INTRODUCTION

Induction of labor is a procedure that is widely used in modern obstetrics, usually performed when continuing the pregnancy poses a risk to fetal or maternal safety. The rate of this procedure has increased worldwide; 18% of women in the USA and nearly one-third of women in the UK currently have their labor induced.\(^1\)\(^2\) Cervical ripening can be carried out by a variety of methods,\(^3\)\(^4\) mainly

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CERVICAL RIPENING WITH MULTIPLE MEDICAL OR COMBINED INDUCTION METHODS: RISKS OF SUBSEQUENT PRETERM BIRTH IN NULLIPAROUS WOMEN

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Abstract

Objective: To determine the impact of combined medical and medical/mechanical methods for cervical ripening on the risk of preterm birth in subsequent pregnancy, in nulliparous women.

Methods: A retrospective cohort study of nulliparous women with term singleton gestations induced by single or combined methods at one center who had their subsequent second birth in the same center. Study groups were compared with a control group of nulliparous women not induced. The primary outcome was risk of preterm labor in the second consecutive birth. Secondary outcomes included neonatal and maternal complications.

Results: Cohort included 1277 nulliparous women who underwent cervical ripening by single or combined methods. The study group consisted of 942 women induced by one dose of prostaglandin E\(_2\), 248 women induced by combined methods, and 87 women induced by a mechanical method. The control group consisted of 3903 women. Demographic data of the groups were comparable. Rates of spontaneous preterm birth and early spontaneous preterm birth in the subsequent births did not differ between the groups.

Conclusion: Cervical ripening with combined methods or multiple medical methods did not increase the rate of subsequent spontaneous preterm births in nulliparous women or change the neonatal and maternal complications rate.

KEYWORDS
combined induction, double-balloon catheter, medical induction, prenatal outcome, preterm birth

1 | INTRODUCTION

Induction of labor is a procedure that is widely used in modern obstetrics, usually performed when continuing the pregnancy poses a risk to fetal or maternal safety. The rate of this procedure has increased worldwide; 18% of women in the USA and nearly one-third of women in the UK currently have their labor induced.\(^1\)\(^2\) Cervical ripening can be carried out by a variety of methods,\(^3\)\(^4\) mainly
depending on the Bishop score. Unfavorable cervix is usually induced medically or by mechanical devices. Prostaglandin drugs, dinoprostone and misoprostol, are the most common preparations used for cervical ripening. In the mechanical method, single- or double-balloon devices are widely used. The proposed mechanism of the double balloon is to apply internal and external pressure on the internal and external cervical os simultaneously, whereas in single balloon the cervical ripening is achieved by direct expansion of the balloon on the cervix and lower uterine segment. In addition, the balloon catheter enhances prostaglandin secretions, which are probably also engaged in cervical ripening.

Preterm birth (PTB) is a serious obstetrics burden responsible for a diversity of obstetrics complications, including almost half of congenital neurologic adverse sequelae and the majority of fetal deaths. Cervical weakness, either congenital or following cervical trauma, is a risk factor for cervical insufficiency, which increases the risk of PTB. Numerous studies have addressed the impact of mechanical or medical induction on risk of PTB in the subsequent pregnancy, but the impacts of combined or repeated doses on subsequent pregnancy have not yet been studied. There is a hypothetical risk that the mechanical stretching of the cervix by multiple medical doses or combined induction methods can lead to cervical tissue damage and potentially increase the risk of PTB in a subsequent pregnancy. In this study we aimed to test whether combined induction methods or multiple doses of prostaglandins could lead to cervical insufficiency, and increase the risk of PTB in the subsequent pregnancy.

2 | MATERIALS AND METHODS

This is a retrospective case–control study of nulliparous pregnant women who delivered in our tertiary care center during 2009–2019. The local ethics committee approved this study (RMB-0310-19). Our study included three groups of women who underwent the following: (1) single round of pharmacologic induction, (2) multiple inductions (i.e. two or more rounds of pharmacologic induction or both pharmacologic and mechanical induction), and (3) mechanical induction; as well as a control group (4) no intervention.

Data were extracted from the hospital’s computerized database and included maternal age, diseases, and both postpartum and neonatal parameters. Data were validated by the authors, all registered MDs, by randomly reviewing the accuracy of data extracted from the written charts. The study groups included nulliparous women who underwent induction of labor by mechanical or medical cervical ripening methods, and delivered their subsequent labor in our medical center. The groups were computer matched to a control group that included nulliparous women who did not undergo induction of labor by any type of cervical ripening method and subsequently delivered in our hospital. Matching ratio was 1:3 in favor of the control group. To minimize the effect of previous pregnancy events on the rate of PTB in a future pregnancy, we only included nulliparous women in our study.

What are the novel findings of this work?

The present study addresses the impact of combined medical and combined medical plus mechanical induction of labor on the risk of preterm birth in a subsequent pregnancy in nulliparous women scheduled for labor induction.

What are the clinical implications of this work?

Our findings highlight that induction of labor by either combined medical or combined medical plus mechanical methods, did not increase the risk of preterm birth in a subsequent delivery by the suspected mechanism of cervical trauma. Physicians should be informed that this approach is safe with no anticipated increase in maternal or neonatal risk.

This study was performed as per the ethical standards set by the Ethical Committee for the human studies, following the 1964 Declaration of Helsinki. The study was approved by the Ethics Committee for human study, Rambam Health Care Campus (Approval number: 0310-19-RMB, Dated June 3, 2019).

Included in our study were pregnant women scheduled for cervical ripening using prostaglandin or double-balloon catheter (Cook Cervical Ripening Balloon, Cook Medical, Bloomington, IN, USA; administered according to the manufacturer’s guidelines). The stated volume (80 ml) of fluid was placed above and below the cervical os. Induction of labor was performed based on department protocol; all women with low Bishop score were induced by prostaglandin or double-balloon catheter. At 24 h following labor induction, pregnant women induced with double balloon without cervical dynamic changes in vaginal examination were treated with prostaglandin, and the labor induction process was continued by additional doses of prostaglandin or double-balloon catheter.

Inclusion criteria included term pregnant women who had labor induction with cervical ripening, with either a medical or a mechanical method. Exclusion criteria included multiple gestation, intrauterine fetal death, and prenatally diagnosed fetal anomalies not compatible with life.

The primary outcome of the study was the rate of PTB in the subsequent labor after cervical ripening by combined methods or multiple doses of prostaglandins.

Secondary outcomes were mode of delivery and additional maternal and neonatal adverse events.

Descriptive statistics in terms of mean, standard deviation, median, interquartile range, and percentages were calculated for all parameters in the study. Normal distribution of the continuous parameters was tested by Kolmogorov–Smirnov test. The results of this test were used in subsequently conducting analysis of variance or Kruskal-Wallis test with multiple comparisons made among groups. Differences between categorical parameters were tested by χ² analysis. Variables statistically significant at the initial analyses,
such as underlying maternal medical conditions, maternal age, and body mass index (calculated as weight in kilograms divided by the square of height in meters) were evaluated in the final multivariable regression model. The threshold of statistical significance was a \( P \) value <0.05. SPSS, version 18 (IBM Corp., Armonk, NY, USA) was used for data management and statistical analysis.

3 | RESULTS

The 1277 women included in the study group were matched with 3903 women in the control group. The study group included 942 women in the single round of pharmacologic induction group, 248 in the multiple attempts at induction group (two or more rounds of pharmacologic induction and either pharmacologic or mechanical induction methods), and 87 in the mechanical induction group. Comparisons of demographic data and clinical characteristics among the groups are presented in Table 1.

There were no significant differences in rates of spontaneous PTB in the study groups compared with the control group in the index pregnancy (4.9% in the single dose group, 2% in the multiple induction group, 6.9% in the mechanical induced group, and 4.3% in the control group). Moreover, the rates of early PTB (<34 weeks) did not differ among the groups (Table 2). After adjusting for confounding variables, using multivariate logistic regression, the rates of subsequent PTB remained non-significant.

The control group had the highest rate of vaginal delivery at first birth (63%, \( P < 0.0001 \)) compared with the study groups, single round of pharmacologic induction group (57%), combined induction group (57%), and mechanical induction group (57.5%).

### TABLE 1 Demographic data: First labor

|                          | 1. Single medical induction; \( N = 942 \) | 2. Multiple inductions; \( N = 248 \) | 3. Mechanical induction; \( N = 87 \) | 4. Control; \( N = 3903 \) | \( P \) value (compared with control)\(^b\) |
|--------------------------|------------------------------------------|--------------------------------------|----------------------------------|--------------------------|---------------------------------|
| Maternal age at first labor, y | 27.48 ± 4.24                             | 27.68 ± 4.09                         | 28.12 ± 5.34                    | 27.39 ± 4.30             | 0.27                            |
| Maternal BMI             | 30.5 ± 4.8                               | 32.13 ± 6.47                         | 30.6 ± 4.9                      | 28.69 ± 4.57             | <0.001                          |
| Indication for induction of labor |                                        |                                      |                                  |                          |                                 |
| Maternal                | 664 (70.5%)                              | 175 (71%)                            | 44 (51%)                        | Irrelevant               |                                 |
| Fetal                   | 278 (29.5%)                              | 73 (29%)                             | 43 (49%)                        | Irrelevant               |                                 |
| Maternal illness during pregnancy\(^c\) | 84 (9%)                                  | 26 (10.4%)                           | 5 (6%)                          | 714 (18.3%)              | <0.001                          |
| Gestational age at delivery at the first labor, week | 40.3 ± 1.74                             | 40.12 ± 1.85                         | 40.1 ± 1.5                      | 39.7 ± 2.04              | 1 vs 4; \( P < 0.001 \) |
| Mode of delivery         |                                          |                                      |                                  |                          | 2 vs 4; 0.013                   |
| Spontaneous             | 537 (57%)                                | 118 (48%)                            | 50 (57.5%)                      | 2475 (63%)               | <0.001                          |
| Vacuum-assisted         | 160 (17%)                                | 37 (15%)                             | 14 (16%)                        | 623 (16%)                | 0.83                            |
| Cesarean section        | 245 (26%)                                | 93 (37%)                             | 23 (26%)                        | 800 (21%)                | <0.001                          |
| Maternal complications at delivery\(^d\) | 76 (8.1%)                                | 18 (7%)                              | 11 (12.6%)                      | 339 (8.7%)               | 0.43                            |
| Fetal outcome           |                                          |                                      |                                  |                          |                                 |
| Apgar score at 1 min >7 | 865 (92%)                                | 229 (92%)                            | 81 (93%)                        | 3690 (95%)               | 0.006                           |
| Apgar score at 5 min >7 | 932 (99%)                                | 245 (99%)                            | 86 (99%)                        | 3849 (100%)              | 0.26                            |
| NICU transfer           | 29 (3%)                                  | 11 (4.4%)                            | 4 (5%)                          | 206 (5.3%)               | 0.075                           |
| Interpregnancy interval, months | 29.4 ± 13.6                              | 30.47 ± 14.56                        | 20.7 ± 6.4                      | 27.9 ± 12.0              | 1 vs 4; 0.012 | 2 vs 4; 0.018 | 3 vs 4; <0.001 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); n, number; NICU, neonatal intensive care unit; NS, not significant.

\(^a\)Values are presented as mean ± standard deviation or as n (%).

\(^b\)\( P < 0.05 \) is considered significant.

\(^c\)Chronic hypertension, gestational and pregestational diabetes, asthma, and endocrine, renal, neurologic, hematologic, and psychiatric disorders.

\(^d\)Retained placenta, postpartum hemorrhage, shoulder dystocia and third- and fourth-degree perineal tears.
cesarean deliveries in the first pregnancy in the multiple induction group was significantly higher compared with the control group (37% vs 21%, \( P < 0.0001 \)). We did not observe any significant maternal or neonatal differences in secondary outcomes.

**4 | DISCUSSION**

In the current study we tested the impact of repeated medical or combined methods of labor induction on the risk of PTB in a subsequent pregnancy among nulliparous women. Our data indicated that repeated attempts, either medical or combined methods, did not increase the rates of PTB in a subsequent pregnancy.

Cervical trauma presents an important reason for cervical incompetence, leading to premature delivery. Numerous studies reported comparable results, concluding that mechanical or medical induction of labor\(^{10-13}\) does not increase the risk of premature labor in subsequent pregnancy. Although, these studies addressed the same research question, no data were available to answer the question of whether repeated attempts or combined methods of labor induction in nulliparous women further weaken the cervix integrity and increase the risk of PTB in a subsequent pregnancy. Furthermore, heterogeneity exists among these studies in term of parity, type of catheters used, volume of fluid placed in the catheter, and whether traction was applied. It is feasible to postulate that iatrogenic cervical ripening may potentially manipulate the normal integrity and strength of the cervix, similar to cases of induced abortion, dilatation and curettage, and cone biopsy, which have a negative effect on cervical competence,\(^{11}\) preventing the cervix from functioning adequately in future pregnancies, which could lead to spontaneous PTB. Such assumptions, addressing the combined induction methods or multiple doses of prostaglandins, had not been tested before.

Zafran et al.\(^{11}\) pointed to several differences found in studies reporting that induction of labor did not increase the rate of premature birth in subsequent pregnancy, such as: (a) the volume of the fluids placed in the catheter and type of catheter placed in the cervix. To strengthen our study, we included only nulliparous women and double-balloon catheter. In accordance with reports claiming that the volume of fluid used to inflate a single-balloon catheter plays an important role in the success of cervical ripening,\(^{13-15}\) we placed a high but set volume of 80 mL of fluid above and below the internal os. Considering factors that increase the cervical weakness, it is rational to assume that repeated medical induction attempts or combined methods (medical and mechanical), where a large volume of fluids is placed in the balloon above and below the internal os, could potentially lead to more cervical tissue injury and therefore have a negative effect on cervical integrity. Our data did not validate this assumption; this approach was shown to be safe with no increase in the rate of premature labor in subsequent pregnancies among nulliparous woman compared with those in the control group.

Almost 250 nulliparous women were treated with multiple doses of prostaglandin or combined medical and mechanical methods, with no cases of PTB before 34 weeks observed in this group. The rate of late PTB between 34.0 and 36+6 weeks gestation was 3.1% in the control group, compared with 2.9%, 1.5%, 6.1%, and 4.6%, in the single medical induction, multiple doses, combined mechanical and medical, and mechanical and mechanical induction groups, respectively. Examining the group induced by prostaglandin and double-balloon catheter, and the double-balloon induction group, we observed a slightly increased rate of PTB during 34–36+6 weeks gestation compared with the other groups. We assume that this difference could be attributed, in part, to the shorter pregnancy interval observed in these two groups. Previous studies have found that short intervals between the birth of one child and subsequent pregnancy are associated with an increased risk of PTB\(^{16,17}\); nevertheless, this slight increase was not statistically significant. Moreover, the neonatal secondary outcomes in term of admission to neonatal intensive care unit or Apgar scores were similar in all groups.

In this study, the mechanical group was induced only by double-balloon catheter. In spite of the large volume of fluid placed in the catheter and the use of traction, comparable with other studies, we did not observe a significantly increased rate of PTB. The similarity in PTB in all groups, regardless of the induction method, favors the hypothesis that the main mechanism of cervical ripening by the double balloon could be related to prostaglandin release from decidual separation as in single-balloon catheters,\(^{7}\) rather than by its mechanical effects.

We observed that cesarean delivery was significantly higher in the multiple induction group compared with the control (Table 1).

### TABLE 2 The relation between type of induction to gestational age at second delivery

|                   | Single medical induction; \( N = 942 \) | Multiple inductions; \( N = 248 \) | Mechanical induction; \( N = 87 \) | Control; \( N = 3903 \) | \( P \) value (compared to control group)\(^{3}\) |
|-------------------|----------------------------------------|---------------------------------|---------------------------------|-------------------|--------------------------------------------------|
| Gestational age at second delivery, wk | 39.8 ± 2.02                        | 40.03 ± 1.46                    | 39.55 ± 2.40                    | 39.83 ± 1.87      | 0.26                                              |
| Delivery before 34 wk | 15 (1.6%)                           | 0                               | 2 (2.3%)                        | 48 (1.2%)         | 0.31                                              |
| Delivery between 34\(^{+6}\) wk | 27 (2.9%)                           | 6 (1.23%)                       | 4 (4.6%)                        | 119 (3.1%)        | 0.77                                              |
| Delivery after 37 wk | 897 (95.5%)                         | 242 (98.77%)                    | 81 (93.1%)                      | 3725 (95.7%)      | 0.77                                              |

Note. Values are presented as \( n \) (%).
\( ^{3} P < 0.05 \) is considered significant.
This difference can be attributed to the following: first, we assume that in the combined induction group more women were exhausted, as the induction process extended to several days compared with the other groups. We believe that exhaustion played an important role in the decision of delivery mode. Furthermore, this group included high-risk pregnant women who underwent labor induction, which can raise the risk of cesarean and instrumental deliveries.

Although this study has the limitation of being retrospective, it has several strengths. It is the first study testing the hypothesis that induction with multiple doses of prostaglandin or with combined methods could have a negative impact on cervical competency, which could lead to PTB in a subsequent pregnancy. This is a large cohort study, using data from one medical center, thus minimizing practice variations in labor induction and delivery protocols. Moreover, we included only nulliparous women to minimize differences among groups.

We conclude that nulliparous women scheduled for labor induction with multiple prostaglandin doses or combined medical plus mechanical methods did not have increased risk of PTB in their subsequent pregnancy.

CONFLICT OF INTEREST
The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by NF and NK. The first draft of the manuscript was written by NK and NF, and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT
Research data are not shared.

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