

# Unsuccessful misoprostol induction in pregnant women: an integrative review

Insucesso de indução por misoprostol em gestantes: revisão integrativa  
Fracaso de la inducción por misoprostol en mujeres embarazadas: revisión integradora

Juliana Oliveira Brito<sup>1</sup>  <https://orcid.org/0000-0002-9871-0240>

Ana Kelve de Castro Damasceno<sup>2</sup>  <https://orcid.org/0000-0003-4690-9327>

Ana Jéssica Silveira Rios<sup>2</sup>  <https://orcid.org/0000-0001-7524-2504>

Jéssica Lourenço Carneiro<sup>2</sup>  <https://orcid.org/0000-0002-1879-2064>

Guilherme Frederico Abdul Nour<sup>1</sup>  <https://orcid.org/0000-0002-5000-6203>

Camila Teixeira Moreira Vasconcelos<sup>2</sup>  <https://orcid.org/0000-0003-4578-4657>

Francisco Herlânio Costa Carvalho<sup>3</sup>  <https://orcid.org/0000-0003-0364-6758>

Emilcy Rebouças Gonçalves<sup>1</sup>  <https://orcid.org/0000-0002-1861-6626>

## How to cite:

Brito JO, Damasceno AK, Rios AJ, Carneiro JL, Nour GF, Vasconcelos CT, et al. Unsuccessful misoprostol induction in pregnant women: an integrative review. Acta Paul Enferm. 2024;37:eAPE02732.

## DOI

<http://dx.doi.org/10.37689/acta-ape/2024AR00027322>



## Keywords

Misoprostol; Labor, induced; Delivery, obstetric; Pregnancy; Cesarean section; Pregnant women

## Descritores

Misoprostol; Trabalho de parto induzido; Parto obstétrico; Gravidez; Cesárea; Gestantes

## Descriptores

Misoprostol; Trabajo de parto inducido; Parto obstétrico; Embarazo; Cesárea; Mujeres embarazadas

## Submitted

December 12, 2022

## Accepted

September 25, 2023

## Corresponding author

Juliana Oliveira Brito  
E-mail: enfajulianaoliveira@gmail.com

## Associate Editor (Peer review process):

Kelly Pereira Coca  
(<https://orcid.org/0000-0002-3604-852X>)  
Escola Paulista de Enfermagem, Universidade Federal de São Paulo, São Paulo, SP, Brazil

## Abstract

**Objective:** To analyze the evidence available in literature regarding unsuccessful labor induction with misoprostol in full-term pregnancies.

**Methods:** This is an integrative review, carried out between January and November 2022, whose research question and descriptors were outlined using the PECO strategy. The searches were carried out in the MEDLINE, Web of Science, CINAHL, EMBASE and Scopus databases by two researchers independently as well as assessment. For the study selection and identification phase, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used. The risk of bias assessment of included articles was carried out using the Newcastle-Ottawa Scale.

**Results:** A total of 3,674 articles were identified, and 84 were read in full, of which 11 comprised the review (n=9,010 pregnant women), published between 2005 and 2021, with the majority in the United States. Regarding the level of evidence, all articles were classified as 2b, assessed according to the design of each study. The study showed evidence regarding the following factors: High BMI (greater than 30 kg/m<sup>2</sup>), nulliparity, immature bishop, cervical length (greater than 30 mm), height, ethnicity (non-Caucasians from southern Europe) and fetal weight (greater equal to 4 kg).

**Conclusion:** The objective study was achieved, having demonstrated six maternal factors and one fetal factor that can lead to unsuccessful induction. It is worth highlighting the need for evidence that incorporates the individuality of each characteristic and the contribution of this study to support the choice of the best conduct for each pregnancy on an individual basis stands out.

## Resumo

**Objetivo:** Analisar as evidências disponíveis na literatura acerca do insucesso da indução do trabalho de parto com misoprostol em gestações a termo.

**Métodos:** Revisão integrativa, realizada entre janeiro e novembro de 2022, cuja pergunta de pesquisa e descritores foram delineados por meio da estratégia PECO. As buscas foram realizadas nas bases de dados MEDLINE; Web of Science; CINAHL; EMBASE e Scopus por duas pesquisadoras de forma independente, assim como a avaliação. Para a fase de seleção e identificação dos estudos foi utilizado o *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA). A avaliação do risco de viés dos artigos incluídos foi realizada através do questionário Newcastle Ottawa Scale.

**Resultados:** Foram identificados 3.674 artigos, 84 foram lidos na íntegra, dos quais 11 compuseram a revisão (n=9.010 gestantes), com publicação entre os anos de 2005 a 2021, sendo a maioria nos Estados Unidos. Quanto ao nível de evidência, todos os artigos foram classificados como 2b, avaliada conforme o delineamento

<sup>1</sup>Maternidade Escola Assis Chateaubriand, Fortaleza, CE, Brazil.

<sup>2</sup>Department of Nursing, Faculty of Pharmacy, Dentistry and Nursing, Universidade Federal do Ceará, Fortaleza, CE, Brazil.

<sup>3</sup>Faculty of Medicine, Universidade Federal do Ceará, Fortaleza, CE, Brazil.

Conflict of interest: nothing to declare.

de cada investigação. O estudo apontou evidências quanto aos seguintes fatores: IMC elevado (maior igual a 30kg/m<sup>2</sup>), nuliparidade, bishop imaturo, comprimento cervical (maior igual a 30mm), estatura, etnia (não caucasianas do sul da Europa) e peso fetal (maior igual a 4kg).

**Conclusão:** Alcançou-se o objetivo do estudo tendo sido demonstrado seis fatores maternos e um fetal que podem levar ao insucesso da indução. Vale ressaltar a necessidade de evidências que incorporem a individualidade de cada característica e destaca-se a contribuição desse estudo para embasar a escolha da melhor conduta para cada gestação de forma individualizada.

## Resumen

**Objetivo:** Analizar las evidencias disponibles en la literatura acerca del fracaso de la inducción del trabajo de parto con misoprostol en gestaciones a término.

**Métodos:** Revisión integradora, realizada entre enero y noviembre de 2022, cuya pregunta de investigación y descriptores fueron definidos mediante la estrategia PECO. Las búsquedas fueron realizadas en las bases de datos MEDLINE, Web of Science, CINAHL, EMBASE y Scopus por dos investigadoras de forma independiente, al igual que la evaluación. Para la fase de selección e identificación de los estudios se utilizó el *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA). La evaluación del riesgo de sesgo de los artículos incluidos se realizó a través del cuestionario *Newcastle Ottawa Scale*.

**Resultados:** Se identificaron 3.674 artículos, 84 se leyeron en su totalidad, de los cuales 11 conformaron la revisión (n=9.010 mujeres embarazadas), publicados entre los años 2005 y 2021, la mayoría en Estados Unidos. Respecto al nivel de evidencia, todos los artículos fueron clasificados como 2b, evaluada de acuerdo con el diseño de cada investigación. El estudio indicó evidencias respecto a los siguientes factores: IMC elevado (mayor igual a 30 kg/m<sup>2</sup>), nuliparidad, bishop bajo, longitud cervical (mayor o igual a 30 mm), estatura, etnia (no caucasoide del sur de Europa) y peso fetal (mayor igual a 4 kg).

**Conclusión:** Se alcanzó el objetivo del estudio y se demostraron seis factores maternos y uno fetal que pueden llevar al fracaso de la inducción. Cabe resaltar la necesidad de evidencias que incorporen la individualidad de cada característica y se destaca la contribución de este estudio para fundamentar la elección de la mejor conducta en cada gestación de forma individualizada.

## Introduction

The purpose of inducing labor is to resolve pregnancy vaginally. The decision to induce labor is made when continued pregnancy is associated with increased maternal and fetal risk and there is no contraindication to vaginal birth. The procedure may be indicated due to fetal attachments, such as premature rupture of membranes (PROM) or ovular infection of the fetus itself (restricted intrauterine growth, fetal death), maternal clinical complications (hypertensive syndromes, diabetes, nephropathies, pneumopathies) and prolonged gestational age, but each service determines its indication protocol.<sup>(1,2)</sup>

In Brazil, there is a recommendation for labor induction from 39 weeks onwards in singleton pregnancies and vertex presentation, with this practice being significantly associated with a reduction in hypertensive disorders of pregnancy, cesarean section birth, meconium fluid and neonatal respiratory problems in compared to expectant management up to 41 weeks. However, medical decision must be based on results of study on pregnant women's preferences and available resources.<sup>(3-5)</sup>

Labor induction is recognized as one of the strategies aimed at increasing vaginal birth rates. The prevalence of this procedure varies considerably from country to country, ranging from 1.4%

to 35.5%. In developed countries, induction is used in about 1 in 5 pregnant women from 37 weeks of gestation.<sup>(6)</sup> In Europe, labor induction rates vary from 7% to 33.0%, with prolonged pregnancy being one of the most common indications. In the United States, it increased from 9.5% to 23% in the last twenty years. In developing countries, these rates are lower, but increasing.<sup>(7)</sup>

The induction method covered in this review was misoprostol, a synthetic analogue of prostaglandin E1, approved by the Food and Drug Administration (FDA) in April 2002 for use in pregnant women with unfavorable cervix. In Brazil, its use is restricted to hospital establishments in accordance with Ordinance 344/1998<sup>(8)</sup> and updated in 2008.<sup>(9)</sup> It has a utero-tonic action, which causes contraction of the myometrium smooth muscle fibers, modifying the cervix, causing softening and distensibility and, subsequently, cervical effacement and dilation.<sup>(10,11)</sup>

Studies show that induction is considered successful when patients progress to vaginal birth and unsuccessful when it ends in cesarean section as well as establishing a time between 24 and 48 hours, with the occurrence of an "uncomplicated vaginal birth", "reaching the active phase of labor" or even relating to the cesarean section rate. However, there is no consensus among guidelines on the concept of successful labor induction.<sup>(12-16)</sup>

In the present study, cesarean section was considered as the outcome of unsuccessful labor induction, and together with this fact there is the challenge of achieving the goals proposed by global policies to control the cesarean section rate between 10% and 15% of all births.<sup>(16)</sup>

Considering the above, the lack of studies that analyze pre-induction maternal and neonatal factors as well as the contribution to the state of the art and strengthening the safe practice of health professionals who work in maternal-fetal care may enable the choice of the best approach to help resolve each pregnancy, predicting and avoiding negative outcomes. This study aimed to analyze the evidence available in literature regarding unsuccessful labor induction with misoprostol in full-term pregnancies.

## Methods

This is an integrative review, which followed the following steps to obtain the results: I- Problem identification; II- Literature search; III- Data assessment; IV- Data analysis; and V- Presentation.<sup>(17)</sup> Therefore, to prepare the guiding question, the acronym PECO was used: P (Population) - full-term pregnancies induced with misoprostol; E/C (Exposure/Comparator) - maternal and fetal factors; O (outcome) - route of birth. The guiding question formulated was: What maternal and fetal factors can lead to unsuccessful induction with misoprostol in full-term pregnancies?

The databases used were the online Medical Literature Analysis and Retrieval System (MEDLINE), Web of Science, CINAHL, EMBASE and Scopus. Access to databases occurred through the Coordination for the Improvement of Higher Education Personnel (CAPES - *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*) Journal Portal, through remote access from the Federated Academic Community (CAFe - *Comunidade Acadêmica Federada*) and registration at the *Universidade Federal do Ceará* (UFC). Articles not found in full by these means were requested via national and international commutation and through

partnership with nurses at Langara College in British Columbia – Canada.

To carry out the search in databases, search strategies were created with controlled descriptors from Medical Subject Headings (MeSH), Emtree and Cumulative Index to Nursing and Allied Health Literature (CINAHL) Subject Headings. Based on the research question and with the set of descriptors selected for each base, the Boolean operators (AND and OR) were used and the following search strategy was constructed: ((“Term Birth” OR “Delivery, Obstetric” OR “Labor, Obstetric” OR “Pregnancy” OR “labor, induced”) AND (misoprostol)) AND (“Cesarean Section” OR “Delivery, Abdominal” OR “Pregnancy Outcome” OR “Abdominal Deliveries”) in MEDLINE; (TITLE-ABS-KEY (“term birth” OR “delivery, obstetric” OR “labor, obstetric” OR “pregnancy”) AND TITLE-ABS-KEY (misoprostol) AND TITLE-ABS-KEY (“cesarean section” OR “delivery, abdominal” OR “pregnancy outcome” OR “abdominal deliveries”)) in Scopus; ALL=(“term birth” OR “delivery, obstetric” OR “induced, labor” OR pregnancy OR “labor, obstetric”) AND ALL=(misoprostol) AND ALL=(“cesarean section” OR “pregnancy outcome” OR “delivery, abdominal”) in Web of Science; (‘term birth’/exp OR ‘obstetric delivery’/exp OR ‘labor induction’/exp OR ‘pregnancy’/exp) AND ‘misoprostol’/exp AND ‘cesarean section’/exp in EMBASE; (“term birth” OR “delivery, obstetric”) AND misoprostol AND (“pregnancy outcomes” OR “cesarean section”) in CINAHL.

We included original articles indexed in the aforementioned databases, in all languages, without restrictions regarding year of publication and that described success percentage regarding using misoprostol alone or in comparison with another intervention, either as a primary outcome or secondary, considering the diversity of its use in different countries, both related to the dose of medication used, route of administration and combination with other induction methods.

Article search and assessment was carried out by two researchers, independently, from January to May 2022, with the help of a reference management tool, Endnote version X7. The researchers standardized

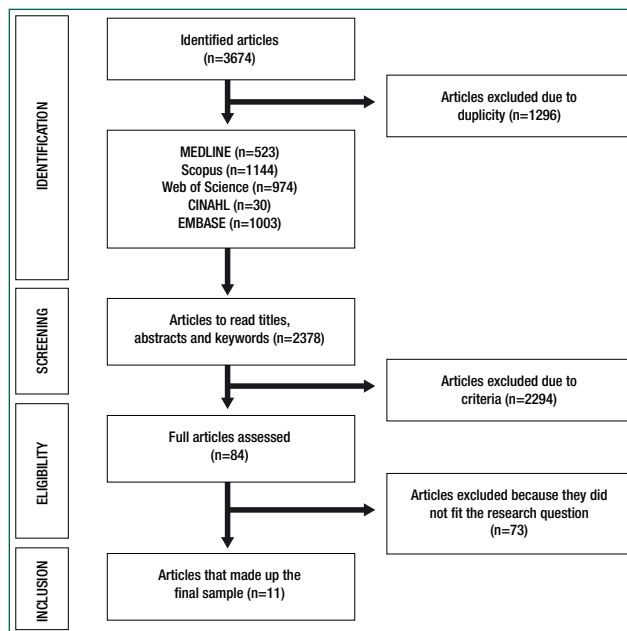
and executed search strategies in each database, with subsequent comparison of results. During the sampling process, duplicate articles were initially excluded. The titles, abstracts and keywords of articles were read, applying the inclusion criteria. The remaining documents were read in full, excluding those that did not answer the research guiding question. The remaining texts made up the final sample. To carry out this process, the study selection and identification flow diagram was used in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Figure 1).<sup>(18)</sup>

All studies that made up the final sample underwent a risk of bias assessment using the Newcastle-Ottawa Scale. The methodological quality of cohort studies was calculated in three categories: Group selection (0 - 4 points); Quality of adjustment for confounding (0 - 2 points); and Assessment of exposure after outcome (0 - 3 points). A score of six to nine represents strong evidence, four to five, moderate evidence, and a score less than four, limited evidence. After selecting the full articles, the instrument adapted from Ursi (2005) was applied to obtain information on article identification (title, language, year of publication, journal name), methodological characteristics, interventions assessed and results found, in addition to level of evidence.<sup>(19)</sup>

The quality of evidence was assessed according to the research design described in the Oxford recommendations, which have levels of evidence 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4 and 5.<sup>(20)</sup> The analysis and integration of results occurred through critical reading of articles based on scientific literature on the topic. The results are presented descriptively, containing the main information in order to answer the research question.

## Results

In the search carried out in databases, in the identification phase, 3,674 articles were obtained, with 1,296 excluded due to duplicity and 2,294 articles after reading the titles and abstracts. Of the 84 publications read in full, a total of 11 articles made up the review (Figure 1).



Source: Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009.

**Figure 1.** Flowchart of the number of publications analyzed at each stage of integrative literature review on maternal and fetal factors related to unsuccessful misoprostol induction in full-term pregnancies

All articles included were in English and the publication period ranged from 2005 to 2021. The countries in which the research was carried out were United States of America (USA) (03), Egypt (02), Geneva (01), Italy (01), Germany (01), South Africa (01), Turkey (01) and Nepal (01). Regarding study design, all were observational, with five prospective cohorts and six retrospective cohorts. Regarding the level of evidence, all articles are 2b according to Oxford. The studies' general methodological quality according to Newcastle-Ottawa Scale scores for cohort studies ranged from 6 to 8, indicating strong evidence.<sup>(20)</sup> The present review consisted of 11 articles, with n=9,010 pregnant women included, which were organized in a chart with the main author, country, year of publication, objective, design, level of evidence, population and risk of bias variables (Chart 1). After reading and analyzing the selected articles, seven factors related to unsuccessful induction were identified, leading to outcome of cesarean section. Of these, six are related to maternal factors and one is linked to the fetus.

**Chart 1.** Synthesis of articles included in the review (n=11)

Article	Country/ year	Objective	Design and LoE	Population	Risk of bias
Ferrazzi et al. <sup>(7)</sup>	Italy 2019	To investigate the impact of maternal age and BMI on the risk of late induction, prolonged induction time and the need for cesarean section after induction.	Retrospective cohort 2b	4618 pregnant women G1 n=4006 spontaneous labor G2 n=612 induced labor	7
Drakopoulos et al. <sup>(21)</sup>	Geneva 2017	To assess the number of doses of misoprostol necessary for cervical maturation and risk factors for cesarean section.	Retrospective cohort 2b	1295 pregnant women induced with misoprostol, dinoprostone or oxytocin.	7
Kehl et al. <sup>(22)</sup>	Germany 2016	To assess the effectiveness of labor induction with a double balloon catheter and oral misoprostol after catheter removal, when necessary, compared to oral misoprostol alone.	Retrospective cohort 2b	1032 pregnant women at term. 830 were induced with oral misoprostol alone and 202 began induction with a double balloon catheter and continued with oral misoprostol.	7
El-Maghraby. <sup>(23)</sup>	Egypt 2021	To compare cervical length measurement on pre-induction ultrasound and detection of insulin-like growth factor binding protein 1 (IGFBP-1) in cervical secretions by the Actim Partus test in predicting successful induction.	Retrospective cohort 2b	140 pregnant women	8
Lassiter et al. <sup>(24)</sup>	USA 2015	To assess the impact of BMI index on labor induction with misoprostol.	Retrospective cohort 2b	329 pregnant women G1 (BMI <30 kg/m <sup>2</sup> ) n=103 G2 (BMI 30-40 kg/m <sup>2</sup> ) n=151 G3 (BMI >40 kg/m <sup>2</sup> ) n=75	7
Ware et al. <sup>(25)</sup>	USA 2000	To compare transvaginal cervical measurement and Bishop score as indicators of labor duration and successful induction.	Prospective cohort 2b	77 pregnant women G1 nulliparous (n=32) G2 multiparous (n=45)	6
Batool S. <sup>(26)</sup>	South Africa 2013	To compare the effectiveness of oral misoprostol in primigravida and multigravida for labor induction.	Prospective cohort 2b	100 pregnant women G1 primigravida (n=50) G2 multigravida (n=50)	6
Beckwith et al. <sup>(27)</sup>	USA 2017	To investigate the effect of maternal obesity on the effectiveness of cervical ripening using misoprostol at the same dose in obese versus non-obese women compared to the effect of maternal obesity on mechanical ripening using oxytocin and a Foley catheter.	Prospective cohort 2b	709 pregnant women G1 misoprostol (n=515) G2 Oxy/Foley (n=194)	7
Caliskan et al. <sup>(28)</sup>	Turkey 2006	To assess cervical length measurement by transvaginal ultrasound to predict the success of labor induction in women with an unfavorable cervix.	Prospective cohort 2b	74 pregnant women G1 nulliparous (n=38) G2 multiparous (n=36)	6
Maged et al. <sup>(29)</sup>	Egypt 2018	To test the hypothesis that there is a higher rate of unsuccessful labor induction in post-term obese pregnant women compared to non-obese women.	Prospective cohort 2b	288 pregnant women G1 obese (n=144) G2 non-obese (n=144)	8
Rijal P. <sup>(30)</sup>	Nepal 2014	To increase knowledge of factors that increase the risk of cesarean section when labor is induced.	Prospective cohort 2b	348 pregnant women G1 vaginal birth (n= 174) G2 cesarean section (n= 174)	6

In the selected articles, there was some variation regarding route of administration and dosage of misoprostol. A total of four studies used misoprostol vaginally (VA), two studies used it orally (OR), two sublingually (SL), one study used OR followed by VA and two studies did not specify the route of administration used. Regarding dosage, four studies cited a dose of 25 mcg (OR, VA, SL); three studies used 50 mcg (VA and SL); one study alternated doses of 20 mcg and 40 mcg; another study alternated doses of 50 mcg and 100 mcg OR and SL, respectively. Another study alternated between 20 mcg and 40 mcg OR. Two articles associated pharmacological induction with misoprostol and mechanical induction. It is worth mentioning that these two studies excluded pregnant women with previous uterine scarring. A total of eight articles specified pregnant women with a previous uterine scar in selection and exclusion criteria; two

did not specify this information; and only one included pregnant women with a previous uterine scar during induction with misoprostol at a dose of 50 mcg VA. Chart 2 shows the synthesis and distribution of studies included.

## Discussion

Although all studies come from international literature, carried out on women from different cultures, races and ethnicities as well as users of different health systems, it is extremely important to incorporate the main maternal and fetal characteristics in individualized decisions regarding the resolution of pregnancy in our country.

Within a clinical context, analyzing the risk of unsuccessful labor induction can bring benefits to care as well as optimizing resources. Therefore, the

**Chart 2.** Distribution of studies according to exposure, variables of interest and maternal and fetal factors related to unsuccessful induction with misoprostol

Article	Exhibition	Variables analyzed	Related factors	Conclusions
Drakopoulos et al., 2017 <sup>(21)</sup>	Misoprostol 20 mg (2 doses) + 40 mg every 2 hours (maximum 320 mg in 18 h)/OR	Primary outcome = Obtaining Bishop $\geq$ 6. Secondary outcomes = Cervical change defined as an increase of at least 2 points in the BS and risk of cesarean section.	Nulliparity BMI $\geq$ 30 Bishop $\leq$ 2	Nulliparity, BMI $\geq$ 30 and Bishop $\leq$ 2 had a significant association with the risk of cesarean section after induction.
Ferrazzi et al., 2019 <sup>(7)</sup>	Misoprostol 25 mcg 4/4 h (maximum 12 doses)/SL	Prolonged induction time (> 24h) and cesarean section rate.	BMI = 25 to 29.9 BMI > 30 Parity Non-Caucasian ethnicity	Overweight, obesity, nulliparity, and ethnicity (non-Caucasian) are significantly associated with cesarean section after induction.
Kehl et al., 2016 <sup>(22)</sup>	Double balloon catheter + misoprostol 50 mcg 4 and 8h/OR. After 48 h: 100 mcg 4, 8, 12 h/VA	Primary outcome = Cesarean section rate. Secondary outcome = Labor induction interval, rate of vaginal births between 24 and 48 hours, unsuccessful induction and neonatal parameters.	BMI Stature Nulliparity	Cesarean section rate significantly associated with BMI (p=0.031) and height (166.3 $\pm$ 6.6 vs. 167.8 $\pm$ 6.9 cm, p=0.004) and nulliparity (p=0.015). Cesarean section rate significantly lower in G2 (catheter + miso) (26.1 vs. 17.3%, p =0.021). Fewer cesarean sections in G2 (37.2% vs. 24.2%, p =0.015) in nulliparous.
Ei-Maghraby., 2021 <sup>(23)</sup>	Misoprostol* + amniotomy with oxytocin	Primary outcome = active phase of labor; dilation cervical $\geq$ 4 cm. Secondary outcome: Interval from induction to labor and newborns' Apgar score.	Cervical length	Significantly greater cervical length in pregnant women who has cesarean section after induction than those who had vaginal birth. Successful induction was significantly correlated with iGFBP-1 detection in cervical secretions.
Lassiter et al., 2015 <sup>(24)</sup>	Misoprostol 25 mcg 4/4 h (max 06 doses)/VA + oxytocin IV	Primary outcome: Interval from induction to labor. Secondary outcomes: Number of misoprostol doses, duration of oxytocin and cesarean section.	BMI < 30 BMI 30–40 BMI > 40	Increased BMI is significantly associated with cesarean section after induction.
Ware et al., 2000 <sup>(25)</sup>	Misoprostol 50 mcg/VA	Primary outcome: Type of birth.	Cervical measurement $\geq$ 3cm Cervical measurement <3cm Bishop $\leq$ 4 Parity	Cervical measurement $\geq$ 3 cm and Bishop score $\leq$ 4 were statistically associated with the outcome of cesarean section. Increased cervical measurement and nulliparity are independent variables that were correlated with cesarean section.
Batool S., 2013 <sup>(26)</sup>	Misoprostol 25 mcg/OR	Outcomes: Number of misoprostol dose, labor induction interval and type of birth.	Parity	The cesarean section rate was higher in primiparous women.
Beckwith et al., 2017 <sup>(27)</sup>	Misoprostol 25 mcg/VA vs. Oxytocin with foley/VA catheter	Primary outcome: Failure to achieve active labor. Secondary outcomes: Cesarean section rate, number of misoprostol doses and need to use other methods (Pit/Fb or dinoprostone).	Obesity (BMI >30)	Pregnant women who are obese were statistically associated with higher cesarean section rates.
Caliskan et al., 2006 <sup>(28)</sup>	Misoprostol 50 mcg/SL	Outcomes: Unsuccessful induction (uterine contraction, Bishop less than 6 or birth not achieved in the first 24 hours after the start of induction), interval from induction to labor and the cesarean section rate.	Cervical length $\geq$ 30 mm Cervical length $\leq$ 30 mm	Cervical length $\geq$ 30 mm was statistically associated with higher cesarean section rates. The 30 mm cut-off point for cervical measurement demonstrated an accuracy of 68%.
Maged et al., 2018 <sup>(29)</sup>	Misoprostol 50 mcg/VA if Bishop > 6	Primary outcome: Cesarean section. Secondary outcome: Interval between labor and birth and the occurrence of postpartum hemorrhage (PPH).	Obesity (gestational BMI >29.9)	Pregnant obese women with Bishop score > 6 showed a statistical association with cesarean section with a risk twice as high.
Rijal P., 2014 <sup>(30)</sup>	Misoprostol* 4/4 h (max 03 doses)	Primary outcome: Marital rate, duration of the latent and active phases of labor. Neonatal parameters.	Bishop $\leq$ 5 Fetal weight >4 kg	Fetal weight > 4 kg is statistically associated with cesarean section, with the risk being almost three times higher in newborns with this weight compared to those weighing less than 4 kg. Bishop score $\leq$ 5 was statistically associated with cesarean section.

\* Did not specify the dose used.

risk should not be a predictor for an elective cesarean section when labor induction is expected to be less favorable or even to accelerate unsuccessful induction diagnosis, but the basis for selecting the best induction method, dose and interval of effective application for each pregnant woman in her individuality.

The studies included in the present review were published over a period of 21 years, in different countries, with the majority in the USA. Accessing scientific production over the long period of publi-

cation in the various work scenarios allowed us to synthesize the main scientific evidence regarding unsuccessful induction with misoprostol. As for the designs, with a prevalence of cohorts, it was possible to carry out a temporal analysis considering the relationship between exposure and effect, i.e., the relationship between induction with misoprostol and unsuccessful vaginal birth.

BMI was the most cited factor in studies in association with unsuccessful labor induction.<sup>(7,21,22,24,27,29)</sup>

Corroborating with a secondary analysis study of data from a randomized clinical trial (RCT) that aimed to predict maternal and gestational characteristics that predict a successful labor induction through the multiple and univariable logistic regression model, it concluded that BMI less than 30 (OR 1.69, 95% CI 1.32-2.22,  $P < 0.001$ ) significantly favors a successful induction.<sup>(31)</sup>

Another factor that had a strong association with unsuccessful labor induction was parity. According to the results of the studies included in this review, we can infer that nulliparity may be a predictor of unsuccessful induction, as women who are pregnant for the first time were more likely to have a cesarean section.<sup>(7,21,22,25,26)</sup>

It was also observed, in the results of this integrative review, that the main induction agent used in nulliparous patients was misoprostol, as they had a Bishop score  $< 6$ , the value necessary for using such a prostaglandin. For some authors, the Bishop score is a reflection of parity and, therefore, of the choice of induction method.<sup>(25)</sup> In this context, it should be noted that immature Bishop was one of the factors identified with the potential to predispose to unsuccessful induction and outcome of cesarean section. It diverged from the findings of the aforementioned systematic review, where the Bishop score did not demonstrate a significant association with the risk of cesarean section due to unsuccessful progression or fetal compromise.<sup>(31)</sup>

A prospective cohort study showed that nulliparous had a lower Bishop score than multiparous, which were associated with prolonged labor and higher cesarean section rates.<sup>(25)</sup> Similarly, in the investigation of another study with the same design, which selected pregnant women with Bishop  $< 6$ , immature Bishop and nulliparity had a significant association with cesarean section in nulliparous compared to multiparous.<sup>(21)</sup>

There was a preference for assessing the cervix using the Bishop score. However, such assessment is subjective and some studies have demonstrated a poor predictive value for the induction outcome.<sup>(23,32)</sup> Cervical length measurement verified by transvaginal ultrasound appears as an alternative for this assessment. The results of this measure were similar

to those of the Bishop score. Nulliparous women were less susceptible to vaginal birth and had prolonged labor compared to multiparous women. Considering the type of birth as an outcome, women with cervical length less than 3.0 cm were more likely to have a vaginal birth ( $p < 0.01$ ).<sup>(25)</sup>

This result was also observed in a prospective cohort of 74 women in Turkey, which used the cut-off point of 30 mm of cervical length to predict the success of induction with 50 mcg of misoprostol, finding a cesarean section rate of 26.1% for women with cervical lengths  $\geq 30$  mm and 7.1%  $\leq 30$  mm ( $P = 0.004$ ).<sup>(28)</sup> Another prospective cohort carried out in Egypt also used cervical length as a predictor of success of induction and vaginal birth, but it did not reveal a statistical association.<sup>(23)</sup>

Other less prevalent maternal factors detected in the present review related to unsuccessful induction with misoprostol were height and ethnicity. A retrospective cohort study assessed using logistic regression analysis and identified that height is associated with cesarean section ( $p = 0.001$ ).<sup>(22)</sup> In another cohort, a significantly higher risk of a cesarean section after induction was observed in non-Caucasian women of southern European descent (adjusted OR 2.39 95% CI 1.28-4.45).<sup>(7,22)</sup>

Fetal weight greater than 4 kg was the only factor associated with the conceptus (fetus) as unsuccessful induction and cesarean section. Cited in only one study in this review, women carrying fetuses weighing more than 4 kg had a higher risk (OR 2.96; 95% 1.532-5.738) of progressing to cesarean section after induction ( $p = 0.003$ ). In the multivariate analysis of significant factors from univariate analysis, the risk remained (adjusted OR 4.384; 95% 1.702-11.109) ( $p = 0.002$ ).<sup>(30)</sup>

A series of RCTs carried out in the Netherlands, comparing various cervical ripening agents, included in the analysis baseline characteristics such as maternal age, BMI, gestational age, parity, maternal ethnicity, Bishop score (before cervical ripening) and indication for induction. The results corroborate the studies included in this review, since maternal age, BMI, parity, ethnicity and birth weight percentile were predictors of cesarean section after induction.<sup>(33)</sup>

As a limitation of this study, the absence of national studies in the sample surveyed stands out, making comparisons with international findings difficult. The methodological quality of the studies included in this review highlighted some limitations regarding confounding variables and strategies to minimize them as well as strategies to minimize losses to follow-up. The different dosages and routes of administration of misoprostol used for induction, the association of the medication with mechanical methods and the different ways of assessing the effectiveness of the method were also considered as limitations.

Given the findings of this review, which demonstrated high BMI as the most cited factor in association with unsuccessful labor induction, experimental research is suggested with the dosage of misoprostol according to pregnant women's weight.

## Conclusion

Based on the evidence found, this study demonstrated that unsuccessful labor induction may be related to pregnant women's high BMI, nulliparity, height, ethnicity, maturity and cervical length, fetal characteristics, and weight. It is pertinent to carry out more studies on this topic, in order to generate evidence that incorporates the individuality of maternal and fetal characteristics in decisions to resolve pregnancy.

## Acknowledgements

To *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)* for the PhD scholarship granted to Jéssica Lourenço Carneiro.

## References

- Scapin SQ, Gregório VR, Collaço VS, Knobel R. Indução de parto em um hospital universitário: métodos e desfechos. *Texto Contexto Enferm*. 2018;27(1):e0710016
- Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Gestão e Incorporação de

Tecnologias em Saúde. Diretrizes nacionais de assistência ao parto normal: versão resumida. Brasília (DF): Ministério da Saúde; 2017 [citado 2023 Ago 17]. Disponível em: [https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes\\_nacionais\\_assistencia\\_parto\\_normal.pdf](https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_nacionais_assistencia_parto_normal.pdf)

- Grobman WA, Rice MM, Reddy UM, Tita AT, Silver RM, Mallett G, Hill K, Thom EA, El-Sayed YY, Perez-Delboy A, Rouse DJ, Saade GR, Boggess KA, Chauhan SP, Iams JD, Chien EK, Casey BM, Gibbs RS, Srinivas SK, Swamy GK, Simhan HN, Macones GA; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. *N Engl J Med*. 2018;379(6):513-23.
- American College Of Obstetricians And Gynecologists (ACOG). Clinical Guidance for Integration of the Findings of The ARRIVE Trial: Labor induction versus expectant management in low-risk nulliparous women. Washington, DC: ACOG; 2018 [cited 2023 Aug 17]. Available from: <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2018/08/clinical-guidance-for-integration-of-the-findings-of-the-arrive-trial>
- Berghella V, Bellussi F, Schoen CN. Evidence-based labor management: induction of labor (part 2). *Am J Obstet Gynecol MFM*. 2020;2(3):100136. Review.
- Mlodawski J, Mlodawska M, Plusajska J, Galuszewska J, Glijer K, Gluszek S. Misoprostol vaginal insert and Foley catheter in labour induction - single center retrospective observational study of obstetrical outcome. *Ginekol Pol*. 2020;91(11):700-3.
- Ferrazzi E, Brembilla G, Cipriani S, Livio S, Paganelli A, Parazzini F. Maternal age and body mass index at term: Risk factors for requiring an induced labour for a late-term pregnancy. *Eur J Obstet Gynecol Reprod Biol*. 2019;233:151-7.
- Brasil. Ministério da Saúde. Portaria Nº 344, de 12 de Maio de 1998. Aprova o Regulamento Técnico sobre substâncias e medicamentos sujeitos a controle especial. Brasília (DF): Ministério da Saúde; 1998 [citado 2023 Mar 31]. Disponível em: [https://bvsms.saude.gov.br/bvs/saudelegis/svs/1998/prt0344\\_12\\_05\\_1998\\_rep.html](https://bvsms.saude.gov.br/bvs/saudelegis/svs/1998/prt0344_12_05_1998_rep.html)
- Brasil. Ministério da Saúde. Portaria Nº 36, de 3 de Junho de 2008. Dispõe sobre Regulamento Técnico para Funcionamento dos Serviços de Atenção Obstétrica e Neonatal. Brasília (DF): Ministério da Saúde; 2008 [citado 2023 Mar 31]. Disponível em: [https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2008/res0036\\_03\\_06\\_2008\\_rep.html](https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2008/res0036_03_06_2008_rep.html)
- Bolla D, Weissleder SV, Radan AP, Gasparri ML, Raio L, Müller M, et al. Misoprostol vaginal insert versus misoprostol vaginal tablets for the induction of labour: a cohort study. *BMC Pregnancy Childbirth*. 2018;18(1):149.
- Varlas VN, Bostan G, Nasui BA, Bacalbasa N, Pop AL. Is misoprostol vaginal insert safe for the induction of labor in high-risk pregnancy obese women? *Healthcare (Basel)*. 2021;9(4):464.
- Raza F, Shams R. Risk of cesarean delivery in induced labour. *Medical Forum Monthly*. 2019;30(6): 55-8.
- Leduc D, Biringer A, Lee L, Dy J; clinical practice obstetrics committee; Special contributors. Induction of labour. *J Obstet Gynaecol Can*. 2013;35(9):840-57.
- Marconi AM. Recent advances in the induction of labor. *F1000Res*. 2019;8:F1000 Faculty Rev-1829. Review.
- National Institute for Health and Clinical Excellence (NICE): Induction of labour. London: NICE; 2008 [cited 2023 Aug 17]. Available from: [https://www.nhs.uk/planners/pregnancy-care-planner/documents/nice\\_induction\\_of\\_labour.pdf](https://www.nhs.uk/planners/pregnancy-care-planner/documents/nice_induction_of_labour.pdf)
- Organização Mundial de Saúde (OMS). Declaração da OMS sobre Taxas de Cesáreas. Suíça: OMS; 2015 [citado 2023 Ago 17]. Disponível em: [https://apps.who.int/iris/bitstream/handle/10665/161442/WHO\\_RHR\\_15.02\\_por.pdf](https://apps.who.int/iris/bitstream/handle/10665/161442/WHO_RHR_15.02_por.pdf)



17. Whittemore R, Knaf K. The integrative review: updated methodology. *J Adv Nurs*. 2005;52(5):546-53.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
19. Ursi ES. Prevenção de lesões de pele no período perioperatório: revisão integrativa da literatura [dissertação]. Ribeirão Preto (SP): Escola de Enfermagem de Ribeirão Preto, Universidade de São Paulo; 2005.
20. Centre for Evidence-based Medicine (CEBM). Oxford Centre for Evidence-based Medicine: levels of evidence (March 2009). Oxford: CEBM; 2009 [cited 2014 Dez 20]. Available from: <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009>
21. Drakopoulos P, Duyck C, Gayet-Ageron A, Fernandez S, Irion O, Martinez de Tejada B. What is the optimal duration of oral misoprostol treatment for cervical ripening? *J Matern Fetal Neonatal Med*. 2017;30(12):1494-9.
22. Kehl S, Böhm L, Weiss C, Heimrich J, Dammer U, Baier F, et al. Timing of sequential use of double-balloon catheter and oral misoprostol for induction of labor. *J Obstet Gynaecol Res*. 2016;42(11):1495-501.
23. El-Maghraby IM. Cervical Length as a Predictor of Success of Induction of Labor. *The Egyptian J Hospital Med*. 2021;85(2):3921-6.
24. Lassiter JR, Holliday N, Lewis DF, Mulekar M, Abshire J, Brocato B. Induction of labor with an unfavorable cervix: how does BMI affect success? (‡). *J Matern Fetal Neonatal Med*. 2016;29(18):3000-2.
25. Ware V, Raynor BD. Transvaginal ultrasonographic cervical measurement as a predictor of successful labor induction. *Am J Obstet Gynecol*. 2000;182(5):1030-2.
26. Batool S. Comparison of oral misoprostol for induction of labour in primigravidas and multigravidas. *Pakistan J Med Health Sciences*. 2013;7(1):239-42.
27. Beckwith L, Magner K, Kritzer S, Warshak CR. Prostaglandin versus mechanical dilation and the effect of maternal obesity on failure to achieve active labor: a cohort study. *J Matern Fetal Neonatal Med*. 2017;30(13):1621-6.
28. Caliskan E, Doger E, Cakiroglu Y, Ozkan S, Öeren S, Çorakçi A. Does cervical length measurement help to predict the success rate of labor induction using misoprostol at term in women with strictly unfavorable cervix? *J Turkish German Gynecol Associat*. 2006;7(3):184-8.
29. Maged AM, El-Semary AM, Marie HM, Belal DS, Hany A, Taymour MA, et al. Effect of maternal obesity on labor induction in postdate pregnancy. *Arch Gynecol Obstet*. 2018;298(1):45-50.
30. Rijal P. Identification of risk factors for cesarean delivery following induction of labour. *J Nepal Health Res Council*. 2014;12(27):73-7.
31. Pevzner L, Rayburn WF, Rumney P, Wing DA. Factors predicting successful labor induction with dinoprostone and misoprostol vaginal inserts. *Obstet Gynecol*. 2009;114(2 Pt 1):261-7.
32. Alanwar A, Hussein SH, Allam HA, Hussein AM, Abdelazim IA, Abbas AM, et al. Transvaginal sonographic measurement of cervical length versus Bishop score in labor induction at term for prediction of caesarean delivery. *J Matern Fetal Neonatal Med*. 2021;34(13):2146-53.
33. Quach D, Ten Eikelder M, Jozwiak M, Davies-Tuck M, Bloemenkamp KW, Mol BW, et al. Maternal and fetal characteristics for predicting risk of Cesarean section following induction of labor: pooled analysis of PROBAAT trials. *Ultrasound Obstet Gynecol*. 2022;59(1):83-92.