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

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Scientific Background

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 post-term pregnancy. Ending a pregnancy can be needed when there is premature rupture of membranes without labor, oligohydramnios, or concerns related to fetal statuses, such as non-reassuring 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 (e.g., Misoprostol), extra amniotic saline infusion (EASI), traction on the cervix with a Foley balloon catheter, and/or hygroscopic cervical dilators are used (3, 4). In nulliparous pregnant women, the cervix has a smooth, round external os. The average time from induction to delivery is between 15 to 20 hours. The cervical ripening phase can take up to 12 hours before the start of labor. Labor may be prolonged by about 10 percent 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 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/liter 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. 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. and Latif et al. demonstrated that glucocorticoids like dexamethasone play a pivotal role in cervical ripening and aid labor induction (2, 8). 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, as 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 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 randomized controlled trial conducted in Kamali Hospital, Karaj, Iran. Kamali Hospital is one of 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 clinicaltrial.gov, NCT05070468.

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

Objectives

The clinical trial investigators and researcher 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 pregnant, having full-term gestation (≥38 weeks), with a singleton pregnancy, between 18 to 35 years of age, and having normal Body Mass Indices (BMI) of 18.5—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 of ≤2 and an estimated fetal weight of 2500-4000 grams. Participants were expected to have had normal Non-Stress Test (NST) results. If the patient's obstetric 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 pre-existing 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, they 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 participants 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 was collected using several tools, including interviews, observations, and a vaginal examination. The research staff designed a 2-page questionnaire which was used, and this included demographic information, i.e., current age, education, job, gravidity, parity, past medical history,

and BMI. The first and second Bishop scores, the latent phase duration, and delivery and intervention type were also recorded for each participant. 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 fourteen 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 obstetric physician undertook the labor induction for the study participants.

There were three 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 of five or more. Third, during labor induction in those participants assigned to the cases group, Misoprostol was administered if they had a Bishop score of less than 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 two separate examiners to verify the result of the vaginal examinations.

Statistical analysis

The statistical analysis collected data from reviewing the participant questionnaires. This was converted for analysis using the SPSS statistical software version 25.0 (IBM Corporation, Chicago, IL, USA). A chi-squared 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 of ($P \leq 0.05$) was considered statistically significant in this study.

1. References:

1. Tenore JL. Methods for cervical ripening and induction of labor. American family physician. 2003;67(10):2123-8.
2. Mohaghegh Z, Faal Siahkal S, Bahmaei H, Sharifipour F, Leyli EK, Zahedian M. The effect of dexamethasone on labor induction: a systematic review. BMC Pregnancy and Childbirth. 2021;21(1):563.
3. Kashanian M, Fekrat M, Naghghash S, Ansari NS. Evaluation of the effect of extra-amniotic normal saline infusion alone or in combination with dexamethasone for the induction of labor. Journal of Obstetrics and Gynaecology Research. 2008;34(1):47-50.
4. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Medley N, Dias S, et al. Which method is best for the induction of labour? A systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess. 2016;20(65).
5. Harrison MS, Ali S, Pasha O, Saleem S, Althabe F, Berrueta M, et al. A prospective population-based study of maternal, fetal, and neonatal outcomes in the setting of prolonged labor, obstructed labor and failure to progress in low- and middle-income countries. Reproductive Health. 2015;12(2):S9.
6. Wadhwa PD, Porto M, Garite TJ, Chicz-DeMet A, Sandman CA. Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. American journal of obstetrics and gynecology. 1998;179(4):1079-85.
7. Cunningham F, Leveno K, Bloom S, Spong CY, Dashe J. Williams obstetrics, 24e: Mcgraw-hill New York, NY, USA; 2014.
8. Abdel Latif EM, Taha WS, Ahmed AARA. Effect of Intra-Muscular Administration of Dexamethasone on the Duration of Induction of Labor in Primigravida Full-Term Pregnancy. The Egyptian Journal of Hospital Medicine. 2018;73(6):6973-82.
9. King BR, Smith R, Nicholson RC. The regulation of human corticotrophin-releasing hormone gene expression in the placenta. Peptides. 2001;22(5):795-801.
10. O'Sullivan J, Iyer S, Taylor N, Cheetham T. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency is associated with a prolonged gestational age. Archives of disease in childhood. 2007;92(8):690-2.
11. Nour El-Din Hashad AM, Yehia AH, Mohammed AA. Effect of Intravenous Dexamethasone on the Duration of Labor Induction: A Randomized Controlled Trial. QJM: An International Journal of Medicine. 2021;114(Supplement_1).
12. Fatemeh L, Negin A, Ameneh B, Farideh M, Ezzatossadat Haj Seyed j. Effect of Intravenous Dexamethasone on Preparing the Cervix and Labor Induction. Acta Medica Iranica. 2015;53(9).
13. Elmaraghy MA-A, El Refaie T, Labib KM, Mohamed MG. Effect of intramuscular administration of dexamethasone on the duration of labor induction. Evidence Based Women's Health Journal. 2018;8(4):311-7.
14. Sammour HM, Ashoush SA, Elhawwary GE, Rekaby SH. Effect of Intramuscular Administration of Dexamethasone on Shortening of the Duration of Induction of Labor. QJM: An International Journal of Medicine. 2021;114(Supplement_1).
15. Elsayed HM, Bahaa AM, Alanwar AA, Mohamed KM. Role of Dexamethasone in Induction of Labor: (A Randomized Clinical Trial). QJM: An International Journal of Medicine. 2020;113(Supplement_1).