〈Regular Article〉

Comparison of uterine artery waveforms during uterine contractions induced by oxytocin and prostaglandin

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ABSTRACT **Background**: Uterine artery waveforms are used as indicators of fetal growth restriction and pregnancy-induced hypertension; however, the findings of most reports were recorded when contractions were absent, leaving the dynamics during labor unclear. This present study aimed to investigate the effects of prostaglandin F2α (PGF2α) and oxytocin administrations on uterine artery resistance and pulsatility.

Methods: This study was approved by the Ethics Committee of Kawasaki Medical School (3632) and was conducted in accordance with the ethical guidelines. The duration of the study was five years from the date of Ethics Committee approval.The participants included were 30 perinatal pregnant women who had no maternal or fetal complications admitted for delivery. The method used in inducing labor was randomly chosen (PGF2α and oxytocin were used in 15 cases each). Transabdominal ultrasonography was performed by a single experienced person to measure the uterine artery pulsatility index (PI) and resistance index (RI). The participants were divided into 3 subgroups based on cervical dilation (2-6 cm, 6-10 cm, and 10 cm to delivery). A univariate analysis was performed to evaluate the mean uterine artery PI and RI, and changes in labor stage were analyzed. The relationship between uterine artery RI and umbilical cord arterial pH was evaluated.

Results: Vaginal delivery occurred in 15 and 11 cases in the oxytocin and PGF2α groups, respectively. Four babies with abnormal fetal heart rates were delivered via emergency cesarean section. There were no differences between the two groups concerning the duration of labor, bleeding during labor, placental weight, birth weight, or in cases of fetal asphyxia based on the Apgar score. No significant differences were observed in PI between the oxytocin and PGF2α groups in any of the three stages of labor($p > 0.05$). In the oxytocin group, uterine arterial blood flow in terms of both RI and PI tended to be the highest at a cervical dilation of 6-10 cm. However, while a similar trend was observed for PI in the PGF2α group, RI was highest at a cervical dilation of ≥ 10 cm. No correlations were found between RI and pH at any

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of the cervical dilation phases($p > 0.05$).

Conclusion: The results of our study showed that the type of labor-inducing agent had no effect on maternal circulation. The total infusion volume of PGF2α was larger than that of oxytocin; thus, it may be preferable to use oxytocin as a conventional induction method.

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Key words：Labor induction, Oxytocin, Prostaglandin, Uterine artery pulsatility index, Uterine artery resistance index, Uterine contraction

INTRODUCTION

Assessments of blood flow velocity waveforms using the ultrasonic Doppler method were introduced in the field of perinatal medicine over 40 years ago. Initially, these examinations were limited to the maternal uterine and umbilical arteries, which could be blindly approached using the continuous wave Doppler method. However, with the introduction of the pulsed Doppler and color Doppler methods, it is currently possible to examine the fetal arterial system, such as the aorta, middle cerebral artery, and renal artery. These techniques enable the evaluation of fetal blood flow dynamics in various pathological conditions, including venous blood flow, such as in the inferior vena cava and ductus venosus. According to previous reports, evaluating blood flow with the resistance index (RI) shows that maternal uterine artery resistance decreases temporarily due to the progression of labor during spontaneous deliveries, and then rises again as full cervical dilation approaches. However, these changes are less apparent during induced deliveries; rather, there is a marked increase in uterine artery resistance from intense contractions. Recently, the changes that occur during painless labor from epidural anesthesia have been reported[1, 2], showing that uterine artery resistance is also higher during this kind of delivery than in spontaneous deliveries. The fetus can experience much stress during delivery, caused by factors such as oxygenation disorders (placenta/umbilical cord dysfunction), physical problems with delivery, and infectious diseases. The supply of oxygenated maternal blood comes from the uterine arteries and penetrate the uterine wall. Strong contractions of the muscles that make up the uterine wall during labor have a great impact on the maternal blood supply to the placenta. During contractions, the oxygen supply to the fetus declines, although its assessment is captured as changes on the fetal side (cardiotocography and blood gas findings). Essentially, fetal hypoxia is caused by impaired maternal blood supply; however, little is known concerning the dynamic changes involved. Uterotonic drugs are used to induce or augment labor due to maternal and fetal factors. Uterotonics used in Japan include oxytocin, prostaglandin F2α (PGF2α), and prostaglandin E2. In general, E2 is administered orally, and there is no particular evidence favoring either of the other two drugs which are easy to control by intravenous drip. The choice of the uterotonic used often based on the physician's discretion. Uterine artery waveforms are used as indicators of fetal growth restriction and pregnancy-induced hypertension, but most reports were recorded when contractions are absent, leaving the dynamics during labor unclear. Evaluating the strength of contractions is often difficult, except for the measurement of intrauterine pressure. Oxytocin and prostaglandin are both effective drugs for labor induction, but caution is needed when excessive pain occurs. In several papers, it has been reported that there is a difference in the pattern of contractions between oxytocin and prostaglandin[3-9]. It was reported that tetanic

contraction, baseline hypertonus, and coupling of contractions were more common with oxytocin[4, 5]. We hypothesized that these differences in uterine contraction patterns may cause changes in the blood flow patterns in the uterine arteries associated with uterine contractions, and that capturing these changes may lead to improved prognosis for the neonate. This present study aimed to investigate the effects of PGF2α and oxytocin administrations on the cycle of contractions, uterine artery resistance and pulsatility, as well as the differences between differences in uterine arterial blood flow according to the degree of uterine opening. Markers of fetal factors such as the umbilical artery and the middle cerebral artery were excluded, and we decided to focus on the uterine artery, which may be involved in maternal factors. The results could further improve safety in induced and painless deliveries and may be useful clinically in selecting among methods of labor induction.

SUBJECTS AND METHODS

This study was approved by the Ethics Committee of Kawasaki Medical School (3632) and was conducted in accordance with the ethical guidelines. The duration of the study was five years from the date of Ethics Committee approval.The participants were perinatal pregnant women admitted for delivery at the Department of Obstetrics and Gynecology at Kawasaki Medical School Hospital and who had no maternal or fetal complications. Indications for labor induction were past the due date, weak contractions, and social background. Patients who provided written informed consent after admission were included in the study. Measurements were taken over time in the same patients. The method used in inducing labor was randomly chosen. Regarding patient factors, we recorded their age, body mass index (BMI), smoking history, weeks of gestation, estimated body weight, placental position, history of pregnancy and delivery, placental weight, umbilical cord blood gas findings, and Apgar score. Transabdominal ultrasonography (ACUSON S2000, Siemens) was used for uterine artery measurements. One person performed all the measurements to ensure no error between measurements. Using a convex probe, the uterine wall was visualized under B mode at 4.0 MHz, and the ascending branch of the uterine artery was identified by the color Doppler method. The angle of incidence was $\leq 60^{o}$ and the sampling volume was 5 mm. Because diastolic blood flow in the uterine artery is maintained even during contractions, an appropriate wall filter was set to remove noise from the vessel wall and surrounding tissue. Once a continuous waveform of at least 3 equivalent heartbeats was assessed visually, each index was calculated for the left and right uterine arteries using the automatic measurement function built in the device. Moreover, measurements were taken at the extreme stage of uterine contraction, and to minimize the burden on the mother, the measurements were completed within 15 seconds on each artery. The subjects were divided into 3 groups based on cervical dilation. The mean left and right uterine artery pulsatility index PI and RI values were calculated for cervical dilation of 2-6 cm, 6-10 cm, and 10 cm to delivery. The required sample size as determined by power analysis based on previous reports was 15 cases each for inducing with oxytocin and PGF2α; thus, a total of 30 cases[10]. Uterine artery PI and RI (mean) was compared between the oxytocin and PGF2α groups, and changes in the labor stage and other factors were analyzed. We also examined the relationship between uterine artery RI (mean) and umbilical cord arterial pH. Statistical analysis was performed using the SAS software (SAS Institute Inc. Version 13.2). Wilcoxon test were performed for the statistical analysis. Statistical data are presented as median and range. A P-value of < 0.05 was considered statistically significant.

RESULTS

Analysis of oxytocin and PGF2α groups

The 30 cases of induced labor with no maternal or fetal complications were randomly divided into the oxytocin and PGF2α groups.

As shown in Fig. 1, vaginal delivery occurred in all 15 cases in the oxytocin group and 11 cases in the PGF2α group. Four cases with abnormal fetal heart rates were delivered via emergency cesarean section.

Maternal characteristics are shown in Table 1. There was no difference between the oxytocin and PGF2α groups in terms of age, gestational age, or BMI. Of the 15 oxytocin cases, the indication for induction of labor was planned delivery in 12 cases and premature rupture of membranes in 3 cases. Regarding the 11 cases of vaginal delivery induced with PGF2α, the indication was planned delivery in nine cases and premature rupture of membranes in two cases. No differences between the two groups

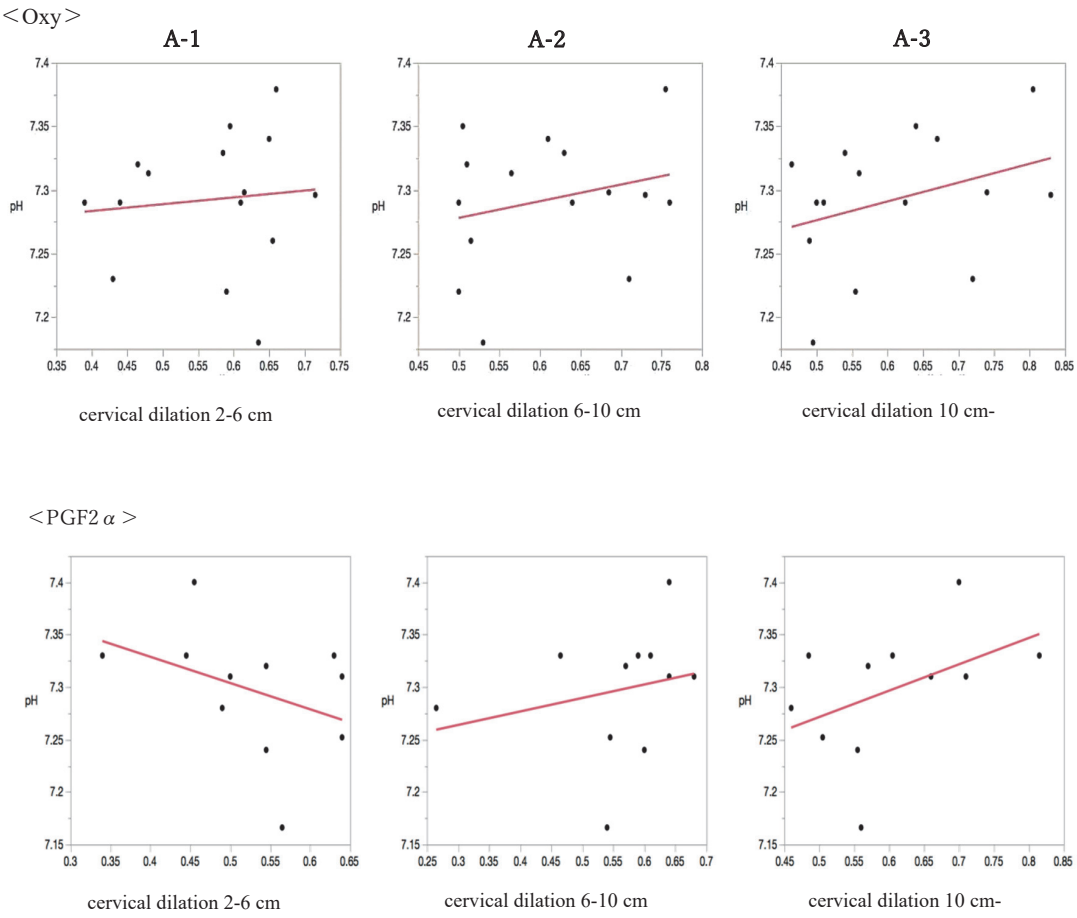

Fig. 1. Comparison of uterine artery RI and umbilical cord blood gas findings by labor stage. The red line in the graph shows the regression line. (A) Oxytocin group, (A-1) cervical dilation 2-6 cm, regression line: pH = 7.26 + 0.05 * RI Average (2-6cm) (P = 0.72, R^2 = 0.01), (A-2) cervical dilation 6-10 cm, regression line: pH = 7.21 + 0.13 * RI Average (6-10cm) (P = 0.37, R^2 = 0.06), (A-3) cervical dilation 10 cm-. regression line: pH = 7.20 + 0.15 * RI Average (10cm-) (P = 0.22, R2 = 0.11), (B) PGF2α group, (B-1) cervical dilation 2-6 cm, regression line: pH = 7.43-0.25 * RI Average (2-6cm), (P = 0.25 R^2 = 0.15), (B-2) cervical dilation 6-10 cm. regression line: pH = 7.23 + 0.13 * RI Average (6-10cm) (P = 0.48 R^2 = 0.06), (B-3) cervical dilation 10 cm-. regression line: pH = 7.15 + 0.25 * RI Average (10cm-) (P = 0.17 R^2 = 0.20) PI, pulsatility index; PGF2α, prostaglandin F2α.

Table 1. Maternal background

	Oxytocin group	Prostaglandin F2α group	p-values
Age (years)	33 ± 0.07	29 ± 0.18	NS
Weeks of gestation	38.5 ± 1.10	39.1 ± 1.28	NS
BMI (kg/m^2)	26 ± 0.34	23 ± 0.83	NS
Response (cases)	Planned delivery: 12 Premature rupture of membranes: 3	Planned delivery: 9 Premature rupture of membranes: 2	
Smoking (cases)	Smoker: 1 Non-smoker: 14	Smoker: 2 Non-smoker: 9	
Primipara/multipara (cases)	9/6	6/5	
Delivery time (min)	465 ± 0.86	325 ± 0.73	NS
Bleeding during delivery (ml)	880 ± 0.14	637 ± 0.36	NS
Placenta weight (g)	580 ± 0.29	555 ± 0.82	NS
Placental attachment site (cases)	Anterior wall: 8 Posterior wall: 7	Anterior wall: 8 Posterior wall: 3	

BMI, body mass index; NS, non-significant

Table 2. Neonatal findings

	Oxytocin group	Prostaglandin F2α group	p-values
Birth weight (g)	2930 ± 279.4	2945 ± 332.1	NS
Apgar score (1st min/5th min) < 7 points: Asphyxia (cases)	0	0	NS
pH	7.29 ± 0.05	7.30 ± 0.06	NS
pCO2	45.8 ± 5.30	46.4 ± 13.6	NS
pO2	15.9 ± 5.94	16.3 ± 7.86	NS
BE	-4.2 ± 1.90	-3.1 ± 1.54	NS

BE, pCO2, partial pressure of carbon dioxide; pO2, partial pressure of oxygen

Table 3. Comparison of uterine artery blood flow PI and RI (mean) between oxytocin and prostaglandin F2α groups

	Uterine arterial blood flow (left-right mean)		p-values
	Oxy	PGF	
PI measurement			
Cervical dilation 2-6 cm	1.45 ± 0.28	1.52 ± 0.33	NS
Cervical dilation 6-10 cm	1.74 ± 0.36	1.85 ± 0.43	NS
Cervical dilation 10 cm-	1.60 ± 0.19	1.75 ± 0.22	NS
RI measurement			
Cervical dilation 2-6 cm	0.56 ± 0.03	0.53 ± 0.03	NS
Cervical dilation 6-10 cm	0.61 ± 0.03	0.56 ± 0.03	NS
Cervical dilation 10 cm-	0.61 ± 0.03	0.60 ± 0.03	NS

Oxy, oxytocin group; PGF, prostaglandin F2α group; PI, pulsatility index; RI, resistance index

were observed in the duration of labor, bleeding during labor, or placental weight. There was no difference in birth weight between the groups or in cases of fetal asphyxia based on the Apgar score (Table 2). The umbilical cord blood gas findings were within the normal range in all cases, and no differences were observed between both groups.

A univariate analysis was performed on the mean uterine artery PI and RI.

There were no significant differences observed in PI between the oxytocin and PGF2α groups in any of the three stages of labor (Table 3). In the oxytocin group, uterine arterial blood flow in terms of both RI and PI tended to be the highest at the cervical dilation of 6-10 cm. However, while a similar trend was observed for PI in the PGF2α group, RI was highest at the cervical dilation of ≥ 10 cm to delivery.

Relationship between uterine artery RI and umbilical cord blood gas (pH) findings

Table 3 shows the correlation between the measurements and umbilical artery pH at each stage of cervical dilation in the oxytocin and PGF2α groups. No correlations between RI and pH were observed at any of the cervical dilation stages.

DISCUSSION

The uterine arteries are blood vessels that nourish the uterus and thus become important nutrient vessels for the fetus during pregnancy. The blood flow in the uterine arteries increases with the establishment of pregnancy. The vascular bed rapidly grows as the placenta forms, which causes thromboblasts to destroy and invade the peripheral spiral arteries of the uterine arteries, expanding the fissures in the syncytiotrophoblast, increasing villi in the blood-filled intervillous space, and reducing peripheral vascular resistance. A decline in peripheral vascular resistance is reflected in the uterine artery waveforms. Uterine artery RI is thought to decrease as pregnancy progresses. However, RI is reported to remain high in conditions such as hypertensive disorders of pregnancy and fetal growth restriction, and it can be used to predict the onset of labor[11–13]. This is contrary to what is expected and suggests that this change is specific to the second trimester and could be used in the future as a predictor of placenta previa[14–16]. Another study examined uterine artery and umbilical artery Doppler in pregnant women with low-level maternal complications at 22-24 weeks and 36 weeks of gestation. An increase in the uterine artery RI was associated with a greater incidence of miscarriage, preeclampsia, and fetal growth restriction, and an increase in the uterine artery PI was associated with low birth weight[15, 16]. Elevated uterine and umbilical artery indicators are thought to be associated with the risk of maternal and fetal diseases.Examination of uterine artery RI values at 20-26 weeks, 27-33 weeks, and 34-40 weeks of gestation in pregnant women without complications showed a decrease in RI values with gestational age, with the 20-26 weeks group differing significantly from the 27-33 weeks and 34-40 weeks groups. However, no difference was observed between 27-33 weeks and 34-40 weeks[17]. In this present study, two uterotonics were used in pregnant women without maternal or fetal complications to investigate the effects of each agent on the maternal uterine arteries. The comparison of the oxytocin and PGF2α groups showed that neither drug affected uterine arterial blood flow. Empirically, the contraction patterns when administering oxytocin and PGF2α show persistent, long uterine contractions with PGF2α administration, which raises concerns about its effects on blood flow. However, the present study found no differences between the two agents, indicating that uteroplacental blood flow is not affected by differences in uterotonic agents used.

There have been no previous reports on the relationship between the uterine artery RI value and cord blood pH, and the present study did not observe a relationship.

There are some limitations in this study. First, the sample size was small; thus, reducing the implication of generalization. Second, because uterotonic drugs were used, the contractions were more regular than actual contractions, and it was difficult to maintain the body position for uterine artery measurements due to the intense contractions. Cesarean section has higher complications for the mother than vaginal delivery, so we believe that the choice should be made after careful assessment of the indications.

In this study, measurements of the uterine arteries, which represent the blood flow to the uterus from the mother, in cases without maternal and fetal complications, have shown that uterotonic drugs have a little direct effect on the uterine arteries. In clinical practice, the choice between oxytocin and

PGF2α is left to the attending physician without distinct criteria. PGF2α is contraindicated in patients with a history of glaucoma or asthma, and because oxytocin does not have such contraindications, it is often used. In some cases where oxytocin is not effective in inducing labor, effective contractions can be obtained by switching to PGF2α.

Our study did not observe significant differences in uterine arterial blood flow between the oxytocin and PGF2α groups, indicating that the type of labor-inducing agent did not affect maternal circulation. It was difficult to clarify the characteristics of uterine contraction by measurement of the uterine artery blood flow. Furthermore, because the total infusion volume of PGF2α is larger than that of oxytocin when the infusion load needs to be considered, it may be preferable to select oxytocin as the conventional induction drug. However, in cases where infusion load does not need to be considered, induction of labor with PGF2α should be considered, and reducing the number of cesarean deliveries as much as possible will reduce the risk to the mother.

Subsequently, we would like to examine more cases, evaluate uterine arterial blood flow based on placental attachment site, and investigate PGE2 vaginal suppositories, which we have recently started using at our hospital.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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