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Delayed versus immediate oxytocin infusion after amniotomy for induction of labour: A randomised controlled pilot trial

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ABSTRACT

Objective: To get a preliminary understanding of the amniotomy-to-delivery interval, patients' experiences and risks by awaiting spontaneous contractions after amniotomy and to explore the need and feasibility for a larger randomised controlled trial.
Methods: We performed a randomised controlled pilot trial in a peripheral teaching hospital in Amsterdam, The Netherlands. Women with term, singleton pregnancy in vertex position undergoing labour induction for one of the five following indications: prolonged pregnancy, mild hypertensive disorders, diabetes, expected macrosomia, maternal request, were randomised to amniotomy with 12-hours delayed oxytocin (DO), or amniotomy with immediate oxytocin (IO).
Results: A total of 64 women was included in the analysis. The median amniotomy-to-delivery interval for the DO-group was 15 h (IQR 8–21), and 6 h (IQR 5–11) for the IO-group (HR, 0.41; 95% CI, 0.24–0.70), with equal patient reported childbirth perception in the overall group (P=0.43). Parous women reported a significantly less positive perception of labour (P=0.02) and used pain relief more often (RR, 2.93; 95% CI, 1.05–8.19) in the DO-group. The proportion of women delivered within 24 h was not significantly different between groups (RR, 0.30; 95% CI, 0.05–1.83). Other delivery and neonatal outcomes did not differ significantly between groups, possibly due to being underpowered.
Conclusion: Preliminary results show that amniotomy-to-delivery interval was prolonged with 9 h in the DO-group, with equal patient reported childbirth perception in the overall group. Parous women have a less positive perception of their delivery and used pain relief more often when oxytocin was delayed. Delaying oxytocin infusion after amniotomy should be further investigated in an adequately powered randomised trial.

Introduction

Induction of labour is performed in 25% of pregnancies in the UK, 23% in the US, and 24% in the Netherlands [1–3]. In women with a favourable cervix standard care is amniotomy and oxytocin infusion immediately. However, a review by Bricker et al. [4] found poor evidence on the optimal time interval between primary (amniotomy alone) and secondary intervention (addition of oxytocin infusion). Since then, two randomised controlled trials showed that amniotomy combined with immediate administration of oxytocin leads to a significantly shorter amniotomy-to-delivery interval in comparison with delaying oxytocin infusion for four hours in both nulliparous and parous women [5,6]. However, there are side-effects to the routine use of synthetic oxytocin during labour: uterine hyperstimulation, and an increased caesarean delivery rate [7,8]. Bell et al. state that synthetic oxytocin may not have the same effects on the maternal body and brain as naturally released oxytocin. They suggest considering the oxytocin system as a whole, not just the immediate clinical result [9].

Several studies have shown when delaying oxytocin administration after amniotomy, administration of oxytocin was not needed at all in 19–68% of all women [5,6,10]. No clinically relevant effects of delaying oxytocin administration, such as patient experience, have been described [5,6,10]. We hypothesize that avoidance of oxytocin infusion in induction of labour could result in higher patient satisfaction and fewer side effects of oxytocin use. By delaying oxytocin for 12 h, we aim to find an optimal timing for starting oxytocin as a secondary intervention after amniotomy.

We conducted a pilot trial to explore the need and feasibility for a larger randomised controlled trial. The objectives of this pilot

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were: [1] To get a preliminary understanding of the amniotomy-to-delivery interval, patient experience and risks of awaiting spontaneous contractions after amniotomy [2]; To assess the clinical feasibility and acceptability to women and caregivers of awaiting spontaneous contractions after amniotomy; and [3] To power further research.

Methods

Design

An unblinded randomised controlled pilot trial was conducted. The trial was performed at the OLVG hospital, Amsterdam, The Netherlands, a secondary teaching hospital where annually about 6000 mid- and high-risk deliveries take place. The study was approved by the Medical Research Ethics Committees United (Nieuwegein).

Participants

During a 5-month period (November 2017 - April 2018) women who met our inclusion criteria have been asked to participate in this trial by the midwife or doctor who planned the induction. Inclusion criteria were: term (≥37 weeks), singleton pregnancies, with viable fetus in cephalic presentation, favourable cervix (bishop score >5), intact membranes, due for induction of labour for one of the following indications: prolonged pregnancy (> 41weeks), mild hypertensive disorder, diabetes, expected macrosomia, or maternal request. Participants had to be ≥18 years old and have sufficient knowledge of the Dutch or English language.

Participants with a previous caesarean section, fetal distress or maternal fever prior to induction were not included in the trial.

Randomisation and blinding

Patients were randomised after written informed consent using Castor EDC [11]. The patients were randomised (1:1) to delayed oxytocin (DO) or immediate oxytocin (IO) infusion after amniotomy. The allocation procedure was blinded via block randomisation with random block sizes. Due to the nature of the intervention patients, obstetrical caregivers and outcome assessors were not blinded to the allocated treatment.

Study protocol

Amniotomy was performed as planned with the induction appointment or after ripening of the cervix was completed. Women in the DO-group waited for spontaneous contractions for 12 h after amniotomy. In case of any contra-indication for awaiting spontaneous contractions, oxytocin was started immediately.

Established labour was defined as 3–4 painful contractions every 10 min and changes of the cervix. If a woman in the DO-group did not establish labour after 12 h she received oxytocin. Oxytocin was administered according to the local induction of labour protocol. Women in the IO-group received standard care and infusion of oxytocin was started immediately (within 30 min) after amniotomy.

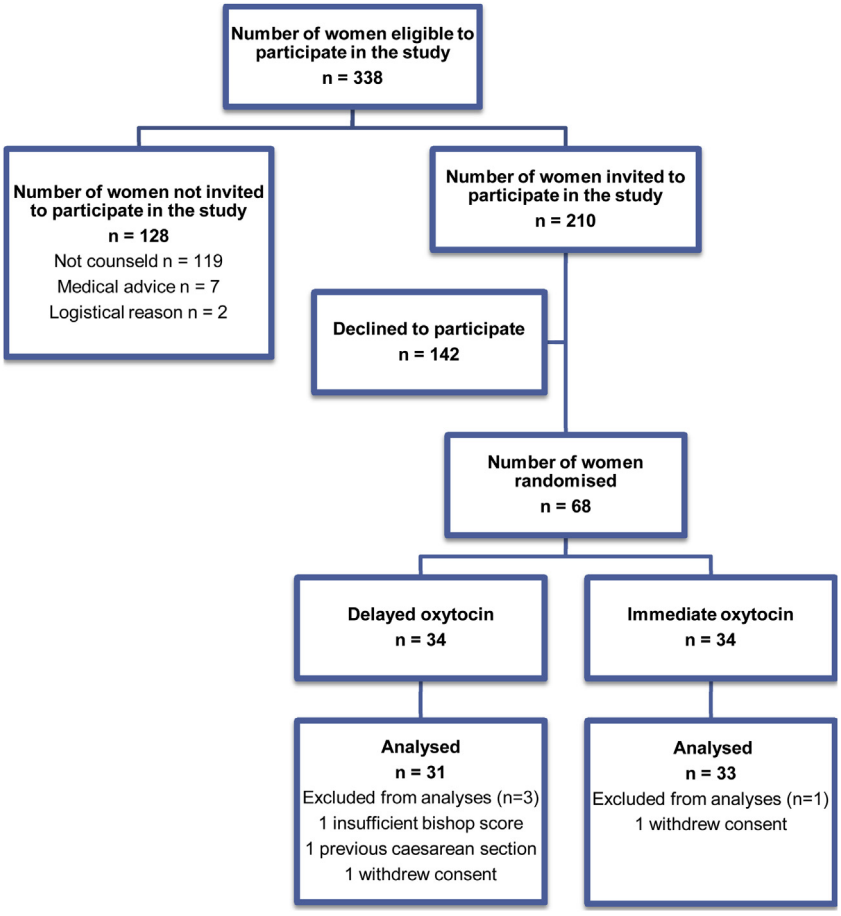

Fig. 1. Flow diagram.

Outcomes

To test our hypothesis, we used two primary outcomes to be able to weigh the possible longer duration of delivery against the effects on patients' birth experience. Primary outcomes were: amniotomy-to-delivery interval and patient reported experience. Patient experience was measured two weeks after delivery with the 'perception of delivery' subscale of the Childbirth Perception Scale (CPS), send to every participant via e-mail invitation [12]. The CPS is a 12-item instrument to assess the patients' perception of delivery and the first postpartum week, developed in The Netherlands. To assess patient reported experience on delaying oxytocin in our trial, the six-item subscale 'perception of delivery' was used. Items were formatted on a four-point scale, ranging from 0 to 3. The total score could range from 0 to 18, higher scores indicated a less positive perception.

Secondary outcomes included: the proportion of women delivered within 24 h, amniotomy-to-established-labour interval, the proportion of women in established labour within 12 h following amniotomy, meconium stained fluid, use of pain relief (epidural anesthesia, patient controlled remifentanil), intrapartum fever (defined as temperature >38.0 C measured rectally), FIGO CTG-classification (normal, no-normal), micro-blood-examination, uterine tachysystole (>5 contractions in 10 min), total oxytocin augmentation time, total oxytocin dose, highest oxytocin dose, mode of delivery, postpartum haemorrhage rate (>1000 ml bloodloss), Apgar <7 at 5 min, neonatal infection (neonatal treatment with antibiotics).

To evaluate the study procedure, we conducted a process evaluation survey to measure the experiences of obstetrical caregivers. Other pilot outcomes included: enrolment rate, rate of violation of the study protocol and amniotomy-to-oxytocin interval.

Data collection & management

Data were collected in a data management system (Castor EDC [11]) and performed according to Good Clinical Practice guidelines. All results could be extracted from the medical records of the participants, except for patient experience. E-mail invitations were sent through Castor EDC, so all data were anonymously linked to the participants record. To prevent missing data in the patient experience measurements, reminders were sent after 2 and 4 weeks.

Analysis

Data were analysed for the two strata (nulliparous and parous women), following the intention-to-treat principle. Time to event data were analysed with a cox proportional hazard analysis. Categorical secondary outcomes were assessed by comparing event rates in the two groups using a Fisher's exact test with a p-value of 0.05. For continuous secondary outcomes, differences between groups were assessed with the Students *t*-test (two-tailed) if the outcome was normally distributed and with a non-parametric Wilcoxon Rank-Sum test if skewed. Data were analysed using R Version 1.0.136 [13].

Results

In total 338 women were assessed eligible for participation. 128 women were not asked to participate in the trial, reasons were: caregiver did not counsel (119/128), medical advice not to participate (7/128), or logistical reasons (2/128). 210 women were invited to participate in the study. 142 women declined to participate.

68 women (20% of eligible women) were included in the study and randomised to the DO-group (n = 34) or to the IO-group (n = 34). After randomisation 4 women were excluded, due to not meeting the inclusion criteria (n = 2) or withdrawing informed consent (n = 2). A total of 64 women were analysed, 31 in the intervention group and 33 in the control group. (Fig. 1)

The maternal characteristics of the two study groups are presented in Table 1.

Amniotomy-to-delivery interval

The primary outcomes are presented in Table 2. The median amniotomy-to-delivery interval for the DO-group was 15 h (interquartile range (IQR) 8–21), for the IO-group it was 6 h (IQR 5–11) (HR, 0.41; 95% CI, 0.24-0.70). Fig. 2 shows the resulting cumulative incidence curve.

Patient reported experience

51 women completed the CPS (80%). Overall there was no difference between the groups in patient reported childbirth perception ($P = 0.43$). However, parous women scored a significantly less positive perception of labour when oxytocin was delayed ($P = 0.02$).

Process of delivery

The secondary outcomes are presented in Table 3. In the DO-group the median amniotomy-to-established-labour interval was 5 h (IQR 2–10), which was significantly longer than the IO-group (3 h (IQR 2–4), HR, 0.41; 95% CI, 0.23-0.74). Overall 74.2% of women in the DO-group were in established labour within 12 h after amniotomy and did not significantly differ from the IO-group (RR, 0.35; 95% CI, 0.10–1.23). Fig. 3 shows the cumulative incidence curve of the amniotomy-to-established-labour intervals. In the first 3 h after amniotomy the cumulative proportion of women in established labour was equal between groups (RR, 0.87; 95% CI, 0.54–1.40).

Significantly more parous women in the DO-group used pain relief, compared to parous women in the IO-group (RR, 2.93; 95%

Table 1
Maternal characteristics.

	Delayed oxytocin (n = 31)	Immediate oxytocin (n = 33)
Maternal age *median (IQR)*	35.0 (31.8–37.3)	34.4 (32.2–37.2)
Ethnicity *n (%)*		
- Caucasian	21 (67.7)	24 (72.7)
- Moroccan	5 (16.1)	5 (15.1)
- Turkish	1 (3.2)	2 (6.1)
- Other non-western	4 (12.9)	2 (6.1)
BMI median (IQR)	22.5 (20.5–28.9)	22.7 (21.1–24.6)
Parity *n (%)*		
- Nulliparous	18 (58.1)	19 (57.6)
- Multiparous	13 (41.9)	14 (42.4)
Gestational age in days *median (IQR)*	279 (270–291)	274 (267–289)
Bishop score *median (IQR)*	7 (6–8)	7 (6–7)
Methods for ripening *n (%)*		
- None	10 (32.3)	11 (33.3)
- Foley	10 (32.3)	18 (54.6)
- Misoprostol	5 (16.1)	1 (3.0)
- Both	6 (19.3)	3 (9.1)
Induction indication *n (%)*		
- Prolonged pregnancy (>41wks of pregnancy)	11 (35.5)	8 (24.2)
- Mild hypertensive disorders	8 (25.8)	8 (24.2)
- Diabetes	4 (12.9)	5 (15.2)
- Expected macrosomia	1 (3.2)	3 (9.1)
- Maternal request	7 (22.6)	9 (27.3)

CI, 1.05–8.19). This was not seen with nulliparous women, nor in the overall group. No difference was found between the groups with regards to meconium stained fluid, CTG classification, micro-blood examinations, or uterine tachysystole.

Use of oxytocin

Overall oxytocin was not used in 22.6% of all women in the DO-group. When treated, women from both groups received comparable doses of oxytocin, for a comparable amount of time.

Outcome of delivery

The proportion of women delivered within 24 h was not significantly different between groups. The frequency of intrapartum fever or neonatal infection were equal between groups.

There was no significant difference between the groups with regard to mode of delivery

or postpartum haemorrhage rate. Apgar <7 after 5 min did not occur in our study.

Pilot

The pilot outcomes are presented in Table 4. 20% of all eligible women were included in this trial. In 46.9% of all women the study protocol was violated. In the DO-group, 35.5% of all women received oxytocin within 12 h after amniotomy without being in established labour yet. In the DO-group, the median amniotomy-to-oxytocin interval was 9 h (IQR 4–13). In 57.6% of all women in the IO-group, oxytocin was not administered within 30 min after amniotomy. The median amniotomy-to-oxytocin interval was 45 min (IQR 20–75) in the IO-group.

Process evaluation shows positive experiences of obstetrical caregivers with the study protocol. Obstetrical caregivers reported that the main reasons for patients declining participations were “Awaiting contractions for 12 h is too long” and “Do not want induction method being subjected to chance”. The most frequently reported reason for administrating oxytocin within 12 h after amniotomy was: “At the request of the patient”.

Table 2
Primary outcomes.

	Delayed oxytocin Total: n = 31	Immediate oxytocin Total: n = 33	
	Nulliparous: n = 18 Parous: n = 13	Nulliparous: n = 19 Parous: n = 14	HR (95% CI)
Amniotomy-to-delivery interval (h)			
median (IQR)	15 (8–21)	6 (5–11)	0.41 (0.24–0.70)
- Nulliparous	18 (7–22)	9 (8–14)	0.50 (0.25–1.01)
- Parous	9 (8–18)	5 (4–6)	0.17 (0.06–0.45)
	Delayed oxytocin Total: n = 24	Immediate oxytocin Total: n = 27	
	Nulliparous: n = 13 Parous: n = 11	Nulliparous: n = 17 Parous: n = 10	*P* Value
Patient reported Childbirth Perception			
Mean total CPS-score (SE)	7.7 (0.8)	6.8 (1.1)	0.43
- Nulliparous	8.0 (1.0)	8.5 (0.9)	0.70
- Parous	7.3 (0.9)	3.9 (1.0)	0.02

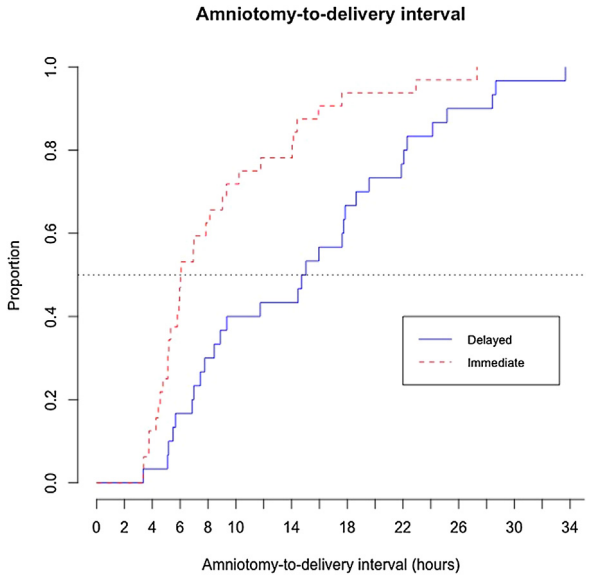

Fig. 2. Amniotomy-to-delivery interval.

Discussion

Main findings

In this study, we found that a 12 -h delay of oxytocin infusion after amniotomy leads to a 9 -h longer amniotomy-to-delivery interval and equal patient reported childbirth perception in the overall group, but with a significantly less positive perception of labour in parous women.

Strengths and limitations

A major strength of our study is the relatively long delay of oxytocin administration after amniotomy, to evaluate the optimal interval between amniotomy alone and oxytocin infusion as a secondary intervention for induction of labour. Moreover, by stratifying our randomisation to parity, we were able to analyse our results for both nulliparous and parous women separately. We used a web-based randomisation, with random block sizes to ensure blinding of randomisation. There were no missing values in our trial and we achieved a high response on patient reported experience of 80%.

The most important limitation of this trial is the small sample size, arguably underpowered. Because being in established labour is a subjective measure diagnosed by an unblinded obstetrical caregiver, this makes interpretation of amniotomy-to-established labour outcome pragmatic, but this needs to be confirmed in a larger trial. The fact that participants were not blinded to the allocated treatment, may have influenced patient reported perception of delivery.

Amniotomy combined with immediate oxytocin is current practice for induction of labour in the OLVG hospital. Therefore, due to voluntary participation, patients included in our trial are more likely to have a high trust in amniotomy alone for induction of labour. This self-selection bias may have resulted in a select group of patients in our trial, with different attitudes towards labour compared to the women who declined participation.

Interpretation

Our first pilot goal was to get a preliminary understanding of the amniotomy-to-delivery interval, patient experience and

Table 3
Secondary outcomes.

	Delayed oxytocin Total: n = 31	Immediate oxytocin Total: n = 33	
PROCES OF DELIVERY	Nulliparous: n = 18 Parous: n = 13	Nulliparous: n = 19 Parous: n = 14	**Effect size*** **(95% CI)**
Amniotomy-to-established-labour interval (h) *median (IQR)*	5 (2–10)	3 (2–4)	0.41 (0.23–0.74)
- Nulliparous	5 (3–10)	3 (3–5)	0.44 (0.20–0.96)
- Parous	4 (2–10)	3 (2–4)	0.37 (0.15–0.94)
In established labour within 12 hrs *n (%)*	23 (74.2)	31 (93.9)	0.35 (0.10–1.23)
- Nulliparous	13 (72.2)	17 (89.5)	0.50 (0.15–1.69)
- Parous	10 (76.9)	14 (100)	
Meconium stained fluid *n (%)*	3 (9.7)	2 (6.1)	1.31 (0.44–3.95)
- Nulliparous	3 (16.7)	1 (5.3)	2.18 (0.39–12.25)
- Parous	0	1 (7.1)	
Use of painrelief *n (%)*	23 (74.2)	19 (57.6)	1.41 (0.89–2.23)
- Nulliparous	14 (77.8)	16 (84.2)	0.80 (0.32–2.01)
- Parous	9 (69.2)	3 (21.4)	2.93 (1.05–8.19)
Intrapartum fever *n (%)*	2 (6.5)	1 (3.0)	1.57 (0.31–7.94)
- Nulliparous	2 (11.1)	1 (5.3)	1.59 (0.31–8.12)
- Parous	0	0	
CTG classification normal *n (%)*	13 (41.9)	15 (45.5)	1.07 (0.67–1.72)
- Nulliparous	6 (33.3)	3 (15.8)	0.58 (0.22–1.55)
- Parous	7 (53.8)	12 (85.7)	2.53 (0.73–8.80)
Micro-blood-examination *n (%)*	7 (22.6)	6 (18.2)	1.15 (0.60-2.18)
- Nulliparous	6 (33.3)	6 (31.6)	1.04 (0.53–2.05)
- Parous	1 (7.7)	0	
Uterine tachysystole *n (%)*	5 (16.1)	8 (24.2)	0.80 (0.48-1.33)
- Nulliparous	5 (27.8)	6 (31.6)	0.92 (0.47–1.78)
- Parous	0	2 (14.3)	
OXYTOCIN			***P* Value**
Use of oxytocin *n (%)*	24 (77.4)	33 (100)	<0.01
- Nulliparous	15 (83.3)	19 (100)	0.11
- Parous	9 (69.2)	14 (100)	0.04
Total oxytocin augmentation time (h) *median (IQR)*	6 (4–10)	5 (4–9)	0.97
- Nulliparous	6 (4–10)	8 (5–12)	0.32
- Parous	7 (2–9)	4 (4–5)	0.75
Total oxytocin dose (mIE) *median (IQR)*	2081 (893–4777)	1686 (819–3110)	0.64
- Nulliparous	2062 (938–4866)	2454 (1514–5650)	0.63
- Parous	2343 (900–4313)	1324 (836–1760)	0.34
Highest oxytocin dose (mIE/min) *median (IQR)*	5.4 (4.5–9.6)	4.8 (3.6–7.2)	0.41
- Nulliparous	4.8 (4.2–8.4)	6.0 (3.6–10.0)	>0.99
- Parous	7.2 (4.8–9.6)	4.8 (4.8–6.0)	0.13
OUTCOME OF DELIVERY			**RR (95% CI)**
Delivered within 24 hrs *n (%)*	25 (80.6)	31 (93.9)	0.30 (0.05–1.83)
- Nulliparous	13 (72.2)	17 (89.5)	0.35 (0.06–2.09)
- Parous	12 (92.3)	14 (100)	
Mode of delivery *n (%)*			
Spontaneous delivery	18 (58.1)	26 (78.8)	1.0
Instrumental delivery	5 (16.1)	2 (6.1)	2.07 (0.62–6.84)
Caesarean section	8 (25.8)	5 (15.1)	1.54 (0.74–3.19)
Caesarean section indications			0.51 (0.30–1.55)
• Labour dystocia	3 (37.5)	4 (80)	
• Fetal distress	5 (62.5)	1 (20)	
- Nulliparous			
Spontaneous delivery	8 (44.5)	12 (63.2)	1.0
Instrumental delivery	4 (22.2)	2 (10.5)	1.80 (0.55–5.90)
Caesarean section	6 (33.3)	5 (26.3)	1.32 (0.63–2.77)
Caesarean section indications			0.42 (0.18–1.73)
○ Labour dystocia	2 (33.3)	4 (80)	
○ Fetal distress	4 (66.7)	1 (20)	
- Parous			
Spontaneous delivery	10 (76.9)	14 (100)	
Instrumental delivery	1 (7.7)		
Caesarean section	2 (15.4)		
Caesarean section indications			
○ Labour dystocia	1 (50)		
○ Fetal distress	1 (50)		
Postpartum haemorrhage *n (%)*	7 (22.6)	4 (12.1)	1.50 (0.66–3.41)
- Nulliparous	6 (33.3)	4 (21.1)	1.39 (0.61–3.19)

Table 3 (*Continued*)

	Delayed oxytocin Total: n = 31	Immediate oxytocin Total: n = 33	
- Parous	1 (7.7)	0	
Apgar <7 at 5 minutes *n (%)*	0	0	
Neonatal infection *n (%)*	1 (3.2)	1 (3.0)	1.03 (0.25–4.21)
- Nulliparous	1 (5.6)	1 (5.3)	
- Parous	0	0	

* For categorical variable: Relative Risk (RR); for time-to-event variable: Hazard Ratio (HR).

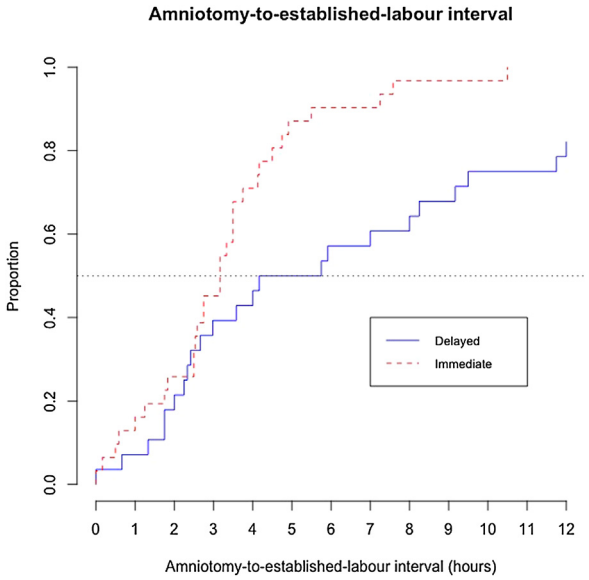

Fig. 3. Amniotomy-to-established labour interval.

Table 4
Pilot outcomes.

	Delayed oxytocin n = 31	Immediate oxytocin n = 33	Overall
Enrolment rate *n (%)*			68/338 (20.1)
Protocol violation *n (%)*	11 (35.5)	19 (57.6)	30/64 (46.9)
Amniotomy-to-oxytocin interval (min) *median (IQR)*	556 (268–757)	44.5 (20–75)	

risks of awaiting spontaneous contractions after amniotomy. Our study supports the findings in a previous study of Moldin et al. [10] that the amniotomy-to-delivery interval is significantly longer when oxytocin administration is delayed for 12 h after amniotomy. Moldin et al. found a median amniotomy-to-delivery interval of 9 h when delaying oxytocin for 12 h, which is shorter than the median amniotomy-to-delivery interval in our study [10]. A possible contributing factor is the relatively higher proportion of parous women in their trial (64%, compared to 42% in our study).

Parous women reported a significantly less positive perception of labour and used pain relief significantly more frequent when delaying oxytocin infusion after amniotomy. Tan et al. [6] studied the effects of delaying oxytocin infusion for 4 h after amniotomy in parous women and also reported significantly more use of epidural analgesia in the delayed group but found no difference in maternal satisfaction with the birth process between groups. Direct comparison of childbirth perception or satisfaction outcomes with trials from other countries may be complicated, due to the unique Dutch obstetrical care system and attitude of Dutch women towards childbirth [14].

The main risk of oxytocin administration during labour is uterine hyperstimulation, which may lead to CTG-abnormalities and fetal acidosis. Our data show relatively more caesareans due to fetal distress in the DO-group and more caesareans due to labour dystocia in the IO-group, although not significant. This contradicts the hypothesis that delaying of oxytocin can prevent uterine hyperstimulation or fetal acidosis.

We found oxytocin administration was not given in 22.6% of all women when delaying oxytocin infusion after amniotomy. Previous studies found oxytocin-avoidance-rates ranging from 19.4% to 68.4% [5,6,10]. The low percentage of no-oxytocin may be a result of the high percentage of protocol violations in our trial.

Due to being a pilot trial, the sample size of our trial was too small to detect any significant differences between groups in expected fetal and neonatal outcomes. To detect possible differences in adverse perinatal outcomes in further research, we suggest using a composite outcome of a 5-minute Apgar <4 and/or an arterial pH < 7.05, meconium aspiration syndrome, intracranial haemorrhage and/or NICU admission.

Our second pilot goal was to assess the clinical feasibility and acceptability to women and caregivers of delaying oxytocin after amniotomy for induction of labour. In our study 20% of all eligible women were included in the trial. 42% (142/338) of all eligible women declined to participate. The main reported reason for not participating was patients found awaiting starting of contractions for 12 h too long.

Our data show that in the first 3 h after amniotomy the cumulative proportion of women in established labour is equal between groups. This might be the optimal timing for oxytocin administration as a secondary intervention. When delaying oxytocin for 3 h, the proportion of women willing to participate in a further trial may be higher.

Our third pilot goal was to power further research. With a power of 80% and an alpha error of 0.05, 1332 women (666 per arm) are needed to detect 2% reduction in the risk of composite perinatal mortality and neonatal morbidity from 3% to 1%. To be able to stratify to parity, a total of 2664 women would be needed. We suggest performing a large multicentre randomised controlled trial, to ensure the feasibility of such a trial.

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The author(s) has(have) no conflicts of interest to disclose.

Declaration of Competing Interest

The author(s) has(have) no conflicts of interest to disclose.

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