Studies on induced labor
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Summary and discussion

Chapter 8
SUMMARY

Induction and augmentation of labor with intravenous oxytocin is one of the most common interventions in obstetrics. Almost one in every four women is induced, mostly for reasons related to increased risk for the mother such as high blood pressure, diabetes or increased risk for the infant such as suspected growth retardation or post term pregnancy. Induction of labor takes place in a clinical setting with a traditional start in the early morning and all women are monitored with cardiotocography for assessment of fetal condition and contractions.

Chapter 1 outlines the history of induction of labor and method to monitor uterine activity and describes the objectives of this thesis.

In Part I timing of start of induction of labor with intravenous oxytocin in the morning is compared to a start in the evening.

In Chapter 2 we present the results of multicenter randomized controlled trial that compared start of induction of labor with oxytocin in the morning with a start in the evening.

Traditionally, in most hospitals, induction of labor starts early in the morning, with the start of the working day. In human and animal studies however, spontaneous onset of labor is proven to have a circadian rhythm with preference for start in the evening. Moreover, when spontaneous labor starts in the evening, total duration of labor shortens and less obstetric interventions are needed. Based on these observations one might assume, that starting induction of labor in harmony with the circadian rhythm of natural birth is more beneficial.

Three hospitals in Amsterdam, the Netherlands participated in the trial, women with an indication for induction of labor with intravenous oxytocin were eligible. Included women were randomized to either the evening group with a start of induction of labor at 21:00 hours, or the morning group with a start at 07:00 hours.

Primary outcome was duration of labor. Secondary outcomes were instrumental delivery rate, adverse neonatal outcome defined as an Apgar score below 7 after 5 minutes, number and indications of pediatric consults and neonatal admissions, duration of second stage, number of intrapartum infections and necessity of pain relief.

We randomised 371 women. Mean duration of labor was not significantly different (primiparae: morning 12 hours and 8 minutes versus evening 11 hours and 22 minutes, P value 0.29; multiparae: morning 7 hours and 34 minutes versus evening 7 hours and 46 minutes, P value 0.70). There were no significant differences in instrumental deliveries rates, number of infections or patient satisfaction. Unexpectedly, neonatal outcome was better in women induced in the evening.
We concluded that induction of labor with intravenous oxytocin in the evening is equally effective and safe as induction in the morning.

In Chapter 3 we present a systematic review titled: morning versus evening induction of labor for improving outcomes. In this review we included three studies that were of high quality with a total of 1150 women randomly allocated to induction in the morning or the evening. There were no other trials on the subject that used intravenous oxytocin and two trials used prostaglandins to induce labor. Prostaglandins are hormones also used for cervical ripening; intravenous oxytocin can be used afterwards to get labor started. Therefore, these two different methods, prostaglandins and intravenous oxytocin, rely on a different mechanism and were assessed separately. This review found no differences in effect between starting induction in morning or evening on outcomes for mother or child. The risk for instrumental vaginal delivery, or risk for a cesarean section or use of epidural anesthesia did not differ between groups. One study reported that women had a preference to start induction of labor with prostaglandins in the morning, and more women in the evening admission group did not like the interruptions to sleep that were associated with the induction protocol. This review, with only three studies with two different comparisons, concludes that induction of labor in the evening is as effective and safe as induction in the morning. However, given the preference of most women, administration of prostaglandins should preferably be done in the morning.

In Part II risks and benefits of use of internal tocodynamometry (IT) for monitoring contractions during oxytocin augmented or induced labor are compared to external monitoring (ET).

In Chapter 4 we present the results of the randomized controlled trial: outcomes after internal versus external tocodynamometry for monitoring labor. It has been hypothesized that internal tocodynamometry, as compared with external monitoring, may provide a more accurate assessment of contractions and thus improve the ability to adjust the dose of oxytocin effectively, resulting in fewer operative deliveries and less fetal distress. However, few data are available to test this hypothesis.

We performed a randomized, controlled trial in six hospitals in the Netherlands to compare internal tocodynamometry with external monitoring of uterine activity in women for whom induced or augmented labor was required. The primary outcome was the rate of operative deliveries, including both cesarean sections and instrumented vaginal deliveries. Secondary outcomes included the use of antibiotics during labor, time from randomization to delivery, and adverse neonatal outcomes (defined as any of the following: an Apgar score at 5 minutes of less than 7, umbilical-artery pH of less than 7.05, and neonatal hospital stay of longer than 48 hours).
We randomly assigned 1456 women to either IT (734) or ET(722). The operative delivery rate was not statistically significant different: 31.3% in the IT group and 29.6% in the ET group. Secondary outcomes did also not differ between the two study groups. No serious adverse events associated with the use of the intrauterine pressure catheter were reported during the trial.

We concluded that internal tocodynamometry during induced or augmented labor, as compared with external monitoring, did not significantly reduce the rate of operative deliveries or of adverse neonatal outcomes.

According to former studies the risk for infection during labor or postpartum is increased when an intra uterine catheter is used for monitoring or for amnioinfusion. In Chapter 5 we reported follow up of randomised controlled trial that assigned women in whom labor was induced or augmented with intravenous oxytocin, to internal or external tocodynamometry. We sought to determine whether use of an intrauterine catheter during labor is related to occurrence of infection in mother or newborn during labor and up to three weeks postpartum. The primary outcome was indication of infection, defined as a composite measure of any clinical sign of infection, treatment with antibiotics or sepsis during labor or in the postpartum period up to three weeks in mother or newborn. We found no indication that use of an intrauterine catheter for monitoring contractions or for amnioinfusion increases the risk of infection during labor or in the postpartum period up to three weeks in mother or newborn.

Although our trial as described in Chapter 4 demonstrated no benefit of intrauterine monitoring, many clinicians continue to use an intrauterine pressure catheter for monitoring contractions, either routinely in oxytocin augmented labors or on an incidental basis. Such management is justified in the belief that when intrauterine activity is ‘adequate’ as defined by an intrauterine pressure of at least 200 Montevideo Units, this will improve labor outcome.

To provide more insight in this mechanisms, we evaluated in Chapter 6 whether measurement of intrauterine pressure has predictive value for the outcome of delivery in oxytocin augmented labor. We performed two secondary analyses on 503 women that had intra-uterine pressure measured in the intervention arm in the trial as reported in chapter 4. First we analyzed outcomes in four strata of women with different ranges of the highest intrauterine pressure registered at any time during labor, women that never reached 100 MU, 100-199 MU, 200-299 MU and women that reached intrauterine pressures 300 MU and higher. Second we assessed the uterine pressure registered at the last vaginal examination in the first stage of labor in two study groups; above and below 200 MU. Outcomes were mode of delivery and a composite neonatal outcome defined as 5-minute Apgar score below 7, an umbilical-artery pH below 7.05, or a neonatal admission longer than 48 hours. Women in the
ranges with lower intrauterine pressures were statistically significant older, had pregnancies with a longer gestational age and had longer labors with children with a higher birth weight. We found a decreasing likelihood for a cesarean section as the intrauterine pressure during labor increased. In the group women that never reached 100 MU the LR for a cesarean section was 1.6, the group between 110 MU and 200 MU the LR was 1.3, the group between 200 MU and 300 MU the LR was 0.85, the group 300 MU and higher the LR was 0.41. Intrauterine pressure measured by intrauterine tocodynamometry was not associated with poor neonatal outcome. Conclusion of this study is that level of intrauterine pressure has a predictive value whether labor will be spontaneous.

In Chapter 7 we summarized literature in a systematic review to evaluate the effectiveness of internal tocodynamometry (IT) compared with external tocodynamometry (ET) when intravenous oxytocin is used for induction or augmentation of labor. Three studies were included in this review. The pooled risk for instrumental delivery was not statistically different between study groups, however in the subgroup of women with augmented labor there was a statistically significant difference in favor of ET. When the variable instrumental delivery was specified into instrumental vaginal delivery or cesarean section, this benefit for ET was not found; moreover we lack a clinical explanation for a possible advantage of external registration of contractions when labor is augmented. This review found insufficient evidence for a benefit of the routine use of IT on rates of adverse neonatal outcomes, rates of instrumental deliveries, use of analgesia, infection, or time to delivery.

In chapter 8 and 9 we discuss our findings and make suggestions for future studies.

**DISCUSSION**

The possibility to end a complicated pregnancy in a controlled and safe way, is one of the blessings of our time and often results in better health outcomes for mothers and infants. Induction of labor allows smart timing of birth in time and place and opens possibilities to plan complicated high risk deliveries in daytime with guaranteed ample availability of pediatric and obstetrical specialists.

A guideline from the Dutch Association of Obstetrics and Gynecology (NVOG) states that ideally uterine activity and course of induced labor should resemble a spontaneous birth. ¹ Onset of spontaneous labor has a circadian rhythm with a preference for the evening. ² In our randomized controlled trial, we compared starting induction of labor with intravenous oxytocin in the morning with starting in the evening, in order to try to resemble natural onset of labor. We found no statistically significant difference in duration of labor between the approaches. This could be related to the fact that the decision to increase dosage of
oxytocin during labor, is a clinical judgement of the frequency of uterine contractions, and not a standard oxytocin dosage according to a medication protocol. Indeed, in our study we found a tendency for increased amounts of oxytocin used during the day time inductions compared to the night and unexpectedly oxytocin dosage was more slowly increased during night time by attending obstetrical personnel. More importantly, in the discussion of her recent thesis, C. Verhoeven strongly advises against use of duration of labor as primary outcome, and against reporting neonatal and maternal outcomes as secondary outcomes, as we did in the above mentioned trial. 3 Although duration of labor can be related to neonatal and maternal outcomes, in fact length of labor is a surrogate outcome for the mother and child, and merely has economic or logistic value for the obstetric ward.

We found no difference in length of labor between the evening and the morning group, but unexpectedly we found that significantly fewer neonates from mothers in the evening group were admitted for pediatric care.

Because our study was not powered to assess a difference in neonatal outcome and the difference was unanticipated and unexplained, we have to be careful to draw conclusions. However, an interesting hypothesis is that because during the night shift the oxytocin dosage was raised more slowly, this might have resulted in less tachysystole and consequently less fetal distress and pediatric involvement. The combination with other non significant factors like shorter second stage of labor and a reduced amount of obstetric interventions needed, could account for a better neonatal outcome in the evening group.

Although the Dutch Association of Obstetrics and Gynecology in her guideline warns against tachysystole during labor and states that a long latent phase up to 12 hours should be accepted, in busy daily labor wards economic motives are undeniably present. 4 The risks involved in the use of intravenous oxytocin and fast increasing doses of oxytocin are often underestimated. A recent editorial comment in the American Journal of Obstetrics gives us a clear warning of risks involved in daily routine use of intravenous oxytocin. 5

Quote : Although considered safe when administered judiciously, the inappropriate use of oxytocin, specifically related to dosing regimens that cause or fail to recognize excess uterine contractions and resultant poor fetal oxygenation, is a common and serious problem. According to a survey of liability cases, approximately 50% of paid liability claims involve alleged misuse of oxytocin.

For these reasons, oxytocin is considered 1 of the 12 most dangerous medications in a hospital. 6

In 2007, the Canadian Institute for Safe Medication Practices added intravenous synthetic oxytocin to their short list of high-alert medications; medications that have a heightened risk of causing significant patient harm when they are used in error. 7 Rare complications of oxytocin are uterine rupture, mostly in women with a scarred uterus, and hyponatremia as result of the anti-diuretic hormone effect. Moreover, recent research hypotheses that synthetic oxytocin given during labor crosses the placental barrier, and fetal exposure to
synthetic oxytocin might have long term effects on behavioural development of the child. \(^8\) Since use of synthetic oxytocin in obstetrics is increasingly common, in 2010 nearly 30% of all labors in the Netherlands were oxytocin augmented \(^9\), further research on this subject is mandatory.

A common complication of oxytocin is hyperstimulation or tachystole, which is defined as either a series of single contractions lasting two or more minutes or a contraction frequency of five or more in 10 minutes. \(^4\) When the contractions are that frequent or long, relaxation time between contractions is too short for the infant to recover and can lead to fetal distress, especially when the reason to induce labor was declining fetal condition. Use of oxytocin almost doubles the likelihood of tachystole with fetal heart rate changes and triples the likelihood of tachystole leading to intervention. \(^10\)

To prevent tachystole, a logical step could be complete discontinuation of oxytocin once active labor is achieved.

The diagnose “active labor” is in this context defined as, four cm dilation with complete effacement and regular contractions every five minutes. In literature there are four randomized trials with low statistical power addressing this issue. \(^11\) - \(^14\)

The most recent trial, Diven et al faced severe inclusion problems and protocol adherence. The trial was stopped after 30 months with 83% of the intended inclusions because of lack of cooperation of the caregivers involved. Furthermore, only 25 of the 125 women that were randomized to discontinuation of oxytocin were treated according to protocol because of what the authors named as “growing clinician anxiety about potentially prolonging the length of labor inductions in a very busy labor unit”. \(^13\) The failure to complete inclusion and treat according to protocol, reflects the impatience caused by circumstances that sometimes urges caregivers to act for no medical reasons. The primary outcome in these studies was the duration of labor or instrumental delivery rate; they found no clinically relevant differences between study groups and were consistent in their conclusion that oxytocin may be discontinued if regular contractions continue to generate cervical change, without increasing the cesarean delivery rate or significantly prolonging labor.

The endpoint of interest, neonatal outcome, was different in the study of Girard et al in the sense that significantly more infants were hospitalized in the neonatology department when oxytocin was continued. The other studies reported no differences in neonatal outcome between study groups. In the study of Ustunyurt et al, the rate of uterine hyperstimulation was significantly higher in oxytocin-continued group but this did not lead to worse neonatal outcomes.

The above mentioned issue certainly merits further investigation with larger sample sizes.

For timely recognition of tachystole caused by overdosing of oxytocin, accurate and preferably graphical simultaneous registration of the fetal heart frequency and uterine activity is of utmost importance. Moreover, correct assessment of uterine activity during use of oxytocin is important to confirm sufficient stimulation.
In our randomized controlled trial (IUPC trial) and the Cochrane systematic review, we concluded that there is no evidence that use of internal tocodynamometry for monitoring contractions in women with induced or augmented labor leads to better outcomes for mother or child. Implementation of this finding in daily practice is however difficult. One argument for clinicians to keep on using internal tocodynamometry is that the attractive precise graphical reproduction of the contractions, must result in better birth outcomes, although studies proved otherwise. Furthermore, the risks associated with use of an intrauterine catheter are often thought to be related to incorrect placement of the catheter. Some clinicians want to continue using intrauterine pressure catheters especially in women with labors after a cesarean section (VBAC), with the expectation that it may facilitate early diagnosis of a uterine rupture. Rodriguez et al studied 39 women that had a uterine rupture during labor and were monitored with an intrauterine pressure catheter. He did not find the classic description of a sudden loss of intrauterine pressure in any of the women. The clinical signs of a uterine rupture, fetal distress, and severe pain are so compelling that diagnosis does not depend on the uterine pressure. Moreover although the risk may be small, one could cause a uterine rupture by and during insertion of the catheter. Apparently introduction of new diagnostic tools or extension of medical interventions are more easy to implement than abandoning an inadequate diagnostic tool caregivers are accustomed to.

Another argument used is that without intrauterine registration of the contractions, the laboring woman might need more attention of her caregivers. Sometimes the registration is vague and one will have to be present in the labor room to assess the contractions by clinical observation, this will be especially the case when the woman is obese. In 2012, after publication of our studies, Rood published a case report of uterine perforation after insertion of an intrauterine pressure catheter in a woman with a body mass index of 45 kg/m². In this case, fortunately mother and child survived after an emergency cesarean section. In our randomised controlled trial we analysed a subgroup of 206 women with a body mass index above 30 kg/m² and found no benefit for use of an intrauterine pressure catheter for these women. However because this analysis was post hoc and the statistical power limited, we cannot draw conclusions.

The proportion of maternal obesity is increasing, in the United States the prevalence of maternal obesity has increased over a 10-year period, from 13% to 22% and the Netherlands will probably follow the same trend. Besides all the risks involved like gestational diabetes and hypertension, obesity of the mother provides a challenge for monitoring contractions during labor, especially because obese women appear to be prone for dysfunctional labor. The caregiver will have to weigh the potential hazardous risks of use of an intrauterine pressure catheter to the (not proven) benefit of an accurate monitoring of contractions for these women.

New technology has been developed that hopefully will overcome the drawbacks of the other methods:
electro hysterography which reports the electrical activity of the myometrium of the uterus through electrodes placed on the maternal abdomen. The method is non invasive and registers contractions accurately regardless of the mothers body mass index. 18-20

Although a randomized trial is considered to be the highest level of evidence, performing one can be time consuming and costly. Both trials published in this thesis were performed without additional financing by the government. The outcomes of the IUPC trial that compared internal tocodynamometry with external tocodynamometry resulted in less use of intrauterine pressure catheters in obstetrics worldwide.
We calculated a saving of 570 000 euro every year in the Netherlands with an implementation of 80% for a onetime investment of 350 000 euro for performing the study. The IUPC trial is a typical example of studies performed by the Dutch Consortium of Obstetrics and Gynecology; relative small investments save the community significant amounts of money on healthcare costs and provide evidence for efficient care for women and their children.

By studies described in this thesis, we aimed to obtain evidence for the effectiveness of a few methods used for labor induction. Ideally, any decision to intervene in medicine should be evidence based, which means with conscientious, explicit and judicious use of current best evidence respecting patient values and expectations of the individual patient. 21 When the decision to induce labor is evidence based, this implicates that the characteristics of the individual woman resemble those of the women in the study for whom the benefits of the intervention, expeditious birth, outweighed the risk of expectant management, continuing the pregnancy.
As an example: women with a complicated pregnancy caused by pregnancy induced hypertension or mild preeclampsia at a gestational age between 36 and 41 weeks, have better maternal outcomes when labor is induced. Results of the HYPITAT trial were quickly implemented in daily practice, especially in the 39 hospitals in the Netherlands that participated in the trial. Maternal outcomes in those hospitals improved within a year after publication; the prevalence of eclampsia decreased from 0.95% to 0.13%, a clear example of improving healthcare as result of well performed and implemented studies. 23 However, reasons to induce labor are not always based on sound evidence but often decided on because of uneasiness to wait and concerns or convenience of parents or caregivers.

Although there can be good reason to do so, nowadays the induction rate is increasing in an excessive way and the elective induction adds its share in the exploding healthcare costs; in developed countries, almost one in every four women is induced. For example, according to data from the Centers for Disease Control and Prevention, the rate of induction in the United States of America in 2009 was 23.3% which represented a 144% increase since 1990. 16 In developing countries, the rates are generally lower, but in some settings they
can be as high as those observed in developed countries. The Netherlands is following the United States with the same growing trend, about one-fourth of all deliveries are induced for the presumed benefit of mother or baby, while in 1993, this intervention apparently was necessary in around 12% of women. There is a large variation between hospitals in percentage of induced labor even when corrected for case-mix. Practice variation of induction and the doubling of inductions in the last 20 years suggest that a lot of these interventions are not based on solid evidence.

Although the World Health Organization recommended in 2011 “Induction of labour should be performed only when there is a clear medical indication and the expected benefits outweigh its potential harms”, a psychosocial indication has become a common rationale for elective induction on maternal request for personal convenience, physical discomfort and provider’s convenience. 24

Elective induction is side effect of medicalization and can lead to a cascade of interventions that frequently accompany labor induction, and puts healthy women and infants at unnecessary risk of complications. 25

The size of risks involved with an elective induction is still under debate, as no prospective trials are available in which healthy women with an uncomplicated medical and obstetrical history and uncomplicated pregnancy are randomised to either expectant management or induction of labor. The definition of elective induction is often unclear and can involve mixed motivations, furthermore the definition of a low risk pregnancy is not unequivocal in international literature. A retrospective comparison of birth outcomes of women with spontaneous onset and induced labor does not account for the specific moment in time the decision for an expectant management or intervention takes place.

Given the exploding healthcare costs and the fact that all interventions bare potential risks, unnecessary medical interventions should be considered like withheld necessary treatment and critically appraised and abandoned if judged not beneficial.

Since at least half of our interventions in childbirth are opinion based, this thesis is hopefully one of many to follow that adds sound evidence for the best care to our clinical practise.

Midwives must be educated in science and encouraged to participate in answering the clinical dilemmas in treatment decisions, and add their expertise on physiology of childbirth to development of multidisciplinary guidelines. For pregnant women and their partners there should be no walls between midwife and gynecologist, home and hospital, physiology and pathology. Ideally, parents to be, should feel free in their choices and experience wide open doors to enter any safe place to deliver after being informed on perinatal care based on proper and transparent evidence.
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