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ORIGINAL RESEARCH

Uterine Reaction to Oxytocin and Maternal-Neonatal Outcomes in Inducing Labor: A Retrospective Cohort Study

Huahua Liu[1,*], Zhanhong Fan[2,*], Fan Wu[2,3,*], Mingbo Wang[2], Ziyi Yang[2], Feng Zhang[2]

[1]Affiliated Maternity and Child Health Care Hospital, Nantong University, Nantong, Jiangsu, People's Republic of China; [2]School of Nursing and Rehabilitation, Nantong University, Nantong, Jiangsu, People's Republic of China; [3]Jiangsu Vocational College of Medicine, Yancheng, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Feng Zhang, School of Nursing and Rehabilitation, Nantong University, Nantong, Jiangsu, People's Republic of China, Tel +86 13814715979, Email zhangfeng820909@163.com

Background: Previous studies did not investigate the effect of gradually increasing the concentration of low-dose oxytocin on mother and newborn outcomes. The purpose of this study was to look at the relationship between oxytocin responsiveness and outcomes for both mothers and newborns during labor induction.

Methods: This retrospective cohort study was conducted at Nantong Maternal and Child Health Hospital, and participants were divided into the early reaction to oxytocin group and the later reaction to oxytocin group based on oxytocin response. Primary outcomes included Apgar score at 1 and 5 minutes, umbilical cord artery pH, neonatal intensive care unit admission, and postpartum hemorrhage. Secondary outcomes assessed the duration of labor. Multiple regression models were used to compare maternal and infant outcomes between the two groups.

Results: A total of 1803 participants were finally included in the statistical analysis, with 1083 in the early reaction to oxytocin group and 720 in the later reaction to oxytocin group. After adjusting for potential confounding factors, the risk of a lower 1-minute Apgar score (OR: 1.924, 95% CI: 1.012–3.655), an increased rate of neonatal intensive care unit admission (OR: 2.064, 95% CI: 1.150–3.703), and a higher incidence of postpartum hemorrhage were observed in the later reaction to oxytocin group (OR: 2.342, 95% CI: 1.631–3.361). Additionally, in this group, the first and second phases of labor were seen to be more drawn out ($P<0.001$, $P<0.001$).

Conclusion: Later reaction to oxytocin was consistently associated with lower 1-minute Apgar scores, an increased number of admissions to neonatal intensive care units, a labor's first and second phases lasting a long time, and an increased occurrence of postpartum hemorrhage. These findings underscore the importance of identifying women who exhibit a delayed response to oxytocin in clinical practice.

Trial Registration: The project was retrospectively registered with the Chinese Clinical Trial Registry (TRN: ChiCTR2100047137; 08/06/2021).

Keywords: oxytocin, labor induction, maternal, neonatal, vaginal delivery

Introduction

Oxytocin, a naturally occurring nine-amino acid hypophysial neuropeptide hormone, is primarily synthesized in the posterior pituitary. It is secreted by various physiological sources, including the pituitary gland, corpus luteum, amnion, decidua, and placenta. Oxytocin plays a multifaceted role in influencing the autonomic nervous system and the immune system, with a broad spectrum of effects on overall health, adaptation, development, reproduction, and social behavior.[1] Oxytocin functions by binding to the oxytocin receptor (OTR) and acting on uterine smooth muscle to induce and enhance uterine contractility during labor.[2,3] Additionally, hormonal changes, such as an increase in estrogen and

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corticotrophin-releasing hormone, can lead to the up-regulation of genes necessary for contractions and various uterotonics, including corticotrophin-releasing hormone and prostaglandins, can stimulate the initiation of human parturition.[4] Emerging evidence suggests that the uterine microenvironment, including immune cell infiltration and chemokine signaling, modulates oxytocin responsiveness. For instance, chemokines like CXCL1 and CCL2 regulate macrophage and T-cell infiltration in uterine tissues, which may influence smooth muscle contractility by paracrine signaling.[5] Moreover, immune-related biomarkers such as RGL4 and MITD1, which are associated with memory B cells and natural killer (NK) cell activity, have been linked to tissue responsiveness to hormonal signals, implying a potential role in oxytocin-mediated uterine contractions.[6,7]

It is generally believed that increased sensitivity to oxytocin is fundamental for the onset of labor at term.[8] Women with reduced sensitivity to oxytocin may experience insufficient uterine activity, uterine atony, and labor extension.[9] Inadequate uterine activity is a significant contributor to the failure to achieve spontaneous vaginal birth. In such cases, exogenous oxytocin is administered to induce contractile efforts and facilitate vaginal delivery.[10] Induction of labor involves stimulating uterine contractions before spontaneous labor begins. Modern obstetric practice routinely employs the administration of oxytocin for labor induction.[11] Common indications for labor induction include post-term pregnancy, premature rupture of membranes, pre-eclampsia, and hypertension.[12]

Exogenous oxytocin has been used for labor induction and enhancement in obstetrics for a very long time,[13] as well as the reduction of uterine bleeding during the third stage of delivery.[14] A synthetic formulation known as exogenous oxytocin is structurally like the endogenous oxytocin released by the pituitary gland.[15] Pharmacokinetic studies have revealed an onset time of 3 to 5 minutes and a half-life of 10 to 12 minutes, with each dose achieving a steady state after 30 to 60 minutes, equivalent to 3 to 5 half-lives.[16] Exogenous oxytocin triggers the labor phenotype through a distinct mechanism observed in natural labor. By activating the OTR, microRNA expression is regulated to facilitate the initiation of labor.[17]

In clinical practice, central oxytocin administration for labor induction is typically achieved through intravenous infusion, enabling precise control over the timing and dosage of oxytocin.[18] Previous research has explored the optimal dosing regimen for oxytocin during labor induction, comparing high-dose and low-dose approaches.[19,20] Dosing regimens have varied across studies, with the American College of Obstetricians and Gynecologists (ACOG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) suggesting initial doses ranging from 0.5 to 2 mU/min for low-dose regimens and 4 to 6 mU/min for high-dose regimens as appropriate for labor induction.[21]

Despite these investigations, a consensus regarding the superiority of high-dose versus low-dose oxytocin regimens remains elusive, with the low-dose regimen currently favored in clinical practice.[22] It is important to recognize that the widespread use of oxytocin during labor is not without potential adverse consequences for both mothers and neonates.[23–25] Surprisingly, the effect of gradually increasing the concentration of low-dose oxytocin on maternal and neonatal outcomes has not been rigorously explored, and limited attention has been given to the impact of oxytocin responsiveness on maternal and neonatal outcomes in the context of labor induction.[26]

Therefore, this study aims to conduct a retrospective cohort analysis to investigate the association between oxytocin responsiveness and maternal-neonatal outcomes in women undergoing labor induction during vaginal delivery. The hypothesis of this study is that different responses of the uterus to oxytocin concentrations have differences in pregnancy outcomes and birth outcomes.

Materials and Methods

Study Design and Setting

A retrospective cohort study was conducted at Nantong Maternal and Child Health Hospital from January 1, 2020, to July 31, 2020. This study was performed in line with the principles of the Declaration of Helsinki, and was approved by Nantong Maternal and Child Health Hospital's Ethics Committee (Y2021002). The need for informed consent was waived by the Nantong Maternal and Child Health Hospital's Ethics Committee (Y2021002). Potential participants' eligibility was established by reviewing their medical records. Because all data were anonymized and de-identified prior

to analysis, informed permission was not required. The project was registered with the Chinese Clinical Trial Registry (ChiCTR 2100047137; 08/06/2021).

Participants

Inclusion criteria encompassed healthy women with normal singleton pregnancies (≧37 gestational weeks) who had vaginal births after receiving oxytocin infusion for labor induction. Exclusion criteria included age<18 years, maternal fever, known hypersensitivity to oxytocin therapy, transfer to cesarean section during vaginal delivery, fetal malformation, fetal distress, contracted pelvis, placenta previa, umbilical cord prolapse, transverse position, and prior uterine rupture.

Grouping

In this study, participants were separated into two groups depending on their oxytocin response. The grouping was determined by a professionally trained midwife, who adjusted the infusion rate every 30 minutes until effective contractions occurred. Effective contractions were defined as three contractions within 10 minutes, each lasting 30 seconds, accompanied by cervical dilation and a contractive pressure of 50mmHg. For both groups, the initial dose consisted of 2.5 units of oxytocin diluted in 500 mL of normal saline, with a 2.64 mU/min starting infusion rate.

The "early reaction" group commenced at 2.64 mU/min and saw a 2.64 mU/min incremental rise every 30 minutes until effective uterine contractions were produced. The maximum rate did not exceed 13.2 mU/min.

If effective uterine contractions were not observed at the maximum infusion rate (13.2 mU/min), a new bag of normal saline containing 3.5 units of oxytocin was employed. The infusion rate was 3.76 mU/min, progressively increasing 3.76 mU/min every 30 minutes until effective uterine contractions occurred. The maximum rate did not exceed 18.8 mU/min. If the women still have no effective uterine contractions, midwives change a new bag of normal saline containing 5 units of oxytocin. The infusion rate starts at 5.36 mU/min and is progressively raised by 5.36 mU/min every 30 minutes until effective uterine contractions arise. The maximum is 26.4 mU/min. Women who still did not exhibit effective uterine contractions after reaching an infusion rate of 13.2 mU/min and an increased oxytocin dose were classified as "later reacting" to oxytocin.

Patient and Public Involvement

No patients or members of the public were involved in the design, conduct, reporting, or dissemination of this study.

Primary Outcomes

The Apgar score is a standardized method for assessing the condition of neonates immediately after birth. Following birth, neonates were evaluated based on their activity, pulse, grimace, appearance, and respiration. A score exceeding seven indicated a favorable or excellent neonatal condition. Both the 1-minute and 5-minute Apgar scores were independently assessed by a proficient midwife and a neonatologist.

Umbilical cord arterial blood with a pH less than 7.0 indicated severe asphyxia, while a pH range of 7.0–7.2 indicated mild asphyxia. Following the baby's birth, double-clamped cord segments were used to collect umbilical cord arterial blood in accordance with standard protocol. Samples were taken by specialized midwives and placed in heparinized syringes. Subsequently, blood gases and lactate levels were measured using a Blood Gas Analyzer (GEM4000). Data were obtained from the medical records of the newborns.

Two physicians, including at least one with a senior professional title, made the decision on whether to admit the infant to the neonatal intensive care unit (NICU). Indications for NICU admission included: 1) Tiny for gestational age newborns, extremely low birth weight infants, and premature infants; 2) The neonates with long duration of intrauterine distress or severe asphyxia; 3) Newborns that require artificial ventilation or endotracheal intubation because to frequent apnea or respiratory failure; 4) Diseases of the central nervous system, intracranial bleeding, and hypoxic ischemic encephalopathy.

Postpartum hemorrhage (PPH) was defined as the loss of ≥500 mL of blood within the first 24 hours following vaginal delivery.[27] A bedpan and perineal sheet were placed beneath the woman's buttocks right after fetal birth to

measure postpartum blood loss. By weighing the bedpan and sheet that had blood on them within the first 24 hours, blood loss was calculated.[28]

Secondary Outcomes

The secondary outcomes measured in this study were the duration of labor. Specifically, the period of time from the start of regular uterine contractions to full cervical dilatation was referred to as the first stage of labor. The interval between full cervical dilatation and fetal birth was referred to as the second stage. Lastly, the third stage was defined as the time from fetal delivery to placental delivery. The progress of labor was assessed through independent observation conducted by two midwives.

Confounding Factors

Patient's electronic medical records were used to gather demographic and pertinent clinical information. Included maternal age, residence, ethnicity, occupation pre-pregnancy BMI, gestational weeks, gravidity, parity, neonatal gender, neonatal weight, and complications of pregnancy. All data has been double-checked and recorded.

Management of Vaginal Delivery

Protocol of Inducing Labor

Labor induction with oxytocin was performed when the bishop score reached six or more. If the Bishop score was below six, labor induction with balloon and oxytocin was initiated and evaluated after 12 hours. If the Bishop score reached six or more, women were considered eligible for labor induction.

Management of the First Stage of Labor

The infusion rate of oxytocin was adjusted by midwives based on obstetricians' assessment of uterine contractions and fetal heart rate. Oxytocin was administered through a constant infusion pump. In the case of tachysystole (more than 5 contractions in 10 minutes, averaged over a 30-minute window), oxytocin was discontinued. Failure to achieve effective uterine contractions after three days of oxytocin administration was considered a failed induction.

Management of the Second Stage of Labor

The team consisted of an obstetrician, two midwives, an anesthesiologist, a neonatologist, and a neonatal nurse. They provided personalized care for postpartum women, closely monitoring labor progress, fetal heart rate, contractions, and fetal descent. They also assisted women in finding a comfortable delivery position. When necessary, forceps were used for interventions to facilitate delivery, ensuring safe and efficient operative vaginal delivery. The decision to use forceps was made by two obstetricians in cases such as prolonged second stage of labor due to maternal exhaustion, fetal compromise requiring prompt delivery, and maternal medical disorders requiring avoidance or minimization of pushing.

Management of the Third Stage of Labor

Midwives assisted with placenta delivery, checked for placenta membrane integrity, monitored uterine contractions, and observed vaginal bleeding. Active management was conducted to reduce the risk of severe postpartum blood loss. These interventions include the prophylactic use of uterine tensioning agents before placental delivery, the control of umbilical cord traction and transection after cord clamping, and uterine massage to promote contractions.

Neonatal Resuscitation

Immediate care for neonates involved drying, warmth, and airway clearance. High-risk infants received specialized care from the neonatal resuscitation team, following the Chinese Guidelines for Neonatal Resuscitation (CNR, 2016), which are based on the 2015 American Academy of Pediatrics Guidelines for Neonatal Resuscitation. Our hospital's neonatal resuscitation team consists of a neonatologist, a midwife, and a doctor of anesthesia.

Administration for Prevention of PPH

To prevent postpartum hemorrhage (PPH), postpartum prophylactic oxytocin was administered (oxytocin 10 units IV or intramuscularly). In cases where women experienced hemorrhage of ≥500 mL within 2 hours of delivery, oxygen and

intravenous access were promptly established, vital signs were closely monitored, and ergometrine and carboprost tromethamine were administered under the supervision of the obstetrician. Uterine tamponade techniques, including the use of an intrauterine balloon catheter, intrauterine tamponade, and vacuum-induced uterine tamponade, were performed in patients with tension or subsegmental hemorrhage.

Sample Size and Statistical Analysis

According to research, approximately 17% of women experience PPH > 500 mL after vaginal delivery.[29] Using the PASS 15 software, the sample size was calculated based on the incidence rate of negative childbirth experiences (π) as 17%, with a margin of error of 0.1π. A two-tailed test was conducted with a significance level of $\alpha = 0.10$. The required sample size was found to be 1379 participants. Considering a 30% dropout rate, the final sample size was set at 1793 participants.

The data were analyzed using statistical software (IBM SPSS Statistics 25.0). Baseline dichotomous data were given as percentages and numbers, whereas baseline continuous data were shown as averages and standard deviations (SD). Variations between groups were analyzed using the Student's *t*-test for continuous data and chi-square for categorical data. Logistic regression models were applied to explore the unadjusted and adjusted odds ratios (ORs) for 1-minute Apgar score, admission to NICU, and postpartum hemorrhage (PPH) associated with the reaction to oxytocin. The length of the first and second phases of labor was examined using multiple linear regressions. A significance level of $P < 0.05$ was used to declare statistical significance.

Results

Mother and Infant Characteristics

A total of 1950 participants were included, and 147 were excluded. Including maternal fever (n=21), known hypersensitivity to oxytocin therapy (n=21), transfer to cesarean section during vaginal delivery (n=15), fetal malformation (n=13), fetal distress (n=25), contracted pelvis (n=14), placenta previa (n=11), umbilical cord prolapse (n=9), transverse position (n=15), and prior uterine rupture (n=3). A total of 1803 participants were finally included in the statistical analysis.

Of the 1803 evaluated mother-infant dyads, 1083 were in the early reaction to oxytocin group, and 720 were in the later reaction to oxytocin group. No difference was found in baseline information between the two groups: marriage (χ^2=0.000, *P*=0.993), residence (χ^2=0.114, *P*=0.735), employment (χ^2=3.715, *P*=0.054), gestational age (t=−0.973, *P*=0.331). Among the 1803 enrolled, women who were later reacting to oxytocin were younger (t=−2.257, *P*=0.024), with higher pre-pregnancy BMI (t=−3.032, *P*=0.002), fewer gravidities (χ^2=8.415, *P*=0.004), lower Bishop score (t=6.690, *P<0.001*), more balloon inducing labor (χ^2=58.759, *P<0.001*) and higher rate of women with clear amniotic fluid (χ^2=13.667, *P*=0.003) (Table 1).

The mean and median total dose of oxytocin of women who were early reacting to oxytocin were 3.44 UI and 2.5 UI, of women who were later reacting to oxytocin were 7.64 UI and 6.0 UI (Z=−37.037, *P<0.001*). The total duration of oxytocin administration was 224.21±115.36 min for women who were early reacting to oxytocin, while 453.69 ±244.61 min (t=−23.496, *P<0.001*) for women who were later reacting to oxytocin.

Maternal and Neonatal Outcomes

There was a decrease in the 1-minute Apgar score in the later reaction to oxytocin group (χ^2=4.512, *P*=0.034). The 5-minute Apgar score (χ^2=0.254, *P*=0.688) and the umbilical cord arterial blood pH (χ^2=2.900, *P*=0.235) had no significant difference between the two groups. There was an increase in the rate of NICU admission in the later reaction to oxytocin group (4.17% vs 1.94%, *P*=0.005). The incidence of PPH was increased in the later reaction to oxytocin group (12.08% vs 5.36%, *P<0.001*).

In the delayed reaction to oxytocin group, the first and second stages of labor lasted longer (429.37±291.36 vs 361.79 ±162.13, *P<0.001*; 50.09±39.81 vs 35.72±28.86, *P<0.001*). The length of the third stage of labor had no significant difference (t=−0.574, *P*=0.566) (Table 2).

Table 1 Demographic Characteristics for Mothers and Neonates (n=1803)

	Early Reaction to Oxytocin Group n=1083 N (%)/$\bar{x} \pm s$	Later Reaction to Oxytocin Group n=720 N (%)/$\bar{x} \pm s$	χ^2 /t	P
Age(years)	27.77±3.88	27.37±3.51	2.257	0.024
Marital status			0.000	0.993
Single	27(2.49)	18(2.50)		
Married	1056(97.51)	702(97.50)		
Residence			0.114	0.735
Countryside	954(88.09)	638(88.61)		
City	129(11.91)	82(11.39)		
Occupation			3.715	0.054
Employed	867(80.10)	549(76.30)		
Unemployed	216(19.90)	171(23.80)		
Pre-pregnancy BMI(kg/m^2)	21.28±2.96	21.74±3.25	−3.032	0.002
Gestational weeks(week)	38.92±1.61	39.00±1.50	−0.973	0.331
Gravidity			8.415	0.004
1–2	905(83.56)	637(88.47)		
≥3	178(16.44)	83(11.53)		
Parity			3.505	0.061
1–2	1060(97.88)	713(99.03)		
≥3	23(2.12)	7(0.97)		
Bishop score	4.98±1.57	4.50±1.39	6.690	<0.001
Balloon inducing labor			58.759	<0.001
Yes	112(10.30)	171(23.70)		
No	971(89.70)	549(76.30)		
Meconium-stained amniotic fluid			13.667	0.003
Clear amniotic fluid	918(84.77)	618(85.83)		
Grade one meconium-stained liquor	44(4.06)	13(1.81)		
Grade two meconium-stained liquor	48(4.43)	21(2.92)		
Grade three meconium-stained liquor	73(6.74)	68(9.44)		
Presentation of fetus			3.791	0.150
LOA	1070(98.80)	704(97.78)		
ROA	8(0.74)	7(0.97)		
Others	5(0.46)	9(1.25)		
Gender of neonate			2.023	0.155
Boy	571(52.72)	355(49.31)		
Girl	512(47.28)	365(50.69)		
Neonatal weight				
Small for gestational age	25	16	2.445	0.295
Normal birthweight	998	651		
Macrosomia	60	53		

Abbreviations: BMI: Body Mass Index; ROA: Right Occiput Anterior; LOA: Left Occiput Anterior.

Adjusted Maternal and Neonatal Outcomes

The unadjusted ORs for 1-minute Apgar score, admission to NICU, and PPH associated with later reaction to oxytocin were 1.976 (95% CI: 1.042–3.748), 2.199 (95% CI: 1.249–3.872), and 2.429 (95% CI: 1.717–3.435).

After adjusting for the pre-pregnancy BMI, age, gravidity, parity, bishop score, balloon inducing labor, meconium-stained amniotic fluid and neonatal weight, later reaction to oxytocin had a significant positive association with 1-minute Apgar score (OR: 1.924, 95% CI: 1.012–3.655), admission to NICU (OR: 2.064, 95% CI: 1.150–3.703), and PPH (OR: 2.342, 95% CI: 1.631–3.361).

Table 2 Maternal and Neonatal Outcomes (n=1803)

	Early Reaction to Oxytocin Group n=1083 N (%)/$\bar{x} \pm s$	Later reaction to Oxytocin Group n=720 N (%)/$\bar{x} \pm s$	χ^2 /t	P
1-minute Apgar score			4.512	0.034
≥8	1066(98.40)	698(96.90)		
0–7	17(1.60)	22(3.10)		
5-minute Apgar score			0.254	0.688
≥8	1080(99.7)	717(99.60)		
0–7	3(0.30)	3(0.40)		
Umbilical arterial blood pH			2.900	0.235
<7.0	8(0.70)	10(1.40)		
7.0–7.2	331(30.60)	235(32.60)		
>7.2	744(68.70)	475(66.00)		
Admission to the neonatal intensive care unit			7.808	0.005
No	1062(98.06)	690(95.83)		
Yes	21(1.94)	30(4.17)		
Postpartum hemorrhage			26.470	<0.001
No	1025(94.64)	633(87.92)		
Yes	58(5.36)	87(12.08)		
First stage of labor(min)	361.79±162.13	429.37±291.36	−6.305	<0.001
Second stage of labor(min)	35.72±28.86	50.09±39.81	−8.340	<0.001
Third stage of labor(min)	6.49±15.28	6.84±6.79	−0.574	0.566

Table 3 Adjusted Maternal and Neonatal Outcomes

	Unadjusted OR (95% CI)/Unstandardized B (95% CI)	Adjusted OR (95% CI)/ Standardized Coefficients Beta (95% CI)
1-minute Apgar score	1.976(1.042–3.748)	1.924(1.012–3.655)
Admission to the neonatal intensive care unit	2.199(1.249–3.872)	2.064(1.150–3.703)
Postpartum hemorrhage	2.429(1.717–3.435)	2.342(1.631–3.361)
First stage of labor(min)	67.367(46.347–88.387) [a]	0.147(0.101–0.192) [b]
Second stage of labor(min)	13.898(10.686–17.110) [a]	0.199(0.152–0.244) [b]

Notes: Multiple regressions adjusted for pre-pregnancy BMI, age, gravidity, parity, bishop score, balloon inducing labor, meconium-stained amniotic fluid and neonatal weight. [a]Unstandardized B (95% CI), calculated from multiple linear regression. [b]Standardized Coefficients Beta (95% CI), calculated from multiple linear regression.

After adjusting for the pre-pregnancy BMI, age, gravidity, parity, bishop score, balloon inducing labor, meconium-stained amniotic fluid and neonatal weight, there was still a significant association between the later reaction to oxytocin and the duration of labor's first and second stages (*P<0.001, P<0.001*) between the two groups (Table 3).

Discussion

In this research, a delayed response to oxytocin was linked to a considerable decline in the 1-minute Apgar score, an increased rate of NICU admissions, and PPH, after adjusting for pre-pregnancy BMI, age, gravidity, parity, bishop score, balloon inducing labor, meconium-stained amniotic fluid and neonatal weight. Compared to women who responded early to oxytocin, those with a later reaction received a higher total dose of oxytocin, and the total duration of oxytocin administration was longer. Additionally, the length of the first and second stages of labor was longer in women with later reaction to oxytocin.

Our research demonstrated that later reaction to oxytocin increased the risk of a 1-minute Apgar score of less than 7 and NICU admission. There was also a slight increase in the incidence of a 5-minute Apgar score of less than 7 in women

with a later reaction to oxytocin (0.4% vs 0.3%), but it did not reach statistical significance. Furthermore, the percentage of women with umbilical cord arterial blood pH≤7.2 was slightly higher in the later reaction to oxytocin group (34%) compared to the early response group (31.3%), nonetheless, this distinction lacked statistical significance. This may be associated with prolonged labor. According to one study, the risk of newborn problems increases when the second stage of labor is prolonged. NICU hospitalization and a 5-minute Apgar score of less than 7 were both more likely in second-stage labor that lasted longer.[30]

The uterine response to oxytocin varied among pregnant women. In near-term pregnant women, there was a significant increase in the number of high-affinity OTR.[31] The uterus exhibited a delayed reaction to oxytocin because a substantial amount of oxytocin was secreted during labor, leading to continuous and prolonged exposure of cultured human myometrial cells to oxytocin. This down-regulated oxytocin receptors and reduced OTR mRNA expression,[32] resulting in the down-regulation and reduction of oxytocin binding sites and decreased responsiveness of myometrial cells, studies have shown that the response time for oxytocin receptor desensitization increases with concentration, taking ≥2 hours for high concentrations (10^{-5} M), ≥4 hours for moderate concentrations (10^{-8} M), and progressively worsening up to 6 hours, beyond which tissue viability declines.[33] Continued increases in oxytocin during prolonged labor could lead to oxytocin receptor desensitization, making oxytocin less effective in producing regular uterine contractions.[34] Desensitization of OTR can manifest as a reduction in oxytocin-induced contractility, contributing to labor progression failure, intrapartum uterine atony, and PPH.[35] It's worth noting that uterine atony was the second most common indication for emergency peripartum hysterectomy and was associated with prolonged labor, significant maternal and perinatal morbidity, and mortality.[36] Similarly, our study found that women with a later reaction to oxytocin had a longer length of the first and second stages. Another study also found that prolonged oxytocin exposure during labor increases the risk of postpartum hemorrhage (PPH) secondary to uterine atony, possibly due to oxytocin desensitization.[37] Likewise, our study found that women with a delayed reaction to oxytocin had an increased risk of PPH.

In addition, oxytocin is an effective uterine agonist widely used to induce labor and shorten its duration. Despite its common use in clinical practice, there is little consensus regarding the optimal oxytocin dose for labor induction.[38] The therapeutic range of oxytocin is narrow, and the ideal infusion rate varies considerably for each laboring woman.[39] Full compliance with the standard oxytocin dosing regimen has been shown to reduce postpartum hemorrhage but increases the risk of cesarean delivery.[40,41] A review has indicated that oxytocin reduces maternal stress levels and inflammation, with some effects on mothers and newborns during and after labor.[42] Therefore, obstetricians should closely monitor the short- and long-term responses to oxytocin in pregnant women and newborns, and should develop personalized oxytocin applications for near-term pregnancies.

The significant finding in our study was the association between a delayed response to oxytocin and maternal and neonatal outcomes in women undergoing labor induction. Therefore, in cases of oxytocin labor induction, it is crucial to assess the response to oxytocin. Identifying individuals with a delayed response as early as possible and providing close monitoring is essential. It is necessary to closely observe the oxytocin infusion dose and uterine contractions for these individuals, paying special attention to the 1-minute Apgar score, PPH, and the duration of labor. Assessing the risk of PPH and developing prevention programs for women with a delayed response to oxytocin can be beneficial. Individualized treatment plans should be developed, and multidisciplinary collaboration should be actively pursued in case of adverse situations. Furthermore, additional research is needed to better understand the mechanisms contributing to adverse perinatal outcomes associated with a delayed response to oxytocin.

This study has several limitations. First, as a retrospective study, there is a potential for selection bias, which may affect the subjective assessment results. Second, participants' "early" and "late" responses to oxytocin were determined based on titration limits, which, although the groupings were determined by professionally trained midwives, may still introduce some bias into the results. Third, individual differences among participants may influence their response to oxytocin. Although adjustments were made for factors such as age, BMI, and number of pregnancies, other factors (such as lifestyle) were not fully controlled for, potentially introducing confounding variables. Finally, this is a single-center study, and the standards for oxytocin use may vary between hospitals or regions, including differences in dosage and titration rate, which could limit the generalizability of the study's results.

Conclusion

We have discovered that a delayed response to oxytocin increases the chance of a lower 1-minute Apgar score, NICU admission, prolonged durations of the first and second stages of labor, and an increased likelihood of experiencing PPH. These associations hold true even after adjusting for variables such as pre-pregnancy factors, age, gravidity, Bishop score, balloon-induced labor, and meconium-stained amniotic fluid. It is both imperative and meaningful to identify women who exhibit a delayed response to oxytocin as early as possible. Subsequent research endeavors should focus on evaluating the impact of this delayed response to oxytocin, including its effects on oxytocin dosage, especially in the context of labor induction for women.

Data Sharing Statement

Data used for analyses, and the analytic code are available from the corresponding author on request.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki, and was approved by Nantong Maternal and Child Health Hospital's Ethics Committee (Y2021002). The need for informed consent was waived by the Nantong Maternal and Child Health Hospital's Ethics Committee (Y2021002). Potential participants' eligibility was established by reviewing their medical records. Because all data were anonymized and de-identified prior to analysis, informed permission was not required.

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

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Disclosure

The authors have stated explicitly that there are no conflicts of interest in connection with this article. Authors' statement that the views expressed in the submitted article are their own and not an official position of the institution or funder.

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