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The Effect of Using Dexamethasone Tablets Vaginally for Improving Cervical Bishop Score in Nulliparous Pregnant Women: A Randomized Clinical Trial

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ABSTRACT

Background: Cervix ripening and labor induction are common interventions in obstetrics. For optimal maternal health, labor may be induced under certain situations to improve fetal survival outcomes. Labor induction of an unripe cervix can lead to complications; therefore, several approaches can facilitate the ripening process.
Methods: This randomized clinical trial was a triple-blind study that involved 84 pregnant nulliparous women enrolled between October 2019 and June 2021 in the labor ward of Kamali Hospital, Karaj, Iran. The pregnant women in the study underwent labor induction and were randomized into 2 groups: 1 group received vaginal dexamethasone and the other group was given a placebo.
Results: There was no significant difference between the groups regarding maternal age, demographic characteristics, and initial Bishop score. The median second Bishop score (6 hours after intervention) was 3.5 in dexamethasone recipients and 3 in placebo recipients ($P=0.48$). The median labor latent phase duration was 4 hours in dexamethasone recipients and 5 hours in placebo recipients ($P=0.57$).
Conclusions: This randomized clinical trial demonstrated that administering dexamethasone tablets vaginally did not significantly improve cervical Bishop scores. (*Curr Ther Res Clin Exp*. 2023; 84:XXX–XXX). ClinicalTrials.gov identifier: NCT05070468.

Introduction

Inducing labor can be required as a therapeutic option. This requires stimulating uterine contractions before the spontaneous onset of labor. The most common indications for labor induction may include gestational or chronic hypertension, severe fetal growth restriction, preeclampsia, eclampsia, gestational diabetes, and postterm pregnancy. Ending a pregnancy can be needed when there is premature rupture of membranes without labor; oligohydramnios; or concerns related to fetal status, such as nonreassuring heart sounds.[1,2] Two primary techniques are used for cervical ripening when the cervix is unfavorable to facilitate the ripening process. The techniques can be mechanical interventions and/or the application of pharmacologic agents. Techniques like the administration of prostaglandins (eg, misoprostol), extra amniotic saline infusion, traction on the cervix with a Foley balloon catheter, and/or hygroscopic cervical dilators are as showed in Figure 1.[3,4] In nulliparous pregnant women, the cervix has a smooth, round external os. The average time from induction to delivery is between 15 and 20 hours. The cervical ripening phase can take up to 12 hours before the start of labor. Labor may be prolonged in about 10% of pregnant women, which can cause maternal and/or fetal risks. These risks include antepartum and postpartum hemorrhage and maternal and/or neonatal infection, leading to maternal, fetal, or

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Figure 1. Types of Induction of labor.

neonatal death.[5] Therefore, labor induction is essential in managing prolonged labor.[6,7]

Corticotropin-releasing hormone (CRH) is a principal regulator of the hypothalamic-pituitary-adrenal axis. CRH is released from the placenta and fetal membranes during pregnancy. Plasma CRH levels observed during labor peak during vaginal delivery (serum levels ranging from 2 to 3000 pmol/L during labor).[6,8,9] The CRH functions as the surveillance and response for the placental. This allows the fetus to detect threats to survival, and if viable, the fetus can adjust its developmental course. In 2007, O'Sullivan et al[10] reported that congenital adrenal hyperplasia in the fetus is associated with 21-hydroxylase deficiency. In addition, a late gestational rise may lead to impaired cortisol production by the fetal adrenal gland.[10]

Studies by Mohaghegh et al[2] and Latif et al[8] demonstrated that glucocorticoids like dexamethasone play a pivotal role in cervical ripening and aid labor induction. Prior studies have used dexamethasone as the chosen glucocorticoid to investigate its role in labor induction. The effect of dexamethasone on the interval length at the beginning of labor induction has been explored because its effects at the beginning of the active phase of labor.[3,8,11–14] However, there is a paucity of studies because of the high heterogeneity among pregnant women. There is a need for double-blind clinical trials to solidify the use of dexamethasone for improving cervical Bishop scores in pregnant women. As outlined, the role of corticosteroids in labor induction remains unclear. The effect of using corticosteroids vaginally for labor induction requires further investigations. Therefore, we undertook a triple-blinded randomized controlled trial (RCT) where dexamethasone was the chosen glucocorticoid used for labor induction. This study aimed to examine the effect of using dexamethasone administered vaginally and whether or not it can enhance the Bishop score and reduce the duration of the latent phase of labor in nulliparous pregnant women.

Methods

Study design

This was a triple-blinded RCT conducted in Kamali Hospital, Karaj, Iran. Kamali Hospital is among the teaching hospital subsets at Alborz University of Medical Sciences. Ethical approval was ceded to the ethical committee of Alborz University. The ethics committee approved the study protocol. The RCT was conducted between October 2019 and June 2021. It was registered as an RCT with the following ID number: IR. ABZUMS. REC1399.067. Additionally, it was registered on ClinicalTrials.gov (NCT05070468).

A sufficient sample size is required to compare the mean of the 2 groups.[15] Using a 95% CI and power of 90%, it was estimated that at least 84 participants were required. The participants were randomly divided into 2 groups of 42 as either cases or controls. The statistician assigned the participants to 2 groups using a balanced block randomization method using allocation into quadruple blocks. There were 6 modes for each case, 2 participants were in the control group, and 2 were in the intervention group. Thus, the participants were selected using the table of random numbers and assigned the numbers 1 to 6 within the groups of 4.

Study selection

The clinical trial investigators and research staff were involved in all aspects of the study design and administration of the RCT. This included screening pregnant patients to assess if they met the study inclusion criteria. These criteria required being a nulliparous Iranian woman and pregnant, having full-term gestation ($\geq$38 weeks), a singleton pregnancy, between ages 18 and 35 years, and having normal body mass index of 18.5 to 24.9. Labor induction was started in the participants when the membranes ruptured without the initiation of labor. The fetus was required to be in cephalic presentation, as shown on an ultrasound; there was a Bishop score $\leq$2 and an estimated fetal weight 2500 to 4000 g. Participants were expected to have had normal nonstress test results. If the patient's obstetrics physician indicated termination of pregnancy, they could be eligible and randomized into case and control groups by a statistician.

Exclusion criteria required the pregnant woman not to take any hormones or herbal medicines (traditional medicines), herbal/natural products, or conventional/prescribed medications during her pregnancy. Those who had the following preexisting diseases, including diabetes mellitus, hypertension, a history of obstetric complications such as preeclampsia or eclampsia, or HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, were excluded. If the pregnant individual had previously presented with fetal immobility/decelerations or a history of maternal bleeding, she could not be enrolled in the clinical trial.

To enroll eligible patients, the investigator explained the study to potential participants and asked them to consider being in the study after considering all the presented information. Written consent was obtained from all recruited patients. Once enrolled, the patients, investigators, and research staff were blinded to which groups the patients were allocated. Dexamethasone and placebo tablets were labeled Tablets A and B and delivered by the hospital pharmacist. The research staff was blinded to which tablets were the study drug. The study design required that the tablets be administered vaginally by the obstetrician. Fourteen dexamethasone tablets (0.5 mg) were administered in group A, and 14 placebo tablets were given in the same manner to the participants in group B.

Data collection

Data were collected using several tools, including interviews, observations, and a vaginal examination. The research staff designed a 2-page questionnaire that was used, and this included demographic information; that is, current age, education, job, gravidity, parity, past medical history, and body mass index. The first and second Bishop scores, the latent phase duration, and delivery and intervention type were also recorded for each patient. The collected information was initially collected on paper forms.

Clinical intervention phase

During the intervention phase, the modified Bishop score was assessed; this comprised a physical examination that evaluated the cervical length, consistency, dilation and position, and fetal head station. Per the study protocol, an obstetrician placed 14 tablets (either Tablets A or B) within the vagina during labor. The fetal heart rate was closely monitored, and any changes in the Bishop score within 6 hours were recorded. During this time, an obstetrics physician undertook the labor induction for the study patients.

There were 3 types of interventions used. The first was when the pregnant woman did not require to be induced. These individuals had effective and robust contractions during labor. Therefore, further induction of uterine contractions was not performed, and labor took its natural course. Second, labor was induced when the pregnant woman did not have strong enough or effective uterine contractions. In these situations, oxytocin was administered to aid in the induction if the patient had a Bishop score $\geq$5. Third, during labor induction in those participants assigned to the cases group, misoprostol was administered to patients with a Bishop score $<$5. Once proper cervix ripening had been achieved, this indicated the termination of misoprostol's effects. Labor induction continued with oxytocin until uterine contractions were satisfactory and strong. At each stage, from initial enrollment into the study, the onset of labor symptoms, and until the end of the latent phase of labor (4 cm dilation), the research staff followed and evaluated the individual women every 30 minutes. To further increase the reliability of the examination results, the patient's cervical dilation was established by 2 separate examiners to verify the result of the vaginal examinations.

Statistical Analysis

The statistical analysis collected data from reviewing the patient questionnaires. This was converted for analysis using the SPSS statistical software version 25.0 (IBM-SPSS Inc, Armonk, New York). A χ^2 test was used to assess any statistical hypotheses. Qualitative variables were reported as percentages and frequency. Through the evaluation of data, the findings were evaluated by using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Additional parametric and nonparametric analyses were performed. The subsequent assessment used the Mann-Whitney or *t* test (depending on the case). A *P* value $\leq$ 0.05 was considered statistically significant in this study.

Results

Study characteristics

The study recruited individual pregnant women at full-term gestation ($\geq$38 weeks). A total of 87 women were initially enrolled in this study, 3 of whom declined to take part further after enrolment. The remaining 84 pregnant women were included in the randomized clinical trial. The women were randomly grouped into 42 cases and 42 controls using a block method with a statistician's oversight. All patients completed the study except 1 pregnant woman from group A receiving dexamethasone. This patient did not complete the study because of maternal and fetal complications. Therefore, she was excluded from the intervention group and further analyses. Figure 2 represented the enrollment of this study. Table 1 illustrated the detailed comparison between the two groups.

The therapeutic approach in the 2 groups

A total of 84 patients with a median age of 24 years (IQR, 22-29 years) were included. In group A, the median age was 25 years (IQR, 22-31 years); in group B, this amount was 23 years (IQR, 21-28.25 years). A *P* value of 0.151 was reported, and no statistically significant difference was observed between the 2 groups. The majority of women in this study (41.7%) passed high school, and in terms of occupation, the majority (91.7%) were unemployed.

The mean gestational age was 40 weeks (IQR, 39-40 years); group A and group B had the same result: 40 weeks (IQR, 39-40 weeks). No statistically significant difference was seen between the 2 groups ($P = 0.691$). In group A, the 42 patients were nulliparous without a history of abortions. In group B, 40 patients were nulliparous with no history of abortions, 1 patient had a history of having had an abortion, and another patient had a history of previously having 2 abortions.

The collected data showed the 25th and 75th percentiles for the first Bishop score in groups A and B were the same. In group A, the second Bishop score was 3.3, and in group B it was 3.1.

The median of the latent phase between group A and group B was 4 and 5 hours, respectively, although in group B the time value of this variable was more; however, there were no statistical differences between both groups. Table 2 presents both groups' detailed first and second Bishop scores and latent phases.

The rate of vaginal birth was 38.1% in group A and 47.6% in group B. It was almost 10% higher in group B, but there was no statistically significant difference between them. When labor induction did not lead to vaginal childbirth, and the cervix remained unripe, a Cesarean section was performed for the safety of the fetus and the mother. A Cesarean section was performed in 61.9% of group A patients and 52.4% of group B patients. Therapeutic intervention (not induced induction with only oxytocin, induction with oxytocin and misoprostol) was almost similar in both groups, and there were no statistical differences between the 2 groups. Table 3 represents a detailed comparison of the type of delivery and the type of intervention between the 2 groups. None of these women received antenatal corticosteroids before induction for fetal lung maturity.

Discussion

Previous studies mainly used 8 mg parenteral dexamethasone.[12] In contrast, the total dose of the inserted tablets in our study

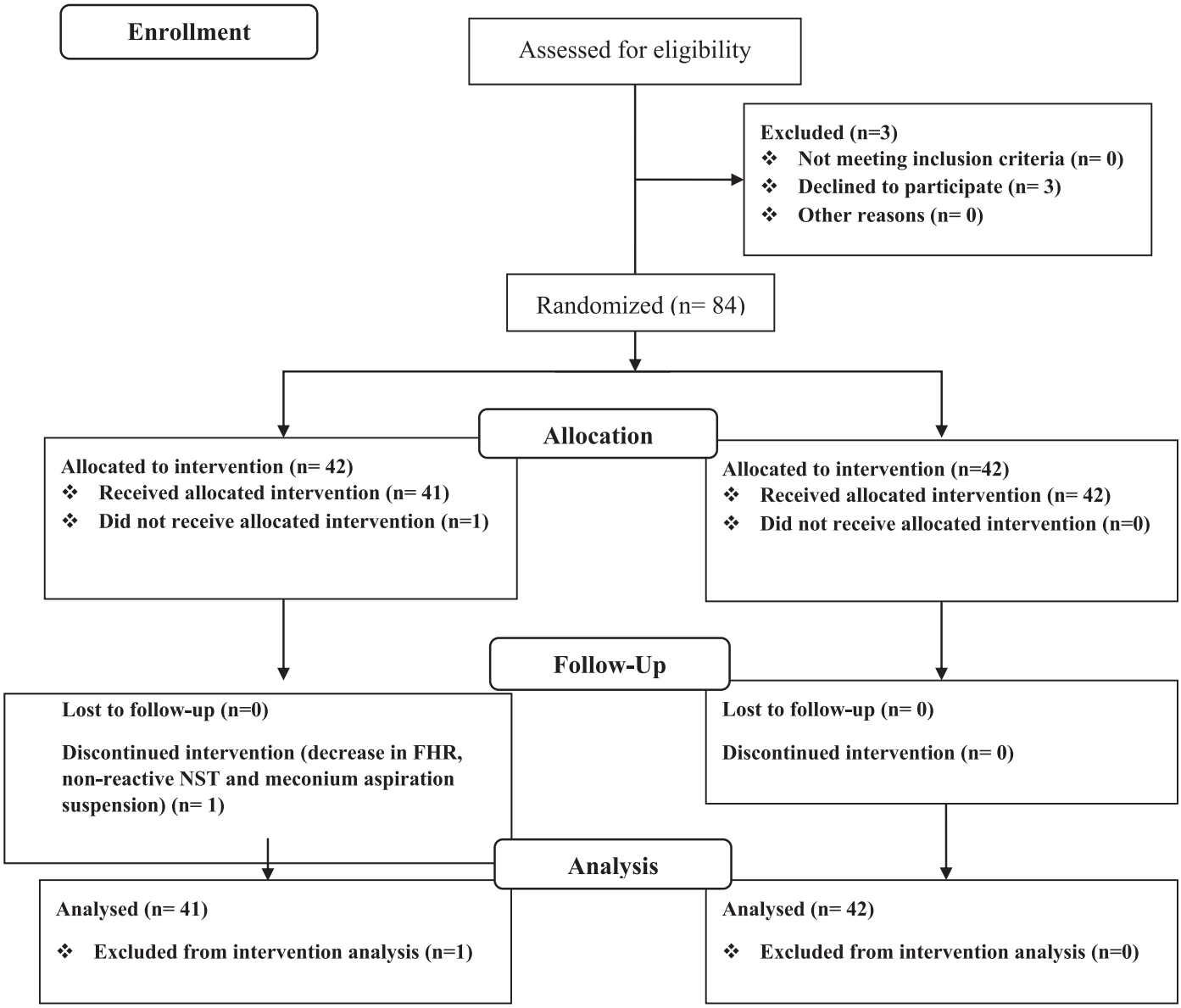

Figure 2. The enrollment of this study.

Table 1
Demographic and obstetric characteristics of participants between the 2 groups.

Parameter		Total		Dexamethasone group		Placebo group		*P* value*
		n	%	n	%	n	%	0.491
Education	Illiterate	10	11.9	4	9.5	6	14.3	
	Primary school	7	8.3	2	4.8	5	11.9	
	Junior school	21	25.0%	14	33.3	7	16.7	
	High school	35	41.7	16	38.1	19	45.2	
	Associate's degree	4	4.8	2	4.8	2	4.8	
	Bachelor's degree or higher	7	8.3	4	9.5	3	7.1	
Job	Unemployed	77	91.7	37	88.1	40	95.2	0.236
	employed	7	8.3	5	11.9	2	4.8	
				Gestational age†, y	40 (39-40)	40 (39-40)	40 (39-40)	0.937
Gravidity and parity	G1ab1	82	97.6	42	100.0	40	97.6	0.359
	G1ab2	1	1.2	0	0.0	1	1.2	
	G1ab3	1	1.2	0	0.0	1	1.2	

G ab = gravidity and abortion.
* All *P* values calculated by χ^2 test except gestational age.
† Gestational age was calculated by Mann-Whitney test and is presented as median (interquartile range).

Table 2
Comparison of Bishop score and latent phase between the 2 groups.

Parameters		Total	Dexamethasone group	Placebo group	*P* value*
First Bishop score	Median	1.0	1.0	1.0	0.618
	25th percentile	1.0	1.0	1.0	
	75th percentile	2.0	2.0	2.0	
Second Bishop score	Median	3.0	3.5	3.0	0.483
	25th percentile	2.0	2.0	2.0	
	75th percentile	4.0	4.0	4.0	
Latent phase	Median	5.0	4.0	5.0	0.571
	25th percentile	.0	.0	.0	
	75th percentiles	8.0	9.0	8.0	

* *P* value calculated by Mann-Whitney test.

Table 3
Comparison of types of delivery and types of interventions between the 2 groups.

Parameter			Dexamethasone group	Placebo group	*P* value*
Type of delivery	Vaginal birth	Number	16	20	0.378
		Percent	38.1	47.6	
	Cesarean section	Number	26	22	
		Percent	61.9	52.4	
	Total	Number	42	42	
		Percent	100.0	100.0	
Typ of intervention	Not induced	Number	10	11	0.943
		Percent	24.3	26.2	
	Induction (oxytocin only)	Number	23	22	
		Percent	56	52.4	
	Induction (oxytocin and misoprostol)	Number	8	9	
		Percent	19.5	21.4	
	Total	Number	41	42	
		Percent	100.0	100.0	

* *P* value calculated by χ^2 test.

was 7 mg. This difference was decided by considering the intravenous/intramuscular dose, the bioavailability of the drug, and possible adverse effects of doses higher than 8 mg. Previous studies have stated that the half-life of dexamethasone did not differ when used orally or intravenously.[16] A recent study reported that a Franz cell diffusion test could measure the permeability of the vaginal mucosa and assess the potential bioavailability of the drug when administered vaginally. Their investigation showed that dexamethasone could permeate the vaginal mucosa, and so can be administered as a noninjectable treatment.[17] Also, Bakhtiari et al[18] suggested that dexamethasone tablets (0.5 mg each) can be absorbed from the mouth mucosa. Because dexamethasone is readily absorbed via the mucosa with a bioavailability of about 80%,[19] we used dexamethasone tablets vaginally for the higher bioavailability.

Recent investigations have clarified that intramuscular dexamethasone can reduce the interval between the induction of labor and the active phase.[13,20–23] Elsayed et al[15] studied 80 pregnant women in a randomized clinical trial. They observed that administration of intramuscular dexamethasone before induction had no statistically significant differences in the active phase of labor between the 2 groups. However, they reported that dexamethasone administration before induction seemed to shorten the induction-active phase interval.[15] These findings showed that dexamethasone administration might reduce labor's latent phase. It was not in concordance with our study. Also, Sammour et al[14] studied 60 pregnant women. A single dose of intramuscular dexamethasone (2 mL) was administered in the case group. They reported that intramuscular dexamethasone shortened the duration of labor induction by decreasing the interval between the start and the beginning of the active phase.[14]

Salman et al[24] studied 60 pregnant women in a randomized, double-blind clinical trial. The control group received vaginal misoprostol, but intravenous dexamethasone was administered to the experimental group. They found that dexamethasone shortened the duration of labor induction by reducing the time interval between the initiation of labor induction and the onset of an active phase ($P < 0.001$).[24] However, in this study, the vaginal use of dexamethasone showed no effect in reducing the latent phase or the induction-active phase interval. These differences in outcomes could be because of the different dexamethasone administration routes (intramuscular/intravenous vs vaginal).

In a meta-analysis, Mohaghegh et al[2] showed that using dexamethasone by intramuscular, intravenous, or extra-amniotic routes can reduce the duration between labor induction and active phase of labor and also improve Bishop scores. In their meta-analysis, vaginal administration of dexamethasone was not studied. They also reported that dexamethasone injection did not affect maternal outcomes or Cesarean rate. In our study, vaginal administration of dexamethasone was not shown to increase the rate of natural vaginal delivery compared with the control group.

Bishop scores after cervical ripening significantly predicted induction success.[25] Kashanian et al. studied 84 pregnant women. They administered 20 mg dexamethasone extra-ovulary plus extra-amniotic saline solution infusion in the case group and extra-amniotic saline solution infusion alone in the control group. They found that the primary Bishop score in the case and control groups were similar.[3]

The effect of vaginal administration of dexamethasone on labor induction or its bioavailability in this form has never been studied; therefore, further investigations are needed in future studies.

Conclusions

In this study, we have described how using dexamethasone tablets vaginally improves Bishop scores in nulliparous pregnant women. The current study showed that administrating vaginal dexamethasone did not affect improving Bishop scores and did not reduce the duration of the latent phase of labor.

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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