

Project title: CONDISOX: Continued versus discontinued oxytocin stimulation of labour in a double-blind randomised controlled trial.

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Objective

The proposed study will investigate the effect of *Syntocinon*® (synthetic oxytocin) to induce labour. The hypothesis to be studied is that once labour is established and the active phase of labour has commenced, *Syntocinon*® can be discontinued and the labour process will continue. The primary outcome will be the rate of caesarean delivery. The main secondary outcomes will be the duration of labour, neonatal conditions, maternal outcomes and satisfaction.

Background

In Denmark approximately 45% of nulliparous women are given stimulation with synthetic oxytocin (*Syntocinon*®) for either induction or augmentation of labour.¹ *Syntocinon*® is used in more than 50% of the deliveries in the United States of America.² Despite the extensive use of *Syntocinon*®, only few studies have focused on how long it needs to be given once labour is established. Currently, there is no consensus whether oxytocin should be continued until delivery or discontinued after the onset the active phase of labour.^{3 4 5 6} Theoretically, once labour contractions are established, the endogenous production of prostaglandin from the endometrium disrupted by the contractions may be enough to maintain appropriate uterine activity without further stimulation with *Syntocinon*®.

The current protocol used in Denmark for induction of labour with *Syntocinon*® is described in the Danish Society of Obstetrics and Gynaecology (DSOG) guidelines⁷. It recommends that the infusion continue until delivery, unless complications (e.g. uterine tachysystole) occur, in which case, the dose being administered should be reduced or discontinued.

Although *Syntocinon*® is used in a high proportion of labours, many professionals underestimate the associated adverse effects. The most frequent complication is tachysystole,⁸ which increases the risk of fetal distress and birth asphyxia, requiring delivery by caesarean section or forceps/ventouse. In addition, the use of *Syntocinon*® increases the risk of uterine rupture.⁸ A continuous high dose of *Syntocinon*® has been associated with a high caesarean delivery rate when compared with a continuous low dose.⁹

It is well established that *Syntocinon*® administration during labour causes down regulation of the oxytocin receptors,¹⁰ which persists postpartum causing an increased risk of postpartum haemorrhage. Initiation and duration of breastfeeding may also be adversely affected in women who undergo

Syntocinon® stimulation.¹¹ Recently it was reported there is an inverse association between stress incontinence (1 year after the first vaginal delivery) and augmentation with *Syntocinon*®.¹²

A few small studies (sample size ranging from 104 to 342) report a reduction in the caesarean delivery rate, when *Syntocinon*® is discontinued at the active stage of labour; however, because of small numbers, this difference was not statistically significant even on meta-analysis.^{3 4 5 6} Recently, a Danish pilot study was conducted to investigate the effects of discontinued *Syntocinon*® infusion compared to continued *Syntocinon*® infusion on labour outcomes¹³. Between 2009 and 2011, two hundred women admitted for induction or augmentation of labour at the Regional Hospital of Randers were randomised to continued or discontinued *Syntocinon*® once active phase of labour had become established. Though not being the primary study outcome, the total caesarean delivery rate for the *Syntocinon*® continued group was 22% compared with 15% in the discontinued group ($p = 0.2745$ by Fisher's exact test). Moreover, in the discontinued group, there were significantly fewer cases of postpartum haemorrhage, uterine tachysystole, and pathological fetal heart rate pattern.

The current study is planned as a double-blind, randomised controlled trial with caesarean section rate as the primary outcome. A power calculation based on the above pilot study shows that with an alpha of 0.05, a beta of 80% and a misclassification of 5 %, 482 women in each group will be needed to test the hypothesis of a caesarean delivery rate of 22% versus 15%. With a drop out of 5%, 506 women will be needed in each group. Therefore we plan to include 600 in each group

Basic demographic data will be presented counts and percentages for categorical variables, with mean and standard deviation for continuous variables, and with median and interquartile range for continuous non-Gaussian variables.

We will use the intention-to-treat principle to compare the designated outcomes between participants with continued or discontinued *Syntocinon*®. We will use multivariate logistic regression with adjustment for differences in baseline characteristics to calculate odds ratios with 95% confidence intervals. Adjustment for multiple comparisons (Bonferroni) will be made in the evaluation of secondary outcomes. The analyses will be stratified by the indication for oxytocin (labor induction or induction due to Premature Rupture of Membranes) and parity (nullipara or multipara).

STUDYDESIGN

Study type:

Double-blind, randomised multicentre trial.

Setting

Sygehus Lillebælt, Kolding, Aalborg University Hospital, Aarhus University Hospital and Randers Regional Hospital, Denmark.

Inclusion criteria:

Women stimulated with *Syntocinon*® infusion for induction of labour (with or without cervical priming by prostaglandin).

Exclusion criteria:

<18 years

Unable to read and understand the Danish language or to give informed consent

Cervical dilatation > 4 cm

Non-cephalic presentation

Multiple gestation

Pathological fetal heart rate pattern (cardiotocogram, CTG) before *Syntocinon*® initiation¹⁴

Fetal weight estimation > 4500 g (clinical or ultrasonic)

Subject declines participation

Gestational age less than 37 completed weeks

Definition: Stimulation following Premature Rupture of Membranes

Stimulation with *Syntocinon*® following Premature Rupture of membranes is induction of labour if there is no cervical change prior to starting the infusion, whereas stimulation with *Syntocinon* after Premature Rupture of Membranes but following the establishment of significant cervical change is augmentation.

Randomisation and blinding:

When the orificium ≥ 6 cm, regular painful contractions (≥ 3 per 10 minutes) and rupture of membranes participants will be randomised in a 1:1 ratio to either the control (continued *Syntocinon*®) or intervention (discontinued *Syntocinon*®) group using an Internet-based randomisation programme. The

randomisation can only be performed when the woman consents to participation. Written consent can be given after the commencement of the *Syntocinon*® infusion, provided the woman previously has received sufficient information for her to give properly informed consent. Random block-sizes of 4 are used, and the participants will be stratified by site (Aarhus University Hospital, Randers Regional Hospital, Sygehus Lillebælt Kolding or Aalborg University Hospital), parity (nulliparous or parous) and indication for *Syntocinon*® infusion (induction or induction due to Premature Rupture of Membranes).

The randomisation number corresponds to number of the project medicine (ampoule). The personnel of the delivery ward will administer the ampoules according to existing guidelines concerning medicine administration^{7 17}.

Projectmedicine

Syntocinon®-ampoules (Producer: Sigma Tau Farmaceuticals Inc.) containing 10 IU/ml and identical placebo-ampoules containing 1 ml 0,9% NaCl (Producer: Hospitalsapoteket, Region Hovedstaden). Apodan Pharma Nordic Packeging A/S will manufacture the placebo ampoules. Hospitalsapoteket Region Hovedstaden will fill the ampoules with isotonic saline and label both ampoules containing *Syntocinon*® and placebo with “CONDISOX – Project number: XXX, EudraCT-nr.: 2015-002942-30”.

Oxytocin stimulation protocol

Existing procedures prior to stimulation will be followed, including use of the existing checklists^{15 16 17}. No further examination will be done prior to inclusion and stimulation, no blood samples nor ECG to identify e.g. unknown QT-syndrome will be performed as this is never performed as a standard procedure prior to induction.

Latent phase: Stimulation will be given according to national DSOG guidelines⁷. Initially 20 ml/hour of 10 IE *Syntocinon*® diluted in 1000 ml 0,9% NaCl. The dose rate will be increased every 20 minutes by 20 ml/hour until appropriate uterine activity of 3-5 contractions per 10 minutes is achieved. The maximum allowed dose rate 180 ml/hour for induction of labour.

Active phase: The woman will be included in the study, when the active phase of labour is established (cervical dilatation ≥ 6 cm, ≥ 3 contractions per 10 minutes, and rupture of membranes). Randomisation

is performed, and the infusion will be replaced by the trial solution, which will be either *Syntocinon*® at the same concentration, or a placebo infusion which will not contain *Syntocinon*®:

1. Control group; 10 IE *Syntocinon*® diluted in 1000 ml 0,9% NaCl infusion
2. Intervention group; 1ml 0,9% NaCl diluted in 1000ml 0,9% NaCl infusion.

The infusion will be continued to achieve uterine activity of 3-5 contractions per 10 minutes. Maximum allowed dose is 180 ml/hour for induction. The procedure for administration of the trial solution is identical with the existing procedure.

Complications:

The infusion will be reduced or discontinued at any point of labour, if the following occur⁷:

- Tachysystole (> 5 contractions per 10 minutes, averaged over a 30-minute window) or hyperstimulation (>5 contractions per 10 minutes, averaged over a 30 minute window during stimulation with projectmedicine¹⁴). A management algorithm is presented in Figure 1.
- Uterine contractions lasting 2 minutes or more
- Pathological fetal heart rate pattern (recurrent variable decelerations, fetal tachycardia or bradycardia, minimal to absent baseline variability, late decelerations)¹⁴
- Suspicion of uterine rupture

These conditions will be managed according to the guidelines of the local delivery wards.

Unconcealment

The primary investigator or a nominated deputy will at all time be able to break the randomisation code and reveal the allocation group, if needed. The Internet Based Randomisation Programme will provide the primary investigator or a nominated deputy with this possibility. (A 24/7 availability of the allocation group is thereby provided).

Dystocia:

If there is failure to progress, defined as less than two cm dilation over 4 hours despite apparently adequate contractions and/or maximal infusion rates (*Syntocinon*® or placebo), the project medicine will be replaced with open-labelled *Syntocinon*® infusion. Stimulation will be given according to national DSOG guidelines⁷. Initially 20 ml/hour of 10 IE *Syntocinon*® diluted in 1000 ml 0,9% NaCl.

The dose rate will be increased every 20 minutes by 20 ml/hour until appropriate uterine activity of 3-5 contractions per 10 minutes is achieved. The maximum allowed dose rate is 180 ml/hour for induction.

Woman receiving open-labelled *Syntocinon*® infusion for 4 hours and continuous failure to progress:
Consider caesarean section.

Outcomes:

Primary outcome:

- Delivery by caesarean section

Secondary outcomes:

- Birth experience and satisfaction 4 weeks postpartum (Childbirth Experience Questionnaire, CEQ1, Dencker 2010)
- Maternal: Instrumental delivery, duration of the active phase of labour (from time of randomisation to delivery), total duration of labour (from initiation time of oxytocin stimulation until delivery.), duration of admission on the delivery ward, tachysystole, hyperstimulation, use of epidural analgesia, dose and duration of oxytocin infusion, episiotomy, rupture of the anal sphincter, uterine rupture, volume of blood loss at delivery and postpartum, need for evacuation of retained products of conception, use of antibiotics during labour, postpartum infection (defined as two measured maternal temperatures of 38°C at least four hours apart), retention of urine requiring catheterisation)
- Neonatal: Birth weight, CardioTocoGram (CTG) classification¹⁴, fetal scalp pH values, Apgar score at 1 and 5 minutes, umbilical cord arterial and venous pH and blood gas values, use of antibiotics, hyperbilirubinaemia, neonatal admission, need for resuscitation (bag and mask or intubation, time to onset of spontaneous ventilation), or death.
- Breastfeeding (time to established feeding and duration of exclusive breastfeeding)

Side effects and risks:

Persistent failure to progress can be expected in 8-46% of the participants in the placebo group versus 3-17% in the control group.^{3 4 5 6}

Based on data from the pilot study, the risk of caesarean section is expected to be 15% in the placebo group versus 22% in the control group. According to the pilot study and previous studies^{3 4 5 6}, the maternal and neonatal complications in the placebo group are expected to be lower than in the control group.

All participants are monitored with continuous electronic fetal heart rate monitoring during labour to detect complications such as uterine tachysystole and pathological fetal heart rate pattern, in accordance with national guidelines.

The personnel of the delivery ward are responsible for registering of adverse reactions and adverse events.

Following adverse reactions and event will be registered immediately in the electronic medical journal of the patient:

- Cesarean delivery
- Postpartum hemorrhage >500 ml
- Manual placenta removal
- Rupture of the anale sphincter
- Urine retention
- Neonatal: pH <7,10 and/or Apgar score ≤ 6 at 5 minutes

Following serious adverse reactions and adverse events will be also registered immediately in the electronic medical journal of the patient:

- Intrauterine dead during labour
- Maternal amniotic fluid emboli or thromboembolic event
- Maternal cardiac arrest
- Maternal Pulmonary edema
- Uterine rupture

The women will be followed for at least 3-6 hours postpartum (termination of project medicine) according current practice on the delivery ward.

The product resume of *Syntocinon*® will be used as reference¹⁸ to determine whether a Serious Adverse Reaction is expected or unexpected. Primary investigator or a nominated deputy will go through the participants medical file 7-30 days postpartum during data management and Primary

investigator will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities concerned, and to the Ethics Committee, and in any case no later than seven days after the knowledge such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

Primary investigator will report to the competent authorities concerned and to the Ethics Committee concerned all other suspected unexpected serious adverse reactions as soon as possible but within a maximum of 15 days of first knowledge.

FORMALITIES

- The GCP unit of Aarhus University and Odense University Hospital will supervise the study at all times.
- The Central Denmark Region Committee on Biomedical Research Ethics has approved the study.
- The Danish Health Authority, (Danish Medicine Agency) has approved the study.
- The study is registered on www.clinicaltrials.gov: **NCT02553226**
- The inclusion is expected to initiate 1th of March 2016. 1 ½ year of enrolment is expected or or until 1200 labouring women have approved participation.

FEASIBILITY

- Recruitment: There are a total of 12.500 births annually at the four Danish centres.
- The Chief midwife at the four Danish centres have given their support for the study

PERSPECTIVE

Caesarean sections are performed frequently in modern practice, and are associated with complications for both mother and child (e.g. maternal haemorrhage and fetal respiratory distress), especially when it is carried out as an emergency. It makes considerable demands on resources, requiring experienced personnel, additional materials needed for surgery and prolonged admission to hospital. The Institute for Safe Medication Practices in USA placed intravenous *Syntocinon*® on the list of high-alert medications in 2007.¹⁹ In 2008 the Danish Patient Insurance reported that *Syntocinon*® stimulation and poor interpretation of CTGs can be primary causes of acquired neonatal brain damage.²⁰ In 2010 the

Danish Patient Insurance paid 38,6 mill DKK for 23 cases of brain injury due to asphyxia in relation to labour.²¹ Thus the potential adverse effects of *Syntocinon*® are correlated with huge social costs, both economic and human. Reducing the duration of *Syntocinon*® stimulation during labour, with a likely decrease in total dosage, may lower the number of neonates with asphyxial sequelae and the number of adverse events during childbirth, and this in turn will reduce the risk of expensive litigation. If the hypothesis of this study is supported by the results of this trial, it is likely to have a major impact on international and Danish clinical practice concerning induction and augmentation of labour.

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