continue or terminate the labor process. In the trial, this decision was left to the attending obstetrician's discretion.

Fetal outcome

In this trial, the neonatal status was evaluated based on three key metrics: umbilical cord pH, Apgar score, and transfer to the neonatal intensive care unit (NICU). A cord pH of less than 7.10 was used as the threshold in this trial, as it is closely associated with severe acidosis. Due to its correlation to infant mortality and the risk of severe neurologic morbidity, a 5-minute APGAR score of less than 7 was used as a predictor in this trial.

3.2. Statistical methods

The analyses were carried out in R 4.3.3. The median and interquartile range were calculated for metric, quasi-metric, and ordinal characteristics. Absolute (numbers) and relative frequencies (percentages) were calculated for nominal characteristics. Due to the large sample, the normal distribution can be approximately assumed for metric and quasi-metric characteristics. Thus, (quasi-) metric characteristics were examined using a t-test for independent samples. For comparisons of an ordinal characteristic between two independent groups, the Mann-Whitney U test was used. In the case of group comparisons concerning a nominal characteristic, Fisher's exact test or its generalization for larger contingency tables

than 2 x 2 was used. The significance level chosen for all analyses was $\alpha = 0.05$. This results in a statistically significant outcome if $p < 0.05$.

4. Results

4.1. Baseline demographic and characteristics

The baseline demographic and characteristics of the study population were analyzed and found to be well balanced between the two study groups (Table 1). These included median age, parity, pre-pregnancy body mass index (BMI), and Bishop score at randomization. Notably, the Angusta-only group had a higher rate of gestational or pre-existing diabetes, whereas a higher rate of small for gestational age or intrauterine growth restriction was observed in the Dilapan-S + Angusta group (study group). Despite the differences, birth weight distribution remained comparable between the two groups. Overall, the baseline characteristics were sufficiently similar, supporting the internal validity of the study.

Table 1: Demographic and baseline characteristics by group allocation

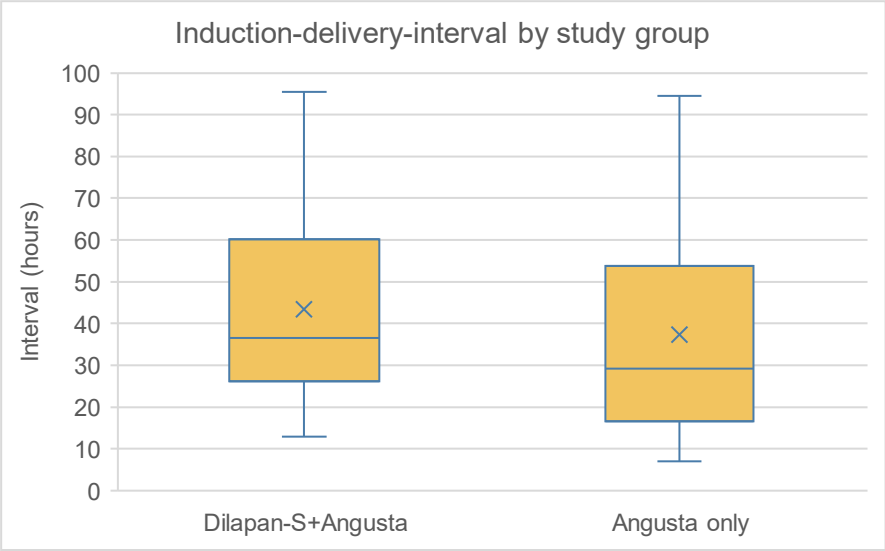
Characteristic	Dilapan-S + Angusta (n = 64)	Angusta only (n = 66)	p-Value
Age, y			
Median	30.0	30.5	0.655
Range	20-41	20-44	
Parity, n, %			
Nulliparous	45 (70.3)	46 (69.7)	1.000
Multiparous	19 (29.7)	20 (30.3)	
GA at randomization, wks, n, %			
40 + 0 or less	35 (54.7)	36 (54.6)	1.000
More than 40 + 0	29 (45.3)	30 (45.5)	
BMI before pregnancy			
Median	27.2	27.6	0.177
Range	17.1 – 43.6	19.8 – 45.7	
Birth weight, gr			
Median	3430	3464	0.980
Range	2208 – 4580	2536 – 4500	
Bishop score at randomization			
Median	2	3	0.732
Range	0 – 6	0 – 6	
Indications for delivery, n, (%)			
Post-term pregnancy	24 (37.5)	22 (33.3)	0.714
Gestational diabetes/pre-existing diabetes type 1/type 2	4 (6.3)	15 (22.7)	0.012
Oligohydramnios/poyhydramnios	3 (4.7)	7 (10.6)	0.325
Hypertensive disorders of pregnancy	7 (10.9)	6 (9.1)	0.777
Small-for-gestational-age/ fetal growth restriction	14 (21.9)	6 (9.1)	0.053
Intrahepatic cholestasis	1 (1.6)	1 (1.5)	1.000
Suspected non-diabetic fetal macrosomia	6 (9.4)	3 (4.6)	0.321
Women’s preference for induction of labor	1 (1.6)	2 (3.0)	1.000
Other	4 (6.3)	4 (6.1)	0.716

4.2. Primary and secondary outcomes

4.2.1. Induction-delivery-interval

The primary outcome, induction-to-delivery interval, did not differ significantly between the two study arms overall. The median duration from induction to delivery was 36.5 hours (range: 13 – 95.5 hours) in the Dilapan-S + Angusta group (study group) and 29.3 hours (range: 7 – 94.5) in the Angusta-only group (control group), with no statistically significant difference observed (p = 0.129).

Graphic 1. Induction-delivery-interval

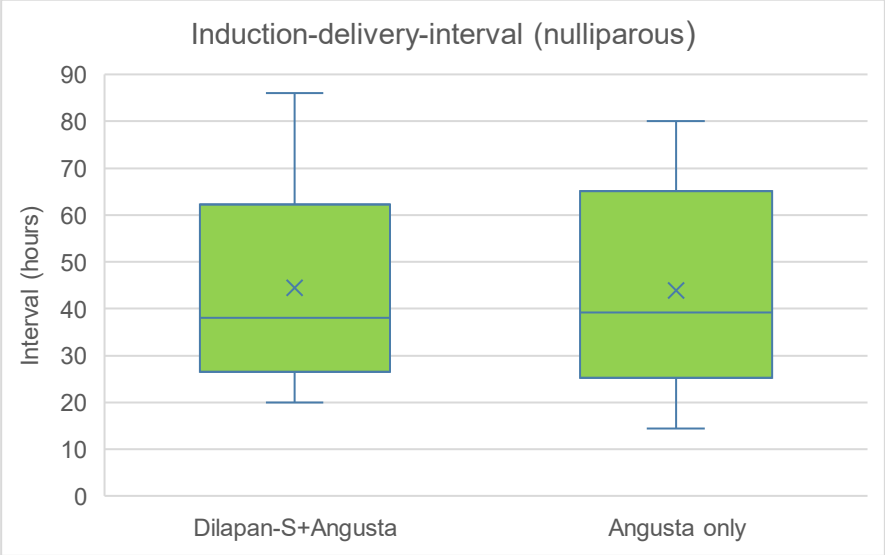


Box plots show median, interquartile range, and range of induction-to-delivery interval. No statistically significant difference was observed (p = 0.129).

A high degree of similarity in the nulliparous subgroup was demonstrated when analyzed by parity: 38.0 hours for participants in the Dilapan-S + Angusta group versus 39.3 hours in the Angusta-only group (p = 1.000). This result suggests that the addition of Dilapan-S resulted in a similarly efficient course of labor, if not slightly more efficient, compared to pharmacological induction alone in this population.

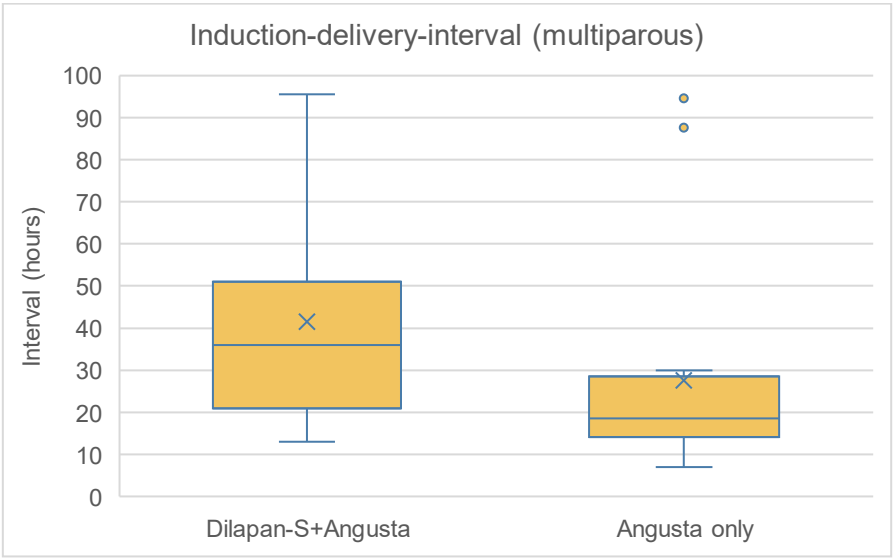
Among multiparous participants, however, a statistically significant difference was observed. The median induction-to-delivery interval was 36 hours in the Dilapan-S + Angusta group compared to 18.5 hours in the Angusta-only group (p = 0.013). This finding suggests a longer induction-to-delivery interval in the study group for this subgroup, without further implications for clinical outcomes.

Graphic 2a. Induction-delivery-interval according to parity (nulliparous)



Box plot of induction-to-delivery interval (hours) in nulliparous participants by study group. No statistically significant difference was found (p = 1.000). Median values are shown by horizontal lines within each box.

Graphic 2b. Induction-delivery-interval according to parity (multiparous)



Induction-to-delivery interval (hours) in multiparous participants. The study group had a significantly longer median interval (36 hours) than the control group (18.5 hours). Boxes represent interquartile ranges; whiskers indicate full data spread. p = 0.013.

Table 2. Primary outcome: Induction-Delivery-Interval

Primary Outcome	Dilapan-S + Ang (n = 40)	Angusta only (n = 41)	p-Value
Induction to delivery interval	36.5	29.3	0.129

Table 3. Primary outcome stratified by parity

Primary Outcome	Nulliparous			Multiparous		
	Dilapan-S + Angusta (n = 25)	Angusta only (n = 25)	p-Value	Dilapan-S + Angusta (n = 15)	Angusta only (n = 16)	p-Value
Induction delivery interval	38 h	39.5 h	1.000	36 h	18.5 h	0.013

4.2.2. Interval of induction and active phase of labor

There was no significant difference between the two subgroups regarding the interval of induction and the active phase of labor. The median duration of the active phase of labor was 33.0 hours in the Dilapan-S + Angusta group (n = 64) and 23.5 hours in the Angusta-only group (n = 66). Although the median duration was numerically shorter in the Angusta-only group, this difference did not reach statistical significance (p = 0.103).

Among nulliparous women, the median active phase duration was 35.0 hours in the Dilapan-S + Angusta group (n = 45) and 33.3 hours in the Angusta-only group (n = 46) (p = 0.283). Despite a modest numerical difference, both groups demonstrated comparable overall labor progression, with no statistically significant delay attributable to the use of Dilapan-S.

Among the multiparous subgroup, the median time spent until the active phase of labor was 29.0 hours in the Dilapan-S + Angusta group (n = 19) and 15.0 hours in the Angusta-only group (n = 20). Although the median time was nearly twice as long in the Dilapan-S group (29.0 vs 15.0 hours), this difference did not reach statistical significance (p = 0.105).

Table 4: Secondary outcomes according to trial group

Outcome	Dilapan-S + Angusta (n = 64)	Angusta only (n = 66)	p-Value
Time to active phase of labor (minutes)			
Medium	33.0	23.5	0.103
Range	0.0 – 177.5	0.0 – 90.0	
Gain of Bishop score			
Median	2	0	0.015
Vaginal birth			
in 36 hours	20 (50)	22 (55)	0.823
in 48 hours	28 (70)	29 (72.5)	1.000
Mode of delivery			
Spontaneous birth	40 (62.5)	40 (60.6)	0.858
Operative vaginal delivery	8 (12.5)	2 (3.3)	0.053
Caesarean section	16 (25.0)	24 (36.4)	0.186
Failed induction of labor			
Percentage (absolute)	3 (4.7)	7 (10.6)	0.325
Dosage of misoprostol			
Median	100	200	< 0.001
Range	0 – 450	50 – 575	
Maternal conditions			
Uterine tachysystole	2 (3.1)	3 (4.6)	1.000
Intervention with oxytocin	28 (43.8)	32 (48.5)	0.603
Triple I	2 (3.1)	0 (0.0)	0.240
Neonatal outcome			
MSAF	2 (3.1)	4 (6.1)	0.680
Non-reassuring fetal heart rate	25 (39.1)	25 (37.9)	1.000
pH < 7.10	3 (4.7)	2 (3)	0.678
APGAR Score <7 at 5’	4 (6.2)	3 (4.6)	0.716
NICU admission	1 (1.6)	2 (3.0)	1.000

Data are n (%) or median (interquartile range)

4.2.3. Gain of Bishop score

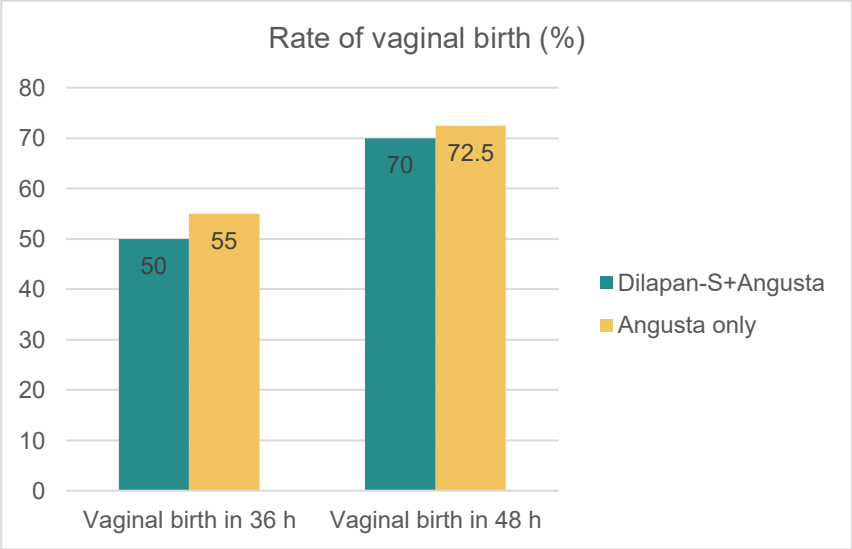
The change in Bishop Score was significantly greater in the Dilapan-S + Angusta group (median = 2) than in the Angusta-only group (median = 0; p = 0.015, Mann-Whitney U test), indicating a more pronounced cervical ripening effect with the combined regimen.

When stratified by parity, nulliparous participants in the Dilapan-S + Angusta group demonstrated a higher median gain in Bishop score than those in the Angusta-only group (2 vs 1; p = 0.051), with statistical significance. A similar pattern was observed in the multiparous subgroup, with median gains of 2 and 1 in the respective groups (p = 0.126), although the differences in both subgroups did not reach statistical significance.

4.2.4. Vaginal births in 36 and 48 hours

The rate of vaginal birth in 36 hours was not significantly different in both groups (p = 0.823). The combination method with Dilapan-S and Angusta resulted in vaginal birth within the time frame in 50% of the participants (n = 20). In comparison, the Angusta-only method achieved this outcome in 55% of participants (n = 22). The difference between the two trial arms was even less pronounced when vaginal birth within 48 hours was observed, with the Dilapan-S + Angusta group achieving 70% (n = 28) and the Angusta-only group achieving 72.5% (n = 29).

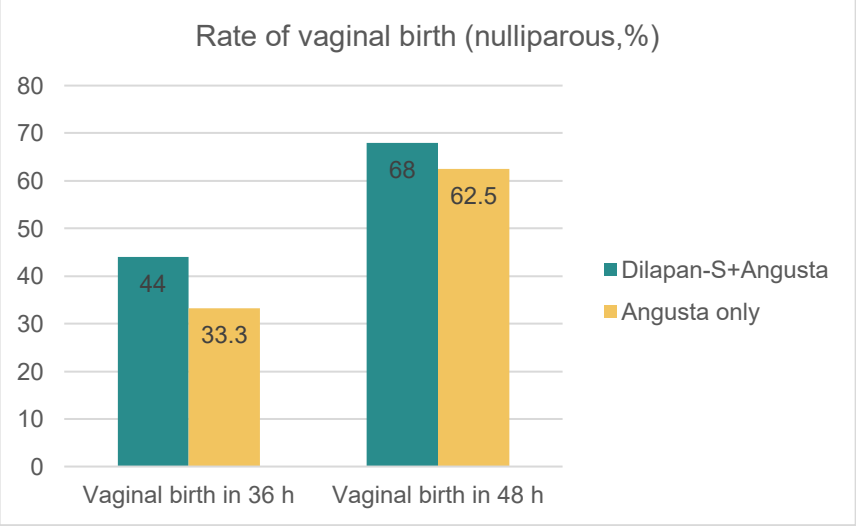
Graphic 3. Rate of vaginal birth by study group



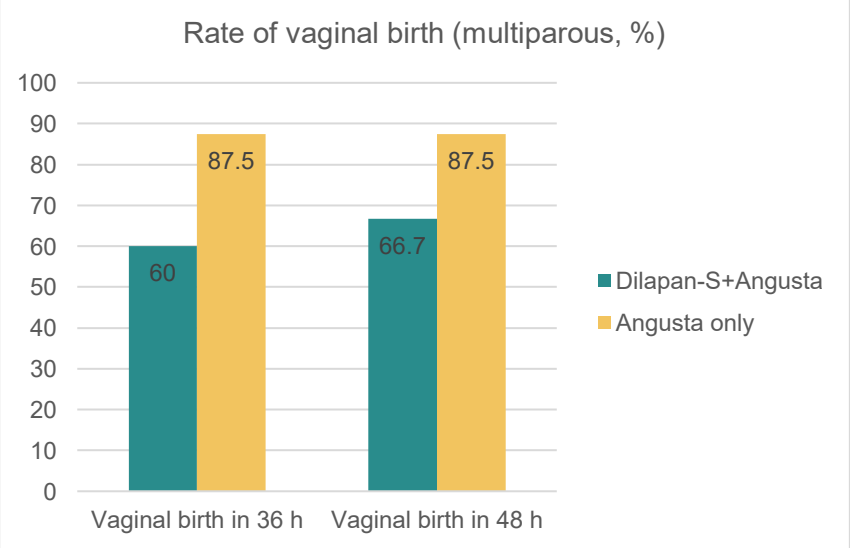
In the nulliparous subgroup, 44% (n = 11) of participants in the Dilapan-S + Angusta group achieved vaginal birth within 36 hours, compared to 33.3% (n = 8) in the Angusta-only group (p = 0.561). Within the 48-hour mark, vaginal birth was achieved in 68% (n = 17) of the Dilapan-S group and 62.5% (n = 15) of the Angusta-only group. Although these proportions were numerically higher in the Dilapan-S + Angusta group, the differences did not reach statistical significance (Fisher's Exact Test, p = 0.759).

Among multiparous women, vaginal birth within 36 hours was achieved by 60% (n = 9) of participants in the Dilapan-S + Angusta group and by 87.5% (n = 14) in the Angusta-only group. Despite this numerical difference, Fisher's Exact Test indicated that the difference was not statistically significant (p = 0.113). Within 48 hours, 66.7% (n = 10) of participants in the Dilapan-S + Angusta group achieved this outcome compared to 87.5% (n = 14) in the Angusta-only group. Thus, in this subgroup, the addition of mechanical cervical ripening with Dilapan-S to pharmacologic induction using Angusta was not associated with a statistically significant increase in the rate of vaginal birth within 36 or 48 hours (p = 0.220).

Graphic 4a. Rate of vaginal birth according to parity (nulliparous)



Graphic 4b. Rate of vaginal birth according to parity (multiparous)



4.2.5. Mode of delivery

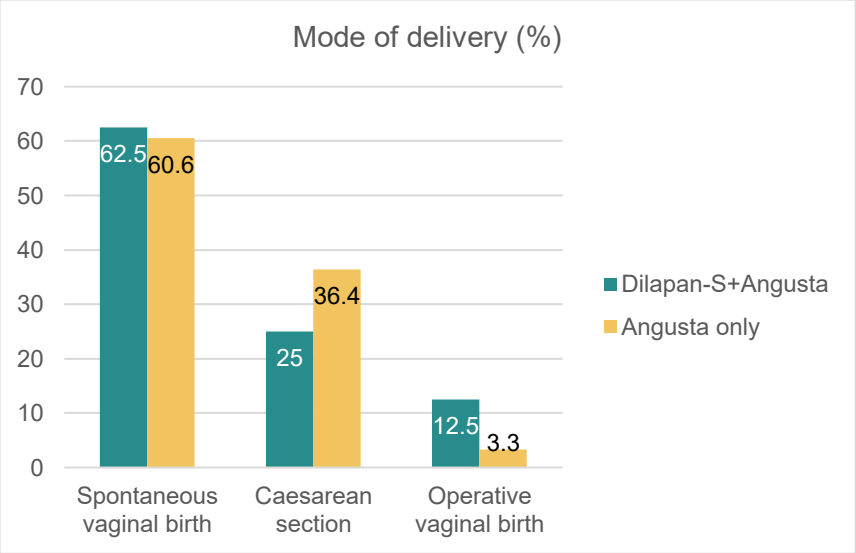
The rate of spontaneous vaginal birth was nearly identical in both trial groups: 62.5% (n = 40) in the Dilapan-S + Angusta group and 60.6% (n = 40) in the Angusta-only group (p = 0.858). This consistency was also observed when analyzed by parity.

While the caesarean section rate was higher in the Angusta-only group (36.4%, n = 24) than in the Dilapan-S + Angusta group (25.0%, n = 16), this difference did not reach statistical significance (p = 0.186). Conversely, the rate of operative vaginal delivery was slightly higher in the Dilapan-S + Angusta group (12.5%, n = 8) compared to 3.3% (n = 2) in the Angusta-only group (0.053).

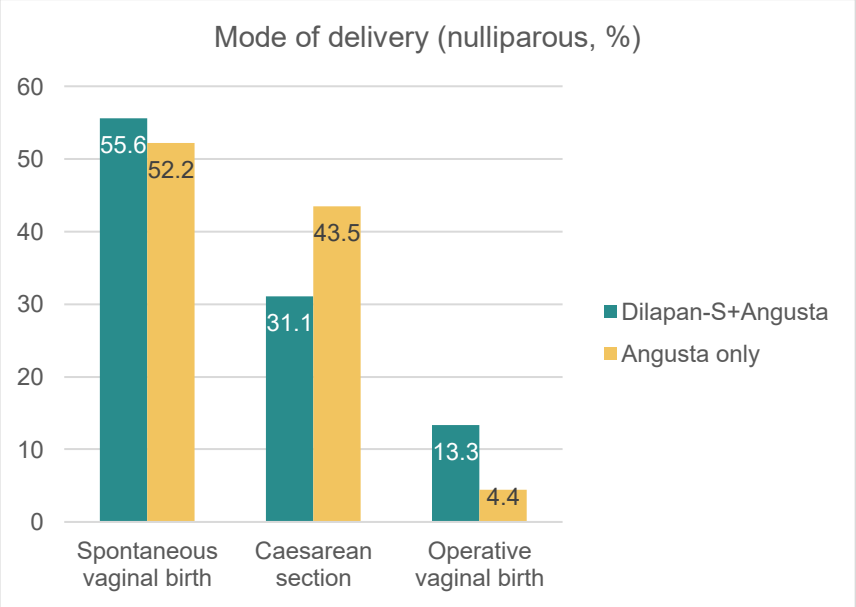
Among nulliparous participants, the rate of spontaneous birth was nearly identical across the two study arms. 55.6% (n = 25) of women in the Dilapan-S + Angusta group and 52.2% (n = 24) in the Angusta-only arm achieved spontaneous vaginal delivery (p = 0.834), indicating no significant difference between the groups. Caesarean section was performed on 31.1% (n = 14) of participants in the Dilapan-S + Angusta group, compared to 43.5% (n = 29) in the Angusta-only group (p = 0.280). While the absolute difference in rates may suggest a trend toward lower caesarean delivery rates in the combination group, the difference did not reach statistical significance. Operative vaginal deliveries were recorded in 13.3% (n = 6) of participants in the Dilapan-S + Angusta arm, whereas 4.4% (n = 2) of women in the Angusta-only group required this intervention (p = 0.156).

In terms of delivery mode among multiparous participants, the rate of spontaneous vaginal birth was highly comparable in both groups. In the Dilapan-S + Angusta group, 78.9% (n = 15) delivered vaginally, closely matching the 80% (n = 16) of participants in the Angusta only group (p = 1.000). Caesarean sections were performed in 10.5% (n = 2) of participants in the study group and in 20.0% (n = 4) of those receiving Angusta alone (p = 0.661), reflecting no statistically significant difference between the groups. Operative vaginal deliveries were required in 10.5% (n = 2) of participants in the Dilapan-S + Angusta arm, while no such intervention occurred in the Angusta-only group (p = 0.156).

Graphic 5. Mode of delivery by study group



Graphic 5a. Mode of delivery according to parity (nulliparous)



Graphic 5b. Mode of delivery according to parity (multiparous)

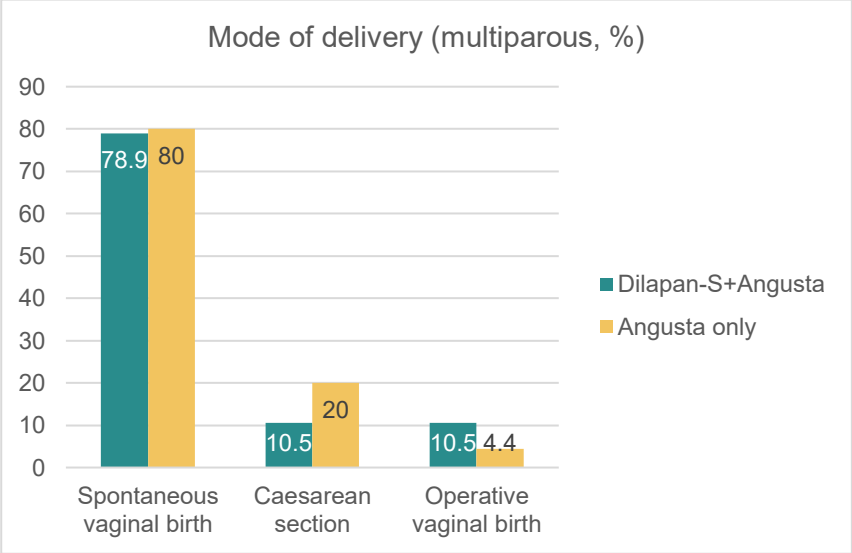


Table 5. Secondary outcomes stratified by parity

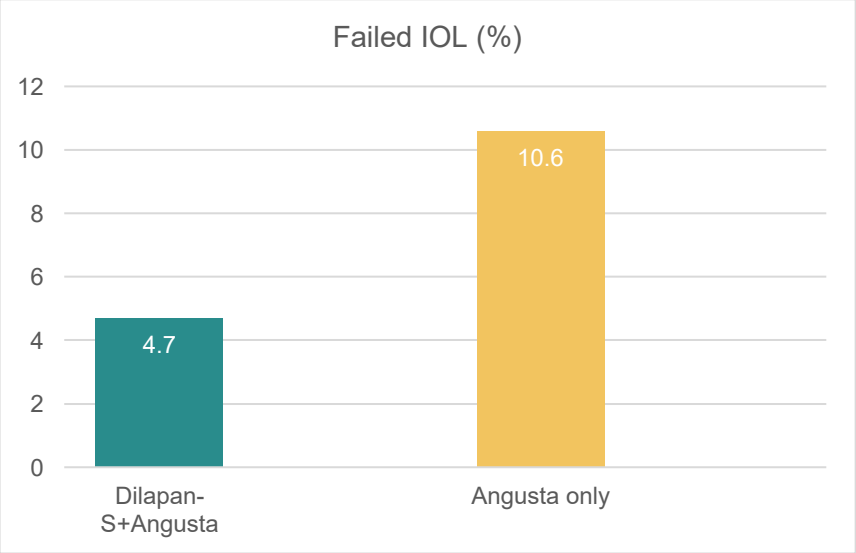
Secondary outcomes	Nulliparous			Multiparous		
	Dilapan-S + Angusta (n = 45)	Angusta-only (n = 19)	p-Value	Dilapan-S + Angusta (n = 46)	Angusta-only (n = 20)	p-Value
Induction-to-active phase-interval	33.0	33.3	0.103	29.0	19	0.105
Gain in Bishop score	2	1	0.051	2	1	0.126
Vaginal births						
in 36 hours	11 (44)	8 (33.3)	0.561	9 (60)	14 (87.5)	0.113
in 48 hours	17 (68)	15 (62.5)	0.759	10 (66.7)	14 (87.5)	0.220
Mode of delivery						
Vaginal delivery	25 (55.6)	24 (52.2)	0.834	15 (78.9)	16 (80)	1.000
Operative vaginal delivery	6 (13.3)	2 (4.4)	0.156	2 (10.5)	0 (0.0)	0.156
Caesarean section	14 (31.1)	29 (43.5)	0.280	2 (10.5)	4 (20)	0,661
Failed induction of labor	2 (4.4)	7 (15.2)	0.158	1 (5.3)	0 (0.0)	0.487
Dosage of misoprostol	100 (0 – 450)	225 (50 – 575)	<0.001	50 (0 – 300)	100 (50 – 350)	0.060
Uterine tachysystole	0	2 (4.4)	0.495	2 (10.5)	1 (5)	0.605
Intervention with oxytocin	23 (51.1)	22 (47.8)	0.835	5 (26.3)	10 (50)	0.470
Suspected triple I	2 (4.4)	0 (0.0)	0.242	0 (0.0)	0 (0.0)	
Fetal outcomes						
MSAF	1 (2.2)	4 (8.7)	0.361	1 (5.3)	0 (0.0)	0.487
Non-reassuring fetal heart rate	17 (37.8)	16 (34.8)	0.829	8 (42.1)	9 (45)	1.000
pH < 7.10	3 (6.7)	1 (2.2)	0.361	1 (5)	0 (0.0)	1.000
APGAR score < 7 at 5’	2 (4.4)	1 (2.2)	0.617	2 (10.5)	2 (10)	1.000
NICU admission	0 (0.0)	1 (2.2)	1.000	1 (5.3)	1 (5)	1.000

Data are in n (%) or median (interquartile range)s

4.2.6. Failed induction of labor

The occurrence of failed induction of labor was slightly higher in the Angusta-only group, with 10.6% (n = 7), compared to 4.7% (n = 3) in the Dilapan-S + Angusta group. The result was not statistically significant (p = 0.325). When analyzed by parity, the advantage of a combined method was even more evident among nulliparous women: only 4.4% (n = 2) nulliparous in the Dilapan-S + Angusta group failed to reach any sign of active labor beyond 72 hours after the start of induction of labor compared to 15.2% (n = 7) in the Angusta-only group (p = 0.158). In the multiparous subgroup, however, one case of failed induction of labor was observed in the Dilapan-S + Angusta group (5.3%), whereas none were reported in the Angusta-only group (p = 0.487).

Graphic 6. Failed induction of labor by the study group



4.2.7. Dosage of misoprostol

An analysis of the total misoprostol dosage used in both trial groups revealed a significantly lower median dose in the Dilapan-S + Angusta group (100 µg [0–475 µg]) compared to the Angusta-only group (200 µg [50–575 µg]), with a statistically significant difference (p = 0.001). Furthermore, the active phase of labor and vaginal birth was reached at a lower median misoprostol dosage in the Dilapan-S group (62.5 µg, n = 40) than in the Angusta-only group (150 µg, n = 40).

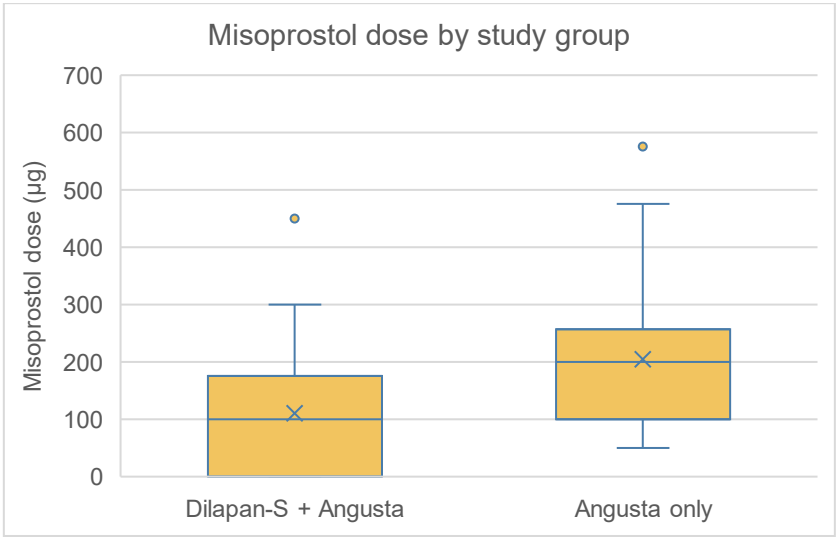
In total, 25% (n = 16) of study participants, equally distributed between the subgroups, achieved active labor and subsequent vaginal birth without requiring any misoprostol administration.

Among nulliparous participants, the total Misoprostol dosage required was significantly lower in the Dilapan-S + Angusta group with a median of 100 µg (range: 0–450 µg) compared to 225

µg in the Angusta-only group (range: 50-575 µg). The difference was statistically significant (p-value < 0.001).

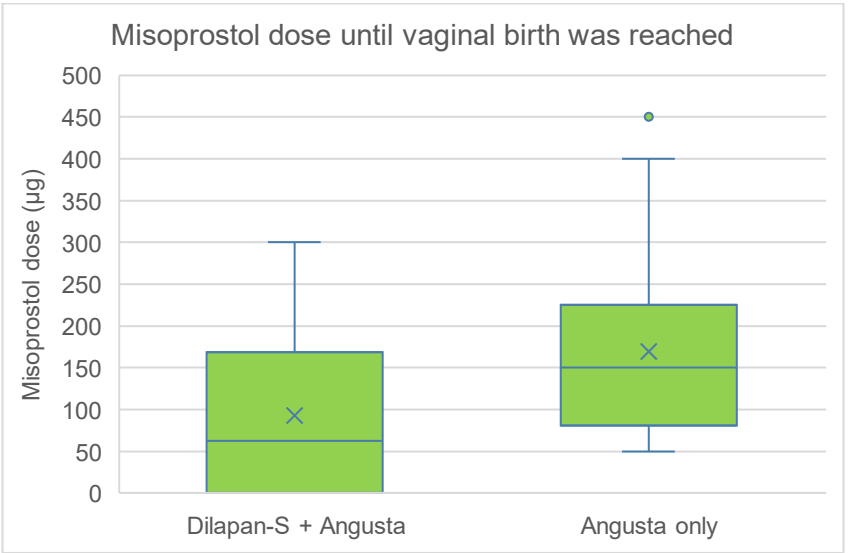
A similar result was observed in multiparous participants, where the median dose of misoprostol required in the Dilapan-S + Angusta group (50 µg [range: 0–300 µg]) was lower than in the Angusta-only group (110 µg [range: 50–350 µg]). However, this difference did not approach statistical significance (p = 0.060, Mann–Whitney U test).

Graphic 7a. Total misoprostol dose by study group



Distribution of total misoprostol dose administered by study group. The Dilapan-S + Angusta group received a significantly lower median dose (100 µg, range: 0–475 µg) compared to the Angusta-only group (200 µg, range: 50–575 µg), p = 0.001 (Mann–Whitney U test). Boxes represent the interquartile range (IQR), horizontal lines indicate the median, and dots represent outliers.

Graphic 7b. Misoprostol dose required to achieve vaginal birth by the study group



The dose of misoprostol required until vaginal birth was achieved, by study group. The median dose was lower in the Dilapan-S + Angusta group (approximately 62.5 µg) than in the Angusta-only group (approximately 150 µg). Boxes represent the interquartile

range (IQR), the line within each box indicates the median, and outliers are shown as dots. The difference was statistically significant (p = 0.001).

4.2.8. Uterine tachysystole

The incidence of uterine tachysystole did not differ significantly between the two groups (3.1% (n = 2) in the Dilapan-S + Angusta group vs 4.6% (n = 3) in the Angusta-only group, p = 1.000). Uterine tachysystole did not occur in the nulliparous participants, whereas 4.4% (n = 2) experienced it in the Angusta-only group (p = 0.495). Among multiparous women, uterine tachysystole was observed in 10.5% (n = 2) of the study group, compared to 5.0% (n = 1) of the control group participants (p = 0.605).

4.2.9. Intervention with oxytocin

A total of 43.8% (n = 28) of patients in the Dilapan-S + Angusta group required oxytocin to augment labor in either the active phase or the second stage, compared with 48.5% (n = 34) in the Angusta-only group. The results did not differ statistically (p = 0.608). When analyzed by parity, intervention with oxytocin was needed in the nulliparous subgroup of both trial groups (51.1%, n = 23 vs 47.8%, n = 22, study group vs control group, p = 0.835). However, an interesting result emerged in the multiparous subgroup: Oxytocin was needed more in the Angusta-only group (50%, n = 10) than in the Dilapan-S vs Angusta group (26.3%, n = 5). Despite the numerical difference, this result did not reach statistical significance (p = 0.470).

4.2.10. Fetal outcome

4.2.10.1. Non-reassuring fetal heart rate

In the trial, the incidence of non-reassuring fetal heart rate was similar between both groups, with 39.1% in the Dilapan-S + Angusta group compared to 37.9% in the Angusta-only group, indicating no significant difference (p = 1.000). A similar outcome was observed in the nulliparous subgroup, with 37.8% (n = 17) non-reassuring fetal heart rate occurring in the Dilapan-S + Angusta group, compared with 34.8% (n = 16) in the Angusta-only group (p = 0.829). In the multiparous subgroup, the rate of the non-reassuring fetal heart rate was evenly distributed between the two groups: 42.1% (n = 8) in the Dilapan-S + Angusta group and 45.0% (n = 9) in the Angusta group (p = 1.000).

4.2.10.2. Meconium-stained amniotic fluid (MSAF)

MSAF was observed in 3.1% of participants in the Dilapan-S + Angusta group and 6.1% in the Angusta-only group (p = 0.680), indicating no significant difference between groups. Among nulliparous women, MSAF occurred in 2.2% (n = 1) of Dilapan-S cases and 8.7% (n = 4) in the Angusta-only group (p = 0.361).

In the multiparous subgroup, a single case (5.3%) of MSAF was reported in the Dilapan-S group, with no cases in the control group (p = 0.487); importantly, this was not associated with any adverse birth outcomes.

4.2.10.3. Suspected Triple I

Suspected Triple I, defined by maternal fever followed by pathological fetal heart rate, was observed in 3.1% (n = 2) of participants in the Dilapan-S + Angusta group, with no cases reported in the Angusta-only group (p = 0.240). Both cases occurred in nulliparous women (4.4%, n = 2; p = 0.242) and resulted in caesarean sections; however, no additional maternal or neonatal complications were reported.

4.2.10.4. pH, APGAR, and NICU admissions

As already shown above, adverse neonatal outcomes were low and comparable between groups. Umbilical cord pH < 7.10 was observed in 4.7% (n = 3) of neonates in the Dilapan-S + Angusta group and 3% (n = 2) in the Angusta-only group (p = 0.678). Among nulliparous women, the incidence was 6.7% (n = 3) and 2.2% (n = 1) in the respective groups (p = 0.361), while in the multiparous subgroup, one case occurred in the Angusta-only group (5%, n = 1) and none in the Dilapan-S + Angusta arm (p = 1.000).

An APGAR score of < 7 at 5 minutes was recorded in 6.2% (n = 4) of neonates in the Dilapan-S + Angusta group and 4.6% (n = 3) in the Angusta-only group (p = 0.716). In nulliparous participants, the rates were 4.4% (n = 2) and 2.2% (n = 1), respectively (p = 0.617). Among multiparous women, both groups showed comparable rates (Dilapan-S + Angusta: 10.5%, n = 2; Angusta-only: 10%, n = 2, p = 1.000).

NICU admission rates were similarly low, with 1.6% (n = 1) of cases in the Dilapan-S group and 3.0% (n = 2) in the control group (p = 1.000). Stratified by parity, one admission occurred among nulliparous participants in the Angusta-only group (2.2%), while none occurred in the Dilapan-S + Angusta group (p = 1.000). In the multiparous subgroup, admission rates were nearly identical (Dilapan-S + Angusta: 5.3%, n = 1; Angusta-only: 5%, n = 1; p = 1.000).

5. Discussion

Induction of labor is one of the most significant workloads in maternity wards and still requires optimization. Up until now, there have been no universal protocols on the most effective approach for the induction of labor. This applies in particular to patients with an unfavorable cervix. An unfavorable cervix is known to be associated with prolonged induction-to-delivery intervals, which is burdensome not only for the patients but also for the already short-handed maternity wards. [4] The need for continuous monitoring of patients undergoing induction of labor places additional weight on already overburdened maternity wards. Mechanical approaches, such as cervical osmotic dilators, offer the option of outpatient care and require less maternal and fetal monitoring. Therefore, it is only reasonable to investigate whether combining mechanical and pharmacological methods results in improved labor outcomes. In this context, the present trial is the first to compare the combination of osmotic dilators (Dilapan-S) and misoprostol (Angusta) with Misoprostol alone as a method for labor induction in patients with an unfavorable cervix, contributing valuable insights into optimizing labor induction strategies.

5.1. Methods

5.1.1. Strengths and limitations of the study

With its single-centered design, the study was conducted with minimal biases due to variability in clinical protocols and standards of procedures across different institutions. This enabled consistency in the induction of labor procedures and patient care and increased the reliability of the results. Additionally, as both osmotic dilators (Dilapan-S) and misoprostol (Angusta) were already established components of the standard protocol for induction of labor at our institution, no additional resources or external funding were required.

Another key strength was the study's prospective, randomized design, which minimized selection bias and allowed a more robust comparison between the two study groups. The distribution of the nulliparous and multiparous subgroups was nearly identical in both groups, so the results are well representative of both clinical conditions.

However, certain limitations must be acknowledged. Vaginal examinations, a critical component of labor assessment, were done by different recruiting obstetricians and midwives; therefore, an intrapersonal variability in the Bishop-Score was unavoidable. Moreover, the attending healthcare provider would manage the labor beyond the initial 48-hour induction period, which could lead to inconsistencies in the decision-making. Despite these limitations, the study provides valuable insights into combining mechanical and pharmacological induction of labor in patients with an unfavorable cervix.

5.1.2. Inclusion and exclusion criteria

The strict inclusion and exclusion criteria were necessary to ensure that the study population baseline was as uniform as possible. In the current trial, the study participants were well-defined as women at term with singleton, cephalic presentation, and no complications that could affect the induction of labor, aiming for reliable and generalizable results. Exclusion criteria were applied to remove potential confounding variables and to ensure the safety of both the mother and the fetus. Women with a history of previous caesarean section or cervical surgery were excluded due to contraindication of misoprostol and increased risk of other labor-related complications. Twin pregnancy status, due to the highly individualized nature of their management regarding mode of delivery, had to be excluded from the trial as well. The same applies to women with PROM, as current studies cannot rule out an increased risk of Triple I when using mechanical induction in this situation. Additionally, conditions such as active vaginal bleeding, non-reassuring fetal status, and known fetal anomalies were also exclusion criteria due to their potential to necessitate immediate obstetric intervention and/or influence the outcomes due to complexities associated with congenital abnormalities.

5.1.3. Primary and secondary endpoints

The efficacy of a labor induction method is not defined by a single universal criterion. Parameters such as caesarean section rates, frequency of failed inductions, or induction-to-delivery interval have been used in previous studies. In this trial, the induction-to-delivery interval, defined as the duration from the initiation of labor induction to spontaneous vaginal birth, was selected as the parameter and the primary endpoint. The reason is that the induction-to-delivery interval not only demonstrated the efficacy of the induction method but also provided insight into potential clinical resource demands and the psychological experience of the patient. Admittedly, the rationale behind measuring only the interval to spontaneous vaginal delivery could be questioned, because the most important goal of inducing labor is the safe delivery of the fetus with little to no adverse maternal condition, regardless of delivery mode. However, in the context of this study, the spontaneous vaginal delivery rate was utilized as a parameter to assess both the efficacy and safety profile of the induction method. In addition to the primary endpoint, a range of secondary endpoints were also evaluated to give a more comprehensive assessment of each induction method. These included the interval from induction to the active phase of labor, gain in the Bishop score, and the rates of vaginal delivery within 36 and 48 hours. Furthermore, other variables that reflect not only maternal but also neonatal well-being were also examined in the trial. Maternal indicators such as suspected Triple I and meconium-stained amniotic fluid were recorded, alongside neonatal outcomes including cord pH, APGAR score at 5 minutes, and admission to the NICU.

5.2. Results

The study compared the efficacy of osmotic dilators (Dilapan-S) combined sequentially with misoprostol (Angusta) versus misoprostol alone for labor induction, with the primary endpoint being the induction-to-delivery interval to spontaneous vaginal birth. While no significant difference was observed in the overall cohort, nulliparous participants — typically provided more clinical challenges during induction — showed comparable induction durations in both groups, which indicates that the combined approach performs equally well in this population. This represents a notable advantage as the regimen allows an outpatient setting. Furthermore, the combined method facilitated vaginal birth within 36 and 48 hours with a comparable efficacy to misoprostol alone, including among nulliparous women. The spontaneous vaginal birth rate was nearly identical between groups. In contrast, the caesarean section rate was lower, with operative vaginal delivery slightly more frequent in the Dilapan-S + Angusta group. This result suggests a trend toward avoiding surgical delivery. Worth noting is also the lower total misoprostol dosage in the Dilapan-S + Angusta group, with 25% of participants achieving vaginal birth without any pharmacological aid. In both study arms, the rate of neonatal adverse outcomes was comparably low. These findings support the safety and effectiveness of the combined method, particularly for nulliparous women, whilst offering the added benefit of suitability for outpatient use.

5.2.1. Demographic

The baseline demographic and clinical characteristics were well balanced between the two groups, supporting the internal comparability of the study arms. Median maternal age, BMI before pregnancy, gestational age at randomization, and Bishop score at study entry did not differ significantly. The distribution of nulliparous and multiparous participants was nearly identical, with 70.3% nulliparous in the Dilapan-S + Angusta group and 69.7% in the Angusta-only group. Noteworthy are the differences in specific baseline indications between the two groups, particularly the higher proportion of gestational or pre-existing diabetes in the Angusta-only group and the presence of small-for-gestational-age/intrauterine growth-restricted fetuses in the Dilapan-S + Angusta group. Despite that, these clinical contrasts were not reflected in neonatal birth weights. The median birth weight was 3430 g in the study group and 3464 g in the control group, without a significant statistical difference ($p = 0.980$). This may suggest that the opposing effects of the two conditions on fetal growth balanced each other out, resulting in similar overall distributions of birth weights. It also highlights that, despite differences in maternal risks, the neonatal baseline in terms of birth weight was broadly comparable between the two induction methods.

5.2.2. Indications for the induction of labor

The induction of labor was generally well balanced between the two groups, with postterm pregnancy being the most frequent reason in both arms (37.5% in the Dilapan-S + Angusta group vs. 33.3% in the Angusta-only group, p = 0.714). However, gestational or pre-existing diabetes was significantly more common in the Angusta-only group (22.7% vs. 6.3%, p = 0.012), which may have some implications for labor progression and fetal weight. Contrariwise, small-for-gestational-age or intrauterine growth restriction was more frequently observed in the Dilapan-S + Angusta group, with a trend toward significance (p = 0.053). These differences, although not reflected in birth weight outcomes, suggest that each group may have contained slightly different clinical profiles in terms of fetal and maternal risk factors. Other indications, including hypertensive disorders (10.9% vs. 9.1%, p = 0.777), suspected (non-diabetogenic) macrosomia (9.4% vs. 4.6%, p = 0.321), and oligohydramnios/polyhydramnios (4.7% vs. 10.6%, p = 0.325), showed no significant differences. The overall distribution supports the clinical comparability of both groups, while underscoring the importance of interpreting outcomes based on the underlying medical indications.

5.2.3. Induction-Delivery-Interval

The induction-to-delivery interval did not differ significantly between the two study groups, with a median duration of 36.5 hours in the Dilapan-S + Angusta group and 29.3 hours in the Angusta-only group (p = 0.129). Although a numerical difference was present, it did not reach statistical significance. Stratification by parity revealed closely aligned median intervals among nulliparous participants (38.0 hours in the study group vs. 39.3 hours in the control group, p = 1.000). This finding suggests that the combined mechanical and pharmacological induction approach performs comparably even in the more challenging setting of labor induction in nulliparous women with an unfavorable cervix (Bishop score < 6). Induction in nulliparous women remains clinically complex, given a longer induction-delivery interval compared to multiparas [79, 80] as well as association with a three- to fourfold higher caesarean section rate compared to multiparas, and in clinical settings where caesarean section rates are intentionally kept low. This often results in extended labor durations, which may, in turn, increase the risk of postpartum hemorrhage. [81]

It is noteworthy that the combination of Dilapan-S + Angusta facilitates outpatient cervical ripening, with most women in this group returning home upon receiving Dilapan-S osmotic dilators and only a minority opting to remain in the hospital. This aspect, although not formally quantified in the study, may contribute to reduced psychological burden on mothers and improved utilization of hospital resources. Supporting this, a UK cost-consequence analysis in 2022 showed that, although Dilapan-S was found to be cost-neutral compared to the control arm, it effectively reduced the workload of midwives by 11%, mainly during the cervical ripening

phase. [82] The feasibility of outpatient induction was supported by a meta-analysis by Dong et al, which demonstrated comparable efficacy, safety, and practicality between outpatient and inpatient mechanical inductions in resource-rich settings and among carefully selected patient populations. [83]

Among multiparous women, the induction-to-delivery interval was significantly longer in the Dilapan-S group (study group 36 hours vs. control group 18.5 hours; p = 0.013). While the literature on the response of the multiparous cervix to mechanical ripening is limited, the findings of this trial suggest a clinically relevant distinction. In this study, the use of osmotic dilators in combination with misoprostol resulted in a greater gain in Bishop score, although not statistically significant, among multiparous women (median gain of the study group 2 vs. the control group 1, p = 0.126). However, this improvement did not translate into shorter labor durations. One possible explanation would be the altered structural properties of the multiparous cervix, which is known to exhibit increased collagen remodeling, reduced fiber alignment, and greater biomechanical compliance due to prior deliveries. Studies have shown that while collagen content may not differ significantly with parity, its spatial distribution and cross-linking may affect cervical strength and responsiveness to stretch-based stimuli [84, 85, 86], as observed in the present study with cervical mechanical dilators. Further research is needed to explore the multiparous cervical tissue and how its responses to mechanical induction, particularly in combination with pharmacological induction, may improve parity-specific protocols for the induction of labor.

Additionally, the study protocol – the sequential start of misoprostol instead of a simultaneous approach – may have impacted this subgroup, contra productive to their otherwise more efficient labor dynamics. It is essential to note that the concurrent administration of mechanical and pharmacological agents to induce labor is not a common clinical practice in Germany. The trial results suggest a potential for greater clinical benefit through the simultaneous administration of mechanical and pharmacological methods, although this remains to be investigated. Further studies, including those involving alternative mechanical methods such as balloon catheters, could help elucidate whether timing and method of combination influence induction efficiency, safety, or patient experience. Such investigations would be especially relevant given the increasing focus on efficiency in hospital resources as well as individualized protocols.

5.2.4. Interval of Induction and Active Phase of Labor

The duration until the onset of the active phase of labor, while numerically longer in the Dilapan-S + Angusta group, did not differ significantly between the two study groups. The median was 33.0 hours using the combination method compared to 23.5 hours in the Angusta-

only group (p = 0.103), which suggests no significant delay in labor progression with the use of mechanical cervical dilators. When stratified by parity, nulliparous women in both groups showed comparable intervals until the active phase (35.0 hours vs. 33.3 hours, p = 0.283), which further supports the notion that the combined method is also effective in this more clinically challenging group. Among multiparous women, the active phase was nearly twice as long in the Dilapan-S + Angusta group compared to the Angusta-only group (29.0 hours vs. 15.0 hours). However, this difference also did not reach statistical significance (p = 0.105). These findings mirror those observed in the induction-to-delivery interval, as previously discussed.

The observed differences in the interval until the active phase must also be interpreted in light of the significantly lower cumulative misoprostol dosage required in the Dilapan-S + Angusta group. Participants in this group received a median dose of 100 µg misoprostol, compared to 200 µg in the Angusta-only group (p = < 0.001), which indicates an adequate cervical ripening and labor progression while reducing the overall need for pharmacological intervention. Among those who reached the active phase and delivered vaginally, the difference was even more obvious, with a median dose of 62.5 µg in the study group as opposed to 150 µg in the control group. It is also noteworthy that 25% of study participants in the study group – equally distributed between the subgroups – reached the active phase and delivered vaginally without requiring any misoprostol administration. While the study design naturally contributed to this outcome, these findings suggest that a combination regimen may reduce pharmacological exposure while potentially contributing to a more gradual onset of labor. This may also offer clinical benefits in terms of lower risk of uterine hyperstimulation and its complications, as well as improved maternal tolerability.

5.2.5. Gain of Bishop score

As already briefly mentioned above, despite the longer induction-to-delivery intervals observed in the Dilapan-S + Angusta group overall, particularly among multiparous participants, the gain in Bishop score was significantly greater in this group compared to the Angusta-only arm (median gain: 2 vs. 0; p = 0.015). This finding suggests a more pronounced cervical ripening effect when mechanical and pharmacological methods are combined. Stratified by parity, again, a similar trend was observed in both the nulliparous and multiparous subgroups, with a higher median Bishop score gain in the combination group. However, these differences did not reach statistical significance. These results appear somewhat counterintuitive when considering the longer intervals to the active phase and delivery, especially among multiparous participants. It is possible that the improved Bishop score in the Dilapan-S + Angusta group reflects anatomical or structural changes on the cervix without necessarily corresponding to faster initiation of labor or uterine contraction. These findings underline the complexity of the

induction process, in which cervical ripening is only one of several factors influencing the pathway of labor.

Taken together, these findings highlight the importance of evaluating labor induction methods not solely by time intervals, but within a broader clinical context. The more pronounced changing in Bishop score observed in the Dilapan-S + Angusta group suggests that the mechanical component of the combination method effectively contributes to cervical ripening, particularly in women with initially unfavorable cervix. While the induction-to-delivery interval was longer in some subgroups, this did not translate into increased maternal or neonatal complications, as will be discussed further. This may reflect the protocol-driven sequencing of mechanical and pharmacological components. Importantly, the combined method allowed for the possibility of outpatient cervical ripening, a practical advantage that supports patient comfort and may reduce strain on inpatient resources.

5.2.6. Vaginal birth rates at 36/48 hours, delivery mode, and failed induction rate

When considering the timing to vaginal birth, no significant differences were observed between groups at either 36- or 48- hour time frame. Within 36 hours, 50% of the participants in the Dilapan-S + Angusta group and 55% of participants in the Angusta-only group delivered vaginally (p = 0.823), with similarly minimal differences at the 48-hour threshold (70% vs, 72.5%). Compared to the observational study by Gupta et al., where 48.4% and 54.7% of women delivered within 36 and 48 hours after 12 hours of Dilapan-S use, our combination method showed slightly higher rates of 50% and 70%, respectively. [87] While the protocols differ, this may point toward a modest additive effect of combining mechanical and pharmacological induction method.

In the nulliparous subgroup, the combined method was favored, with higher rates of vaginal birth being achieved within both 36 hours (44% vs. 33,3%; p = 0.561) and 48 hours (68% vs. 62.5%; p = 0.759), although these results did not reach significance. In multiparas, the pattern was reversed, with the Angusta-only group achieving higher rates of vaginal delivery within 36 hours (87.5% vs. 60%, *p* = 0.113) and 48 hours (87.5% vs. 66.7%, *p* = 0.220). These results reflect the overall trend seen in the induction-to-delivery intervals, where the combination method may be associated with a slower onset of labor in multiparous women.

The mode of delivery observed in this study supports the overall safety of and clinical comparability of the two induction methods. Rates of spontaneous vaginal birth were nearly identical in both groups – 62.5% in the study group vs. 60.6% in the control group – a pattern that stayed true across parity subgroups. These results show that the Dilapan-S + Angusta regimen achieves comparable success in facilitating vaginal birth while offering more

advantages. Among nulliparous participants, spontaneous delivery was achieved in over half of patients in both arms (55.6% vs 52.2%; p = 0.834), while among multiparas, the rates were consistently high (78.9% vs. 80.0%; p = 1.000).

Although not statistically significant, caesarean section was less frequent in the Dilapan-S + Angusta group across all analyses, with an absolute difference of more than 10 percentage points in the nulliparous subgroup (31.1% vs. 43.5%; p = 0.280). This finding aligns partially with the findings of Saad et al., whose pooled analysis of four RCTs demonstrated Dilapan-S was at least noninferior and marginally superior in reducing the caesarean section rates, especially among multiparous women. [88] Interestingly, in contrast to their findings, the trend toward reduced caesarean delivery in our study was observed among nulliparous women, suggesting that the combined method of Dilapan-S and Angusta may also lower the caesarean delivery rate in this subgroup. However, a higher rate of operative vaginal deliveries was observed in the Dilapan-S + Angusta group (12.5% vs. 3.3% overall; 13.3% vs. 4.4% in nulliparas), though this too did not reach significance. This could indicate that, when complications arose, they were more often managed successfully with operative vaginal birth in the Dilapan-S + Angusta group without having to resort to surgical deliveries.

Notably, the rate of failed induction was slightly higher in the Angusta-only group (10.6%) compared to 4.7% in the Dilapan-S + Angusta group (p = 0.325). This trend was even more pronounced among nulliparous participants: only 4.4% in the Dilapan-S group failed to reach the active phase of labor within 72 hours and required a caesarean section, compared to 15.2% in the Angusta-only group (p = 0.158). Although these differences did not reach statistical significance, they suggest improved responsiveness with the combined method in women with an initially unfavorable cervix. Among multiparous women, only one case of failed induction occurred in the Dilapan-S group (5.3%), while no cases were reported in the Angusta-only group (p = 0.487), and consistent with previous evidence supporting the high efficacy of misoprostol alone in this population. The rate of failed induction of labor was found to be heterogenous in various past studies, given the fact that the term itself lacks a universally approved definition. [89, 90, 91]

Importantly, none of these variations in delivery mode or induction outcome were associated with increased maternal or neonatal morbidity, and the overall delivery outcomes prove effectiveness of the combined regimen across a range of clinical scenarios. The added benefit of outpatient cervical ripening, as feasible with the Dilapan-S + Angusta approach, may further support its use in individualized care models aiming to optimize maternal experience without compromising delivery outcomes.

5.2.7. Uterine tachysystole and intervention with oxytocin

Despite the higher total dosage of misoprostol used in the Angusta-only group, the incidence of uterine tachysystole remained low and comparable between the two groups (3.1% in the Dilapan-S + Angusta group vs. 4.6% in the Angusta-only group, $p = 1.000$). Tachysystole did not occur among nulliparous participants in the study group, whereas two cases (4.4%) were observed in the Angusta-only group ($p = 0.495$). Among multiparas, the incidence was slightly higher in the Dilapan-S group (10.5% vs. 5.0%, $p = 0.605$), although the small sample size limits definitive interpretation. Importantly, all cases of tachysystole in the study group were managed conservatively, and both patients proceeded to spontaneous vaginal birth without major complications — except for one case involving a transiently low APGAR score. In contrast, tachysystole in the Angusta-only group was associated with more serious maternal and fetal outcomes, including emergency caesarean section, placental abruption, atonic bleeding, and cervical laceration. Although the numbers were small and the differences did not reach statistical significance, these observations suggest that when tachysystole does occur, it may be more clinically eventful in the misoprostol-only protocols. Familiari et al. supported this observation in their meta-analysis, where a reduction of uterine tachysystole was shown in a group that was induced with mechanical methods (3.8%) compared to misoprostol (7.5%) and dinoprostone (13.8%). [92] While the study populations differ, the tendency toward a higher safety profile with mechanical induction is consistent. Another similar finding was reported by Nasioudis et al., whose meta-analysis demonstrated that a combination method resulted in a lower rate of uterine tachysystole with changes in fetal heart rate, likely due to the lower doses of misoprostol when mechanical methods are used in conjunction. [93]

A similar pattern of non-significant but potentially relevant trends was seen in the use of oxytocin for labor augmentation. While nearly half of the participants in both groups required oxytocin administration (43.8% vs. 48.5%, $p = 0.608$), the subgroup analysis among multiparous women revealed an interesting discrepancy: only 26.3% of participants in the Dilapan-S + Angusta group required oxytocin, compared to 50% in the Angusta-only group. Although this difference was not statistically significant, it may suggest a more efficient or sustained cervical response following mechanical ripening in multiparous women that can reduce the need for additional uterotonics. This observation is supported by Baev et al., in their pilot prospective study involving 120 women, demonstrating that a combination of osmotic dilators and mifepristone reduced the need for oxytocin by 12% [94]. This supports the idea that combined methods may improve cervical readiness and reduce the need of pharmacologic intervention. These findings, together with the low overall incidence of uterine hyperstimulation and adverse fetal outcomes presented below, reinforce the safety profile of the combined method and suggest that the addition of mechanical ripening may provide physiological

benefits not fully captured by standard endpoints alone. Further studies with larger cohorts would be valuable for confirming these trends and better defining their clinical relevance.

5.2.8. Fetal outcomes

Neonatal outcomes in this trial were overall reassuring and comparable between the two induction methods. The incidence of non-reassuring fetal heart rate was similar across groups and parity subgroups, with no statistically significant differences observed. Likewise, the occurrence of meconium-stained amniotic fluid remained low and did not differ significantly, nor was it associated with adverse neonatal outcomes. While two cases of suspected Triple I were reported in the Dilapan-S + Angusta group — both among nulliparous participants — no additional maternal or neonatal complications occurred, and the overall infection rate remained low. Umbilical cord pH values below 7.10, low APGAR scores at five minutes, and NICU admissions were rare and evenly distributed between groups. Notably, there were no instances of NICU admission among nulliparous women in the Dilapan-S + Angusta group. Consistent with these findings, a large trial by Levine et al. comparing combination, mechanical-only, and pharmacological-only induction methods found no differences in neonatal outcomes between the groups [95]. Taken together, these results suggest that a combined mechanical and pharmacological induction approach does not increase the risk of neonatal morbidity.

6. Conclusion

The combined use of Dilapan-S and misoprostol demonstrated comparable efficacy to misoprostol alone for labor induction, including in nulliparous women. While induction-to-delivery intervals and vaginal birth rates were similar, the combined method required significantly less misoprostol and enabled outpatient cervical ripening. These findings support its utility as a safe and resource-efficient alternative for selected patient populations.

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