Evaluation of Paraoxonase 1 Oxidative Stress Enzyme in Cord Blood of Newborn to Patients Delivered with Oxytocin Induced Labor

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Abstract

Background   The use of labor induction to shorten the duration of a pregnancy has increased steadily during the last few decades. Paraoxonase 1 levels were observed to be higher in the oxytocin-induced group than in the spontaneous labor group.

Objective   To compare the influence of induced labor on fetal Apgar score and birthweight, and to measure the level of oxidative stress (paraoxonase 1) experienced during labor by the neonates of pregnant women undergoing induced or spontaneous birth.

Methods   A case control study that was conducted in the Department of Obstetrics and Gynecology, Azadi Teaching Hospital, Kirkuk during a period of nine months from 10th of February till 10th of November 2019. It included 60 healthy pregnant women with singleton pregnancy and viable fetus attending the labor room of the hospital. They were divided into two groups: Case group included 30 pregnant women who underwent oxytocin-induced labor and control group included 30 pregnant women underwent spontaneous vaginal delivery in latent phase of first stage labor without oxytocin induction. A five ml of blood was drawn from the umbilical artery to measure Paraoxonase 1 level. Pregnancy outcome was also monitored.

Results   The mean of Paraoxonase 1 enzyme was significantly higher in women who underwent oxytocin-induced labor than that in women who underwent vaginal delivery without oxytocin induction. No significant differences between study groups regarding birthweight, Apgar score 1 min, Apgar score 5 min, packed cell volume, and hemoglobin F.

Conclusion   Serum Paraoxonase 1 as a marker was elevated in neonates of pregnant women who underwent oxytocin induced labor without a significant effect on Apgar score of neonates or its birthweight.

Keywords   Paraoxonase 1, labor induction, oxidative stress, pregnancy outcome

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List of abbreviations: BMI = Body mass index, C/S = Cesarean section, HbF = Fetal hemoglobin, PCV = Packed cell volume, PON = Paraoxonase

Introduction

Labour is a physiological process, in which the fetus, membranes, umbilical cord, and placenta are ejected from the uterus [1]. A spontaneous vaginal delivery occurs when the baby is born without the need for doctors to utilize instruments to help pull the baby out [2]. Induction of labor is the procedure of stimulating the uterus artificially to start labor. It's usually accomplished by administering oxytocin or prostaglandins to the pregnant mother, or by manually rupturing the amniotic membranes. The use of labor induction to shorten the duration of a pregnancy has increased steadily during the last few decades

[3]. In developed countries, the proportion of infants born at term after induction of labor can be as high as one out of every four births [4]. The most commonly used pharmacologic drug for labor induction and augmentation is oxytocin. Oxytocin regimens can be classified as high-dose or low-dose based on the initial dose and the amount and rate of subsequent dose increases [5]. Paraoxonase (PON) is a hydrolytic enzyme with a broad substrate range and the capacity to protect lipids from oxidation. They are a group of mammalian enzymes that act as aryl-di-alkyl phosphatases. PON isozymes are enzymes that are involved in the hydrolysis of organophosphates. There are three types of PON isozymes. The majority of research on the PON family has focused on the PON 1 type, leaving much to learn about the other two [6]. PON have been discovered to perform a variety of biological roles, while the basic function of this family of enzymes is yet unknown. Anti-inflammatory, anti-oxidative, anti-atherogenic, anti-diabetic, anti-microbial, and organophosphate-hydrolyzing capabilities have been discovered in some of the identified roles [7]. Although the specific antioxidant mechanism of PON is unknown, it is known that it is neither mediated by copper ion chelation or possible lipid transfer from low density lipoprotein (LDL) to high density lipoprotein (HDL) [8]. Intrauterine oxidative stress was reported to develop in women who gave delivery or experienced induction of labor [9]. There are studies in the literature that use cord blood to measure oxidative state. Nitric oxide, asymmetrical dimethylarginine, PON, total oxidative state, and total antioxidative status, on the other hand, have yet to be cited in the literature as indicators. Labor triggered by oxytocin raises stress markers but has little effect on Apgar scores. Antioxidative systems may be activated in pregnant women as a result of oxidative stress [10]. For a good pregnancy, the mother's vascular anatomy and vessel activity within the placental bed should be normal. At this stage, PON's antioxidant properties become more essential. PON has potent antioxidant properties and is found at 3-

to 4-fold higher levels in females than males, providing increased protection against oxidative stress [11].

This study aimed to compare the influence of induced labor on fetal Apgar score and birthweight, and to measure the level of oxidative stress (PON 1) experienced during labor.

Methods

A case control study conducted at Department of Obstetrics and Gynecology at Azadi Teaching Hospital, Kirkuk during a period of nine months from 10th of February till 10th of November 2019. This study was approved by the Council of Iraqi Board of Medical Specialization and the Department of Obstetrics and Gynecology at Azadi Teaching Hospital.

The study included 60 healthy pregnant women with singleton pregnancy and viable fetus attending the labor room of the hospital. They were informed about the nature of the study and verbal consent was obtained from them. Women with history of hypertensive disorder of pregnancy, diabetes (gestational or pre-gestational), history of intrauterine growth retardation, history of cardiac diseases, aberrant complete blood count and blood biochemistry test results, pregnancies that occurred as a result of assisted reproductive procedures, history of smoking and using of antioxidant drugs, history of cesarean section (C/S) or uterine surgery and abnormal presentation, and congenital anomalies of the fetus were excluded from the study. They were divided into two groups:

1. Case group: Included 30 pregnant women who underwent labor induced by oxytocin.
2. Control group: Included 30 pregnant women without a previous history of C/S nor uterine surgery with cephalic presentation underwent vaginal delivery without oxytocin induction after matching for age and gestational age with case group. All in latent phase of first stage labor.

Assessment and estimation of gestational age was done depending on the date of last

menstrual cycle, and/or early ultrasound scan. Detailed history by questionnaire, obstetrical history, past medical and surgical histories were taken in both groups. General examination and vital signs also monitored. Abdominal examination was done to assess uterine contraction, also we assessed fundal height, fetal heart. Fundal grip, lateral grip and pelvic grip techniques to assess engagement of fetal head.

Internal examination (per vaginal examination) for consistency, length, dilatation and effacement of cervix and engagement of presenting part in both groups. Labor was followed by partogram, fetal monitoring done by cardiotocography (CTG). Investigation as complete blood count, liver and renal function tests, and serum uric acid were done. Postnatal assessment was done by calculating the Apgar score for all newborns at the first and fifth minute' systemic physical examination. Birthweight was measured by a pediatric scale and blood sent for packed cell volume (PCV) and fetal hemoglobin (HbF).

Induction of labor in case group
Five IU/ml of synthetic oxytocin liquid ampoule was prepared by adding it into 500 ml of 0.9% NaCl fluid and given as initial dose of 2 mIU/mint. Intravenously until effective contractions were achieved, then increasing infusion dose by 2 mIU/mint. Every 20 mints. highest dose average was 20 mIU/min. The induction agent dose and contractions formed during labor were recorded [12].

Sample collection and oxidative stress marker test procedure
After delivery of fetus, from all study participants, the fetal cord was clamped. Then a five ml of blood was drawn from the umbilical artery and put into a plain tube and left for two hours at room temperature to clot.

Then centrifugation was done at 5000 rpm for five minutes. Then the serum was stored at – 80° C until the analysis time [12]. Human PON1 was measured by a kit using enzyme linked immune sorbent assay (ELISA) based on sandwich technology. The detection range is 0.16-10 ng/ml.

Statistical analysis
Statistical Package for Social Sciences (SPSS) version 26 was used to analyze the data. The information is displayed in the form of a mean, standard deviation, and ranges. The continuous variables were compared using a two-tailed independent t-test. Pearson's correlation test (r) was used to assess correlation between continuous variables accordingly. A level of P-value less than 0.05 was considered significant.

Results
In this study, study participants age was ranging from 19-41 years with a mean of 29.16 ± 6.0 years. Mean of human PON1 was significantly higher and mean of serum uric acid was significantly lower in women who underwent oxytocin-induced labor than that in women who underwent vaginal delivery without oxytocin induction (10.14 versus 8.08 mg/ml, P=0.045; and 3.5 versus 2.87 mg/dl, P=0.009 respectively). No significant differences (P≥0.05) between study groups regarding age, gestational age, body mass index (BMI), parity, and all other biochemical parameters (Table 1).

No significant differences (P≥0.05) between study groups regarding birthweight, Apgar score 1 min, Apgar score 5 min, PCV, and HbF as shown in table (2).

No significant correlations (P≥0.05) between human PON1 and all of maternal age, BMI, birthweight, Apgar score 1 min, and Apgar score 5 min as shown in table (3).

Table 1. Comparison between study groups by general biochemical parameters, and human PON1 marker

Variable	Case Mean±SD	Control Mean±SD	P - Value
Age (Year)	29.1±6.3	28.72±4.9	0.804
GA (Week)	38.5±1.1	38.1±0.7	0.132
BMI (kg/m^2)	23.5±2.5	23.7±2.1	0.694
Parity	1.33±0.5	1.42±0.4	0.791
SGOT (U/L)	37.33±11.8	35.78±7.4	0.549
SGPT (U/L)	35.6±8.6	36.25±8.4	0.771
ALP (IU/L)	108.0±25.4	113.5±16.8	0.332
B. Urea (mg/dl)	31.0±7.1	31.3±8.9	0.891
S. Creatinine (mg/dl)	0.48±0.2	0.46±0.2	0.705
S. Uric acid (mg/dl)	2.87±1.0	3.5±0.7	0.009
Human PON1 (mg/ml)	10.14±4.5	8.08±3.1	0.045

GA = Gestational age, BMI = Body mass index, ALP = Alkaline phosphatase, SGOT = Serum glutamic-oxaloacetic transaminase, SGPT = Serum glutamate-pyruvate transaminase

Table 2. Comparison between study groups by pregnancy outcome characteristics

Variable	Case Mean±SD	Control Mean±SD	P - Value
Birthweight (kg)	3.44±0.4	3.29±0.3	0.131
Apgar 1 min	6.06±1.2	6.46±1.3	0.237
Apgar 5 min	8.26±1.1	8.03±1.5	0.487
PCV of baby (%)	57.35±7.6	60.89±7.8	0.089
HbF (gm/dl)	16.71±1.0	17.21±1.4	0.141

PCV = Packed cell volume, HbF = Fetal hemoglobin

Table 3. Correlation between human PON1 marker and certain parameters

Variable	Human PON1 (mg/ml)	
	r	P - Value
Maternal age (Year)	0.104	0.431
BMI (kg/m^2)	0.105	0.427
Birthweight (kg)	0.03	0.765
Apgar 1 min	- 0.2	0.125
Apgar 5 min	- 0.197	0.131

BMI = Body mass index

Discussion

Maintaining the fetus's proper development during intrauterine life and achieving birth with minimal maternal-fetal trauma has become two of obstetrics' key goals. The birth process involves a sequence of cellular, molecular, and hormonal activities [11]. Induction to start labor is required in about 20-30% of all births.

Intravenous oxytocin is the most extensively used and acknowledged method for inducing labor in third-trimester pregnancies at the moment [12]. The current study is part of a small body of work that looks at the impact of oxytocin induction on oxidative stress and subsequent maternal and fetal adverse effect. This study showed that human PON1 was significantly higher in case group than that in control one and no correlation detected between human PON1 and maternal age, BMI level, birthweight, Apgar score 1 and 5 min. This result agreed with a study done by Karaçor et al. in 2017 who concluded that PON1 has an antioxidant function; thus, the presence of a defensive mechanism against the stress experienced by the mother is indicated by high levels of PON1. These findings suggest that using oxytocin to induce labor increases oxidative stress, and that anti-oxidative mechanisms are activated as a result [12]. PON1 deficiency promotes the oxidation of both high- and low-density lipoproteins, and is consequently linked to a variety of cardiac vascular diseases, including atherosclerosis [13]. Both the mother's vascular structure and vessel activities within the placental bed should be normal for a successful pregnancy. The antioxidant effect of PON1 becomes more important at this time [14]. In this study, mean of serum uric acid was significantly higher in control group than that in case group and this is agreed by Karaçor et al. study in 2017. Uric acid possesses antioxidant properties and is an important determinant of total plasma antioxidant capacity [12]. Oxytocin is the drug most frequently linked to avoidable perinatal complications. Indications, timing, dose, and monitoring of maternal and fetal effects are all ambiguous in recommendations for this drug's use. Precise, evidence-based guidelines for the intrapartum administration of oxytocin can be generated based on a review of current clinical and pharmacologic data. If implemented, such processes may reduce the risk of patient harm [15]. This study showed no statistically significant differences between study groups regarding birthweight, Apgar score 1 min,

Apgar score 5 min, PCV, HbF. This is agreed with a result found by Karaçor et al. study in 2017 [12], Hidalgo-Lopezosa et al. study in 2016 [16], and Heimstad et al. study in 2007 [17]. Different result obtained in Gülmezoglu et al. study in 2018 as Apgar score is less than seven at five minutes in the induction groups compared with expectant management [18]. The variations in results might attributed to the sample size enrolled in each study, gestational age (since post-term is associated with higher perinatal morbidity and mortality), type and dosage of stimulants, associated co-morbid diseases, and parity (In fact, because labor is frequently longer, more painful, and can present more difficulties in primiparous women) [19]. Interventions with oxytocin, especially at high doses, have the potential to harm both the mother and the fetus, such as uterine tachy-systole and fetal heart rate disruption [15]. During contractions, blood flow to the intervillous space is reduced or interrupted, resulting in this condition [20]. The majority of fetuses tolerate contractions in typical births; but, if the contractions are particularly frequent and/or lengthy, there is a danger of fetal hypoxemia and acidemia [21]. Interventions during the physiological birth process, according to some authors, increase the risk of alterations for the mother and the fetus in the absence of problems. They argued that evidence-based clinical practice should be used to promote physiological delivery, as well as the avoidance of unnecessary labor inductions and regular care interventions, as well as unnecessary limits [22].

In conclusion, neonates of pregnant women who underwent oxytocin induced labor showed elevated serum human PON1 as antioxidant marker without a significant effect on Apgar score of neonates or its birthweight.

Author contribution
Dr. Ghalib: Put the research plan. Dr. Ahmed: Did the sampling, wrote the manuscript and did the statistical work.

Conflict of interest
Authors declare no conflict of interest.

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