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ORIGINAL ARTICLE

The effect of slow-release vaginal dinoprostone on maternal and fetal oxidative stress in term pregnancies complicated by oligohydramnios: Prospective cohort study

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Abstract

Background: To evaluate changes in oxidant status using thiol/disulfide homeostasis in mothers and fetuses after induction of labor with slow-release vaginal dinoprostone inserts.

Methods: A total of 70 pregnant women were divided into two groups. Thirty-five women in whom labor was induced with slow-release vaginal dinoprostone inserts (10 mg of prostaglandin E2, group A) were compared before and after the administration. The other 35 women, who were followed up spontaneously during labor (group B), were included as a control group. Both groups were diagnosed with isolated oligohydramnios without signs of placental insufficiency. The thiol/disulfide homeostasis parameters were calculated before medical induction and after removal of the insert at the beginning of the active phase of labor. Maternal and cord blood values were measured in both groups.

Results: Although the balance shifted to the antioxidant side after the slow-release vaginal dinoprostone insert was applied, there was no significant difference in maternal oxidative load compared to the pre-application status (5.32 ± 014/5.16 ± 0.15, $p = 0.491$). Despite the shift toward the antioxidant side, maternal antioxidants were still significantly lower in the group that received slow-release vaginal dinoprostone at the beginning of the active phase of labor than in the control group (295.98 ± 13.03/346.47 ± 12.04, respectively, $p = 0.009$). There was no statistically significant difference in terms of oxidative balance or newborn Apgar score ($p > 0.05$).

Conclusion: Induction of labor with slow-release vaginal dinoprostone inserts in pregnancies with isolated oligohydramnios does not cause further oxidative stress and is safe for both mothers and neonates in terms of oxidant load by thiol/disulfide homeostasis.

Keywords: Dinoprostone; Disulfide; Homeostasis; Labor; Oxidant

1. INTRODUCTION

Induction of labor (IOL) is commonly used worldwide in cases in which delivery is considered safer than continuing.[1] It is usually performed to reduce maternal morbidity in high-risk pregnancies, or to reduce fetal/neonatal morbidity in cases such as post-term pregnancy, oligohydramnios, and intrauterine growth restriction (IUGR).

Oligohydramnios is defined as low amniotic fluid volume for gestational age and complicates 4.4% of all pregnancies at term and may be caused by maternal, fetal, or placental reasons.[2,3] If the cause is not defined, it is called idiopathic or unexplained oligohydramnios. Most cases of oligohydramnios seen in the third trimester are in this form and are associated with better outcomes.[4]

The American College of Obstetricians and Gynecologists (ACOG) suggested IOL be considered in term pregnancies complicated by oligohydramnios.[5] Slow-release vaginal dinoprostone is widely used for IOL in singleton pregnancies with a cervical score of ≤5. In many studies, the use of slow-release dinoprostone for IOL was found to be safe and effective.[6–8]

Reactive oxygen species (ROS) are produced in human cells as a result of aerobic respiration and metabolism. Various enzymatic and antioxidant mechanisms have been developed to control ROS production and eliminate its harmful effects. An imbalance between ROS production and antioxidant systems is known as oxidative stress (OS). It is an unstable and toxic cellular condition that leads to disruption of intracellular functions. High levels of ROS are observed in all developmental stages of pregnancy. OS has been examined in cases of fibroids, assisted reproduction, pregnancy loss, gestational diabetes, preeclampsia, IUGR, nuchal cord, and fetal death.[9–15]

Thiols (RSH) are a class of organic compounds that can undergo oxidation reactions via oxidants and form disulfide bonds. Under conditions of OS, dynamic thiol/disulfide homeostasis is maintained, and it plays critical roles in antioxidant protection, detoxification, signal transduction, apoptosis, regulation of enzymatic activity, transcription factors, and cellular

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signaling mechanisms.[16,17] Thiol/disulfide homeostasis can be measured automatically by a new method and is associated with several diseases.[18,19]

Dinoprostone is a phenolic compound.[20] It is a flavonoid with significant antioxidant activity.[21] If the cervix is immature in term pregnancies complicated by oligohydramnios, slow-release vaginal dinoprostone is one of the best options for IOL. Therefore, we aimed to evaluate changes in oxidant/antioxidant balance and possible negative effects by measuring thiol/disulfide levels in mothers and neonates after labor induction with slow-release vaginal dinoprostone.

2. METHODS

This prospective cohort study included women diagnosed with isolated oligohydramnios who underwent medical IOL with slow-release vaginal dinoprostone (prostaglandin E2, 10 mg) inserts in the obstetrics department of a tertiary hospital in Ankara. Samples were collected over 2 years. The study was approved by the Hospital's Ethics Committee (E1-20-248) and written informed consent was obtained from each participant.

Thirty-five pregnant women who were diagnosed with isolated oligohydramnios in late-term pregnancy and underwent medical IOL with slow-release vaginal dinoprostone (10 mg of prostaglandin E2) (group A) were compared before application of the insert and after its removal at the beginning of the active phase of labor (5-6 cm opening, 80% effacement). For the control group, 35 pregnant women of similar ages, gestational weeks, and body mass index (BMI), without membrane rupture, and with isolated oligohydramnios who were followed up spontaneously at the beginning of the active phase of labor were selected (group B). None of the participants had any additional chronic diseases. A total amniotic fluid index (AFI) of <5 cm in transabdominal ultrasound was considered to indicate oligohydramnios. According to the ACOG recommendation, the diagnosis of oligohydramnios in term pregnancies is an indication for delivery, and labor induction should be started as soon as the diagnosis is made. Among the pregnant women who participated in the study, those in group A were diagnosed with oligohydramnios at the time of hospitalization and had a Bishop score of <5. The pregnant women in group B were admitted to the hospital with spontaneous labor pain and were diagnosed with oligohydramnios at that time. AFI begins to decrease steadily after 40 weeks' gestation. Especially in clinical practice, IOL is more common after these gestational weeks. Therefore, the study was planned in gestational age 41 0/7 to 41 6/7 weeks to ensure standardization. Oligohydramnios was noted in both groups with no signs of placental insufficiency, intrauterine growth retardation, or chromosomal anomaly. Patients with abnormal laboratory tests, gestational or pregestational hypertension, IUGR, oligohydramnios due to specific causes, multiple gestations, malpresentation, nonvertex presentation, diabetes mellitus (gestational or pregestational), chronic diseases, infections, prematurity, failed induction, cesarean section for any reason, ruptures of membranes before the active phase, or fetuses with any kind of defects were excluded from the study. Those in whom assisted reproductive techniques associated with pregnancies had been applied were also not included. Patients who had to take any kind of medication or were addicted to drugs or consuming alcohol or tobacco were also excluded. During follow-up, patients were excluded from the study if uterine hyperstimulation developed, the vaginal insert was spontaneously dislodged, the presence of meconium-stained amniotic fluid was observed, or fetal distress developed at any stage during delivery. For sample size, with an effect width value of 0.50 at a 5% margin of error and 80% power level, the total number of patients was determined as 35 in the study group and 35 in the control group. Until the sample size's patient count was attained, in group A, IOL with a slow-release vaginal dinoprostone insert application was stopped, and participants were excluded from the study due to hyperstimulation in 2 of the 45 pregnant women, the existence of meconium-stained amniotic fluid when the membrane was ruptured in 2 women, and spontaneous expulsion from the vagina in one of them. Five pregnant women from both groups were excluded from the study due to fetal distress. The thiol/disulfide homeostasis parameters of the pregnant women in the study group were compared between before the application of the slow-release vaginal dinoprostone and after the insert was removed at the beginning of the active phase of labor. In the control group, these parameters were evaluated at the beginning of the active phase of labor. Those who delivered via successful induction in group A and had a vaginal delivery in both groups were included in the study. Umbilical cord venous blood samples were taken from both groups. Additionally, the groups were compared according to their 1- and 5-minute Apgar scores. In group A, the mean value of slow-release vaginal dinoprostone administration time was 11.82 hours while the median value was 12 hours.

Maternal venous blood and umbilical cord venous blood samples were collected from volunteers in plain tubes. The sera were separated by centrifugation at 1600 × *g* for 10 min and stored at −80°C until analyzed. Thiol/disulfide homeostasis tests were performed using the automated spectrophotometric method described by Erel and Neselioglu.[19] After the determination of native and total thiols, disulfide amounts and disulfide/native thiol percentage ratios (SS/SH) were calculated.

As our study was preliminary, power analysis was not performed before it started. Post-hoc analysis of 70 patients showed a power of 0.80 when we accepted the effect size of 0.5 with an α of 0.05 significance level. The data were evaluated using visual (histograms) and statistical methods (Kolmogorov-Smirnov test and Shapiro-Wilk test) to determine whether the data were normally distributed. Descriptive analyses were performed using the mean and standard deviation (mean ± SD) for the normally distributed variables. Because the data were normally distributed, independent sample *t* tests, one-way analysis of variance (ANOVA), and paired sample *t* tests were used to compare the parameters between the groups. Correlation analyses were performed using Pearson's correlation coefficient. An overall type 1 error of 5% was used to infer statistical significance. The statistical analyses were performed using SPSS version 20 (SPSS Inc. Chicago, IL).

3. RESULTS

The demographic and postpartum variables of groups A and B are summarized in Table 1. Age, parity, BMI, gestational weeks, 1- and 5-minute Apgar scores, and birth weights were similar between the two groups ($p > 0.05$).

Table 2 shows the thiol/disulfide parameters of both groups. In the thiol/disulfide balance, the amount of native and total thiol indicates the antioxidant status, while the amount of disulfide indicates the oxidant status. The balance is stated as the % ratio of the two (index%). According to Table 2, although antioxidant levels were lower in group A, using slow-release vaginal dinoprostone, the balance was not significantly different from that in group B (5.16 ± 0.15, 5.04 ± 0.25, respectively, $p = 0.726$).

The cord blood thiol/disulfide homeostasis parameters are summarized in Table 3. Although the antioxidant level in the cord blood tended to be lower in group A, the balance was insignificantly different compared to that in group B (4.45 ± 0.24, 4.73 ± 0.22, respectively, $p = 0.426$).

Table 1

Demographic and pregnancy characteristics of groups A and B

Variables	Slow-release vaginal dinoprostone (n = 35)	Control group (n = 35)	*p*
Age, y	26.91 ± 4.23	27.20 ± 4.92	0.782
Gravidity	1.47 ± 1.02	1.98 ± 1.27	0.046
Parity	0.44 ± 0.89	0.84 ± 0.97	0.061
Body mass index, kg/m^2	29.76 ± 4.02	28.34 ± 2.92	0.064
Gestational week	41.07 ± 0.22	41.12 ± 0.14	0.295
Apgar scores at 1st, min	7.53 ± 0.50	7.42 ± 0.60	0.374
Apgar scores at 5th, min	9.06 ± 0.34	9.16 ± 0.54	0.302
Birth weight, g	3306 ± 394	3416 ± 360	0.199

Table 2

Thiol/disulfide profiles of maternal venous blood in groups A and B

Variables	Group A[a]	Group A[b]	*p*	Group A[b]	Group B[c]	*p*
Native thiol, μmol/L	285.13 ± 8.44	295.98 ± 13.03	0.271	295.98 ± 13.03	346.47 ± 12.04	0.009[d]
Total thiol, μmol/L	315.27 ± 9.04	325.92 ± 14.03	0.301	325.92 ± 14.03	380.45 ± 12.87	0.008[d]
Disulfide, μmol/L	15.07 ± 0.46	14.96 ± 0.61	0.960	14.96 ± 0.61	16.99 ± 0.94	0.135
Index (disulfide/native thiol, %)	5.32 ± 014	5.16 ± 0.15	0.491	5.16 ± 0.15	5.04 ± 0.25	0.726

[a]Slow-release vaginal dinoprostone-before insertion.
[b]Slow-release vaginal dinoprostone after the insert is removed-beginning of the active phase of labor.
[c]Control group beginning of the active phase of labor.
[d]A significant difference with $p < 0.05$.

Table 3

Thiol/disulfide profiles of umbilical cord blood in groups A and B

Variables	Group A Slow-release vaginal dinoprostone group (n = 35)	Group B Control group (n = 35)	*p*
Native thiol, μmol/L	361.47 ± 16.89	392.81 ± 17.98	0.240
Total thiol, μmol/L	393.20 ± 18.09	428.27 ± 18.71	0.210
Disulfide, μmol/L	15.86 ± 0.98	17.73 ± 0.82	0.157
Index (disulfide/native thiol, %)	4.45 ± 0.24	4.73 ± 0.22	0.426

4. DISCUSSION

To the best of our knowledge, this is the first study to evaluate the effect of IOL with slow-release vaginal dinoprostone on thiol/disulfide homeostasis in term deliveries complicated by oligohydramnios and it demonstrated that IOL with slow-release vaginal dinoprostone might not cause further OS in mothers and fetuses.

Slow-release vaginal dinoprostone is a common IOL method used for cervical changes and uterine contractions when the cervix is unripe and delivery is decided on. It offers many advantages like being less invasive, easily administered, quickly removed, and well suited for women, allowing dose control and a sufficient single application. The most significant adverse effect is uterine hyperstimulation, which occurs in 5% to 15% of patients. Apart from the symptoms observed during IOL with slow-release vaginal dinoprostone, some molecular changes such as oxidation may occur in the cellular defense systems. Thiol groups are antioxidants in the form of -SH and they play a role in cell defense. They are mainly found in proteins and can be oxidized to functional and reversible disulfide bonds, -SS. As a result of oxidation in the cytoplasm, native thiol turns into disulfide forms. In the case of excessive ROS production, this reversible balance is disturbed, which is called failed thiol/disulfide homeostasis, resulting in OS. This damages the structure, stability, and activity of various proteins, including enzymes.[22] Studies related to thiol/disulfide homeostasis and pregnancy-related conditions, such as recurrent pregnancy loss, gestational diabetes, preeclampsia, and hyperemesis gravidarum, have shown that levels of serum native thiol, which means antioxidants, are significantly lower.[23–25] These studies have shown that the measurement of thiol/disulfide in obstetric pathologies indicates oxidative status. In a study by Eryilmaz et al,[26] medical IOL with oxytocin was found to be safe for both the mother and fetus in terms of OS according to thiol/disulfide parameters.

As mentioned above, dinoprostone is a phenolic compound and a flavonoid with significant antioxidant activity.[20,21] Therefore, the question arises as to whether this antioxidant IOL method creates a different oxidative status in the mother and newborn. When we examined the pregnant women in the study, they were similar in terms of age, BMI, and gestational weeks. Native and disulfide thiol levels were compared before and after the slow-release vaginal dinoprostone insert application in women diagnosed with isolated oligohydramnios and unripened cervix. In the control group, these parameters were evaluated at the beginning of the active phase of labor. Cord blood levels were measured in the study and control groups to assess fetal status immediately after delivery. In the thiol/disulfide balance, the amount of native and total thiol indicates

the antioxidant status, while the amount of disulfide indicates the oxidant status. The balance is stated as index% (ratio%). When oxidant stress is higher in the body, the antioxidant mechanism works harder to balance, and the index value shows this balance. Native and total thiol levels increased as expected in the pregnant women who received vaginal dinoprostone. However, this increase was not statistically significant (p = 0.271, p = 0.301, respectively). When we evaluated antioxidant levels in the control group, who were followed up spontaneously, they were significantly higher than those in the slow-release vaginal dinoprostone-treated group in the same phase of labor. When we compared the oxidative balance before and after insert application, although the balance seemed to shift in the oxidant direction, it did not cause a statistically significant difference (p = 491). When groups A and B were compared in terms of oxidative balance, no significant difference was observed ($p > 0.05$).

The cord blood thiol/disulfide homeostasis parameters were also evaluated in our study. Although the antioxidant level in the cord blood tended to be lower in group A, it was insignificantly different compared to that in group B. When the groups were compared, index levels in the cord blood and the 1- and 5-minute Apgar scores were statistically similar.

Based on these data, we determined that application of an insert containing antioxidant dinoprostone may not cause any increase in oxidative load in mothers and newborns. However, our study had some limitations. Only those in whom induction was successful and those who delivered vaginally from both groups were evaluated to ensure standardization. Moreover, the thiol values of the control group were not measured before the active phase of labor because these pregnant women were in the low-risk group and had no indications for hospitalization while the cervix was unripe.

In conclusion, according to the results, IOL with a slow-release vaginal dinoprostone insert in term pregnancies complicated by isolated oligohydramnios, which is one of the best choices for an unripened cervix, does not result in OS for the mother or the fetus in terms of oxidant levels using thiol/disulfide balance.

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