Oxytocin Discontinuation During Induced Labor in Pregnancies With Suspected Fetal Growth Restriction

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Research article

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Abstract

Objective: Although fetal growth restriction (FGR) is associated with an increased risk of cesarean delivery during induced labor, there is little evidence to guide labor management in such cases. This study aimed to investigate whether discontinuation of oxytocin infusion affects the cesarean delivery rate and the risk of maternal and neonatal complications associated with induced labor in pregnancies with suspected FGR.

Methods: This was a retrospective cohort study of singleton pregnancies with vertex presentation and indications for labor induction due to FGR after 34.0 weeks of gestation at our institution from January 2010 to December 2017. Two parallel groups were compared: women who received oxytocin continuously until delivery (continuation group) and women whose oxytocin was discontinued at the beginning of the active phase of labor (discontinuation group).

Results: There were 74 women in the continuation group and 51 women in the discontinuation group. The incidence of cesarean deliveries was higher (5.4% vs 2.0%) in the continuation group, but this difference was not statistically significant. However, the incidence of uterine tachysystole (23.0% vs 9.8%) was significantly higher in the continuation group than in the discontinuation group. Differences in labor management did not affect the lengths of the active phase and second stage of labor (mean, 136 ± 122 minutes and 34.2 ± 45 minutes, respectively; 122 ± 104 minutes and 48.8±67 minutes in the continuation group and discontinuation group, respectively). The incidence of postpartum hemorrhage and adverse neonatal outcomes were not significantly different between groups.

Conclusions: Oxytocin can be safely discontinued after the active phase of labor in women undergoing labor induction for FGR without an increased risk of cesarean delivery or other unfavorable outcomes. Therefore, this strategy may be considered an alternative to continued oxytocin infusion.

Background

When a fetus is diagnosed with growth restriction, the main priority is to deliver that fetus in optimum condition. Because fetal growth restriction (FGR) is possibly associated with fetoplacental insufficiency, the pregnancy should be considered at high risk and managed as such. Furthermore, the possibility of hypoxic fetal status and the timing of delivery should be considered. FGR is associated with an increased risk of cesarean delivery in circumstances of non-reassuring fetal status (NRFS) during induced labor, but there is no indication for elective cesarean delivery because of FGR alone [1]. Previous studies have focused on delivery timing and outcomes according to delivery mode for FGR [1–4]. Although these indications for labor induction are common, there is little evidence to guide labor management in such cases.

Oxytocin has been the most commonly used agent to induce labor, although its use has been associated with an increased risk of labor complications, including uterine tachysystole, water intoxication, and uterine rupture [5, 6]. Although there is no consensus regarding the method of administration at the time

of induction, it is common practice to adjust the dosage while observing uterine contractions to prevent adverse events. Recent reports have suggested that discontinuation of oxytocin infusion during the active phase of labor significantly lowered the risk of uterine tachysystole and cesarean delivery [7–15]. Uterine tachysystole is considered to affect fetuses with FGR more adversely than fetuses whose size is appropriate for gestational age (AGA). However, to the best of our knowledge, there are no previous studies of oxytocin discontinuation during the active phase of labor in women undergoing labor induction for FGR. Therefore, it is necessary to establish a method of safely using oxytocin during induced labor for FGR. This study investigated whether oxytocin discontinuation after the active phase of labor in cases of FGR at or near term affected the cesarean delivery rate and the risk of maternal and neonatal complications, including uterine tachysystole.

Methods

This study was a retrospective cohort study of women who underwent labor induction because of FGR at or near term at Osaka University Hospital from January 2010 to December 2017. The study protocol was approved by the Osaka University Ethics Committee and conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was not obtained because of the retrospective study design. The data were anonymized.

FGR was defined as fetal growth < 1.5 standard deviations (SD) below the mean estimated fetal body weight (EFBW) according to gestational age, and it was calculated based on the Japanese standard using ultrasonography data [16]. Women were included if the gestational age was at least 34 0/7 weeks, if they were scheduled for labor induction because of FGR, and if they carried a singleton fetus in vertex presentation. Initial exclusion criteria included stillbirth, multiple gestations, fetuses with congenital malformations or chromosomal abnormalities, previous cesarean delivery, and serious maternal complications. Subsequent exclusion criteria included women who delivered without oxytocin, who had cesarean deliveries before achieving the active phase of labor, and who delivered after the discontinuation of oxytocin before the active phase of labor.

We extracted information regarding the maternal obstetric history, antepartum records, and labor and delivery records. Doppler velocimetry was performed by experienced obstetricians. Flow-velocity waveforms were obtained from the umbilical artery (UmA) and the middle cerebral artery (MCA). The cerebroplacental ratio (CPR), a known predictor of the perinatal prognosis for FGR, was calculated as the ratio between the MCA pulsatility index (PI) and the UmA PI. Regarding the timing of delivery, delivery was performed at 38 0/7 to 39 6/7 weeks of gestation in cases of isolated FGR and at less than 37 6/7 weeks of gestation in cases of FGR with additional risk factors, such as oligohydramnios, abnormal UmA or MCA Doppler study results, and maternal comorbidities [17]. At our institution, women who undergo labor induction require cervical ripening with intracervical balloon placement (usually filled with 30 mL of water) the day before oxytocin administration and are continuously monitored during this time. Women with a favorable Bishop score are induced with oxytocin alone.

From January 2010 to December 2013, oxytocin was routinely and continuously administered at the same dose at the beginning of the active phase of labor (continuation group). Oxytocin was administered until delivery unless there was an indication for discontinuing infusion. From January 2014 to December 2017, oxytocin was discontinued, or the dose was reduced by half at the beginning of the active phase of labor (discontinuation group). Oxytocin infusion was restarted or administered at an increased dose when labor stalled. The “active” phase was defined as cervical dilatation ≥ 4 cm with regular uterine contractions for both primiparous and multiparous women. The starting dose of oxytocin infusion was 2 mIU/min, which was increased by 2 mIU/min every 30 min. The maximum dose of oxytocin was 20 mIU/min until regular contractions at a rate of three to five every 10 min were achieved. The timing of cervical examinations was decided by the attending physicians during the latent phase of labor unless changes in the fetal status or maternal labor symptoms indicated the need for more frequent assessments.

We determined the primary and secondary outcomes prior to data extraction. The primary outcome was between-group differences in the cesarean delivery rate. Secondary outcomes of interest were broadly divided into labor and delivery-related outcomes and neonatal outcomes. The former group included uterine tachysystole (defined as > 5 contractions per 10 minutes averaged over a 30-minute period), mode of delivery, indications for cesarean delivery, postpartum hemorrhage, and duration of labor for women who delivered vaginally (active phase and second stage of labor). The latter group included Apgar score and umbilical artery pH. Additionally, because there were women who had continued oxytocin infusion in the discontinuation group, and because there were women who had discontinued oxytocin infusion in the continuation group, analyses were performed based on actual treatment that the women received.

We performed a power analysis, which estimated that 152 women were needed to detect a difference in the cesarean delivery rate of 15% between groups to achieve 80% power and an α-value of 0.05. Based on previous studies, a 15% difference between groups was selected [11, 18]. A statistical analysis was performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA). Data were presented as the mean ± SD, and statistical comparisons between groups were performed using the Student t-test, chi-squared test, or Wilcoxon rank-sum test. $P < 0.05$ was considered statistically significant.

Results

During the study period, 163 women underwent labor induction due to FGR with a singleton fetus in vertex presentation after 34 gestational weeks. Of these women, 38 were excluded because they had deliveries without oxytocin, cesarean deliveries before the active phase of labor, or deliveries involving the discontinuation of oxytocin before the active phase of labor (Fig. 1). A total of 125 women were included in this study, and they were separated into the continuation group (n = 74) and the discontinuation group (n = 51). Oxytocin was continued in 85.1% (63/74) of women in the continuation group; however, oxytocin was discontinued in four women and reduced by half in seven women in that group. Oxytocin was discontinued or reduced by half in 62.7% (32/51) of women in the discontinuation group; however, in that

group, 8 women needed reinfusion of oxytocin due to labor arrest and 12 women did not need oxytocin reinfusion (Fig. 1).

Characteristics of all the women are presented in Table 1. There were no significant differences in maternal age, parity, body mass index, Bishop score, and cervical ripening between groups. Table 2 shows the fetal ultrasound and Doppler study results within 2 weeks of delivery. There were no significant differences in the timing of the scan, EFBW, SD for the EFBW, and CPR. The between-group difference in the primary outcome (the cesarean delivery rate) did not reach statistical significance (5.4% vs 2.0% for the continuation group and discontinuation group, respectively; p = 0.33) (Table 3). Regarding the secondary outcomes, the uterine tachysystole rate was significantly higher in the continuation group than in the discontinuation group (23.0% vs 9.8%; p = 0.04). The spontaneous vaginal delivery rate was more than 80% in both groups. There were no statistically significant between-group differences in NRFS and non-progression of labor rates. The vacuum extraction rate was slightly lower in the continuation group, but it was not statistically significant. The postpartum hemorrhage rate was similar in both groups. There were no significant differences in neonatal outcomes, including birthweight, small for gestational age percentage, Apgar score, and umbilical cord pH (Table 4). The active phase of labor was longer by 14 minutes and the second stage of labor was shorter by 14 minutes in the continuation group (70 women reached the active phase of labor and delivered vaginally) compared to the discontinuation group (50 women), but these differences were not statistically significant (Table 5).

Table 1
Baseline maternal characteristics

Characteristic	Continuation group (n = 74)	Discontinuation group (n = 51)	*P* value
Maternal age (years)	31.5 ± 5.1	32.1 ± 5.2	0.59
Parity, n (%)			
Nulliparous	42 (56.8)	36 (70.6)	0.11
BMI (before pregnancy)	21.1 ± 4.1	19.8 ± 2.4	0.08
Gestational age (weeks)	37.4 ± 1.2	37.6 ± 1.5	0.09
Smoker, n (%)	4 (5.4)	4 (7.8)	0.58
ART, n (%)	8 (10.8)	4 (7.8)	0.58
Epidural analgesia, n (%)	4 (5.4)	4 (7.8)	0.58
Oligohydramnios, n (%)	4 (5.4)	5 (9.8)	0.27
Hypertensive disorders, n (%)	10 (13.5)	7 (13.7)	0.97
Cervical ripening, n (%)	68 (91.9)	41 (80.4)	0.05
Bishop score ≥ 4, n (%)	12 (16.2)	12 (23.5)	0.34
Amniotomy, n (%)	44 (59.5)	25 (49.0)	0.25
Data were analyzed using the Student t-test, chi-squared test, Fisher exact test, or Wilcoxon rank-sum test, as appropriate.			
Results are provided as n (%) or mean ± standard deviation (SD).			
BMI, body mass index. ART, artificial reproductive technology.			

Table 2
Ultrasound and Doppler findings of the fetuses

Parameter	Continuation group (n = 74)	Discontinuation group (n = 51)	*P* value
GA at ultrasound (weeks)	36.4 ± 1.3	36.6 ± 1.8	0.51
EFBW (g)	2147 ± 289	2186 ± 307	0.54
EFBW (SD)	-1.86 ± 0.6	-1.78 ± 0.5	0.52
CPR	1.61 ± 0.5	1.47 ± 0.4	0.17
CPR < 5 percentile, n (%)	11 (14.9)	11 (21.6)	0.33
Data were analyzed using the Wilcoxon rank-sum test, as appropriate.			
Results are given as mean ± standard deviation (SD).			
GA, gestational age; EFBW, estimated fetal body weight; CPR, cerebroplacental ratio.			

Table 3
Labor and delivery outcomes

	Continuation group (n = 74)	Discontinuation group (n = 51)	*P* value
Uterine tachysystole, n (%)	17 (23.0)	5 (9.8)	0.04
Abnormal fetal heart rate, n (%)	26 (35.1)	20 (39.2)	0.64
Mode of delivery, n (%)			
Spontaneous vaginal delivery	62 (83.8)	41 (80.4)	0.62
Instrumental delivery	8 (10.8)	9 (17.7)	0.27
Cesarean delivery	4 (5.4)	1 (2.0)	0.33
Indications for cesarean delivery, n (%)			
NRFS	1 (1.4)	1 (2.0)	0.79
Non-progression of labor	3 (4.1)	0 (0)	0.15
Postpartum hemorrhage (mL)	373 ± 234	395 ± 226	0.41
Maximal dose of oxytocin (mU/min)	12.4 ± 4.9	12.3 ± 5.8	0.88
Duration of oxytocin infusion (min)	417 ± 192	417 ± 386	0.06

Data were analyzed using the Student t-test, chi-squared test, or Wilcoxon rank-sum test, as appropriate. Results are provided as n (%) or mean ± standard deviation (SD).

NRFS, non-reassuring fetal status.

Table 4
Neonatal outcomes

	Continuation group (n = 74)	Discontinuation group (n = 51)	*P* value
Birthweight (g)	2136 ± 360	2184 ± 348	0.26
SGA, n (%)	52 (70.3)	39 (76.5)	0.44
Apgar score < 7 at 1 min, n (%)	6 (8.1)	2 (3.9)	0.35
Apgar score < 7 at 5 min, n (%)	0 (0)	2 (3.9)	0.09
Umbilical artery pH < 7.10, n (%)	1 (1.4)	3 (5.9)	0.16
Umbilical artery pH	7.30 ± 0.08	7.29 ± 0.07	0.42
Data were analyzed using the Student t-test, chi-squared test, or Wilcoxon rank-sum test, as appropriate. Results are provided as n (%) or mean ± standard deviation (SD).			
SGA, small for gestational age.			

Table 5
Length of labor for women who delivered vaginally

Time interval (min)	Continuation group n = 70	Discontinuation group n = 50	*P* value
Active phase of labor	136 ± 122	122 ± 104	0.50
Second stage of labor	34.2 ± 45	48.8 ± 67	0.39
From induction until delivery	431 ± 188	499 ± 391	0.77
Data were analyzed using the Wilcoxon rank-sum test, as appropriate.			
Results are given as mean ± standard deviation (SD).			

Finally, an analysis was performed based on the actual treatment received by the women. During the study period, 82 women received continuous oxytocin and 43 women received discontinued oxytocin or a half-dose of oxytocin. The uterine tachysystole rate was significantly higher in the continuation group than in the discontinuation group (23.2% vs 7.0%; p = 0.02). The abnormal fetal heart rate incidence was also significantly higher in the continuation group than in the discontinuation group (42.7% vs 25.6%; p = 0.04). However, the cesarean delivery rate was similar in both groups (4.9% vs 2.3% for the continuation group and discontinuation group, respectively) (Table 6).

Table 6
Labor and neonatal outcomes of women according to the actual treatment received

	Continuation group (n = 82)	Discontinuation group (n = 43)	*P* value
Uterine tachysystole, n (%)	19 (23.2)	3 (7.0)	0.02
Abnormal fetal heart rate, n (%)	35 (42.7)	11 (25.6)	0.04
Mode of delivery, n (%)			
Spontaneous vaginal delivery	67 (81.7)	36 (83.7)	0.78
Instrumental delivery	11 (13.4)	6 (14.0)	0.93
Cesarean delivery	4 (4.9)	1 (2.3)	0.49
Indications for cesarean delivery, n (%)			
NRFS	2 (2.4)	0 (0)	0.30
Non-progression of labor	2 (2.4)	1 (2.3)	0.97
Indications for cesarean and instrumental delivery, n (%)			
NRFS	12 (14.6)	4 (9.3)	0.40
Non-progression of labor	3 (3.7)	3 (7.0)	0.41
Maximal dose of oxytocin (mU/min)	12.3 ± 5.5	12.5 ± 4.8	0.80
Duration of oxytocin infusion (min)	373 ± 290	345 ± 291	0.56
Active phase of labor (min)	133 ± 117	125 ± 110	0.49
Second stage of labor (min)	41.6 ± 59	38.0 ± 49	0.63
Data were analyzed using the Student t-test, chi-squared test, or Wilcoxon rank-sum test, as appropriate.			
Results are provided as n (%) or mean ± standard deviation (SD).			
NRFS, non-reassuring fetal status.			

Discussion

To our knowledge, this study is the first to report outcomes associated with oxytocin discontinuation after the active phase of labor that was induced because of FGR. Our findings suggest that the cesarean delivery rate does not change based on whether oxytocin is continued or discontinued. However, compared to the continuation group, the incidence of uterine tachysystole was lower in the

discontinuation group. Discontinuation of oxytocin was not associated with a longer duration of the active phase of labor and the second stage of labor when compared to the equivalent metric in the continuation group. Oxytocin can be safely discontinued after the active phase of labor without increasing the risk of cesarean delivery or other unfavorable outcomes.

Previous studies have reported that because the delivery of newborns with FGR is associated with NRFS, the rate of cesarean delivery is high (14-40.9%) [18–23], particularly in cases with low CPR [23]. The indication for cesarean delivery was fetal distress in 9.5–29% of these cases [18–20]. In our study, because women who experienced cesarean delivery before the active phase of labor were excluded, the cesarean delivery rate was only 4% (5/127). However, after including women who have experienced cesarean delivery before the active phase of labor, the total cesarean delivery rate was 14.1% (23/163), which is consistent with previous reports. Regarding the decision to induce labor in cases of FGR, the choice to perform cesarean delivery due to NRFS is often made before the active phase of labor. In our study, the cesarean delivery rate was lower than expected for women who had entered the active phase labor, and the majority of women delivered vaginally. As a result, we could not find a significant difference in the cesarean delivery rates of the continuation group and discontinuation group. However, the frequency of uterine tachysystole was lower in the discontinuation group than in the continuation group. A previous meta-analysis of nine randomized controlled trials compared continuation and discontinuation of oxytocin after the active phase of labor and its effect on labor induction and labor augmentation [7–15, 24]. In that meta-analysis, oxytocin discontinuation after the active phase of labor significantly lowered the cesarean delivery rate (9.3% vs 14.7%) and uterine tachysystole rate (6.2% vs 13.1%) compared with oxytocin continuation until delivery [24]. When labor enters the active phase, further oxytocin administration does not seem to have any benefit except for shortening the labor length. However, it is associated with some adverse events; therefore, decreased use of oxytocin is encouraged [25, 26]. Because the cause of FGR is associated with placental dysfunction, and because FGR is a risk factor for fetal heat rate abnormalities, uterine tachysystole associated with the inappropriate or excessive use of oxytocin should be reduced.

Discontinuing oxytocin did not prolong the active phase of labor or second stage of labor. On the contrary, the duration of labor in cases of FGR was short compared to what is generally considered to be the induction time for AGA fetuses, and we had to use caution because of the rapid progression of labor. It has been reported that the rate of precipitous delivery, defined as delivery of the fetus within less than 3 hours of the commencement of regular contractions, of infants with low birthweight (less than 2500 g) is high (28.5%) [27]. Precipitous delivery is concerning because it is a known risk factor for fetal stress and respiratory distress in newborns [28], and insufficient time for newborn resuscitation is a possibility. A short delivery time is by no means an advantage in labor induction for FGR. In our study, although we could not reduce the length of labor and delivery, uterine tachysystole was reduced, thus leading to the possibility of less fetal distress. In 2014, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommended that the definition of active phase of labor should be revised to include cervical dilatation of 6 cm [29]. However, this recommendation does not distinguish between a fetus with FGR and a fetus with AGA. We identified one previous study that investigated labor

progression in preterm deliveries [30] and reported that the median traverse time from 5 to 6 cm of cervical dilation was less than 30 minutes for nulliparous and multiparous women. After achieving 6 cm of dilatation, both groups rapidly progressed to 10 cm (median, 18 minutes). Therefore, the authors speculated that the true active phase of labor begins at 5 cm of cervical dilatation in preterm births. Regarding labor and delivery, it is possible to infer that the onset of the active phase of labor occurs earlier in cases of FGR at or near term than in cases of AGA at term. Therefore, the definition of the active phase of labor as cervical dilatation ≥ 4 cm was suitable for our study. After cervical dilatation ≥ 4 cm with labor induction for FGR, attention should be focused on the rapid progression of labor and clinicians should consider discontinuing or reducing oxytocin infusion to prevent uterine tachysystole.

There were some limitations associated with this study. First, this was a retrospective cohort study based on data from a single institution where a limited number of women fulfilled the inclusion criteria. The population included both parous and nulliparous women. Stratification according to parity would have been beneficial, but the study population was too small. Moreover, oxytocin could not be discontinued in some women assigned to the discontinuation group (19/51; 37%). Furthermore, oxytocin had to be discontinued in some women assigned to the continuation group due to NRFS or rapid progression of labor (11/74; 15%). Because of the rapid progression of labor with FGR and the need to be cautious because of the possibility of fetal heartrate abnormalities, fewer women were able to adhere to the protocol. When we evaluated the actual treatment received, the tachysystole rate and abnormal fetal heart rate incidence were significantly higher in the continuation group than in the discontinuation group. However, the cesarean delivery rate was not different between groups. Second, because oxytocin has a half-life of approximately 3 minutes, tachysystole is perhaps one of the easier tocodynametric issues to resolve; however, it remains unclear whether this method can reduce the cesarean delivery rate. Therefore, further large prospective studies adhering to the protocol involving discontinuation of oxytocin are required to determine whether this approach can reduce the cesarean delivery rate.

Conclusion

For singleton pregnancies near term or at full-term with FGR, oxytocin can be safely discontinued after the active phase of labor without increasing the risk of cesarean delivery or other unfavorable outcomes. Therefore, oxytocin discontinuation when entering the active phase of labor may be considered a safe management option for women undergoing labor induction for FGR.

Abbreviations

FGR: fetal growth restriction;

NRFS: non-reassuring fetal status;

AGA: appropriate for gestational age;

SD: standard deviations;

EFBW: estimated fetal body weight;

UmA: umbilical artery;

MCA: middle cerebral artery;

CPR: cerebroplacental ratio;

PI: pulsatility index

Declarations

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Authors' contributions

SI contributed to study design, data acquisition, data analysis, and writing and revising the manuscript. KM contributed to study design, data analysis, and revising the manuscript. ME, YK, AK, TM, SM, TT and TK contributed to data acquisition and revising the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not Applicable

Ethics approval and consent to participate

The study protocol was approved by the Osaka University Ethics Committee and conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was not obtained, because this study was a retrospective study design based on database, it will not affect the routine

procedures of the examination, nor will it cause any harm to pregnant women and fetuses. This article does not contain any studies with animals performed by any of the authors.

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Figures

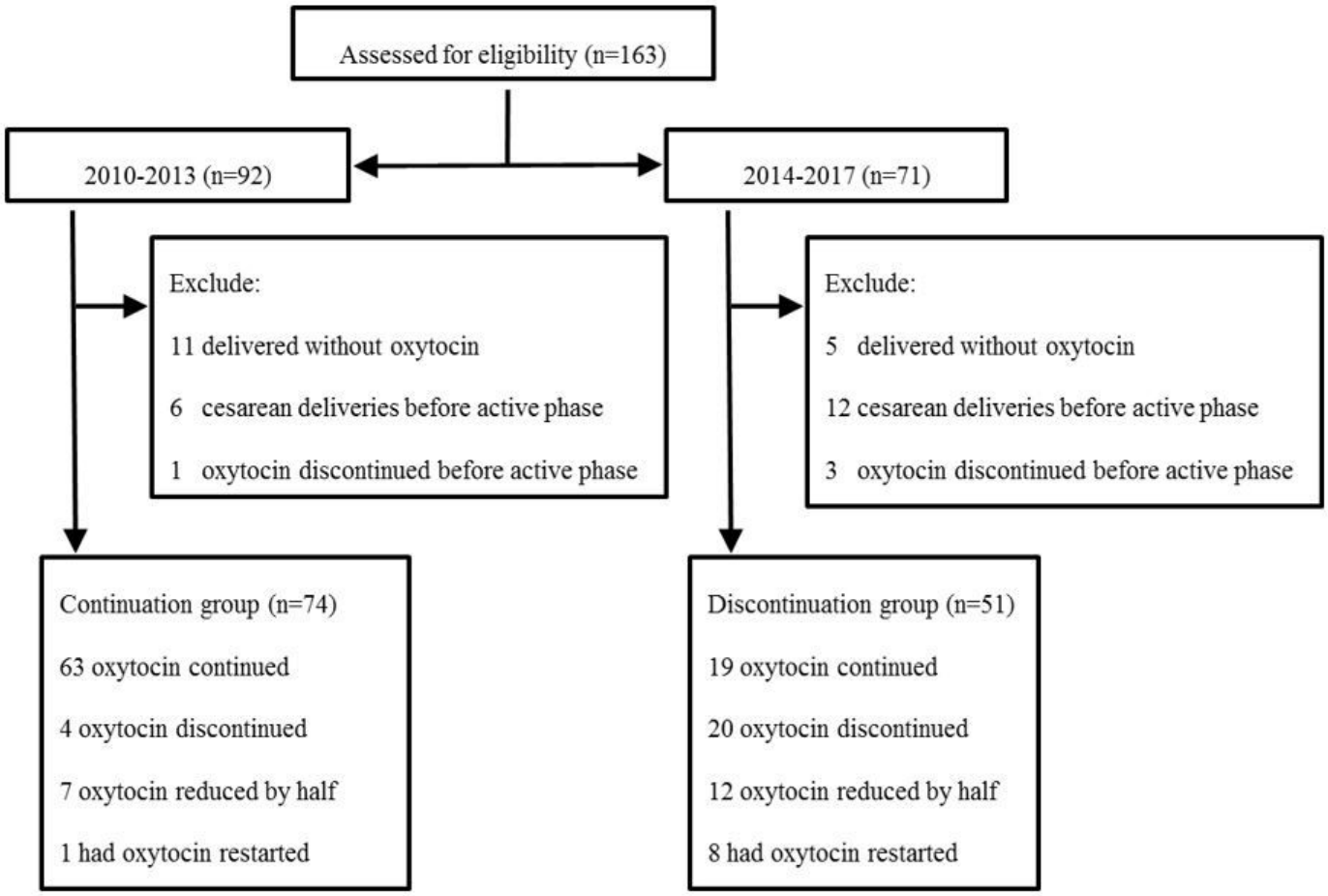

Figure 1

Flow diagram of the inclusion process