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Synopsis

High or low dose oxytocin for nulliparous women delayed in the first stage of labour: the HOLDS RCT

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Abstract

Background: Delay in the first stage of labour occurs in approximately 20% of nulliparous women. Recommended treatment is intravenous oxytocin, which shortens labour but does not affect the mode of birth. There is some evidence that a higher dose regimen may decrease the need for caesarean section.

Objective: The primary objective was to establish if a high-dose regimen of oxytocin compared to the current standard-dose regimen reduced the need for caesarean section for nulliparous women with confirmed delay in the first stage of labour.

Design: Multicentre, randomised double-blind controlled trial.

Setting: Twenty-one maternity units in the United Kingdom.

Participants: Consenting nulliparous women who had a singleton cephalic pregnancy, gestation of 37–41 weeks inclusive, confirmed delay in labour in first stage, ruptured membranes and for whom the clinical decision has been made to prescribe oxytocin.

Interventions: Standard-dose regimen of oxytocin (2 mU/min increasing every 30 minutes to a maximum of 32 mU/min) compared with high-dose regimen (4 mU/min increasing every 30 minutes to a maximum of 64 mU/min).

Main outcome measures: The primary outcome was the rate of caesarean section. Secondary outcomes included maternal and neonatal birth outcomes and safety.

Results: One hundred and eighteen women were successfully randomised via third-party minimisation from an intended sample size of 1500 between 30 June 2017 and 14 November 2022.

The caesarean section rate in the standard-dose group was 34% (20/58) and 27% (16/60) in the high-dose group. The intervention was provided as intended in 96% (113/118) of participants. There was no obvious suggestion that the high-dose regime was unsafe (all neonates were discharged home with mother), but this size of sample prohibited any definitive conclusions.

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Limitations: The trial did not meet its intended sample size due to a number of challenges. It was difficult for busy clinical staff to recruit women in labour in this acute, but not emergency, situation. The legislative requirements of undertaking research using interventional medicinal products imposed further constraints, and we encountered challenges in the production, blinding and monitoring required.
Changes in clinical practice since trial design and commencement 10 years ago have resulted in fewer women going into spontaneous labour (reduced from 66% to 47%), and therefore potentially becoming eligible, due to more women having labour induced (22%–33%) or elective caesarean sections (12%–20%). These challenges were further compounded by a falling birth rate and the impact of the COVID-19 pandemic.
Conclusions: The question of the optimum dose of oxytocin for nulliparous women delayed in the first stage of spontaneous labour remains an important unanswered clinical question, and the major challenge is how best to address this within the current regulatory framework.
Future work: Future studies should consider whether the option of delayed consent would be suitable in this acute, but not emergency, situation.
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A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/MALP6685.

Rationale for research and background

Delay in the first stage of labour is not uncommon on UK Delivery Suites and how best to care for these women is currently unclear. The only recommended treatment for delay in the first stage of labour is an intravenous infusion of oxytocin which has been used since the 1960s and is licensed for this specific indication. This treatment is used worldwide, and all regimens of oxytocin for confirmed delay gradually increase the dose to increase the frequency and strength of uterine contractions with an aim of achieving vaginal birth. The dose is titrated for each woman based on her response and that of the fetus. An optimal response is achieved if three to four uterine contractions occur for every 10 minutes and there is progressive cervical dilatation without adverse effects on the fetus (manifesting as abnormal fetal heart patterns).

There is evidence from one Cochrane systematic review that considered women delayed in spontaneous labour[1] comparing high- versus low-dose oxytocin regimens. The review included four trials and 644 women and while indicating a trend towards reduced rates of caesarean section (CS) with the high-dose regimen, the evidence was not conclusive (relative risk: 0.67, 95% confidence interval 0.38 to 1.18; $p = 0.2$). It highlighted the lack of robust evidence regarding the high-dose regimen and strongly concluded that further research was needed, reinforcing the need for confirmatory evidence from a large, randomised trial. While it did compare a low-dose oxytocin with a high-dose regimen, the recent publication of a Swedish trial by Selin[2] did not answer the question as women were recruited up to 4 hours earlier in labour than the timing recommended by the National Institute for Health and Care Excellence (NICE) guidance. This means that many of the women in the Selin trial were not delayed in labour according to the NICE definition, and the initiation of oxytocin (whether high or low dose) could not be expected to improve outcome while at the same time risking adverse side effects. This is supported by the very low rate of CS seen in the Selin trial (12.3% vs. the expected 17.5% they included in their sample size calculation) and lower than the 32% we anticipated in the women joining the high- or low-dose syntocinon (HOLDS) trial.

Reducing the rate of unplanned CS is important for women, as it is associated with longer stays in hospital, higher risk of infection, increased bleeding and thrombosis and increased risk of CS in subsequent pregnancies.

The question of when the active phase of labour begins remains controversial. In the USA, the Consortium of Safe Labor had published data that suggest that the duration of labour appears to be longer today than in the past[3] and that a cervical dilation of 6 cm appears to be a better marker for the start of the active phase of labour. This has been adopted by the American College of Obstetricians and Gynecologists with the Society for Maternal-Fetal Medicine in their consensus statement for 'Safe Prevention of Primary Caesarean Section'[4] as part of a number of strategies designed to reduce the CS rate. In this statement, they suggest that the intervention for delayed labour should not start until the cervix is > 6 cm dilated, and it is not clear what the standard oxytocin dose regimen should be. Using the data collected as part of the work undertaken by the Consortium of Safe Labor, an observational study[5] found no difference in CS rates with a so-called high-dose oxytocin compared to a low dose. However, this study is open to methodological biases,

the exact oxytocin dose regimens are unclear and, as they are presented within the paper, all the regimens would be considered as standard-dose regimens in the UK. Uptake of this evidence and the Consensus Statement[4] has been controversial in the USA[6] and does not appear to have influenced practice in the UK. Indeed, the most recent NICE intrapartum care of healthy women and babies update[7] does not suggest any change to the definitions of established or delayed labour. We incorporated a subgroup analysis of women commencing treatment < 6 cm and ≥ 6 cm into our a priori statistical analysis plan to ensure that the trial results were of worldwide interest and relevance.

Objectives

HOLDS was funded by the Health Technology Assessment (HTA) programme in March 2016 (HTA 14/140/44). The primary objective was to establish if a high-dose regimen of oxytocin compared to the current standard-dose regimen reduced the need for CS for nulliparous women with confirmed delay in the first stage of labour.

Secondary objectives were to assess the effect on maternal and neonatal outcomes and to explore any variation in effect in women randomised with cervical dilation < 6 cm and ≥ 6 cm. Furthermore, we aimed to assess the safety of high-dose oxytocin, as oxytocin can cause excess contractions (tachysystole), which can lead to abnormalities of the fetal heart rate (hyperstimulation). A full description of the trial design can be found in the protocol [https://fundingawards.nihr.ac.uk/award/14/140/44 (accessed 3 April 2025)].

Setting

Obstetric departments in 21 UK hospitals.

Participants

Consenting nulliparous women (aged 16 years+) who had a singleton cephalic pregnancy, gestation 37–41 weeks inclusive, confirmed delay in spontaneous labour in the first stage, ruptured membranes and for whom the clinical decision had been made to prescribe oxytocin for augmentation of labour.

For all women, labour is established when there are regular painful contractions and progressive cervical dilation from 4 cm (NICE 2014).[7] The definition of confirmed delay is as follows:

- For women with cervical dilation between 4 and 7 cm, inclusive delay is suspected when cervical dilation of < 2 cm in 4 hours occurs. Delay is confirmed when progress of < 1 cm in 2 hours is found on repeat vaginal examination.
- For women with cervical dilatation of 8 and 9 cm (whether or not membranes are ruptured), re-examination occurs in 2–4 hours (depending on local guidance and practice), and if the cervix is not fully dilated, the labour should be considered as delayed.

Women were excluded if they had reached full dilation of the cervix (10 cm), underwent induction of labour, had a body mass index (BMI) > 40 at booking or had multiple pregnancies. Several other exclusion criteria relating to existing disease status or known contraindication to oxytocin therapy were also applied.

Screening and randomisation

Information was sent to women in the late antenatal period. Participants were recruited by clinical staff once delay in labour was confirmed. Once consent and eligibility were confirmed, randomisation was via a web-based central service based at the University of Aberdeen to allocate women in a 1 : 1 ratio using a minimisation algorithm.

Interventions

High-dose regimen of oxytocin (4 mU/min increasing every 30 minutes to a maximum of 64 mU/min) compared with a standard-dose regimen (2 mU/min increasing every 30 minutes to a maximum 32 mU/min) was followed (*Table 1*). Both treatment regimens were manufactured to have an identical appearance, with the intention of blinding participants, midwives and any treating clinicians throughout, as knowing treatment allocation could influence care of the mother.

Outcomes

The primary outcome was CS. Secondary outcomes are explained below:

Maternal (clinical) outcomes

- Epidural use during labour
- Duration of first, second and third stages of labour.
- Time to birth from randomisation.
- Mode of birth [spontaneous vaginal birth (SVB), instrumental or CS].
- Degree of perineal trauma (first, second, third and fourth degrees).
- Reason for CS and decision to delivery interval for CS.
- Confirmed urinary retention requiring catheterisation and pulmonary oedema.

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TABLE 1 Dose regimens used in HOLDS

60 women randomised to blinded standard-strength oxytocin solution (10 IU in 50 ml)		60 women randomised to blinded high-strength oxytocin solution (20 IU in 50 ml)	
Time after starting (minutes)	**Milliunits a minute**	**Time after starting (minutes)**	**Milliunits a minute**
0	2	0	4
30	4	30	8
60	8	60	16
90	12	90	24
120	16	120	32
150	20	150	40
180	24	180	48
210	28	210	56
240	32	240	64

IU, International Units.

- Tachysystole (uterine contractions > 5 in 10 minutes for 20 minutes) requiring reduction in oxytocin and/or tocolysis.
- Hyperstimulation (uterine contractions > 5 in 10 minutes for 20 minutes resulting in non-reassuring or abnormal fetal heart rate).
- Fetal blood sampling (FBS) during labour or significant ST analysis (STAN event (for those units that use ST waveform analysis for intrapartum fetal monitoring).
- Abnormal cardiotocogram leading to immediate birth without fetal blood sample.
- Incidence of possible maternal morbidity (anaphylaxis, pulmonary oedema, postpartum haemorrhage, shoulder dystocia, chorioamnionitis and uterine rupture/hysterectomy).
- Active management of third stage of labour.
- Length of time after birth in hospital (days).
- Admission to high dependency unit (HDU) /intensive therapy unit (ITU).
- Maternal death.

Process outcomes

- Time from randomisation to commencement of allocation.
- Total oxytocin dose.
- Time to maximum oxytocin rate.
- Maximum oxytocin dose reached.

Neonatal outcomes

- Gender and birthweight.
- Apgar score at 5 minutes.
- Arterial and venous cord blood gases when collected.
- Breastfeeding rates on discharge from hospital.
- Length of time after birth in hospital (days).
- Resuscitation.
- Reason for neonatal review on ward (excluding routine baby check).
- Reason for admission to neonatal unit (NNU) and level of care received (levels 1–3), including intensive care.
- Duration of respiratory support.
- Days to full suck feeds.
- Seizures.
- Neonatal encephalopathy [SARNAT (classification scale for hypoxic–ischaemic encephalopathy of the newborn) grade].
- Therapeutic hypothermia (cooling) if required.
- Intrapartum still birth.
- Early neonatal death (within 7 days of birth).

Statistical considerations

The sample size assumed a CS rate of 32% in the standard-dose group and aimed to have at least 90% power ($p = 0.05$) to detect a 25% relative reduction in the high-dose group by recruiting 1500 participants. Due to the premature closure of the trial due a number of recruitment and logistical issues (see *Results* and *Discussion/interpretation*), it was felt that any formal analysis would not be appropriate. Summary statistics for all outcomes are provided below.

Results

Recruitment took place over three periods (30 June 2017–17 October 2017, 27 June 2018–2 August 2018 and 30 May 2022–14 November 2022) from 21 maternity units across the UK.

The trial began recruitment on 30 June 2017 and was suspended for the first time on 17 October 2017 due to two unanticipated drug-related issues. The trial restarted recruitment on 27 June 2018, but it was suspended for a second time on 2 August 2018 after a further 7 women had been recruited (total 102 women recruited).

Following discussions with the HTA between October 2018 and October 2020, additional funds were secured, and the HOLDS grant was reactivated in July 2021. Due to COVID-19-related delays (see *COVID-19*), sites reopened on 30 May 2022. During the subsequent five months, a total of 18 women were recruited before the trial was finally closed on 14 November 2022 as part of the Research Reset programme when it became increasingly evident that the trial was not going to meet pre-determined internal pilot recruitment criteria. In the context of this paper, when we refer to women, we are including pregnant people and birthing parents who may not identify as women.

In total, 120 women were randomised, although 1 participant had to be excluded due to failure to gain consent and a further participant was excluded due to incorrectly being randomised twice (*Figure 1* and *Table 2*). Participants had an average age of 28.7 years and BMI of

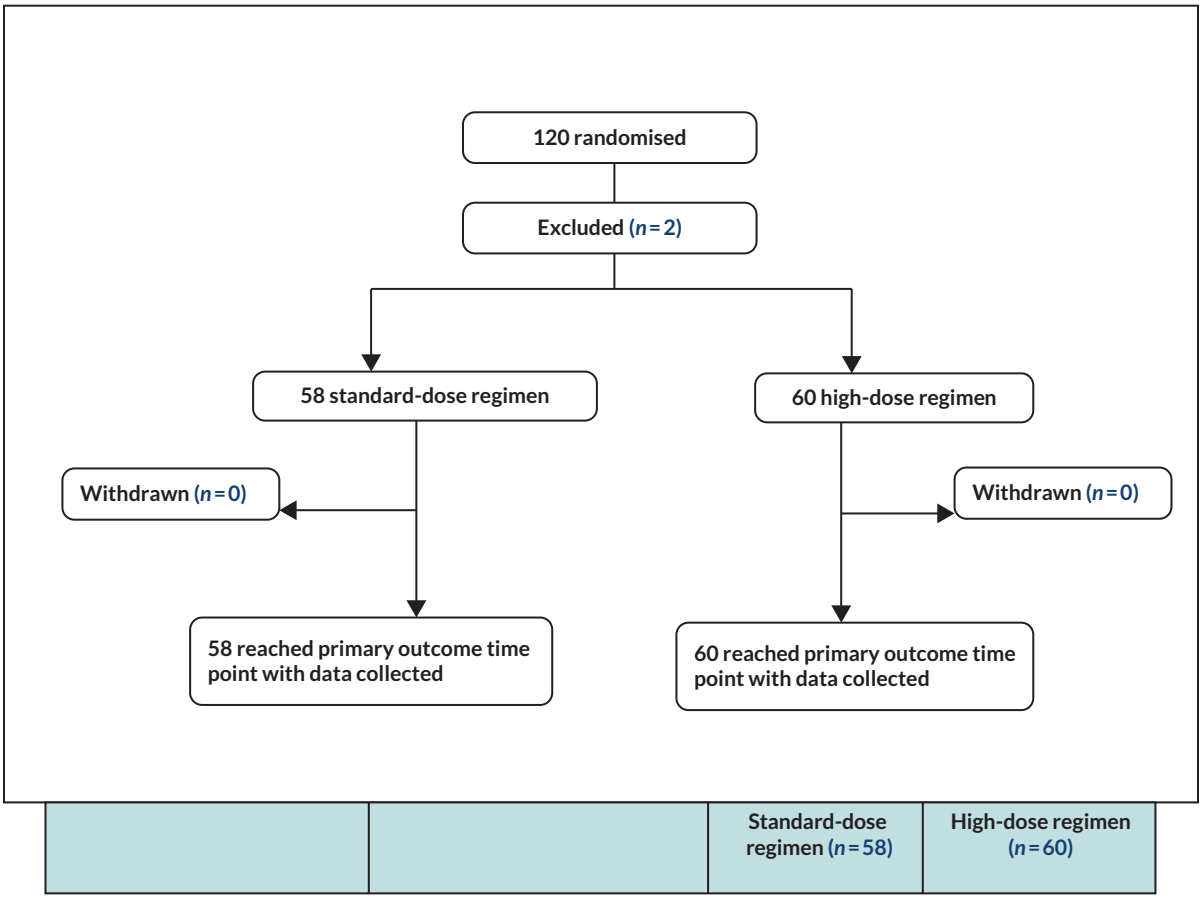

FIGURE 1 Consolidated Standards of Reporting Trials flow diagram.

TABLE 2 Participant trial exit (attrition)

	n = 120
Number excluded[a]	2 (2%)

a Two participants at one centre have been excluded from analysis for the context of this report due to issues during randomisation; and during data collection, one participant did not give consent and a second was randomised twice and it was unknown which treatment she received.

25.1 kg/m^2; 78% were of White ethnicity, and there was an even split on the degree of cervical dilation, with 53% (62/118) ≥ 6 cm at the time of randomisation. The groups appeared balanced for other baseline characteristics (*Table 3*).

Primary outcome data were successfully attained for all participants (see *Figure 1*). The CS rate in the standard-dose group was 34% (20/58) and was 27% (16/60) in the high-dose group; 10% (6/58) versus 8% (5/60) were

TABLE 3 Participant baseline characteristics

		Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Minimisation variables			
Degree of cervical dilation (cm)	< 6 cm	28 (48%)	28 (47%)
	≥ 6 cm	30 (52%)	32 (53%)
Age (years)	< 20	4 (7%)	5 (8%)
	≥ 20 to < 30	27 (47%)	29 (48%)
	≥ 30 to < 40	27 (47%)	26 (43%)
	≥ 40	0 (–)	0 (–)
Maternity unit	St Mary's Hospital Manchester	8 (14%)	9 (15%)
	Sunderland Royal Hospital	8 (14%)	7 (12%)
	Birmingham Women's Hospital	6 (10%)	6 (10%)
	University Hospital of Wales	6 (10%)	4 (7%)
	St James University Hospital	4 (7%)	5 (8%)
	West Middlesex University Hospital	5 (9%)	2 (3%)
	The James Cook University Hospital	3 (5%)	3 (5%)
	The Royal Victoria Infirmary	1 (2%)	4 (7%)
	Royal Preston Hospital	2 (3%)	3 (5%)
	Royal Cornwall Hospital (Treliske)	3 (5%)	1 (2%)
	University Hospital of North Tees	3 (5%)	1 (2%)
	Liverpool Women's Hospital	1 (2%)	3 (5%)
	The Princess Royal Maternity Unit	1 (2%)	2 (3%)
	Burnley General Hospital	1 (2%)	2 (3%)
	St Thomas Hospital	1 (2%)	1 (2%)
	Derriford Hospital	0 (–)	2 (3%)
	Leeds General Infirmary	2 (3%)	2 (3%)
	The Great Western Hospital	1 (2%)	1 (2%)
	Stoke Mandeville Hospital	1 (2%)	1 (2%)
	The Princess Royal Hospital (Maternity)	0 (–)	1 (2%)
	Queen's Medical Centre	1 (2%)	0 (–)
Participant demographics			
Age (years)	Mean (SD)	28.7 (5.6)	28.7 (5.4)
Ethnic group, *n* (%)	UK (White)	46 (79%)	46 (77%)
	South Asian (Asian)	4 (7%)	3 (5%)

TABLE 3 Participant baseline characteristics (*continued*)

		Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
	Southern and other European (White)	3 (5%)	4 (7%)
	Northern European (White)	2 (3%)	2 (3%)
	South East Asian (Asian)	0 (–)	3 (5%)
	African or African-Caribbean (Black)	1 (2%)	1 (2%)
	Other non-European (other)	0 (–)	1 (2%)
	Do not know/not available	2 (3%)	0 (–)
Other baseline variables			
Cervical dilation (cm)	Median (IQR)	6 (4–7)	6 (4–7)
BMI (mg/kg^2)	Mean (SD)	24.7 (4.7)	25.6 (5.2)
	Missing	0	2
Gestational age at randomisation (weeks)	Median (IQR)	39 + 4 (39 + 1 – 40 + 1)	39 + 3 (38 + 6 – 40 + 1)

IQR, interquartile range; IU, International Units; N/A, not available; SD, standard deviation.

Notes
Data are either mean (SD), median (IQR) or number (%).
The intervention was successfully delivered in 96% (113/118) of participants, with the remaining 5 receiving either the site-standard oxytocin regimen or no intervention. As intended, this translated to the high-dose group delivering a faster (median oxytocin dose rate per group: 9.2 mU/min vs. 7.0 mU/min; median time to maximum dose: 120 minutes vs. 150 minutes) and higher maximum dose (medium: 16 mU/min vs. 12 mU/min) than the standard-dose group but similar total amount of oxytocin (median: 3.3 IU vs. 3.0 IU) (*Tables 4–8*).

TABLE 4 Treatment adherence

Time point		Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Initial allocation	Number that received randomised allocation	55 (95%)	58 (97%)
	Number that received standard oxytocin treatment	1 (2%)	1 (2%)
	Number that received no intervention[a]	2 (3%)	1 (2%)

a Of the three participants who did not receive any intervention: in the standard-dose arm, two participants did not receive the investigational medicinal product (IMP) as the baby was already born, and in the high-dose group, one participant did not continue due to clinical decision.

TABLE 5 Average oxytocin rate (mU/min)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Average oxytocin dose rate by arm (mU/min), mean (SD)	7.6 (4.5)	12.0 (8.5)
Median (IQR)	7.0 (4.3–10.2)	9.2 (6.7–16.1)
Missing	4	2

IQR, interquartile range.

categorised as requiring the highest level of urgency (immediate threat to life) (*Tables 9* and *10*).

There was no obvious suggestion that the high-dose regime was unsafe, with the obvious caveat that this size of sample would prohibit any definitive conclusions. Uterine tachysystole and uterine hyperstimulation were common in both groups [31% (18/58) vs. 40% (24/60) and 24% (14/58) vs. 27% (16/60) in the standard- and high-dose groups, respectively]. Six babies in total (three in

TABLE 6 Time to maximum oxytocin dose (minutes)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Time to maximum dose by arm (minutes), mean (SD)	192 (140)	191 (251)
Median (IQR)	150 (90–240)	120 (60–180)
Missing	3	1

IQR, interquartile range.

TABLE 7 Maximum oxytocin dose (mU/min)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Maximum dose by arm (mU/minutes), mean (SD)	12.3 (6.5)	18.4 (11.1)
Median (IQR)	12 (8–16)	16 (8–24)
Participants reaching a maximum dose over 32 mU/min	1 (2%)	7 (12%)
Participants reaching a maximum dose over 64 mU/min	0 (–)	1 (2%)
Missing	2	1

IQR, interquartile range.

TABLE 8 Total amount of oxytocin administered (IU)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Total amount of oxytocin administered by arm (IU)	3.5 (3.3)	5.2 (5.6)
Median (IQR)	3.0 (1.6–4.2)	3.3 (1.7–6.6)
Missing	2	2

IQR, interquartile range; IU, International Units.

TABLE 9 Summary of primary outcome measure

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
CS	20 (34%)	16 (27%)
Mode of delivery of other births		
Instrumental	20 (34%)	24 (40%)
SVB	18 (31%)	20 (33%)

each group) were admitted to a NNU, four of which were due to suspected infection and one due to respiratory distress (one reason missing). All babies were discharged home with their mother (*Tables 11–16*).

Discussion/interpretation

While obtaining evidence about the optimal dose regimen of oxytocin for nulliparous women with confirmed delay in the first stage of spontaneous labour presents an important clinical question, this trial experienced a number of challenges; some of which were expected and some which were not.

Change in practice over time

Since the trial was conceived 10 years ago, the proportion of women having their labour induced has increased from 22% to 33%,[8] and similarly, those having an elective CS has also increased from 12% to 20%. This means that there are fewer women going into spontaneous labour (from 66% to 47%), and therefore, combined this with a falling birth rate means that less women were eligible for the HOLDS trial.

TABLE 10 Caesarean section details

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Category of urgency		
Cat 1: immediate threat to the life of mother or fetus	6 (10%)	5 (8%)
Cat 2: maternal or fetal compromise that was not immediately life-threatening	11 (19%)	11 (18%)
Cat 3: the mother needed early birth, but there was no maternal or fetal compromise	3 (5%)	0 (–)
Reasons for CS[a]		
Delay in first stage	13 (22%)	11 (18%)
Delay in second stage	2 (3%)	2 (3%)
Maternal request	1 (2%)	0 (–)
Hyperstimulation	1 (2%)	1 (2%)
CTG concerns without resort to FBS (incl. significant STAN event)	16 (28%)	14 (23%)
Abnormal FBS	0 (–)	1 (2%)
Failed instrumental	5 (9%)	0 (–)
Unsuitable for instrumental	10 (17%)	10 (17%)
Other[b]	3 (5%)	2 (3%)

CTG, cardiotocography.
a Participants can select more than one reason.
b Other reasons include cord wrapped around baby's neck, pre-eclampsia symptoms and maternal sepsis × 3.

TABLE 11 Secondary outcomes

Outcome		Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Maternal outcomes			
Epidural use during labour		47 (81%)	46 (77%)
Duration of first stage of labour (minutes)[a]	Mean (SD), *n*	818 (221), 41	888 (249), 42
	Missing	2	2
Duration of second stage of labour (fully dilated to birth) (minutes)[a]	Mean (SD), *n*	144 (64), 43	150 (77), 44
Duration of third stage of labour (birth to expulsion of placenta and membranes) (minutes)	Mean (SD), *n*	8 (16), 58	8 (7), 60
Time from randomisation to birth (minutes)	Median (IQR), *n*	431 (349–548), 57	368 (242–608), 60
	Missing	1	0
Mode of birth	SVB	18 (31%)	20 (33%)
	Instrumental birth	20 (35%)	24 (40%)
	CS	17 (29%)	16 (27%)
	CS following failed instrumental birth	3 (5%)	0 (–)

continued

TABLE 11 Secondary outcomes (*continued*)

Outcome		Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Degree of perineal trauma[b]	None (intact perineum)	14 (24%)	20 (33%)
	First degree	2 (3%)	3 (5%)
	Second degree	17 (29%)	16 (27%)
	Third degree	2 (3%)	1 (2%)
	Fourth degree	0 (–)	1 (2%)
	Missing	3	3
Confirmed urinary retention requiring catheterisation or pulmonary oedema		1 (2%)	1 (2%)
	Missing	4	2
FBS during labour or significant STAN event	*N* (%)	9 (16%)	12 (20%)
No. of occasions FBS procedure performed (successful or not)	Median (IQR), *n*	1.5 (1–2), 8	1 (1–2), 11
Abnormal cardiotocogram leading to immediate birth without fetal blood sample	*N* (%)	13 (22%)	18 (30%)
Women with blood loss > 500 ml (PPH)	*N* (%)	27 (47%)	25 (42%)
IV antibiotics for suspected or confirmed chorioamnionitis	*N* (%)	3 (5%)	1 (2%)
Active management of third stage of labour	*N* (%)	55 (95%)	55 (92%)
Length of time after birth in hospital (days)	Median (IQR), *n*	1.5 (1–3), 58	1 (1–2), 60
Admission to HDU/ITU	*N* (%)	2 (3%)	1 (2%)[c]
Maternal death	*N* (%)	0 (–)	0 (–)
Instrumental birth outcomes[d]			
Rotation required		7 (12%)	4 (7%)
Ventouse	No	19 (33%)	20 (33%)
	Successful	3 (5%)	2 (3%)
	Failed	1 (2%)	2 (3%)
Forceps	No	4 (7%)	2 (3%)
	Successful	15 (26%)	22 (37%)
	Failed	3 (5%)	0 (–)
Primary reason for instrumental birth	CTG concerns without resort to FBS (incl. significant STAN event)	18 (31%)	12 (20%)
	Abnormal fetal scalp blood sampling (FBS) (≤ 7.20)	0 (–)	1 (2%)
	Delay in second stage	14 (24%)	15 (25%)
	Pushing challenges	2 (3%)	1 (2%)
	Other	1 (2%)	2 (3%)

TABLE 11 Secondary outcomes (*continued*)

Outcome		Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Neonatal outcomes			
Gender	Female	31 (53%)	29 (48%)
	Male	27 (47%)	31 (52%)
Birthweight (kg)	Mean (SD), *n*	3.52 (0.44), 58	3.51 (0.42), 60
Apgar score at 5 minutes	Median (IQR), *n*	10 (9–10), 58	9.5 (9–10), 60
Arterial cord blood gases when collected (pH)	Mean (SD), *n*	7.22 (0.10), 32	7.22 (0.09), 34
Venous cord blood gases when collected (pH)	Mean (SD), *n*	7.27 (0.09), 35	7.29 (0.07), 39
Breastfeeding rates on discharge from hospital		42 (72%)	50 (83%)
Discharged home with mother		58 (100%)	60 (100%)
Length of time after birth in hospital (days)	Median (IQR), *n*	1.5 (1–3), 58	1 (1–2), 60
	Range	0–7	0–7
Resuscitation		8 (14%)	6 (10%)
Reason for neonatal review on ward (excluding routine baby check)	Infection	13 (22%)	6 (10%)
	Other[e]	5 (9%)	7 (12%)
	Baby not reviewed	36 (62%)	45 (75%)
	Missing	4	2
Admitted to NNU		3 (5%)	3 (5%)
Length of time in NNU (days)	Median (IQR), *n*	1 (1–5), 3	4.5 (4–5), 2
	Missing	0	1
Reason for admission to NNU	Hypoglycaemia	0 (–)	0 (–)
	Hypothermia	0 (–)	0 (–)
	Poor feeding	0 (–)	0 (–)
	Jaundice	0 (–)	0 (–)
	Suspected Infection	3 (5%)	1 (2%)
	Intrauterine growth restriction	0 (–)	0 (–)
	Respiratory distress (incl. meconium aspiration syndrome)	0 (–)	1 (2%)
	Missing	0	1
Level of care received	Transitional care	2 (3%)	1 (2%)
	Special care (level 1)	0 (–)	1 (2%)
	High-dependency care (level 2)	1 (2%)	0 (–)
	Intensive care (level 3)	0 (–)	0 (–)[f]
	Missing	0	1

continued

TABLE 11 Secondary outcomes (*continued*)

Outcome		Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Ventilation support given		0 (–)	0 (–)
	Missing	0	1
Duration of non-invasive respiratory support (BiPAP, CPAP, high-flow O_2) (days)	Median (IQR), *n*	0 (0–1), 3	0 (0–0), 2
	Missing	0	1
Oxygen given		0 (–)	0 (–)
	Missing	0	1
Days to full suck feeds	Median (IQR), *n*	0 (0–0), 3	0.5 (0–1), 2
	Missing	0	1

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CTG, cardiotocography; IQR, interquartile range; PPH, postpartum haemorrhage.
a Outcome only for participants whose cervix reached full dilation after randomisation.
b Number of participants who did not have a CS: *n* = 82.
c One participant recorded admission to HDU/ITUon the birth + discharge form; however, on a serious adverse event (SAE) form, this was recorded as not admitted to HDU/ITU and site could not be contacted to verify.
d Number of participants who either had an instrumental birth or a failed instrumental birth: *n* = 47.
e Other reasons for neonatal review include: breathing × 2, infection × 2, jaundice, meconium, resuscitation at birth, shoulder dystopia, poor tone, bilious vomit, bruise on eye and maternal pyrexia post delivery.
f An additional baby was reported as admitted to the neonatal ITU on a SAE form; however, no neonatal form was ever completed for the participant and it was deemed as unobtainable.

TABLE 12 Adverse events (maternal)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Headache	1 (2%)	0 (–)
Nausea	7 (12%)	5 (8%)
Vomiting	5 (9%)	6 (10%)
Tachycardia/bradycardia	12 (21%)	6 (10%)
Mild or moderate hyponatraemia	0 (–)	0 (–)

TABLE 13 Adverse events (labour)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Uterine tachysystole (defined as more than five contractions in 10 minutes for 20 minutes)	18 (31%)	24 (40%)
• Single episode	5 (9%)	16 (27%)
• Multiple episode	13 (22%)	8 (13%)
Action taken[a]		
• No action/unresolved	3 (5%)	4 (7%)
• Reduced oxytocin	15 (26%)	20 (33%)
• Stopped oxytocin	6 (10%)	3 (5%)
• Tocolysis	0 (–)	0 (–)

TABLE 13 Adverse events (labour) (*continued*)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Uterine hyperstimulation (defined as tachysystole with non-reassuring or abnormal features of the fetal heart rate)	14 (24%)	16 (27%)
• Single episode	8 (14%)	13 (22%)
• Multiple episode	6 (10%)	3 (5%)
Action taken[a]		
• No action/unresolved	2 (3%)	2 (3%)
• Reduced oxytocin	12 (21%)	14 (23%)
• Stopped oxytocin	4 (7%)	5 (8%)
• Tocolysis	0 (–)	0 (–)

a Multiple actions taken to resolve possible.

TABLE 14 Serious adverse events (maternal)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Events requiring expedited reporting		
Maternal anaphylaxis	0 (–)	0 (–)
Serious maternal hyponatremia in labour or 48 hours following delivery	0 (–)	0 (–)
Pulmonary oedema	0 (–)	0 (–)
Uterine rupture/hysterectomy	0 (–)	0 (–)
Postpartum haemorrhage that triggers the massive obstetric haemorrhage protocol	3 (5%)	1 (2%)
Maternal admission to HDU/ITU	2 (3%)	0 (–)
Maternal death	0 (–)	0 (–)
Other events[a]		
Other[b]	4 (7%)	1 (2%)

a Prior to an amendment in the protocol, there were other events reported to the trial office that are no longer considered as SAEs requiring reporting to Birmingham Clinical Trials Unit.
b Other reasons include category 2 CS for deep transverse arrest, traumatic delivery, sepsis × 3.

TABLE 15 Serious adverse events (neonatal)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Events requiring expedited reporting		
Unexpected provision of neonatal intensive care	0 (–)	1 (2%)
Neonatal seizures	0 (–)	0 (–)
Neonatal encephalopathy	0 (–)	0 (–)
Need for neonatal therapeutic hypothermia	0 (–)	0 (–)
Intrapartum stillbirth	0 (–)	0 (–)

continued

TABLE 15 Serious adverse events (neonatal) (*continued*)

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Neonatal death (within 7 days)	0 (–)	0 (–)
Other events[a]		
Suspected sepsis	6 (10%)	2 (3%)
Jaundice	1 (2%)	0 (–)
Other[b]	4 (7%)	3 (5%)

a Prior to an amendment in the protocol, there were other events reported to the trial office that are no longer considered as SAEs requiring reporting to Birmingham Clinical Trials Unit.
b Other reasons include erythemal toxicum rash, antibiotics × 2, prolonged rupture of membranes and meconium stained liquor, suspected infection × 3, shoulder dystocia.

TABLE 16 Safety summary

	Standard-dose regimen (*n* = 58)	High-dose regimen (*n* = 60)
Total number of SAEs	20	8
Total number of maternal SAEs	9	2
Total number of neonatal SAEs	11	6
Total number of participants (mother or baby) experiencing a SAE[a]	15 (26%)	7 (12%)
Total number of women experiencing SAE	7 (12%)	2 (3%)
Total number of babies experiencing SAE	11 (19%)	6 (10%)
Total number of SUSARs	0 (–)	0 (–)
Total number of participants experiencing a SUSAR	0 (–)	0 (–)

SUSAR, suspected unexpected serious adverse reaction.
a Both mother and baby could experience SAEs but would count as one participant overall.

When we undertook the pilot study in 2010,[9] the NICE guidance regarding suspected and confirmed delay had been released in 2007. Data from the pilot suggested that a third of women with suspected delay made progress in the subsequent 2 hours and did not have delay confirmed and did not require oxytocin.[9] We were clear that only women with confirmed delay would be eligible for the HOLDS trial. Our more recent experience has suggested that this NICE guidance is not adhered to as rigorously as previously and that oxytocin is being prescribed more commonly earlier in labour. Just before the trial was stopped, we had decided to be more inclusive in the eligibility criteria to include all women for whom oxytocin was prescribed as part of the management of delayed labour, but this was too late (see *Report Supplementary Material 1* for a full list of protocol changes).

We have previously emphasised the importance of training of clinical staff in both the identification and recruitment of eligible women, and due to staffing pressures[10] that have been clearly identified within maternity services, the training of clinical staff has been more challenging and this may well have influenced the more recent recruitment (May–November 2022) to HOLDS.

Reflections

Reductions in the number of women going into spontaneous labour (due to increases in induction of labour and elective CS) combined with the falling birth rate undoubtedly had an effect as fewer women were potentially eligible to be recruited to HOLDS. Our original remit was to include women with confirmed delay as discussed above, so we were possibly too reluctant to change our eligibility criteria.

Researchers undertaking similar work may wish to monitor more systematically changes in the numbers of women potentially eligible and in clinical practice to enable them to respond more promptly. We had discussed monitoring these issues with sites, but the variations in data collection

and the complexity of collecting the numbers of women with suspected and confirmed delay proved this to be impractical.

Obtaining informed consent in labour

We adopted a pathway for obtaining informed consent developed during the pilot for HOLDS RfPB PB-PG-0407-13193 (June 2010–January 2012) in line with national guidance[11] and found this to be acceptable to women.[8] This involved giving antenatal information to women and then conducting discussions as requested by the woman. Detailed discussions with women would take place once it was recognised that the labour was not progressing normally, after at least 4 hours of labour, when a midwife undertook an assessment.

At that stage, delay would be suspected (when cervical dilation of < 2 cm in 4 hours was found) and obstetric intervention is usually not required. During the 2-hour period until progress is reassessed, the midwife is likely to suggest interventions which would facilitate progress such as encouraging the woman to mobilise, consider hydration (e.g. a sports drink) and discussing appropriate and effective pain relief. Artificial rupture (amniotomy) would also be advised if the fetal membranes were still intact. During this 2-hour window, the HOLDS trial would be discussed.

If after a further 2 hours, the progress remained slow, then delay was confirmed, obstetric review was requested and a decision about management was made, including the use of oxytocin. At this point, trial eligibility would be confirmed by a HOLDS-trained obstetrician, and the woman consented to trial participation. Thus, not only had women been in labour for at least 6 hours, but potentially they were also in pain and some distress as labour was not now progressing normally. The window of opportunity was also relatively short as participants needed to be randomised after delay had been confirmed and before oxytocin was commenced, usually about 30 minutes.

To address the issues identified during the pilot that made recruitment in these circumstances challenging, we developed a summary of the trial for use in labour with women. We focused on the training of the clinical staff so that they would be able to introduce the trial and answer any questions the women may have as well as randomise the participant.

While there was an identified HOLDS midwife within each maternity unit, their role focused on training and supporting clinical staff as recruitment could occur at any point 24/7, so they relied on consent and randomisation being undertaken by clinical staff as additional tasks. Many trials rely on research staff who recruit participants and undertake the required research tasks outside clinical duties, but this was not a model that could be used and was a further challenge we faced.

Reflections

Other researchers undertaking work in the acute phases of maternity care (in labour) may wish to carefully consider when information is given to women and when consent is obtained for intrapartum research in the acute situation.

A recent study[12] looking at intrapartum consent to trials was included in a Cochrane review of 'Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis'. This suggested that the timing of the provision of information and request of consent are most feasible at the time of admission to the maternity unit. However, practices of informed consent showed variability and substandard reporting. More recently, Alvarez *et al.*[13] undertook a qualitative study with midwives and women recruited to the ASSIST II trial and have proposed a framework for good practice, which aims to place women at the centre of the recruitment process using the following principles: that every woman be provided with the opportunity to participate in research, the promotion of women's autonomy, acknowledging vulnerability, avoiding professional gatekeeping and supporting the understanding of research information. This includes the provision of information regarding the trial to all women before admission as HOLDS did. They stressed the importance of discussion and suggested that a decision about in-principal participation should be made prior to labour.

However, ASSIST II used research staff to recruit participants, which HOLDS was not able to do due to recruitment needing to take place 24/7. In-principle consent prior to labour was something we considered, but this is problematic for a trial like HOLDS as this would mean approaching many women who would not become delayed in labour and therefore eligible. As described earlier only, about 20% of women who go into labour spontaneously become delayed and there have been increases in women having labour induced or an elective CS. Raising the possibility of abnormal labour with women who are anticipating labouring normally may also not be appropriate and can cause unnecessary anxieties. While the pilot study confirmed that our recruitment methods were acceptable to women, we did rely on clinical staff undertaking trial procedures (information, consent, randomisation and data collection), and we believe that

the current acute staffing situation within maternity care impacted recruitment.

One solution which would lessen the burden on clinical staff would be to use a model of deferred consent. It may be that this is more appropriate for this acute but not emergency situation. This would mean that research staff would undertake most research tasks and may result in better recruitment. Undoubtedly, this idea would need to be explored with women to ensure that it is acceptable.

Sharp services

The production (blinding labelling, packaging and distribution) of a drug for use in a clinical trial has to be handled by a company who are licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) – for this, HOLDS contracted with Sharp Services [www.sharpservices.com/facilities/united-kingdom/ (accessed 2 October 2023)]. All IMPs must be manufactured or imported by organisations holding a Manufacturers Authorisation and should have a qualified person (QP). QPs have personal and legal responsibilities as defined by the EU Clinical Trial Directive (2001/20/EC).

We used two ampoules of 5 International Units (IU) oxytocin as the standard-dose arm and two 10 IU as the higher dose arm. The ampoules must be stored in 2–8 °C, and if the temperature deviated to between 8 and 30 °C, it must be used within a maximum of 3 months after which time it must be discarded. As there are no stability data, if the temperature deviates to < 2 or > 30 °C, then oxytocin cannot be used and must be destroyed.

At the beginning of the trial in 2017, the pharmacy-specific HOLDS guidance stated that the monitoring of the Delivery Suite fridge temperature should be done in line with the local trust's guidance, as that is what was done during the pilot study without any issues. The clinical staff, and not research midwives, normally do this as part of usual monitoring, as the treatment packs are usually stored in the routine fridge used for the standard drugs on Delivery Suite (which would include oxytocin). The treatment packs are stored there to facilitate recruitment.

The trial began recruiting on 30 June 2017, and recruitment was suspended for the first time on 17 October 2017 due to two unanticipated issues:

- A site alerted us that clinicians could remove the label from the ampoule, thus potentially unblinding the randomised treatment. The manufacturer resolved this by removing the original label and relabelling the ampoules for the 900 treatment packs still stored with them, but 438 treatment packs had to be destroyed.
- Routine monitoring processes uncovered a total of 233 temperature deviations outside the recommended range of 2–8 °C across 84% (16/19) of active sites. Extensive revisions to the guidelines for IMP monitoring and storage were introduced, including the use of buffered thermometers. Deviations were reduced to 38 across 29% (7/24) of sites. The buffered thermometers are set up to alarm if the temperature is recorded < 2 or > 30 °C (where there are no stability data and the ampoules cannot be used). The clinical staff would phone the 24/7 telephone randomisation system to halt recruitment in the site.

This issue was submitted to the MHRA as a serious breach, which was resolved when we submitted an amendment to restart the trial to Health Research Authority (HRA) and the MHRA on the 20 February 2018. HRA approval was received on 8 June 2018. Local research and development approval was obtained, and we restarted recruitment on 27 June 2018.

In August 2018, it was identified that the IMP had been packaged in November 2016 by Sharp Services at ambient temperatures outside those recommended (2–8 °C), meaning potentially it should have been discarded and not used. The trial was suspended again and the matter was referred to the MHRA. In mid-September 2018, the matter was resolved when the MHRA decided that this process would not have had any detrimental effect on participants. However, the trial awarded time and funding had been exhausted, so we could not reopen. The Trial Steering Committee (TSC), Data Monitoring Committee and the HTA were kept informed of each issue and approved their resolution.

Reflections

It is hard to identify what we could have done differently as we had complied with the legislation regarding the production and distribution of the trial drug.

We advise researchers, adopting the routine procedures and processes for monitoring the storage of the trial drug that these may not be rigorous enough and to be responsible themselves for this. We responded as soon as we realised the extent of the problem, but the trial was delayed as a result. However, the rigorous temperature monitoring we had to introduce was an additional burden on staff, and it may not be so rigorously applied in routine practice outside of a research environment.

We did consider moving supplier earlier, but we were concerned that doing so would delay us further.

COVID-19

Further funding was identified in October 2020 for HOLDS and the intention was to run HOLDS concurrently with high- or low-dose syntocinon induction (iHOLDS) (HTA 17/137/02). The iHOLDS trial was a commissioned call by the HTA, which was funded at the beginning of 2019. Funding started in October 2019, with recruitment due to begin in July 2020, however we were delayed by the impact of the COVID-19 pandemic.

This randomised, double-blind trial will recruit 2400 women from 30 maternity units over 36 months – 21 months recruiting – with an 8-month internal pilot in 20 maternity units. We will compare the standard-dose regimen of oxytocin with a high-dose regimen to test the hypothesis that, in nulliparous women who require oxytocin as part of induction of labour, a high-dose regimen reduces the rate of CS by at least 20% compared with a standard-dose regimen. While separate in terms of approvals, permissions and funding from iHOLDS, the trials ran concurrently in the same maternity units to provide economies of infrastructure and staffing, which benefited HOLDS.

Between March and July 2020, NHS England paused all research except for COVID-19 or only treatment options. We recruited a senior trial manager for both trials in June 2020 when funds were drawn from the allocated resources. The Delta wave of COVID-19 meant that the NHS was focusing on the care of patients with COVID-19 and the maternity units collaborating could not start set up due to capacity issues beyond our control.

The National Institute for Health and Care Research then had a managed research recovery plan, which focused on completing existing trials and not on starting new trials. We appointed the lead midwife in July 2021 to start set up in the autumn of 2021. COVID-19 particularly affected maternity services and the combination of low staffing levels and high sickness rates, together with the additional scrutiny resulting from the Ockenden Report[14] further impacted capacity.

We were able to start recruitment to both trials in June 2022, and both trials had a 9-month pilot stage – it was during this time that HOLDS was closed, but iHOLDS has successfully moved to the main trial.

Patient and public involvement

Aim

Ultimately, patient and public involvement (PPI) engagement aims are to undertake research 'with women', and not 'on women',[15] to develop a trial that is acceptable to women in labour and that we assess whether a higher dose regimen of oxytocin for confirmed delay in the first stage of labour did reduce CS.

Methods

This research topic was originally prioritised by the NICE Intrapartum Care Guideline in 2007, which included a strong PPI element. One of the service users on the Guideline Development Group became a co-applicant in our pilot study (PB.PG.0407.13193). Her involvement, and the qualitative work undertaken as part of the pilot, has been integral to the research design, consent and recruitment processes and information for women developed during the pilot and proposed for this trial. This individual has stepped down due to family commitments and was replaced by Ruth Hewston. She is an equal member of the co-applicant group. We involved Ruth in every aspect of trial development and set up, and she reviewed all the trial participant documentation, staff training materials and the website.

We also have PPI representation on the TSC, from the National Childbirth Trust. Using social media to promote the trial has been discussed by the coinvestigator group and with the TSC, but due to the nature of the research and acuteness of the timing of recruitment, this was felt to have a limited impact and was not something we pursued.

Reflections of patient and public involvement input

Pregnancy studies have historically had the benefit of active PPI, and for a study in an acute intrapartum setting, this was particularly important to all the investigators. We needed to clearly explain the balance between risks and benefit to both mother and baby. Additionally, we had the challenge of presenting information about a drug routinely used in clinical practice, where a thorough explanation of the risks and benefits of its use may not be given routinely. The pilot study enabled us to design the recruitment processes and participant materials to be as helpful as possible to potential participants and to provide a clear account of potential benefits and harms in an unalarming way. So, in that respect, PPI has been only a positive and essential guiding influence.

Having only one PPI member of the coinvestigator group has sometimes limited the input due to availability, so having access to a number of women, ideally with lived experience of delay in labour, would have been helpful. Future researchers should consider how best to address this for their particular study needs.

Equality, diversity and inclusion

The study enrolled 118 pregnant women from 21 maternity units in England, Scotland and Wales.

A total of 78% of women were from UK White ethnic groups [following Office for National Statistics (ONS) ethnic group descriptors]. In ONS data on live births in 2017[16] (the year of majority recruitment into the HOLDS trial), 71% of women were from a UK White ethnic group. In HOLDS, 9% were White European and 11% were from ethnic minority groups, and 2% were not stated. We recruited 8% Asian or Asian British, 2% Black and 1% mixed ethnic groups and other. Comparison with ONS data shows 9% Asian or Asian British, 4% Black and 11% mixed ethnic groups, so the main difference is in the mixed group of women. This suggests that this small sample was reasonably representative of the wider pregnancy population. We are not aware of any published data on ethnicity groupings specifically for nulliparous women with delay in the first stage of spontaneous labour (between 37 + 0 and 41 + 6 weeks gestation) in the UK between 2017 and 2022 to ascertain whether or not our participants were representative of the wider population.

However, our wide geographical diversity of maternity units and inclusive approach to recruitment suggest that clinical and research staff enabled participation by a diverse group of women.

Implications for decision-makers

The HOLDS aimed to provide robust evidence of clinical effectiveness of a high-dose regimen compared to the current standard-dose regimen of oxytocin in reducing the need for CS for nulliparous women with confirmed delay in the first stage of labour, but unfortunately this was not possible.

The optimum treatment for women delayed in the first stage of labour remains an important unanswered clinical question.

Research recommendations

We identified the following questions for future research and have indicated the area of research to which they relate.

Primary research

Does a high-dose regimen of oxytocin prescribed for nulliparous women with delay in the first stage of labour reduce the incidence of CS?

Prognostic factors

Are there any antenatal clinical factors or signs in early labour that best determine whether the labour progress is delayed?

If a woman has cervical dilatation of < 6 cm or > 6 cm when delay is diagnosed and oxytocin commenced, does it affect the CS rate?

Women's and families' perspectives

What is the optimal timing of consent and recruitment and whether the option of delayed consent would be suitable in this acute but not emergency situation?

What do women and their families consider as the most important when undertaking shared decision-making around the use of oxytocin for delayed labour?

How can we best support women and their families when delay is diagnosed during labour and beyond?

Meta-analysis with other similar studies

What are the maternal and infant outcomes when a high-dose oxytocin regimen is prescribed for delay in the first stage of labour (compared with standard-dose regimen) when included with other studies in an individual patient data meta-analysis?

Intervention in other healthcare settings

How does the impact of high-dose regimens of oxytocin for delay in the first stage of labour compared with standard-dose regimens differ across varied healthcare settings (e.g. in low- and middle-income countries)?

Wider clinical uncertainties

Are there other policies/interventions/treatments which are as effective as standard-dose regimens of oxytocin in promoting normal birth when labour becomes delayed in the first stage?

Conclusions

The question of the optimum dose of oxytocin for nulliparous women delayed in the first stage of spontaneous labour remains an unanswered important clinical question and the major challenge is how best to address it.

The trial was not feasible between 2017 and 2022, and there is a need to explore the best approach to recruiting participants in this acute, but not emergency, situation.

Additional information

CRediT contribution statement

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Sponsor

This study was sponsored by the Birmingham Women's and Children's NHS Foundation Trust; monitoring and audit teams were led by Liz Adey and Sarah Hadfield.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted after review.

Ethics statement

The trial initially received clinical trial authorisation (CTA 21375/0207/001-0011) from the Medicines and Healthcare products Regulatory Authority (MHRA) and ethical approval from the West Midlands – Edgbaston Research Ethics Committee (REC) (16/WM/0014) on 24 February 2016 (IRAS ID 193293).

Information governance statement

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/MALP6685.

Primary conflicts of interest: Sara Kenyon (Chief Investigator), Tracey Johnston, Jason Waugh, Kim Hinshaw, Julia Sanders, Andrew Ewer, Lee Middleton, Ruth Hewston and Peter Brocklehurst also hold the iHOLDS grant (NIHR HTA 17/137/02).

Sara Kenyon was also co-applicant on the following studies – HSDR Listen2Baby study NIHR134306; HSDR NIHR151802 – Factors influencing the implementation of the Midwifery Continuity of Carer (MCoC) model of care in England; Improving Parental Engagement in Child Death Review RfPB NIHR203045 and leads the Maternity Theme of the Applied Research Collaborative (ARC) West Midlands (Maternity Theme) programme (NIHR grant 970014). She was a member of HTA MNCH Panel from 1 March 2013 to 31 March 2017 and of HTA Prioritisation Committee C (Mental health, women and children's health) from 1 March 2017 to 31 July 2019 and is a NIHR Senior Investigator.

Kim Hinshaw was a co-applicant on the following studies – ROTATE trial (NIHR 127818) – funding as a grant co-applicant (September 21 for 4 years); COPE trial – The Carboprost or Oxytocin Postpartum haemorrhage Effectiveness study. (NIHR 16/16/16) – funding as a grant co-applicant (September 2017 for 4 years – ended in September 2021).

Julia Sanders was a co-applicant on the following studies – HSDR Listen2Baby study NIHR134306; HSDR NIHR151802 – Factors influencing the implementation of the Midwifery Continuity of Carer (MCoC) model of care in England; Cervical Ripening at Home or In-Hospital – prospective cohort study and process evaluation (CHOICE Study) NIHRDH-NIHR127569; The effectiveness and cost-effectiveness of Assets-based feeding help Before and After birth (ABA-feed) for improving breastfeeding initiation and continuation NIHRDH-NIHR129182; Calcium Supplementation for Prevention of Pre-eclampsia in High Risk Women: CaPE Trial NIHR 127325; and Chief Investigator on The POOL Study. Establishing the safety of waterbirth for mothers and babies: A cohort study with nested qualitative component NIHR 16/149/01.

Peter Brocklehurst was a co-applicant on the following grants – CaPE: Calcium Supplementation for Prevention of Pre-eclampsia in High Risk Women (NIHR HTA 127325); ROTATE: Rotation of the fetal head at full cervical dilation (NIHR HTA 127818); LAVA: Laparascopic versus Abdominal hysterectomy (NIHR HTA 128991); GIANT PANDA: Pregnancy AntihyperteNsive Drugs; Which Agent is best? (NIHR HTA 128721); eMOTIVE: Early detection of postpartum haemorrhage and treatment using the World Health Organization MOTIVE 'first response' bundle: a cluster randomised trial with health economic analysis and mixed-methods evaluation (Gates Foundation); ADEPP: AntiDEpressants for the Prevention of depression following first episode Psychosis (NIHR HTA 127700); The POOL Study: Establishing the safety of waterbirth for mothers and babies: A cohort study with nested qualitative component (NIHR HTA 16/149) and C-STICH 2: Rescue Cervical Cerclage To Prevent Miscarriage and Preterm Birth a Randomised Controlled Trial (NIHR HTA 13/04/107). He was also a member of CTUs funded by NIHR until 31 August 2021, HTA Efficient Study Designs – 21 November 2015–31 July 2016, HTA Efficient Study Designs Board 13 October 2014–17 December 2014, HTA MNCH Panel 1 December 2014–30 June 2018, HTA Commissioning Committee 29 March 2010–30 April 2012.

Clive Stubbs, Versha Cheed, Hannah Summers, Adrian Wilcockson, Kate Siddall and Dee Wherton have no interest to declare.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

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This synopsis provided an overview of the research award *High Or Low Dose Syntocinon for delay in labour (HOLDS)*. For other articles from this thread and for more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/14/140/44).

About this synopsis

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List of supplementary material

Report Supplementary Material 1
History of amendments to HOLDS protocol

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/MALP6685).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

BMI	body mass index
CS	caesarean section
FBS	fetal blood sampling
HOLDS	high- or low-dose syntocinon
HRA	Health Research Authority
HTA	Health Technology Assessment
iHOLDS	high- or low-dose syntocinon induction
IMP	investigational medicinal product
ITU	intensive therapy unit
IU	International Units
MHRA	Medicines and Healthcare products Regulatory Agency
NNU	neonatal unit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
ONS	Office for National Statistics
PPI	patient and public involvement
QP	qualified person
SVB	spontaneous vaginal birth
TSC	Trial Steering Committee

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