Continuation versus Discontinuation of Oxytocin Infusion during the Active Phase of Labour:

A Double Blinded Randomized Controlled Trial

Thesis

Submitted for Partial Fulfillment of Master Degree in Obstetrics and Gynecology

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Heba Gaber Saad

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List of Abbreviations

ACOG	:	American College of Obstetricians and Gynecologists
IMPS	:	Investigational medicinal products
IU	:	International unit
OTR	:	Oxytocin receptor
OT	:	Oxytocin
mRNA	:	Messenger Ribonucleic acid
VP	:	Vasopressin
HELLP	:	Hemolytic anaemia elevated liver enzyme low platelet count
NICHD	:	National Institute of Child Health and Human Development
FHR	:	Fetal heart rate
CTG	:	Cardiotocography

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Protocol of Thesis

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Introduction

Since oxytocin was first synthesised in 1953, it has become one of the most widely used medications in obstetrics to induce and augment labour ***(Oscarsson and Amer-Wahlin, 2006).*** In many delivery units, oxytocin is used in more than 50% of deliveries ***(Simpson et al., 2009).***

In 1954, Vincent du Vigneaud managed to isolate and synthetize oxytocin, an octapeptide amine, which evolved to the most widely used obstetrical agent for inducing or augmenting labor ***(den Hertog et al., 2001).*** Two previous studies show that after 10h of oxytocin usage the myometrium receptor concentration diminishes and further oxytocin administration has no or negative impact on this effect ***(Phaneuf et al., 2000) (Robinson et al., 2003).*** Interestingly since then this field has not been investigated. In contrast, oxytocin administration has been broadly adopted by the international community and established in daily practice.. Despite the widespread usage of oxytocin, there is still no consensus on its mode of administration. Therefore, the infusion rate is mainly titrated after observing the uterine contractility pattern to prevent peripartum complications ***(ACOG Practice Bulletin, 2009).***

The U.S. Food and Drug Administration describes oxytocin as a drug that carries a heightened risk of causing significant patient harm ***(ISMPs list of high alert medications, 2008).*** *As* the use of oxytocin during labour may result in a number of maternal adverse effects including hypotension, tachycardia, arrhythmias, nausea, vomiting,

headache and flushing ***(Dansereau et al., 1999).*** Rarely, large doses of oxytocin may cause water retention, hyponatraemia, myocardial ischaemia, seizures and coma ***(Begum et al., 2009).*** Furthermore, a long duration of labour induction or augmentation due to use of oxytocin decreases the efficacy of labour induction as the sensation of myometrium decreases gradually and inversely with duration of oxytocin infusion and also increases complication rates ***(Phaneuf et al., 2000; Ozturk et al., 2015).***

Aim of the Work

As expected, discontinuation of oxytocin infusion will prolong the duration of the active phase of labour. Yet neither this will affect expected maternal and fetal outcome, it need to be investigated.

Research question:

Is there a benefit from oxytocin infusion discontinuation during the active phase of labor over continuation of the oxytocin as regards maternal and fetal outcomes?

Research hypothesis:

Although oxytocin infusion discontinuation will prolong active phase of labour, yet it will result in better of some maternal and fetal outcomes.

Patients and Methods

Study design: a double blinded randomised controled trial

Settings: Labour wards at Maternity Hospitals of Ain Shams University& Glaa Teaching Hospital

Time:

Methods:

Any pregnant women with single living cephalic fetus presented to labour ward either early in labour (cervix < 3cm) or with an indication for labour induction will be included in the study. On the other side, any patient with contraindication for trial of normal delivery or labour induction will be excluded, for example: placenta previa, multiple gestation, previous uterus scar, Grand Multipara, severe medical illness of mother which may need urgent Cs, malpresentation fetus, pathological CTG, estimated fetal weight more than 4kg, gestational age less than 32 weeks.

History should be taken precisely. Physical examination will be done and vital signs will be taken. Abdominal examination will be important to assess fetal size, weight, gestational age and presentation. Vaginal examination will be performed by senior Obst&Gyn Resident as an initial assessment when women enter the delivery unit. Also CTG will be applied for 20 minute as an initial assessment.

All women will initially receive oxytocin infusion when cervix dilatation is less than or 3cm according to the local oxytocin guidelines which present in Ain Shams Maternity Hospital. Amniotomy will be performed in those

with intact membranes at the beginning of the active phase.

Vaginal examination will be performed by the same resident each 2 hours during the labour according to the study protocol in order to assess the degree of opening of the cervix, as well as cervical effacement, rotation and descent of the fetal head to evaluate the progress in labour. Fetal monitoring will be assessed either by Doppler every 15–20 minutes or intermittent CTG

At the beginning of the active phase, which was defined as 6-cm cervical dilatation and the presence of regular contractions at 3 min intervals, all of the infusion solutions will be stopped and the patients will receive either placebo or oxytocin according to the computer randomization which distributes the patients into 2 groups , group A will receive oxytocin and group B will receive placebo .Also , these 2 groups will be subdivided into 2 groups according to the parity (primi gravida and multi gravida) . The solutions will be prepared by a resident who doesn't participate in monitoring of the patients in an attempt to reduce the bias. Patients won't know anything about the protocol that will be used for induction.

All patients will be monitored throughout the labor and maternal vital signs will be recorded routinely. A reassuring fetal heart rate pattern is defined as a baseline between 110 and 160 b.p.m., with long-term variability between 5 and 25 b.p.m., and either no decelerations or only early decelerations. A non-reassuring fetal heart rate

pattern is defined as any fetal heart rate pattern that does not meet criteria for a reassuring fetal heart rate pattern. Uterine contractions will be recorded during labor in all patients using external electronic fetal monitoring. Hyper stimulation will be diagnosed if there are six or more contractions in 10 min intervals. Arrest of labor is defined as no cervical change for 2 h despite adequate contractions. Oxytocin will be decreased or discontinued because of hyper stimulation or severe fetal heart rate abnormalities or no progress for 4hrs, and those patients will be excluded from the study.

Outcomes:

1) Primary outcome:

- Rate of uterine hyperstimulation
- Fetal distress assessed by CTG

2) Secondary outcome:

- Duration of the active phase of labour
- Rate of postpartum hemorrhage
- Rate of perineal tear
- Neonatal depression assessed by Apgar scores, and admission to neonatal care unit.
- Mode of delivery of the pregnant women involved in the study, as the study mainly aim to decrease the rate of caesarean sections and increase the rate of normal vaginal delivery.

Sample size calculation

Sample size was calculated using PASS® version 11 program, setting the type-1 error (α) at 0.05 and the power (1-β) at 0.8. Results from a previous study **(*por et al, 2015*)** showed that the rate of uterine hyperstimulation was 12% in the continued group but 2% in the discontinued group, which was statistically significant (RR 5.62; 95% CI 1.28– 24.65; P < 0.008). Calculation according to these values produced a **minimal** sample size of 100 cases per group.

Randomization:

Patients fulfilling inclusion and exclusion criteria will be divided into 2 groups.

Assuming a drop-out rate at (10%) a total number of 110 patients will be recruited.

Methods of randomization :

Randomization will be done using computer generated randomization sheet using MedCalc© Version 13

Allocation concealment

Sequentially numbered, opaque, sealed envelopes will be used.

Reference for program:

Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. PRIMI GRAVIDA A GROUP (n=50)