
OBSTETRICS

Cesarean Section Rate in Oxytocin Infusion between Continuous Until Delivery and Discontinuation at Active Phase of Labor: A randomized controlled study

Lalida Chookijkul, M.D.*,
Sinart Prommas, M.D.*,
Piyawan Pariyawateekul, M.D.*,
Nawaporn Orungrote, M.D.*,
Buppa Smanchat, M.D.*,
Komsun Suwannaruk, M.D.**.

* Department of Obstetrics and Gynecology, Bhumibol Adulyadej Hospital, Bangkok 10220, Thailand

** Department of Obstetrics and Gynaecology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand

ABSTRACT

Objective: To compare the cesarean section rate between discontinuing oxytocin infusion for labor induction or augmentation when the active phase of labor is established and continuing oxytocin infusion until delivery.

Materials and methods: This was a prospective randomized controlled trial of 340 pregnant women who underwent labor induction or augmentation at Bhumibol Adulyadej Hospital during February 2014 to January 2015. Parturient were randomly and equally allocated into two groups. The continued group received oxytocin infusion throughout all stages of labor. The discontinued group received oxytocin infusion and early discontinued when the active phase of labor had begun. Intention to treat analysis was used in this study.

Results: Three hundred and forty pregnant women were enrolled for the study. They were assigned randomly into two groups, 170 patients for each group. Cesarean section rate in continued and discontinued group were 31.8% and 27.7%, respectively ($p = 0.40$). The infusion of intravenous fluid in CG group was stopped due to non-reassuring fetal heart rate pattern in 15 women and total oxytocin doses used were significantly higher than that in DG group. In DG group, additional oxytocin was required due to poor uterine contraction. Duration of each stage of labor, maternal complications and adverse neonatal outcomes were not significantly different. There were only two cases of postpartum hemorrhage in discontinued group that was successfully managed by medical treatment.

Conclusion: There was not sufficient evidence to support whether discontinuation or continuation of oxytocin in active phase of labor influenced cesarean section rate. However, higher doses of oxytocin used was found in continuation group. Future well-randomized design with enough sample size is needed.

Keywords: cesarean section rate, oxytocin, labor

Introduction

Oxytocin has been used for decades to induce or augment labor⁽¹⁾. It is an effective drug to improve uterine activity⁽²⁾. Oxytocin receptor antagonists have been introduced in clinical practice since 1998⁽³⁾. Phaneuf et al showed that continuous use of oxytocin negatively stimulated its receptors in laboratory. From previous study, the concentration of myometrial oxytocin receptors and the steady state of its mRNA were measured in patients undergoing cesarean sections before or during spontaneous or induced labor. The concentration of receptors decreased during prolong oxytocin infusion. The results showed that larger doses and longer time infusion of oxytocin caused desensitization or down regulation of receptors. Continuous use of oxytocin infusion for long duration may result in postpartum uterine atony and hemorrhage⁽⁴⁾.

Results from prior ten-year studies supported discontinuing oxytocin infusion when the active phase of labor has begun (early discontinuing protocol). Cesarean section rate did not increase in the studies⁽⁵⁻⁹⁾. The conclusion was not widely used in clinical protocols. There were two randomized controlled trials (RCTs) of which one RCT concluded that discontinuation of oxytocin in active phase lead to longer duration of active phase⁽¹⁰⁾, in contrast, another RCT concluded that continuation of oxytocin lead to hyper-stimulation and abnormal fetal heart⁽⁶⁾. As a result, whether continuation or discontinuation of oxytocin in active phase of labor is inconclusive. The objective of this study was thus to compare the cesarean section rate between discontinuing oxytocin infusion for labor induction or augmentation when the active phase of labor is established and continuing oxytocin infusion until delivery. The conclusion of this study might be useful for developing a protocol or standard regimen for obstetric practice. Study hypothesis was early discontinuing protocol did not increase the cesarean section rate.

Materials and Methods

This was a prospective randomized controlled trial design. Three hundred and forty pregnant women who underwent labor induction or augmentation were enrolled. Study period started from February 2014 to January 2015 at Bhumibol Adulyadej Hospital, Thailand. The hospital ethical review board approved this protocol. Written informed consent was obtained from all patients. Inclusion criteria were gestational age of 37 to 42 weeks, singleton with cephalic presentation, latent phase of labor, estimated fetal weight < 4,000 g by Leopold's maneuver or ultrasonography and bishop score > 4. Exclusion criteria were fetal malpresentation, previous cesarean section or uterine scar such as previous myomectomy, placenta previa, placental abruption, persistent non-reassuring fetal heart rate pattern, active phase of labor, premature rupture of membrane (PROM), documented fetal anomalies, severe maternal diseases or maternal complications such as severe preeclampsia, diabetes mellitus, heart diseases, HIV infection, genital lesions that obstruct passage of labor such as large genital wart, active genital herpes and contracted pelvis.

The primary outcome was the rate of cesarean section between the parturient in the continued group and discontinued oxytocin group. The secondary outcomes were the duration of each stage of labor such as latent phase, active phase and second stage of labor including duration from membrane rupture to delivery, total oxytocin doses which measured from intervention started to end of delivery, intrapartum and postpartum complications such as chorioamnionitis and postpartum hemorrhage, adverse events following labor induction and augmentation such as non-reassuring fetal heart pattern, neonatal outcomes such as Apgar score, neonatal birth weight and Neonatal Intensive Care Unit Admission rate.

Subjects were randomly and equally assigned to either continued (CG) or discontinued group (DG) by

block randomization. The block of four was generated by computer statistical program STATA version 12 (Bangkok, Thailand) and put in sealed and opaque envelopes.

This study was conducted at labor room, Department of Obstetrics and Gynecology. Oxytocin and placebo was prepared by one pharmacist who did not attend or take responsibility for attending cases. It was labeled by running number. The code can be opened for patient safety by attending physician in emergency conditions.

External electronic fetal monitors were used for recording uterine activity and fetal heart rate in all cases. Induction or augmentation of labor was performed by oxytocin infusion according to the hospital protocol. Oxytocin dose was titrated to get 3-4 contractions in a 10 minute period. Uterine contractions and fetal heart rate were monitored and evaluated as protocol. Cervical progression examination was performed every two hours and anytime as necessary according to clinical indications. When active phase of labor defined as 4 cm or more of cervical dilatation with good uterine contraction was established, intravenous fluid match with sealed envelope number was started instead of oxytocin. Labor was monitored until delivery or other managements were performed according to obstetric indications by responsible physician blindingly. Active phase was defined as 4 cm or more of cervical dilatation with good uterine contraction. It was assessed by the physician. If there was no progression of labor or indication for cesarean delivery, the oxytocin was restarted for good uterine contractions or progression of labor was assessed at two hours later. Amniotomy was performed in both groups to enhance labor progression in active labor.

Sample size estimation was done with a power of 80% and alpha level of 0.05. Sample size of 163 patients per group was needed to show an increase in the cesarean section rate from a baseline rate of 25% to 40% for patients in discontinued group⁽⁸⁾. SPSS version 18.0 (Chicago, IL) was used to analyze data. Statistical analysis to compare groups was performed with the χ^2 analysis for categorical variables and the student t test or the Mann Whitney U test for continuous

variables. Statistical analysis was aimed to intention to treat.

Results

Three hundred and forty cases were enrolled into the study. All of them were randomized into two groups as shown in Fig. 1.

Mean age of parturient in this study was 25 years old. Two thirds of them were nulliparous. Medical diseases (asthma and thyroid diseases) were found in CG and DG at 4 (2.4%) and 5 (2.9%), respectively. Both CG and DG had a similar basic demographic feature as presented in Table 1. There were gestational diabetes mellitus (GDM) which was significantly different between both groups. There were 11 and 3 cases who had GDM in CG and DG, respectively with statistical significant ($p = 0.03$). Approximately five percent of both groups had pregnancy induced hypertension (PIH).

Mean gestational age at delivery was 39 weeks in both groups. Seventy five percent of cases in this study had spontaneous labor onset. The median Bishop score was 7 in both groups. Half of cases had favorable cervix (Bishop Score ≥ 9). Three fourths of cases underwent amniotomy as shown in Table 1.

Cesarean section rate in CG and DG were 31.8% and 27.7%, respectively ($p = 0.40$). Indications of cesarean sections were not significantly different. Abnormal labor progression leading to perform cesarean delivery in CG and DG were 75.9% (41/54) and 74.5% (35/47), respectively without statistical different. Cesarean section rate due to non-reassuring or abnormal fetal heart rate pattern were 24.1% and 25.5% cases in CG and DG, respectively.

Operative vaginal delivery was performed at percentage of 7.1 and 4.7 in CG and DG, respectively ($p = 0.35$). Labor progression pattern in both groups had no statistical significance as presented in Table 2. Oxytocin usage in CG was significantly higher than DG (1021.1 mU and 647.9 mU, respectively, $p < 0.001$).

In CG, oxytocin was continuously titrated until good uterine contraction achieved. There were fifteen cases who had to stop oxytocin from non-reassuring fetal heart rate pattern. Twelve cases were delivered

by vaginal delivery. Others underwent cesarean delivery from abnormal labor progression.

In DG, there were sixteen cases who had to restart oxytocin from poor uterine contraction in active phase of labor. Ten cases were delivered by vaginal delivery. Others underwent cesarean delivery. Indications were abnormal progression of labor and fetal heart rate pattern: 4 and 2 cases, respectively.

There was no intrapartum complication in this study. Only two cases in DG had postpartum hemorrhage (PPH) complication after delivery. Both parturients underwent medical treatment without

hysterectomy and completely recovered. Mean number of cervical examination during intrapartum monitoring in CG and DG were 4.5 and 4.8, respectively. No chorioamnionitis case was found.

Neonatal outcomes (Apgar score at 1 and 5 minutes) were equally excellent in both groups. Low birth weight ($< 2,500$ g) and large newborns ($\geq 4,000$ g) were 12/10 cases and 3/2 cases in CG and DG, respectively. Both groups showed similar rate of neonatal intensive care unit (NICU) admission as presented in Table 2.

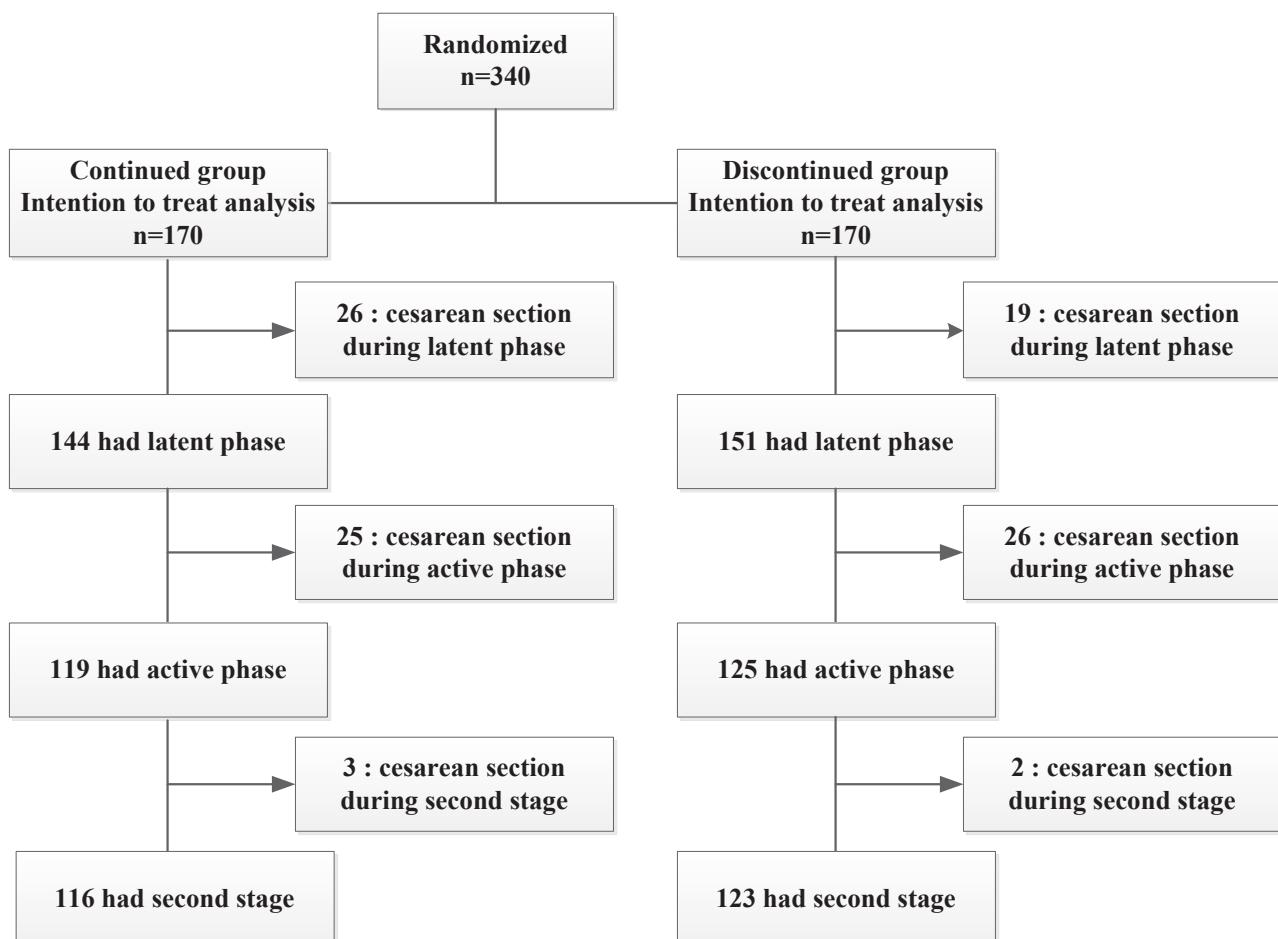


Fig. 1. Participant flow.

Table 1. Demographic data and characteristics.

Characteristics	CG (n = 170)	DG (n = 170)	P
Age (yr.)	25.5 ± 6.2	24.9 ± 6.6	0.42
Nulliparity*	100 (58.8)	101 (59.4)	0.91
BMI (kg/m ²)	27.3 ± 4.8	26.8 ± 4.1	0.35
Obesity (BMI ≥ 30)*	36 (21.2)	38 (22.4)	0.79
GDM*	11 (6.5)	3 (1.8)	0.03
PIH*	11 (6.5)	8 (4.7)	0.48
GA (wk.)	39.5 ± 1.3	39.6 ± 1.2	0.30
Indication*			0.33
Augmentation	123 (72.4)	134 (78.2)	
Induction	47 (27.6)	36 (21.8)	
Amniotomy*	124 (72.9)	130 (76.5)	
Amniotomy*	124 (72.9)	130 (76.5)	0.68

Data were analyzed with the student t test or the χ^2 test as appropriate.

CG: Continued Group, DG: Discontinued Group, *n (%)

BMI: body mass index, GDM: gestational diabetes mellitus

PIH: pregnancy induced hypertension, GA: gestational age

Table 2. Maternal and neonatal characteristics.

Characteristics	CG (n = 170)	DG (n = 170)	P
Cesarean delivery*	54 (31.8)	47 (27.7)	0.40
Non-reassuring fetal heart rate*	26 (15.3)	21 (12.4)	0.43
PPH*	0	2 (1.2)	0.49
Latent phase of labor (hr.)**	5.59 (0.50 - 14.42)	5.27 (0.33 - 16.00)	0.30
Active phase of labor (hr.)**	1.56 (0.08 - 7.43)	1.82 (0.08 - 10.00)	0.13
Second stage of labor (hr.)**	0.40 (0.03 - 1.95)	0.44 (0.02 - 3.03)	0.18
Time (hr.)	3.43 (0.17 - 21.33)	3.55 (0.10 - 12.03)	0.69
Total oxytocin dose (mU)***	1,021.1 (1000.2)	647.9 (668.4)	0.00
BW (g)	3,159.4 ± 399.7	3128.0 ± 403.9	0.47
NICU admission*	4 (2.4)	5 (2.9)	1.00

Data were analyzed with the Mann Whitney U test, the χ^2 test as appropriate.

CG: Continued Group, DG: Discontinued Group

*n (%), **results are given as mean (min-max), ***results are given as mean (sd)

PPH: postpartum hemorrhage, Time: time from membrane rupture to delivery

BW: neonatal birth weight, NICU: Neonatal Intensive Care Unit

Discussion

Oxytocin is considered as a high-alert medication by the Institute for Safe Medication Practices. It has been widely used in obstetrics for induction and augmentation of labor⁽²⁾. Oxytocin is associated with

hazard effect (hypotension, tachycardia and myocardial ischemia)⁽¹¹⁾. Myocardial infarction may be resulted from bolus dose of oxytocin administration⁽¹²⁾. Increased oxytocin dosing is associated with uterine atony and PPH⁽¹³⁾.

Recent labor management protocol has focused on evaluation of the lowest effective dose of oxytocin that minimizes adverse maternal outcomes⁽¹⁴⁾. Reducing the oxytocin dose could decrease its cardiovascular and dose-related side effects⁽¹⁵⁾. Good protocol implementation would result in lower intrapartum oxytocin doses without increasing cesarean section and PPH rate.

However, two cases of PPH in DG were found. One had uterine atony which was associated to oxytocin. The other had retained placenta. From this result, clinicians should aware of PPH and closed postpartum monitoring should be done.

Primary outcome was cesarean section rate which revealed no statistically significantly difference between both groups. This could be explained by low-risk pregnant women enrolled in our study or lower difference of cesarean section rate between intervention groups than expected in sample size calculation leading to more sample size required. The average age was 25 in both groups, three quarter had spontaneous onset of labor and half of them had favorable cervical condition.

Although the demographic data were similar between both groups except for the number of GDM which were significantly higher in CG. However, adverse neonatal and overall outcomes were not significantly different. Amniotomy also was performed per guideline protocol in three fourth of cases.

The results of the present study were similar to the findings of the studies from Israel, Turkey and Bangladesh^(5,6,9). Israel and Turkey's study paid attention on induction of labor's cases. Our study and Bangladesh's study studied in women who underwent induction and augmentation of labor. All three reports included parturient with PROM and enrolled the cases with 5 cm or more of cervical dilatation for active phase. PROM case was excluded in the present study. While our study enrolled the cases who had cervical dilatation for 4 cm or more. The result from previous and present studies revealed lower cesarean section rate in DG with lack of statistical difference.

The differences of inclusion criteria were found in the study from France⁽⁷⁾ and Iran⁽¹⁶⁾. The study from

France included singleton pregnancy with vertex presentation of over 34 gestational weeks, presenting a medical indication of induction of labor and the study from Iran included pregnancy with gestational age over full 36 weeks who had labor induction. However, the result of the cesarean section rate was not different between CG and DG.

The US study had additional methods for induction of labor⁽⁸⁾. Cervical ripening (either misoprostol or intracervical Foley bulb) was performed in unfavorable cervix's cases. The different result was chorioamnionitis which was found more cases in DG (12.8%) compared to CG (5.5%). It might be associated with placing intrauterine pressure catheter in their study which found higher in DG.

The different findings between our study and a study from Turkey⁽¹⁰⁾ may be explained by different outcome measurement. The Turkey's study found a shorter time from active phase until delivery without increasing non-reassuring fetal heart rate pattern and hyperstimulation in CG group. However, these outcomes were opposite in the findings of our study which might be due to different inclusion criteria, oxytocin dose adjustment or other managements.

So far, the conclusion on whether the oxytocin should be continued or discontinued and which doses of oxytocin should be adjusted was not clear⁽¹⁷⁾. Any clinical practice would be performed with caution.

Strength of the study was the study design. Double blinded randomized controlled study was performed. Patient allocation to treatment was blinded from investigator and other health personnel in the labor room. The results were analyzed without bias.

The limitations of the study were the starting time for determining active phase of labor, it may vary, depended upon when cervical examination performed. It was difficult to specify when to exactly perform the examination after a good uterine contraction emerged.

Conclusion

There was not sufficient evidence to support whether discontinuation or continuation of oxytocin in active phase of labor influenced cesarean section rate. However, higher doses of oxytocin used was found in

continuation group. Future well-randomized design with enough sample size is needed.

Declaration of interest

The author declares no conflict of interest in this study.

Ethical approval

The study was approved by Bhumibol Adulyadej Hospital Review Board, Royal Thai Air Force.

Acknowledgements

Authors would like to thank the staff and medical personnel of the Department of Obstetrics and Gynecology, Bhumibol Adulyadej Hospital for their support in this study. The fund for this study was supported by the Bhumibol Adulyadej Hospital Research Fund. The trial was registered in Thai Clinical Trials Registry (TCTR). Study ID: TCTR20150503001 (<http://www.clinicaltrials.in.th/>).

References

1. Cunningham FG, Leveno KJ, Bloom SL, et al. Induction and augmentation of labor. In: Williams Obstetrics. 24th ed. New York: Mc Graw Hill; 2014. p. 523-34.
2. Nadir CH, Backstrom T, Ulmsten U. Ineffectiveness of oxytocin on intercellular communication between term pregnant human myometrial cells before labour. *Am J Obstet Gynecol* 1998; 174(4):855-61.
3. Goodwin TM and Zograbyan A. Oxytocin receptor antagonists. Update. *Clin Perinatol* 1998; 25(4):859-71.
4. Phaneuf S, Rodriguez LB, TambyRaja RL, MacKenzie IZ, Lopez BA. Loss of myometrial oxytocin receptors during oxytocin-induced and oxytocin-augmented labour. *J Reprod Fertil* 2000; 120(1):91-7.
5. Spiegel DE, Weiner Z, Shlomo IB, Shalev E. For how long should oxytocin be continued during induction of labor?. *BJOG* 2004;111:331-4.
6. Ustunyurt E, Ugur M, Ustunyurt BO, Iskender TC, Ozkan O, Mollamahmutoglu L. Prospective randomized study of oxytocin discontinuation after the active stage of labor is established. *J Obstet Gynaecol Res*. 2007; 33(6):799-803.
7. Girard B, Vardon D, Creveuil C, Herlicoviez M, Dreyfus M. Discontinuation of oxytocin in the active phase of labor. *Acta Obstet Gynecol Scand* 2009;88:172-7.
8. Diven LC, Rochon ML, Gogle J, Eid S, Smulian JC, Quinones JN. Oxytocin discontinuation during active labor in women who undergo labor induction. *Am J Obstet Gynecol* 2012; 207:471.e1-8.
9. Begum LN, Sultana M, Nahar S, Begum B, Barua S. A randomized clinical trial on the need of continuing infusion in active phase of induced labor. *Chattogram Maa-O-Shishu Hospital Medical College Journal* 2013; 12(2):23-30.
10. Ozturk FH, Yilmaz SS, Yalvac S, Kandemir O. Effect of oxytocin discontinuation during the active phase of labor. *J Matern Fetal Neonatal Med* 2015;28(2):196-8.
11. Dyer RA, Butwick AJ and Carvalho B. Oxytocin for labour and caesarean delivery: implications for the anaesthesiologist. *Curr Opin in Anaesthesiol* 2011; 24:255-61.
12. Svanstrom MC, Biber B, Hanes M, Johansson G, Naslund U, Balfors EM. Signs of myocardial ischaemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methylergometrine during caesarean section. *Br J Anaesth* 2008;100:683-9.
13. Grotegut CA, Paglia MJ, Johnson LN, Thames B, James AH. Oxytocin exposure in women with postpartum hemorrhage secondary to uterine atony. *Am J Obstet Gynecol* 2011; 204(1):56.e1-6.
14. Dyer RA, van Dyk D, Dresner A. The use of uterotonic drugs during caesarean section. *Int J Obstet Anesth* 2010;19:313-9.
15. Jonsson M, Hanson U, Lidell C, Norden-Lindeburg S. ST depression at caesarean section and the relation to oxytocin dose. A randomised controlled trial. *BJOG* 2010; 117:76-83.
16. Bahadoran P, Falahati J, Shahshahan Z, Kianpour M. The comparative examination of the effect of two oxytocin administration methods of labor induction on labor duration stages. *Iran J Nurs Midwifery Res* 2011; 16(1):100-5.
17. Patka JH, Ladolce AE, Johnston AK. High-versus low-dose oxytocin for augmentation or induction of labor. *Ann Pharmacother* 2004;39(1):95-101.

การศึกษาเปรียบเทียบระหว่างอัตราการผ่าตัดคลอดบุตรเมื่อให้ยาออกซิโตซินตลอดระยะเวลาคลอด เทียบกับการหยุดยาออกซิโตซินในระยะปากมดลูกเปิดเร็ว

ลลิตา ชูภิจกุล, สินาท พรมมาศ, ปิยะวรรณ ปริยวาทีกุล, นวกรรณ ออรุ่งโรจน์, บุปผา สมานชาติ, คอมสันต์ สุวรรณฤกษ์

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบอัตราการผ่าตัดคลอดบุตรเมื่อหยุดยาออกซิโตซินในระยะปากมดลูกเปิดเร็ว เทียบกับการให้ยาออกซิโตซินตลอดระยะเวลาคลอด

วัสดุและวิธีการ: งานวิจัยนี้เป็นการศึกษาแบบสุ่มไปข้างหน้า ในสตรีตั้งครรภ์เดี่ยวจำนวน 340 ราย ที่นัดมารับการซักน้ำการคลอดหรือสามารถให้ยาออกซิโตซินเพื่อส่งเสริมการคลอดได้ ที่โรงพยาบาลภูมิพลอดุลยเดช ตั้งแต่ฤกษ์มาพันธ์ 2557 ถึงมกราคม 2558 โดยแบ่งสตรีตั้งครรภ์แบบสุ่มเป็นสองกลุ่มจำนวนเท่ากัน คือ กลุ่มที่ได้รับยาออกซิโตซินตลอดระยะเวลาคลอด และกลุ่มที่หยุดยาออกซิโตซินในระยะปากมดลูกเปิดเร็ว โดยวิเคราะห์แบบ *Intention to treat*

ผลการศึกษา: สตรีตั้งครรภ์เดี่ยวจำนวน 340 คน ถูกแบ่งออกเป็น 2 กลุ่ม กลุ่มละ 170 คน อัตราการผ่าตัดคลอดบุตรในกลุ่มให้ยาออกซิโตซินตลอดระยะเวลาคลอด และกลุ่มที่หยุดยาออกซิโตซินในระยะปากมดลูกเปิดเร็วเท่ากับ 31.8% และ 27.7% ตามลำดับ ซึ่งไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p=0.40$) การให้สารน้ำที่มียาออกซิโตซินในกลุ่มให้ตลอดระยะเวลาคลอด จำเป็นต้องหยุดจำนวน 15 ราย เนื่องจากอัตราการเต้นของหัวใจทางผิดปกติ และจำนวนของยาออกซิโตซินที่ใช้มีปริมาณมากกว่าอย่างมีนัยสำคัญทางสถิติ สำหรับกลุ่มที่หยุดยาออกซิโตซินมีการให้ออกซิโตซินเพิ่มเติมเนื่องจากภาวะดีดตัวของมดลูกไม่ดี ระยะเวลาที่ใช้ในการคลอดภาวะแทรกซ้อนของมารดาและทารกแรกเกิด ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ มีสตรีที่ตกลีดหลังคลอด 2 ราย ในกลุ่มที่หยุดยาออกซิโตซินในระยะปากมดลูกเปิดเร็ว แต่สามารถรักษาได้โดยใช้ยา

สรุป: ไม่มีหลักฐานเพียงพอที่จะสนับสนุนว่าการหยุดหรือให้ยาออกซิโตซินในระยะปากมดลูกเปิดเร็วมีผลต่ออัตราการผ่าตัดคลอดบุตรหรือไม่ อย่างไรก็ตามพบว่ากลุ่มที่ได้รับยาออกซิโตซินตลอดระยะเวลาคลอด มีการใช้ยาในขนาดที่สูงกว่า ในอนาคตควรมีการศึกษาแบบสุ่มไปข้างหน้าด้วยขนาดตัวอย่างที่มากขึ้น
