Studies on Induced labor
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Introduction
INTRODUCTION

Rationale

Most women in their reproductive years are healthy and their pregnancies end with the spontaneous onset of labor and uncomplicated delivery of a healthy child at a gestational age between 259 and 294 days. However, when continuation of pregnancy is considered to increase the risk for adverse outcome for mother or child, the clinician can decide to intervene and induce labor before its spontaneous onset.

Guidelines are developed by professional organizations on how to induce labor and which methods are safe to be used.\(^1,2\) Induction of labor is one of the most common interventions in obstetrics and since associated risks involved are under debate, it is necessary to reconsider the practice of induction of labor. In this thesis we discuss several aspects of induction of labor with intravenous oxytocin and how it is performed in obstetrical practice.

According to the national Dutch guideline on induction of labor, one should aim to imitate ‘physiological’ uterine activity and therefore a long period of time (until 12 hours) should be accepted before the acceleration phase of labor starts and progression can be expected with regular frequent contractions and ongoing dilatation of the cervix.\(^2\) However, if one aims to imitate natural course of labor, one should consider to start induction in the evening, in accordance with the physiological circadian rhythm.\(^3\) This clearly is in contrast with routine management of labor induction in hospitals starting in the early morning.

During induced or augmented labor with oxytocin, condition of the fetus and frequency of contractions must be monitored by cardiotocography in order to obtain good progression and prevent "hyperstimulation" of uterine activity which may result in fetal distress or uterine rupture. Since the introduction of intrauterine tocodynamometry for monitoring contractions, its use became a routine and was even expanding to deliveries with spontaneous contractions. The possibility to assess intrauterine pressure expressed as Montevideo Units was thought to reflect strength of contractions and allow the clinician to better titrate oxytocin. Although at that time two small randomized controlled trials were available that showed no benefit for use of intrauterine monitoring, the precise graphical depiction of contractions was thought to obviously result in better birth outcomes.\(^4,5\)

Although use of an intrauterine pressure catheter is considered safe, numerous case reports link its use to rare but serious complications, like abruptio placentae, uterine perforation, placental vessel perforation and even maternal anaphylactic shock resulting in neonatal or near maternal deaths.\(^6-11\)

Aim of the thesis

This thesis addresses the following questions:

- Does induction with intravenous oxytocin starting in the evening, in agreement with the endogenous circadian rhythm of spontaneous onset of labor, improve birth outcomes compared with care as usual, the starting induction of labor in the morning?
• Does use of an intrauterine pressure catheter for monitoring contractions lead to better neonatal or maternal outcomes when labor is induced or augmented with intravenous oxytocin?
• Does use of an intrauterine catheter during labor relate to occurrence of infection in mother or newborn during labor and up to three weeks postpartum?
• Does measurement of intrauterine pressure have predictive value for the outcome of delivery in oxytocin augmented labor?

In the following paragraphs some historical and related aspects of induction of labor are given with relevance to the above questions.

Induction

In ancient times women and medical workers already tried to influence the natural course of labor and provoke contractions by using herbs, tonics and other remedies; Hippocrates described mammary stimulation and mechanical dilatation of the cervical canal as a method to stimulate labor. From the second through the 18th century, mechanical methods to induce labor came into use. In 1756, at a meeting held in London, physicians discussed the efficacy and ethics of early delivery by rupturing the membranes to induce labor. In 1810, James was the first in the United States to utilize amniotomy to induce preterm labor. Amniotomy and other mechanical methods like laminaria or inflating balloons remained the most commonly employed methods of labor induction until the 20th century.

Oxytocin: historical aspects

In 1913 Bell reported powerful contractions of the pregnant, puerperal and menstruating uterus, caused by an extract of the pituitary gland. He was one of the first, maybe the first, to use pituitary extracts in a clinical setting. He described the effect of a single injection during cesarean section: “the naked-eye effect of a single injection is immediate and convincing, the uterus contracts into a blanched ball”. After the introduction of pituitary extract as a hormonal method of labor induction in 1913, use of this method gained acceptance among obstetricians. However, due to the use of too large doses and the impurity of the extract that also could contain vasopressin, numerous adverse effects were reported like cardiac arrest, uterine rupture and abruptio placentae. Gradually, as the number of reported cases increased, use of the pituitary extract became discredited in many centers. Later in 1953, the molecular structure of oxytocin was discovered, and synthetic oxytocin produced by pharmaceutical companies, became one of the most common pharmaceuticals used in obstetrics. Nowadays, synthetic oxytocin is used worldwide for induction or augmentation of labor, either alone or in combination with other drugs usually preceded by artificial rupture of the membranes.
Oxytocin physiology

Endogenous oxytocin is produced in the maternal hypothalamus and secreted into the bloodstream by the posterior pituitary gland but is also produced in other parts of the brain, several organs and by the fetus. Knowledge on the role of oxytocin in the physiology of human parturition, its pharmacological use and its interactions are still limited. We know that besides stimulating uterine activity, oxytocin also promotes milk ejection and influences behaviour like mother-child bonding and social interaction. For this thesis we only focus on the role of oxytocin in uterine activity.

Oxytocin metabolic clearance rate is increased in human pregnancy and appears to vary between individuals possibly related to the activity of the placental enzyme oxytocinase (EC 3.4.11.3, cysteine aminopeptidase). Oxytocin attaches to specific oxytocin receptors in the myometrium that increase in number towards the end of pregnancy and during active labor. When the receptors are occupied with oxytocin, the myometrium is stimulated to contract and prostaglandin is formed in the decidua. Oxytocin release from maternal hypothalamus occurs in pulses and timing, frequency, and amplitude of these pulses differ when delivery is nearby.

Most likely, there is also a mechanism that down regulates the oxytocin receptors, meaning that when oxytocin is overdosed the number of oxytocin receptors decreases and oxytocinase mRNA production is increased.

It agrees with the course of labor of women who end up with a failed induction. They seem to be resistant for oxytocin and despite long and high doses of synthetic oxytocin for prolonged periods of time, they don’t develop efficient contractions and progression of dilation. Interestingly in this respect is the observation of Cral et al, that showed in a small study on 10 women with arrest of labor that uterine response was increasing with a fixed rate oxytocin infusion but when prolonged for more than 90 minutes resulted in decreasing uterine activity.

Spontaneous onset of labor has a circadian rhythm with a preference to start labor in the evening with a diurnal rhythm in plasma oxytocin levels, with a nocturnal peak. This peak correlates with a decrease in the oestrogen/progesterone ratio in plasma. An increased oxytocin receptor density and oxytocin concentrations during night-time, makes the myometrium of the uterus more sensitive for maternal oxytocin in the night than during daytime. When onset of labor starts with spontaneous contractions in the evening, total duration of labor and delivery tends to shorten and less obstetric interventions are needed.

Protocols

The nonapeptide oxytocin cannot be administered orally because it is rapidly metabolized within the gastrointestinal tract. At first oxytocin was given by intramuscular injection, but it became quickly clear that every woman reacts differently, necessitating precise titration.
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of the medication by an intravenous drip to gain effect on the one hand and avoid unwanted side-effects on the other.

In daily clinical practice during the continuous infusion of oxytocin for the induction or augmentation of labor, the time to uterine response is three to five minutes, and effects on uterine activity, fetal condition and progress of labor are used to guide the amount of oxytocin needed.

It is given according to local hospital protocols, in a clinical setting with continuous monitoring of the fetal heart rate and frequency of contractions for an effective titration of the medication.\textsuperscript{31,32}

Too little oxytocin will unnecessarily prolong the duration of labor and thus increase the risk of interventions or an operative delivery. Too much oxytocin, in contrast, can lead to excessively frequent contractions and short relaxation time in between contractions and may subsequently lead to decreased fetal oxygen saturation level and fetal heart rhythm changes such as decreased variability and late decelerations as expression of fetal distress. This hyperstimulation of the uterus is preferably called, “tachysystole”, and is defined as more than five contractions in ten minutes, averaged over a 30-minute window.\textsuperscript{33,34} For timely recognition of tachysystole, accurate simultaneous and preferably graphical registration of the fetal heart rhythm and uterine activity is of utmost importance.

Despite its widespread use, there is no uniform and optimal protocol for oxytocin use for induction of labor. Oxytocin protocols can be divided into high-dose and low-dose protocols depending on the initial dose and the amount and rate of sequential increase in dose.

A Cochrane review reports high-dose protocols for augmentation to be associated with a reduction in the length of labor and cesarean section rates, but also concludes that there is insufficient evidence to draw conclusions for other maternal and neonatal outcomes, and how women experience the higher doses of oxytocin.\textsuperscript{35}

The Dutch Association of Obstetrics and Gynecology does not recommend high or low dosage of oxytocin as there is no consensus on which protocol is the best, and the clinician is advised to understand the trade-offs involved and how those trade-offs could relate to the clinician’s local situation.\textsuperscript{32}

Uterine activity

Also in other professional fields of Obstetrics and Gynecology, like in treatment of women with dysmenorrhea, understanding of uterine activity has proven to be important in development of new therapies and medication. In this thesis we focus on uterine activity measured during labor.

Palpation of the gravid uterus by hand, gives a impression of frequency, duration and strength of the contractions, and recognizing the bowel alike movements of the expelling uterus visible by eye, confirms start of the second phase of labor. Arrabal et al compared the accuracy of the impression of the caregiver of strength of contractions by palpation to simultaneously recorded intrauterine pressure readings.\textsuperscript{36} Caregivers of varying experience
were asked to assess contractions and were blinded for the intrauterine readings; 49% of the observations turned out to be less reliable. So, driven by the wish for objective and accurate registration of uterine activity, much research has been done and different methods developed to assess and register uterine activity.

The first graphical recording of uterine activity was made by a kymograph developed by Hendricus in 1889. The Latin word “kymograph” translates as “wave writer,” referring to the graphical representation of the instrument. A stylus registers on paper pressure, sound or motion on one axis, and time elapsed on the other axis. When these variables change, they look like waves when plotted. The early precursor of our extra-abdominal tocodynamometer is a construction introduced in 1930 by Crodell in which a little stylus writes movements of the mother’s belly on a plate placed against the abdomen. Many improved versions were developed and presented since.

Nowadays, we use an extra-abdominal tocotransducer attached to mother’s abdomen by elastic stripes or stickers and recently wireless connection to the monitor allows the mother to walk around and even take a bath. External registration of contractions has the advantage of being inexpensive, non-invasive, re-usable and in general provide reliable information about the frequency of contractions. It does give however no information about the strength of the contractions and can be unreliable in obese or restless women.

Internal methods

Even before the first external registration of contractions, much research was already done on internal methods for registration of uterine activity.

Some methods look rather obscure in our eyes, like injecting lipiodal, a contrast liquid, into the non gravid uterus and take serial x-rays up to every five seconds thus obtaining a description of uterine muscle contraction by comparing the sequential photographs. Attempts to record uterine activity during labor by electrodes tracing action potentials by attaching one electrode to the cervix and the other placed in the rectum at the level of the fundus of the uterus or by injecting CO2 puncturing a cannula through the uterus wall and so directly measuring pressure change, were other areas of interest, though not applicable in daily obstetrical practice.

In 1861 Kristeller attached a kind of dynamometer to a forceps in order to assess uterine contractions. Many different concepts followed until the intrauterine balloon method was developed to the method we use today, a small flexible tube that is inserted into the cavum of the uterus, its tip laying between the baby and the uterine wall. This intrauterine catheter allows us to calculate frequency and gives a quantification of uterine pressure of every single contraction. Caldeyro-Bancia et al defined the amount of uterine pressure per unit of time in Montevideo Units; product of frequency and peak pressure over a 10-minute period. An uterine pressure of 200 Montevideo Units in active labor is considered to be adequate. Use of an intrauterine pressure catheter for monitoring...
contractions gives an accurate graphical registration of contractions, independent of
position, movements or body mass index of the mother.
Most of the historical medical instruments belong into a museum, and the knowledge
 gained deserves not to be forgotten, let it be solely for the women who volunteered for
such experiments. It formed the basis for the modern catheters that we tested finally for
their effectiveness in obstetrical practice.

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GENERAL INTRODUCTION

1 REFERENCE LIST


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