Heliyon 9 (2023) e13055

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Maternal and perinatal outcomes of failed prostaglandin induction of labour: A retrospective cohort study

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ARTICLE INFO

Keywords:
Cervical ripening
Prostaglandins
Failure
Risk factors
Adverse outcomes
Induction of labor

ABSTRACT

Background: Induction of labor is performed in up to 25% of pregnant women. When the cervix is unfavorable, cervical ripening may be safely and effectively performed using slow-release vaginal inserts of prostaglandin E2. However, the risk factors, management, and outcome of patients who fail to respond remain unclear.

Objective: To evaluate the outcomes of women who fail to respond to cervical ripening with prostaglandins.

Methods: A retrospective cohort analysis (2013–2019) was conducted. Women with a singleton gestation who underwent induction of labor due to post-date pregnancy using a slow-release prostaglandin E2 vaginal insert for cervical ripening were included. Data on clinical and outcome factors were derived from the medical files, and findings were compared between patients who achieved ripening within 24 h of treatment onset and those who did not. The primary outcome measure was the vaginal delivery rate following the ripening process. Secondary outcome measures were adverse composite maternal and neonatal outcomes. A model combining maternal characteristics and response rates to ripening was constructed.

Results: The final cohort included 1285 women: 1202 responded to cervical ripening (93.54%) and 83 (6.46%) did not. Compared to non-responders, responders had higher rates of vaginal delivery (96.51% vs. 66.27%, $P < 0.001$); lower rates of adverse maternal composite outcome (12.81% vs. 24.10%, $P = 0.031$) and adverse neonatal composite respiratory outcome (1.33% vs. 6.02%, $P = 0.009$). Responders were younger than non-responders (mean 30.03 years vs 31.73 years, $P = 0.005$) and had a lower nulliparity rate (50.99% vs 76.92%, $P < 0.001$). On multivariate analysis, failure to achieve cervical ripening was an independent risk factor for intrapartum cesarean delivery due to prolonged labor (aOR 11.90, 95% CI 6.13–23.25).

Conclusion: Women who achieve cervical ripening with prostaglandin E2 vaginal inserts are younger and more often multiparous than women who fail to respond. Good response to the cervical ripening process is associated with lower rates of intrapartum cesarean delivery and of adverse outcomes.

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https://doi.org/10.1016/j.heliyon.2023.e13055
Received 18 October 2022; Received in revised form 28 December 2022; Accepted 13 January 2023
Available online 16 January 2023

Abbreviations

BMI	Body mass Index
NICU	Neonatal intensive care unit
PGE2	Prostaglandin E2

1. Introduction

Induction of labor is a common obstetric procedure, performed in up to 25% of pregnant women [1,2]. When the cervix is unfavorable (i.e., Bishop score <6), cervical ripening is indicated [3,4]. Slow-release vaginal inserts of prostaglandin E2 (PGE2; PROPESS) are safe, efficient, and widely used method for cervical ripening [5]. However, the labor induction process, which is occasionally lengthy and painful, can have both medical and psychological impacts on patients, and some women may fail to respond. Studies have reported specific characteristics of women who fail induction, namely older age, higher rate of nulliparity, and higher rates of overweight and obesity [6]. The preferred management of women who fail induction is moot, with possible second-line treatment by either extra-amniotic Foley balloon catheter, repeated prostaglandin application, or cesarean delivery [7–11]. The lack of uniform data impairs the ability of clinicians to offer evidence-based counseling to women undergoing labor induction.

The aim of the present study was to better define the characteristics of women who fail to achieve cervical ripening with prostaglandins and to evaluate their obstetric outcomes. The findings are intended to assist both women and clinicians at decision-making junctions during the induction process.

2. Materials and methods

2.1. Design

A retrospective cohort study was conducted in a single, university-affiliated medical center between January 2012 and December 2018.

2.2. Study population

Women presenting with an unfavorable cervix (Bishop score <6) [3], who were admitted for cervical ripening with PROPESS due to prolonged gestation (40 + 0 weeks and more) were included in the study. Eligibility was limited to those between 18 and 45 years of age with singleton gestations who gave birth to a live neonate. Women with prior cesarean delivery, premature rupture of the membranes at admission, multifetal gestation, or known fetal anomaly were excluded. Women who underwent cesarean delivery prior to the 24-h evaluation (due to non-reassuring fetal heart rate/opted for cesarean delivery) were excluded as well, as were women in whom cervical ripening was terminated prior to the 24-h evaluation point (due to tachysystole, meconium-stained amniotic fluid, or intractable pain). The final cohort was divided into two groups according to cervical status at 24 h of treatment: (A) responders - women who achieved cervical ripening and continued to artificial rupture of the membranes and oxytocin augmentation; (B) non-responders - women who did not achieve cervical ripening (Bishop score <6). Non-responders were furthermore divided into two subgroups: (B1) partial non-responders - women who had rupture of the membranes or some degree of cervical response, i.e. changed cervix from admission but not to ≥8 point in Bishop score; and (B2) complete non-responders - women who did not respond at all and required an additional ripening method (extra-amniotic balloon).

2.3. Procedures and definitions

Gestational age was calculated according to last menstrual period and confirmed by the first trimester ultrasound with a fetal crown-rump length measurement. Post-date pregnancy was defined as gestational age over 40 + 0 weeks [12].

According to our departmental protocol, women with low-risk post-date pregnancies are offered induction of labor when active labor is not observed and there is no contraindication for vaginal delivery. Vaginal examination is performed to assess cervical status and determine the Bishop score [4] based on the following parameters: dilatation, effacement, consistency, location, and position. A Bishop score <6 mandates cervical ripening. The most common ripening method used in our center is the PROPESS vaginal delivery system (Ferring Pharmaceuticals, Saint-Prex, Switzerland), consisting of a 10 mg slow-release insert of PGE2 (dinoprostone) which is introduced into the posterior vaginal fornix. After the insert is placed, the patient is evaluated for regular contractions, rupture of membranes, and suspected fetal compromise every 12 h, up to 24 h. The assessment includes a nonstress test and, if indicated, vaginal examination. The PROPESS is removed at the 24-h mark. It may be removed in the event of non-reassuring fetal heart rate, or tachysystole (≥5 contractions in 10 min), prior to achieving cervical ripening. Women who achieve cervical ripening at or prior to 24 h of treatment are admitted to the labor and delivery floor. Women who do not achieve cervical ripening and whose membranes do not rupture undergo second-line ripening by transcervical insertion, of a 22 F Foley balloon inflated with 60 ml saline. The catheter is attached to the patient's thigh with traction and removed after 24 h, or earlier if spontaneous expulsion or rupture of the membranes occurs. The patient is then transferred to the labor and delivery floor.

The augmentation process on the labor and delivery floor is the same for all women. After the patient is transferred, labor is augmented by artificial rupture of the membranes, followed by oxytocin infusion, starting with 2mU and increasing by 2mU every 30 min.

Failed induction of labor is defined as a failure to go into the active stage of labor at least 18 h after rupture of the membranes, with regular contractions every 2–3 min, lasting at least 30 s.

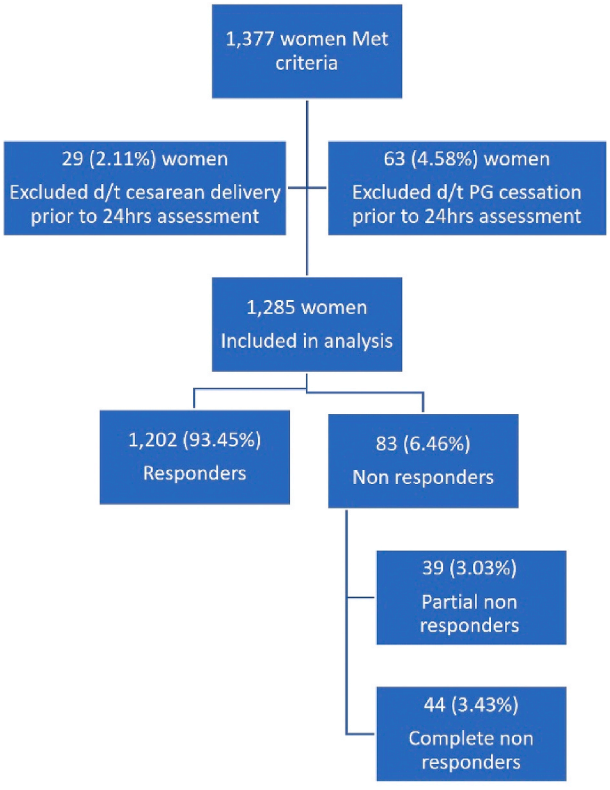
Failure to progress in labor is defined as an unchanged cervix in active labor more than 4–6 h after rupture of the membranes and establishment of adequate contractions.

Arrest of descent is defined as a failure of the presenting part to descend in the pelvis after 2 h of pushing for multiparous women and 3 h of pushing for nulliparous women.

2.4. Data collection and outcome measures

Data were obtained from the electronic medical records, including the perinatal database, maternal-fetal clinic records, and delivery ward charts. The following variables were recorded: maternal age, pre-pregnancy body mass index (BMI), parity, mode of conception, gestational age at delivery, and maternal co-morbidities. Labor characteristics such as anesthesia, meconium-stained amniotic fluid, and neonatal birthweight were recorded as well. The primary outcome measure of the study was the rate of vaginal delivery. Secondary outcome measures were rates of adverse composite maternal and neonatal outcomes. Adverse maternal composite outcome was defined as the presence of any of the following: intrapartum fever, obstetric anal sphincter injuries, postpartum hemorrhage, and need for transfusion of blood products. Adverse neonatal composite outcome was defined by the presence of any of the following: 5-min Apgar score <7, asphyxia, neonatal intensive care unit (NICU) admission, need for phototherapy, and composite respiratory complications (transient tachypnea of the newborn, respiratory distress syndrome, oxygen enrichment, mechanical ventilation, and/or meconium aspiration syndrome).

Postpartum hemorrhage was defined as on of the above: blood loss greater than 500 ml in a vaginal delivery or 1000 ml in a



Study Design

Overall, 1,377 women at post-dates (≥40w0d) were admitted for cervical ripening with a PGE-2 slow-release vaginal insert (PROPESS). Of those 92 (6.68%) were excluded from the study according to following: 29 (2.11%) were excluded from the study as they underwent a cesarean delivery prior to the 24 hours PROPESS assessment d/t various reasons; 63 (4.58%) were excluded from the study as the process was ceased for them prior to the 24 hours assessment. Thus 1,285 women were included in the final analysis. Of those, 1202 (93.45%) achieved cervical ripening with PROPESS and 83 (6.46%) did not. Of the 83 who did not achieve cervical ripening- 39 (3.03%) were partial non responders and 44 (3.43%) were complete non responders who required a second ripening method with extra amniotic balloon.

Fig. 1. Study design.

cesarean delivery; hemodynamic instability or signs of hypovolemia attributed to blood loss.

2.5. Statistical analysis

Statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA). Student t-test was used to compare continuous variables between groups, and $\chi 2$ test was used to compare categorical data. A probability value < 0.05 was considered significant. Multivariate logistic regression was performed to detect independent risk factors for cesarean delivery after controlling for possible confounders, including maternal age, overweight and obesity, and nulliparity. To predict the risk of cesarean delivery, a model combining maternal age, overweight and obesity, and nulliparity with response to ripening was constructed, and the area under the receiver operating characteristic (ROC) was calculated.

2.6. Ethics approval and consent to participate

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Rabin Medical Center (approval number RMC-0224-18). The IRB waive the need for informed consent due to the retrospective design of the study.

3. Results

During the study period, 1377 women meeting the inclusion criteria were admitted for cervical ripening with the PROPESS due to post-date pregnancy. Excluded from the analysis were 92 women (6.68%): 29 (2.11%) in whom cesarean delivery was performed before the 24-h cervical assessment, and 63 (4.58%) in whom PGE2 treatment was stopped prior to completion. The remaining 1285 women formed the final cohort: 1202 (93.54%) responded to the induction process (group A) and 83 (6.46%) did not (group B; Fig. 1). Non-responders were further divided into partial non-responders (n = 39, 3.03%) and complete non-responders (n = 44, 3.43%).

On group comparison, the patients who responded to the cervical ripening process were significantly younger than the non-responders (30.03 years vs 31.73 years, $P = 0.015$) and had a significantly lower nulliparity rate (50.99% vs 77.11%, $P < 0.001$). They also had a lower rate of overweight/obesity, but the difference did not reach statistical significance (18.72% vs 26.51%, $P = 0.11$). There were no between-group differences in the other background parameters evaluated (Table 1).

Labor characteristics, including rates of use of anesthesia, intrapartum fever, and meconium-stained amniotic fluid were similar in the two groups (Table 2).

The responders had a significantly higher rate of vaginal delivery than the non-responders (96.51% vs 66.27%, $P < 0.001$), and their intrapartum rate of cesarean delivery was significantly lower (3.49% vs 33.73%, $P < 0.001$). The main reason for intrapartum cesarean delivery in the non-responder group was failed induction of labor (Table 2).

The non-responders had a higher rate than the responders of adverse maternal composite outcome (24.10% vs 12.81%, $P = 0.031$), mostly attributable to postpartum hemorrhage (Table 2), and adverse neonatal composite respiratory outcome (6.02% vs 1.33%, $P = 0.009$). The groups did not differ in any other neonatal parameters including NICU admission, birthweight, 5-min Apgar score, phototherapy, and asphyxia (Table 2).

A sub-analysis was performed between the two subgroups of non-responders: partial non-responders (did not require a second method of cervical ripening but did not reach an adequate Bishop score, group B1) and complete non-responders (required a second ripening method with an extra-amniotic balloon catheter, group B2). The complete non-responders showed a trend toward even higher rates of intrapartum cesarean delivery (36.36% vs 30.77%, $P = 0.819$). The finding, however, was not statistically significant, most probably because of the small sample size.

On multivariate logistic regression analysis adjusted for maternal age, nulliparity, and overweight or obesity, failure to respond to the cervical ripening process was an independent risk factor for intrapartum cesarean delivery (aOR 11.90, 95% CI 6.13–23.25, $P < 0.001$) (Table 3). Other risk factors identified were maternal age above 30 years (aOR 2.30, 95% CI 1.24–4.27, $P = 0.008$) and nulliparity (aOR 9.90, 95% CI 4.13–23.81, $P < 0.001$) (Table 3).

A model was constructed combining non-response to PGE2, maternal age >30 years, BMI $\geq$25 kg/m^2, and nulliparity to predict the risk for intrapartum cesarean delivery. The area under the curve on ROC analysis was 0.73 (Fig. 2). Women who were nulliparous,

Table 1
Maternal baseline characteristics.

Characteristics	Responders (n = 1202, 93.54%)	Non-responders (n = 83, 6.46%)	*P* value
Age, years	30.03 ± 5.02	31.73 ± 4.96	**0.015**
Pre-pregnancy BMI ≥25 kg/M^2	225 (18.72)	22 (26.51)	0.11
Nulliparity	613 (50.99)	64 (77.11)	< **0.001**
ART	28 (2.33)	1 (1.20)	1.0
Gestational age at delivery, weeks	41.21 ± 0.50	41.33 ± 0.53	**0.003**
GDM	71 (5.91)	4 (4.82)	1.0

Data are presented as mean ± standard deviation for continuous variables and number (percent) for categorical variables.
BMI, body mass index; ART, assisted reproductive technology; GDM, gestational diabetes mellitus.

Table 2
Maternal and neonatal outcomes.

Outcomes	Responders (n = 1202, 93.54%)	Non-responders (n = 83, 6.46%)	*P* value
Labor characteristics			
Epidural	776 (64.56)	56 (67.47)	0.411
Meconium	198 (16.47)	12 (14.46)	1.0
Intrapartum fever	19 (1.58)	3 (3.61)	0.194
Vaginal delivery	1160 (96.51)	55 (66.27)	< **0.001**
Cesarean section	42 (3.49)	28 (33.73)	< **0.001**
Failed IOL	6 (14.29)	15 (53.57)	< **0.001**
Failure to progress	30 (71.43)	11 (39.26)	**0.002**
Other	6 (14.29)	2 (7.14)	0.07
Birthweight, g	3464.94 ± 382.04	3480.36 ± 351.04	0.599
LGA	100 (8.32)	6 (7.23)	1.0
SGA	41 (3.41)	2 (2.41)	1.0
Maternal complications			
Composite[a]	154 (12.81)	20 (24.10)	**0.031**
OASIS	10/1160 (0.86)	1/55 (1.82)	0.56
PPH	114 (9.48)	14 (16.87)	0.094
Blood products	11 (0.92)	2 (2.41)	0.229
Neonatal complications			
Composite[b]	128 (10.65)	16 (19.28)	0.504
5 min APGAR <5	8 (0.67)	1 (1.2)	0.375
Umbilical cord pH < 7.2	63 (5.24)	4 (4.82)	0.814
NICU	34 (2.83)	4 (4.82)	0.304
Phototherapy	7 (0.58)	2 (2.41)	0.11
Respiratory composite[c]	16	5	**0.009**

Data presented as mean ± standard deviation and n (%).
IOL, induction of labor; LGA, large for gestational age; SGA, small for gestational age; OASIS, obstetric anal sphincter injuries; PPH, postpartum hemorrhage; NICU, neonatal intensive care unit.
[a] Maternal composite: OASIS, PPH, need for blood transfusion, and/or intrapartum fever.
[b] Neonatal composite: 5-min APGAR <7, umbilical cord pH < 7.2, NICU admission, respiratory composite, and/or phototherapy.
[c] Neonatal respiratory composite: apnea, transient tachypnea of newborn, respiratory distress syndrome, oxygen enrichment, mechanical ventilation, and/or meconium aspiration syndrome.

Table 3
Adjusted odds ratio for cesarean delivery.

Variables	Adjusted odds ratio	95% confidence interval	*P* value
Non-responder	11.90	6.13–23.35	< **0.001**
Age >30 years	2.30	1.24–4.27	**0.008**
BMI ≥25 kg/m^2	1.08	0.45–1.91	0.83
Nulliparous	9.90	4.13–23.81	< **0.001**
BMI, body mass index			

older than 30 years, with BMI ≥25 kg/m^2 who failed to achieve cervical ripening with prostaglandins had a 60% chance of undergoing intrapartum cesarean delivery due to either failed induction or failure of labor to progress.

4. Discussion

4.1. Main findings

The present study demonstrated that failure to achieve cervical ripening was a significant independent risk factor for intrapartum cesarean delivery. Women who did not respond to the PROPESS induction process were older than the responders and more frequently nulliparous and had a tendency towards a higher BMI.

5. Results

Induction of labor occasionally fails at the initial phase of cervical ripening. In our study, the overall failure rate was 6.46%, lower than the 10%–30% reported in the literature [8,13,14]. A possible reason for the low rate might be our use of a single ripening method (PROPESS) and, more importantly, a single indication for cervical ripening (post-date gestation), with a clear and clinically relevant definition of failed ripening. Whereas some studies defined the outcome of ripening as failure to deliver vaginally within 24 h of induction initiation, we defined it as failure to achieve a minimal Bishop score within 24 h of treatment onset.

Several studies previously described predictors for cervical ripening failure. Melamed et al. [6] and Pevzner et al. [15], in

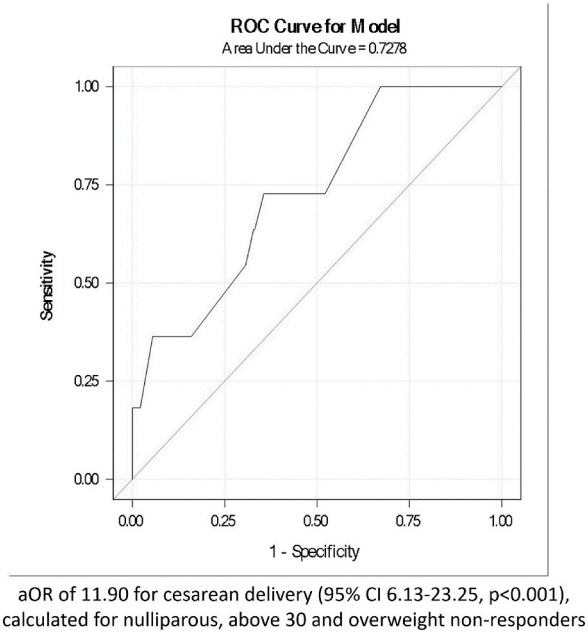


Fig. 2. ROC curve analysis.

concordance with our results, demonstrated that older, nulliparous, overweight women have higher PGE2 failure rates. The explanation for these findings may lie in an important, albeit rarely addressed, issue, namely, the pharmacokinetics of the prostaglandins used for labor induction. Prostaglandins are detected in the plasma after vaginal administration, indicating systemic absorption via the vaginal mucosa. The distribution differs depending on the use of gel or tablets [16]. In addition, current treatment protocols and dosage are based on clinical response (i.e., cervical softening, dilatation, and uterine contractions) rather than plasma level titrations, but use of slow-release vaginal inserts, unlike gels and tables, precludes dosage adjustment by clinical response. Hence, the difference between studies in the response to cervical ripening may be associated with differences in prostaglandin absorption, distribution, and excretion, all of which may, in turn, be influenced by maternal age and weight.

As for nulliparity, it is well established that nulliparity is a risk factor for prolonged labor [17], need for operative vaginal delivery, and intrapartum cesarean delivery [18–20]. Our results support these findings and perhaps imply that for nulliparous women, the treatment protocol should be modified to allow for longer exposure to the medications or a combined method for cervical ripening should be used.

Other previous studies tried to offer second-line treatment in the event of cervical ripening failure. However, the results were inconclusive, and the treatments varied, including extra-amniotic Foley balloon catheter, repeated prostaglandin application, and cesarean delivery.[7–11]

5.1. Clinical implications

Our study found women who fail to respond to cervical ripening have an idependt risk factor to end up with an intrapartum cesarean delivery. Women who are nulliparous, older (>30 years), and overweight women (BMI >25) and fail to respond to prostaglandins cervical ripening, have up to a 60% chance of intrapartum cesarean delivery. This finding should not be overlooked when counseling women for induction continuation or cessation at the decision-making point.

5.2. Research implications

Accurate identification of patients with post-date pregnancy who have a high likelihood of responding to PGE2 cervical ripening will improve physician decision-making at critical points in the induction process. Further studies are needed to investigate the risks and outcomes of response failure to first-line treatment and to develop efficient, uniform second-line methods of induction in this patient group. Future studies should focus onto assessing plasma level of prostaglandins among women with successful versus failed induction of labour with the aim of adjusting the dose response or deciding on switching to an alternative method.

5.3. Limitations and strengths

Our study is limited by its retrospective design. First, we could not account for some probable confounders, such as gestational weight gain. Second, we were unable to detect significant differences between complete and partial non-responders owing to the small

sample size.

Be that as it may, our study has several strengths. We included a relatively large cohort undergoing standardized practice using a single pharmacological agent for a solitary indication in a single tertiary center. We focused on a common, but not well resolved dilemma regarding the outcomes of failed cervical ripening.

6. Conclusions

Women with a post-date pregnancy who fail to achieve cervical ripening within 24 h of onset of PGE2 treatment have not only higher rates of cesarean delivery due to lack of response to labor induction and augmentation efforts, but also an increased risk for maternal and some neonatal adverse outcomes. This is particularly significant in older, nulliparous patients.

Author contribution statement

Alexandra Berezowsky: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Gil Zeevi: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Eran Hadar: Conceived and designed the experiments; Wrote the paper.
Eyal Krispin: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Additional information

Supplementary content related to this article has been published online at [URL].

The study at a glance

A. Why was the study conducted?

To characterize patients who fail to respond to cervical ripening with prostaglandins and evaluate their risk of cesarean section due to labor dystocia.

B. What are the key findings?

Failure to respond to cervical ripening with prostaglandins is an independent risk factor for a cesarean delivery due to labor dystocia. Older, primiparous patients with elevated body mass index who require a second method of cervical ripening after a failed response to prostaglandins have up to a 60% chance of undergoing cesarean section due to labor dystocia and should be appropriately counseled.

C. What does this study add to what is already known?

The study adds data on the patient group at risk of failure of cervical ripening and elaborates the independent consequences of this failure. The findings will aid clinicians in providing evidence-based counseling to patients and in selecting the right path at decision-making points in the induction process.

Acknowledgements

We thank Dr Lior Topaz for helping us with the data collection process.

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