

## Project description

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

### Objective

The proposed study will investigate the effect of *Syntocinon*® (synthetic oxytocin) to induce or augment 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.<sup>1</sup> *Syntocinon*® is used in more than 50% of the deliveries in the United States of America.<sup>2</sup> 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.<sup>3 4 5 6</sup> 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 augmentation and induction of labour with *Syntocinon*® is described in the Danish Society of Obstetrics and Gynaecology (DSOG) guidelines<sup>7</sup>. 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,<sup>8</sup> 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.<sup>8</sup> A continuous high dose of *Syntocinon*® has been associated with a high caesarean delivery rate when compared with a continuous low dose.<sup>9</sup>



It is known that *Syntocinon*® administration during labour causes down regulation of the oxytocin receptors,<sup>10</sup> 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.<sup>11</sup> Recently it was reported there is an inverse association between stress incontinence (1 year after the first vaginal delivery) and augmentation with *Syntocinon*®.<sup>12</sup>

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.<sup>3 4 5 6</sup> Recently, a Danish pilot study was conducted to investigate the effects of discontinued *Syntocinon*® infusion compared to continued *Syntocinon*® infusion on labour outcomes. 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 non-reassuring fetal heart.

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 %, 600 women in each group will be needed to test the hypothesis.

## **STUDYDESIGN**

### ***Study type:***

Double-blind, randomised multicentre trial.

### ***Setting***

Aarhus University Hospital and Randers Regional Hospital, Denmark.



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***Inclusion criteria:***

Women stimulated with *Syntocinon*® infusion for induction of labour (with or without cervical priming by prostaglandin) or for augmentation of slow labour in the latent phase (regular contractions for at least four hours and a cervical dilatation of  $\leq 4$ cm).

***Exclusion criteria:***

<18 years and >45 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*® initiation<sup>13</sup>

Fetal weight estimation > 4500 g (clinical or ultrasonic)

Subject declines participation

Gestational age less than 37 completed weeks

***Randomisation and blinding:***

Once they consent to participate, 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. This randomisation will be performed as soon as the woman consents, which can be up to four hours after the commencement of the *Syntocinon*® infusion, provided the woman has previously been given sufficient information for her to give properly informed consent.

Random block-sizes of 2, 4, and 6 are used, and the participants will be stratified by site (Aarhus University Hospital, Palle Juul-Jensens Boulevard or Randers Regional Hospital), parity (nulliparous or parous) and indication for *Syntocinon*® infusion (induction or augmentation).

***Oxytocin stimulation protocol***

Latent phase: Stimulation will be given according to national DSOG guidelines<sup>7</sup>, 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 120 ml/hour for augmentation and 180 ml/hour for induction.

Once the woman is established in the active phase of labour (cervical dilatation  $\geq 6$  cm), 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; 0,9% NaCl infusion.

The infusion will be continued to achieve uterine activity of 3-5 contractions per 10 minutes. Maximum allowed dose is 120 ml/hour for augmentation and 180 ml/hour for induction.

### **Complications:**

The infusion will be reduced or discontinued at any point of labour, if the following occur<sup>7</sup>:

- Tachysystole (> 5 contractions per 10 minutes, averaged over a 30-minute window) or hyperstimulation (>5 contractions per 10 minutes and non-reassuring CTG<sup>13</sup>). A management algorithm is presented in Figure 1.
- Uterine contractions lasting 2 minutes or more
- Non-reassuring CTG (recurrent variable decelerations, fetal tachycardia or bradycardia, minimal to absent baseline variability, late decelerations)<sup>13</sup>
- Suspicion of uterine rupture

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

### **Dystocia:**

If there is failure to progress, defined as less than one cm dilation over 4 hours despite apparently adequate contractions and/or maximal infusion rates (*Syntocinon*® or placebo), the randomisation code will be broken and the allocation group revealed to the supervising clinician by the primary investigator or their nominated deputy (this is necessary to provide 24/7 availability of the allocation group). The following actions will then be considered:

1. Woman had been receiving *Syntocinon*®: Consider caesarean section
2. Intervention (placebo): *Syntocinon*® infusion.



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### **Outcomes:**

#### *Primary outcome:*

- Delivery by caesarean section

#### *Secondary outcomes:*

- Maternal: Instrumental delivery, duration of the active phase of labour, total duration of labour (from commencement of induction or time of onset of regular contractions if spontaneous onset), 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) classification<sup>13</sup>, 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 or any breastfeeding)
- Birth experience and satisfaction (Questionnaire made of components of existing validated Danish questionnaires)
- Urinary incontinence after 6 months (Questionnaire: The International Consultation of Incontinence Questionnaire Short Form (ICIQ-SF))

#### **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.<sup>3 4 5 6</sup>

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<sup>3 4 5 6</sup>, the maternal and neonatal complications in the placebo group are expected to be lower than in the control group



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

### FORMALITIES

- The GCP unit of Aarhus University will supervise the study at all times.
- The Central Denmark Region Committee on Biomedical Research Ethics has approved the study.
- The study will be registered prospectively on [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- The infusions will be prepared and labeled with project numbers by the Pharmacy of Randers Regional Hospital.

### FEASIBILITY

- Recruitment: There are a total of 6,500 births annually at the two centres.
- The Chief midwife at the two 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.<sup>14</sup> In 2008 the Danish Patient Insurance reported that *Syntocinon*® stimulation and poor interpretation of CTGs can be primary causes of acquired neonatal brain damage.<sup>15</sup> In 2010 the Danish Patient Insurance paid 38,6 mill DKK for 23 cases of brain injury due to asphyxia in relation to labour.<sup>16</sup> 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



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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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- <sup>9</sup> Mori R, High dose versus low dose oxytocin for augmentation of delayed labour, The Cochrane Collaboration 2011
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STAN nomenclature: <http://www.dsog.dk/sandbjerg/stan%20guideline%202008.pdf>
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- <sup>16</sup> [www.patientforsikringen.dk](http://www.patientforsikringen.dk)