

# Impact of discontinuing oxytocin in active labour on neonatal morbidity: an open-label, multicentre, randomised trial



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## Summary

**Background** Oxytocin is effective in reducing labour duration but can be associated with fetal and maternal complications that could potentially be reduced by discontinuing the treatment during labour. We aimed to assess the impact of discontinuing oxytocin during active labour on neonatal morbidity.

**Methods** STOPOXY was a multicentre, randomised, open-label, controlled, superiority trial conducted in 21 maternity units in France. Participants who received oxytocin before 4 cm dilation were randomly assigned 1:1 to either discontinuous oxytocin (oxytocin infusion stopped beyond a cervical dilation equal to or greater than 6 cm) or continuous oxytocin (administration of oxytocin continued until delivery). Randomisation was stratified by centre and parity. The primary outcome, neonatal morbidity, was assessed at birth using a composite variable defined by an umbilical arterial pH at birth less than 7·10, a base excess greater than 10 mmol/L, umbilical arterial lactates greater than 7 mmol/L, a 5-min Apgar score less than 7, or admission to the neonatal intensive care unit. Efficacy and safety was assessed in participants who were randomly assigned (excluding those who withdrew consent or were deemed ineligible after randomisation) and had reached a cervical dilation of at least 6 cm. This trial is registered with ClinicalTrials.gov, NCT03991091.

**Findings** Of 2459 participants randomly assigned between Jan 13, 2020, and Jan 24, 2022, 2170 were eligible to receive the intervention and were included in the final modified intention-to-treat analysis. The primary outcome occurred for 102 (9·6%) of 1067 participants (95% CI 7·9 to 11·5) in the discontinuous oxytocin group and for 101 (9·2%) of 1103 participants (7·6 to 11·0) in the continuous oxytocin group; absolute difference 0·4% (95% CI -2·1 to 2·9); relative risk 1·0 (95% CI 0·8 to 1·4). There were no clinically significant differences in adverse events between the two groups of the safety population.

**Interpretation** Among participants receiving oxytocin in early labour, discontinuing oxytocin when the active phase is reached does not clinically or statistically significantly reduce neonatal morbidity compared with continuous oxytocin.

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## Introduction

Oxytocin is one of the most commonly used drugs worldwide, and is used either as part of induction of labour or for augmentation of labour.<sup>1-5</sup> It is effective in increasing frequency and intensity of uterine contractions and therefore in reducing labour duration.<sup>6,7</sup> Obstetric situations requiring oxytocin administration before 4 cm of dilation are induction of labour, with or without previous cervical ripening, and labour dystocia (ie, non-progression of the cervical dilation).<sup>2,8,9</sup> With the current trend of increased rates of induction of labour, particularly for nulliparous women at 39 weeks without medical indication,<sup>10</sup> it is essential to evaluate the use of medication such as oxytocin cautiously and consider the importance of reducing unnecessary interventions.

The most common side-effect of oxytocin infusion is uterine tachysystole, which might occur in more than 30% of women induced with oxytocin.<sup>11-14</sup> Oxytocin-induced tachysystole is associated with significant oxygen desaturation and non-reassuring fetal heart rate patterns, contributing to neonatal acidosis.<sup>11,15</sup> Acidosis accounts for a substantial proportion of term neonatal morbidity due to related complications leading to hospitalisation in neonatal intensive care units, but also cerebral palsy or neonatal death in the most severe cases. In addition, the effectiveness of oxytocin in decreasing the caesarean delivery rate has not been demonstrated.<sup>16,17</sup> Moreover, its administration is potentially associated with maternal complications, such as postpartum haemorrhage.<sup>18</sup>

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## Research in context

### Evidence before this study

Previous studies have demonstrated the effectiveness of oxytocin in reducing labour duration by increasing uterine contractions. However, oxytocin is also associated with uterine tachysystole which can lead to abnormal fetal heart rate patterns and neonatal acidosis. Despite the routine use of oxytocin in maternity settings, with over 80% of women who have labour induced and 15–40% of women in spontaneous labour receiving this treatment, the optimal duration of oxytocin administration and its potential effects on neonatal and maternal outcomes remain areas of uncertainty. We conducted a comprehensive literature review to assess the existing evidence on the use of oxytocin during labour and the potential benefits of discontinuing its administration during the active phase. A systematic search was performed in PubMed from inception to June 1, 2023, using relevant keywords related to “oxytocin”, “labor”, “discontinuation”, “uterine hyperstimulation”, “neonatal morbidity”, “neonatal acidosis” and “cesarean delivery”. No language restrictions were applied. The search included randomised controlled trials, observational studies, systematic reviews, and meta-analyses. The quality of the retrieved evidence varied, considering factors such as study design, sample size, methodological rigour, and risk of bias. We did not identify any clinical trials specifically investigating the impact of discontinuing oxytocin during the active phase of labour with neonatal morbidity as the primary outcome. Most studies and all meta-analyses have indicated that discontinuing oxytocin during the active phase of labour might be associated with a reduced risk of uterine tachysystole, neonatal acidosis, adverse neonatal outcomes, and caesarean delivery. However, a large trial conducted in 2021 found contrasting findings to those of previous literature. This trial revealed a slight increase in caesarean deliveries when oxytocin was discontinued, but the difference was neither clinically nor statistically significant. It is noteworthy that this trial focused solely on neonatal outcomes as secondary endpoints and found no significant differences in low pH, low Apgar scores, and neonatal intensive care unit admission rates between the discontinuous oxytocin and continuous oxytocin groups. Nonetheless, all these previous studies were underpowered to detect differences in neonatal morbidity rates. The available evidence, including previous studies and systematic reviews, has provided some insights into the potential benefits and risks of discontinuing oxytocin during labour. However, there is a lack of robust

evidence addressing the discontinuation of oxytocin during the active phase of labour and its effect on neonatal morbidity and maternal complications.

### Added value of this study

The current study addresses this research gap by conducting a large, multicentre, randomised controlled trial powered to evaluate neonatal morbidity. Our study adds to the existing evidence by examining the effect of discontinuing oxytocin during the active phase of labour on neonatal morbidity and other important outcomes. The findings of our study, which did not demonstrate a significant reduction in neonatal morbidity with discontinuous oxytocin compared with continuous oxytocin, provide important insights for clinical practice, by showing that there is no scientific basis for systematically discontinuing oxytocin to improve neonatal morbidity. They also highlight the need for individualised care and consideration of patient-specific factors. By assessing the effects of discontinuing oxytocin during the active phase of labour on a comprehensive range of outcomes, including neonatal morbidity, mode of delivery, course of labour, maternal complications, and birth experience, our study aims to contribute significant insights to the existing evidence base and provide valuable guidance for clinical practice and future research. Furthermore, our study emphasises the need for updated meta-analyses as it reinforces the finding that discontinuous oxytocin does not reduce the risk of caesarean delivery.

### Implications of all the available evidence

The results suggest that discontinuing oxytocin when the active phase of labour is reached does not significantly reduce neonatal morbidity compared with continuous oxytocin in participants receiving oxytocin before 4 cm of cervical dilation. Furthermore, we did not find any lower risk of caesarean delivery with discontinuous oxytocin use. These findings have important implications for obstetric practice, highlighting the need to carefully consider the individualised management of oxytocin use during labour. As our study and a previous large trial by Boie and colleagues (2021) showed, the discontinuation of oxytocin might not offer significant benefits in reducing the risk of caesarean delivery. Given the complexities of labour management and the potential variability in individual responses to oxytocin, further research is warranted to optimise oxytocin administration protocols.

One assumption is that, once women requiring oxytocin during the latent phase enter the active phase, natural oxytocin takes over from synthetic oxytocin.<sup>19</sup> Thus, in the active phase, oxytocin could be discontinued, reducing exposure duration, and therefore reducing the risk of complications, in particular neonatal complications such as hypoxia, without compromising the chances of vaginal delivery. It can therefore be hypothesised that discontinuation of oxytocin in the

active phase of labour (from 6 cm of dilation) in women who received oxytocin in the latent phase or for an induction of labour could reduce neonatal morbidity and severe maternal complications such as postpartum haemorrhage. Previous studies evaluating discontinuation of oxytocin in the active phase of labour have been underpowered to detect a significant difference in neonatal morbidity rates, highlighting the need for further research.<sup>20,21</sup>

A meticulous approach to the administration of oxytocin, particularly given the increasing rates of labour induction, possesses the potential to recalibrate obstetric practices by prioritising judicious interventions. This approach attends to the wellbeing of both mothers and neonates.

Thus, our aim was to measure the impact of discontinuing oxytocin in the active phase of labour on the neonatal morbidity rate. Secondary objectives included measuring the impact of discontinuing oxytocin on low arterial cord pH and need for hypothermia for neuroprotection, mode of delivery, course of labour, maternal complications, and birth experience.

## Methods

### Study design

STOPOXY was a multicentre, randomised, open-label, controlled, superiority trial conducted in 21 maternity hospitals across France (centres and patient numbers are in the appendix p 1). The trial design is published online,<sup>22</sup> and the trial protocol (appendix pp 2–45) was approved by the National Agency for Drug Safety, the Committee for Protection of Persons Involved in Biomedical Research, and the French Data Protection Authority.

### Participants

Eligible participants were pregnant women aged 18 years or older, with a singleton term pregnancy ( $\geq 37$  weeks) and a fetus in cephalic presentation, receiving oxytocin before reaching 4 cm of cervical dilation, regardless of mode of onset of labour. Women with a scarred uterus, a fetus with growth less than the third percentile for gestational age or congenital abnormality, abnormal fetal heart rate at randomisation, participating in another trial involving medication, or who were not able to communicate fluently in French or have medical insurance were not eligible for inclusion in this trial. Informed written consent was obtained from all participants.

### Randomisation

Before participants had cervical dilation of 6 cm they were randomly assigned using a 4-size permuted block randomisation with a 1:1 ratio to either discontinuous oxytocin or continuous oxytocin with the use of a computer-generated randomisation sequence. Randomisation was stratified by the centre and participant parity (nullipara/multipara). The randomisation procedure was carried out in the labour ward by either the midwife or the obstetrician, who were certified in Good Clinical Practice for research, and was completed online via the CleanWeb interface accessible 24 h a day.

### Procedures

The trial information was initially delivered to participants before labour during their last prenatal visits, as well as during outpatient clinic visits and birth preparation classes. Additionally, posters were displayed

in waiting rooms, emergency rooms, and the outpatient clinic to disseminate information. Further screening and informed consent took place during labour induction or the onset of spontaneous labour in the labour ward. The informed consent was signed before inclusion, typically after the onset of oxytocin infusion.

Participants were included if they received oxytocin before 4 cm of cervical dilation; subsequently, randomisation took place before reaching 6 cm of cervical dilation. This process ensured that some participants could be included but not randomly assigned either because of a caesarean delivery before 6 cm of cervical dilation, or because of an abnormal fetal heart rate. In all centres, oxytocin was administered according to national guidelines (ie, low dose oxytocin infusion of less than 4 mUI/min with increments every 30 min, without exceeding a 20 mUI/min flow rate).<sup>8</sup>

After randomisation, in the discontinuous group, oxytocin infusion was stopped beyond a cervical dilation equal to or greater than 6 cm. If necessary, health-care professionals were instructed that oxytocin could be restarted after 2 h of labour arrest (no progression of the cervical dilation or no progression of the fetal head). In the continuous oxytocin group, oxytocin was continued during the active phase and during the second stage. If necessary, it could be stopped because of an abnormal fetal heart rate pattern or uterine tachysystole.

To prevent any cross-contamination between the groups and ensure adherence to the allocated treatment, we prospectively monitored the total dose and duration of oxytocin administration for every 20 included participants in each participating centre. This monitoring process was conducted by an independent trial monitoring team.

Although this trial took place during the COVID-19 pandemic, the recruitment, randomisation, study conduct, and outcomes were not impacted by the pandemic.

### Outcomes

The primary outcome was neonatal morbidity assessed at birth using a composite variable defined by an umbilical arterial pH at birth of less than 7·10, a base excess greater than 10 mmol/L, umbilical arterial lactates greater than 7 mmol/L, a 5-min Apgar score less than 7, or admission to the neonatal intensive care unit. This composite outcome allowed for the evaluation of neonatal morbidity potentially associated with uterine tachysystole induced by oxytocin, which might lead to respiratory, metabolic, or mixed acidosis and clinical implications necessitating neonatal intensive care unit admission. Each criterion represents neonatal morbidity and is recognised as an indicator of adverse outcomes. The chosen thresholds are commonly reported in the literature for assessing neonatal acidosis at birth.<sup>23–25</sup> No specific cord clamping recommendations were specified in the trial protocol. The primary outcome was assessed by the investigators.

See Online for appendix

Secondary outcomes included neonatal pre-acidosis, acidosis and its severity (defined as umbilical arterial cord pH at birth of  $<7.20$ ,  $<7.10$ , and  $<7.00$ , and need for hypothermia for neuroprotection), other neonatal complications (need for resuscitation at birth, admission to neonatal intensive care unit, and length of hospital stay in neonatal intensive care unit), mode of delivery (spontaneous delivery, instrumental vaginal or caesarean delivery), indication (rates for caesarean delivery and instrumental delivery for abnormal fetal heart rate), course of labour characteristics (such as median active phase duration, defined as duration from 6 cm to full dilation, second stage and active phase to delivery duration, defined as duration from 6 cm to delivery, occiput-posterior presentation at delivery, and occurrence of uterine tachysystole defined by periods with more than five uterine contractions in 10 min or hypertonus requiring medical treatment), maternal fever during labour (defined as a maternal temperature  $>38^{\circ}\text{C}$ ), and postpartum haemorrhage (defined as an estimated blood loss  $>500$  mL regardless of the mode of delivery). The assessment of uterine tachysystole, as well as the monitoring of oxytocin doses and the reasons for treatment discontinuation or resumption, were documented using a specific sheet designed for this purpose.

Women's birth experience was evaluated at day 2 postpartum using the Labour Agency Scale (LAS), where higher scores indicate a greater sense of control during the birthing process.<sup>26</sup> Additionally, at 2 months postpartum, women's wellbeing was assessed using the Edinburgh Postnatal Depression Scale.<sup>27</sup> These assessments were conducted via email. A score of greater than 12 on the Edinburgh Postnatal Depression Scale is indicative of a higher likelihood of experiencing depressive symptoms of varying severity.<sup>27</sup>

During the study, the investigators reported four serious adverse events: postpartum haemorrhage, characterised by an estimated blood loss of more than 1000 mL; need for neonatal hypothermia; maternal death; and newborn death. These events were communicated without delay and throughout the participants' involvement in the study (2 months postpartum). Any other unexpected adverse event was reported by the investigators or the participants and documented by means of review of medical files transmitted by the participant or the physician.

### Statistical analysis

Sample size calculations were based on estimated effect of discontinuous oxytocin on neonatal morbidity. In a prospective population-based cohort study conducted in France in 2015, among women receiving oxytocin under standard care, 8% of neonates had at least one criterion of the primary endpoint of the current trial.<sup>28</sup> We hypothesised a clinically relevant decrease from 8% in the continuous oxytocin group (ie, standard care) to 5% in the discontinuous oxytocin group, representing a 3% absolute

difference in the neonatal morbidity rate (relative risk [RR] 0.62 [95% CI 0.45–0.86]). To calculate the required sample size, we used a two-sided test with a power of 80% and a significance level of 0.05, along with Yates' continuity correction. We considered an allocation ratio of 1:1 between the discontinuous oxytocin group and the continuous oxytocin group. Thus, the total sample size required was 2250 participants (1125 in each group). To ensure adequate power and account for potential dropouts due to caesarean deliveries before reaching 6 cm dilation (preventing participants from receiving the studied intervention), the protocol provided for an increase in the required sample size by 10% in each group (225 participants in total), bringing the total required sample size for inclusion in the study to 2475 women.

The main analysis of the primary and secondary outcomes was performed in the modified intention-to-treat population (mITT). The mITT population included participants who underwent randomisation (excluding those who withdrew consent or were deemed ineligible after randomisation) and had reached a cervical dilation of at least 6 cm, making them eligible for the intervention. We also analysed two other populations: the intention-to-treat (ITT) population which included all randomised participants, regardless of whether they reached 6 cm dilation, except for those who withdrew consent or were considered ineligible after randomisation; and the per-protocol population, which included the participants from the mITT population who received the allocated intervention as intended by the protocol.

The safety population included all participants from the mITT population, with participants divided into discontinuous oxytocin and continuous oxytocin groups based on their actual experience during the active phase of labour. Participants who had a discontinuation of oxytocin and a restart during labour were considered in the discontinuous oxytocin group to assess any potential adverse outcomes related to the reduction of oxytocin usage.

The baseline maternal and pregnancy characteristics of the trial participants were described with qualitative variables expressed as proportions and quantitative variables as medians with IQR. The two-sided 95% CIs for the primary outcome were computed using the Wilson method. The comparison of the primary and secondary outcomes between the randomised groups was performed using the RR for binary variable, or the median difference for quantitative variables, along with their 95% CI. The two-sided 95% CIs for the RR were computed using the log-binomial regression model, and bootstrapping was employed for the median difference. Additionally, for the primary outcome the absolute difference between the two groups was calculated, and its 95% CI was also determined.

Two preplanned subgroup analyses were performed: according to the mode of onset of labour (induced or spontaneous), and according to parity (nullipara or multipara). For these subgroup analyses, we used the

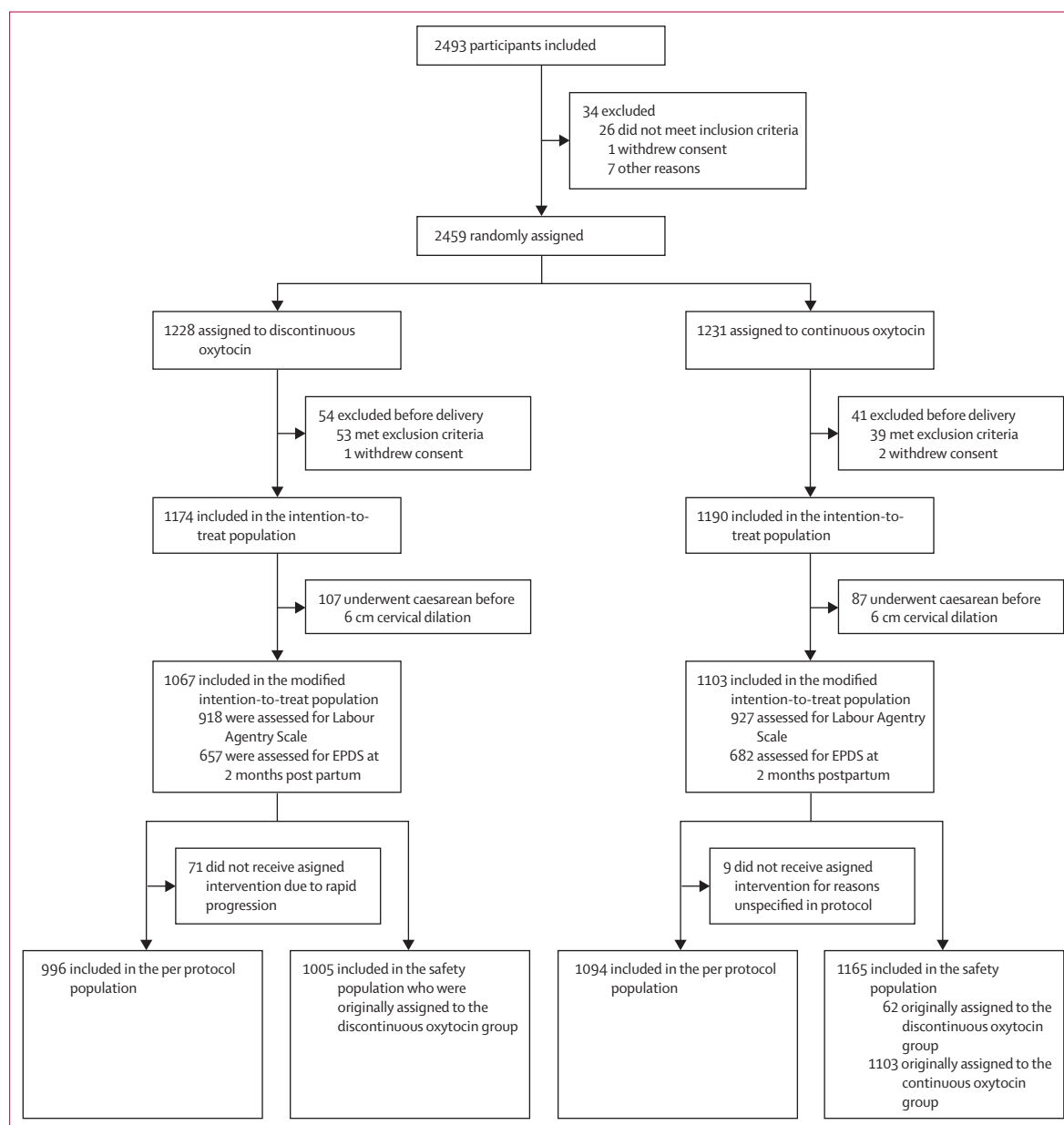
same statistical methods as the main analysis and compared primary and secondary outcomes. The same analyses were also repeated in the ITT population and per protocol population. For the safety analyses we reported the proportions of occurrence of the severe and unexpected adverse events and compared them between the two groups using the risk difference with its 95% CI using Wilson's method. Our statistical analysis plan did not include a plan to adjust for multiple comparisons of secondary outcomes or subgroups. Across the entire trial population, missing data were observed in less than 1% of cases. Given the negligible amount of missing data and its

distribution across both study arms we did not conduct the planned sensitivity analyses to explore the effects of missing data.

All tests were bilateral with a significance level of 5%. All analyses were performed using SAS software, version 9.4.2 and R software (version 3.5). This trial is registered with ClinicalTrials.gov, NCT03991091.

#### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.



**Figure: Trial profile**

EPDS=Edinburgh Postnatal Depression Scale.

## Results

Between Jan 13, 2020, and Jan 24, 2022, 2493 participants were included, 34 participants were not randomly assigned due to eligibility criteria errors. 2459 participants were randomly assigned to discontinuous oxytocin (n=1228) or continuous oxytocin (n=1231) in the active phase of labour (figure). Of the randomly assigned participants, 53 in the discontinuous oxytocin group and 39 in the continuous oxytocin group were excluded because they did not meet randomisation criteria. Of the remaining 2364 participants, 194 (7.9%) underwent caesarean delivery before reaching a cervical dilation of 6 cm which resulted in a mITT population of 2170 participants (1067 in the discontinuous oxytocin group and 1103 in the continuous oxytocin group; figure, table 1).

According to study protocol, in the discontinuous oxytocin group, oxytocin was restarted in

432 (40.5%) of 1067 participants, and in the continuous oxytocin group, oxytocin was stopped in 58 (5.3%) of 1103 participants (table 2).

There was no clinical or statistical difference between the two groups in the mITT analysis for the primary outcome. Neonatal morbidity occurred in 102 (9.6%) of 1067 participants (95% CI 7.9 to 11.5) in the discontinuous oxytocin group and 101 (9.2%) of 1103 participants (7.6 to 11.0) in the continuous oxytocin group; absolute difference 0.4% (-2.1 to 2.9); RR 1.0 (0.8 to 1.4; table 3). Apgar score and admission to the neonatal intensive care unit were available for all participants, and cord pH was available for 2015 (92.9%) of 2170 participants. Base excess and lactate levels were not measured in all centres; when the variable was not available, it was considered a missing data item.

There were no differences between the two groups for the rates of neonatal secondary outcomes (table 3). No differences were observed in the mode of delivery, with a caesarean delivery rate of 114 (10.7%) of 1067 participants in the discontinuous oxytocin group and 109 (9.9%) of 1103 in the continuous oxytocin group, RR 1.1 (95% CI 0.8–1.3). Participants in the discontinuous oxytocin group had longer median active phase of labour (100 min [IQR 50–208] in the discontinuous oxytocin group vs 90 [45–150] in the continuous oxytocin group, median difference 10.0 [95% CI 0.0–16.0]), median second stage (120 min [IQR 33–184] vs 83 min [23–166], median difference 37.0 [95% CI 21.0–51.0]), and median active phase to delivery (244 min [IQR 122–386] vs 197 [93–317], median difference 47.0 [95% CI 24.0–65.5]) durations than participants in the continuous oxytocin group. Uterine tachysystole was less frequent in the discontinuous oxytocin group than the continuous oxytocin group (62 [6.3%] of 978 participants vs 106 [10.4%] of 1019 participants); RR 0.6 [0.4–0.8]; table 3).

Both the completion rate of the LAS at day 2 postpartum (1845 [85.0%] of 2170 participants) and the completion rate of the Edinburgh Postnatal Depression Scale at 2 months postpartum (1339 [61.7%] of 2170 participants) were comparable between the two groups. There were no differences in the median scores of the LAS or the rate of scores greater than 12 in the Edinburgh Postnatal Depression Scale between the two groups (table 3).

The appendix (pp 46–48) provides baseline and oxytocin characteristics for each subgroup of the mITT population. The results of the subgroup analyses concerning mode of onset of labour and nulliparous women were consistent with the main analysis (appendix pp 46–51). In the multiparous subgroup, the discontinuous oxytocin group had higher rates of neonatal morbidity (27 [5.2%] of 521 participants) versus the continuous oxytocin group (13 [2.5%] of 521; RR 2.1 [95% CI 1.1–4.0]; appendix p 51).

The results of the analyses in the ITT population and the per protocol population yielded similar results and are presented in the appendix (pp 53–62).

	Discontinuous oxytocin group (n=1067)	Continuous oxytocin group (n=1103)
<b>Individual characteristics</b>		
Maternal age, years	31 (28–35)	32 (28–35)
Pre-pregnancy BMI, kg/m <sup>2</sup>	24.0 (21.0–28.0)*	24.0 (21.2–28.2)*
Smoking during pregnancy	99/1050 (9.4%)	96/1089 (8.8%)
Nulliparous	521/1067 (48.8%)	521/1103 (47.2%)
<b>Pre-existing pathology</b>		
Chronic hypertension	18/1065 (1.7%)	20/1101 (1.8%)
Diabetes	11/1065 (1.0%)	18/1101 (1.6%)
<b>Pathology during pregnancy</b>		
Hypertensive disorder (gestational hypertension or pre-eclampsia)	53/1066 (5.0%)	47/1100 (4.3%)
Gestational diabetes	226/1066 (21.2%)	231/1101 (21.0%)
<b>Labour onset</b>		
Induction of labour	864/1067 (81.0%)	917/1103 (83.1%)
Indication for labour induction		
Ruptured membranes	183/864 (21.2%)	156/916 (17.0%)
Postdate pregnancy	180/864 (20.8%)	188/916 (20.5%)
Suspected macrosomia	97/864 (11.2%)	114/916 (12.4%)
Maternal pathology	179/864 (20.7%)	170/916 (18.6%)
Maternal request	103/864 (11.9%)	128/916 (14.0%)
Other indications†	122/864 (14.1%)	160/916 (17.5%)
First method of induction		
Amniotomy	68/864 (7.9%)	100/913 (11.0%)
Oxytocin	386/864 (44.7%)	375/913 (41.1%)
Dinoprostone vaginal slow-release system	126/864 (14.6%)	143/913 (15.7%)
Misoprostol	130/864 (15.0%)	98/913 (10.7%)
Balloon catheter	124/864 (14.3%)	162/913 (17.7%)
Prepidil or prostin gel	30/864 (3.5%)	35/913 (3.8%)
Epidural analgesia	1044/1067 (97.8%)	1081/1103 (98.0%)
Data are n/N (%) or median (IQR). *Data on pre-pregnancy BMI were missing for 21 participants in the discontinuous oxytocin group and 12 in the continuous oxytocin group. †Oligohydramnios, reduced fetal movements, fetus growth below the tenth percentile and above the third percentile for gestational age, late-pregnancy bleeding, or maternal anxiety.		
<b>Table 1: Baseline participant and pregnancy characteristics in the modified intention-to-treat population</b>		

The most common adverse events were moderate postpartum haemorrhage, which was present in 23 (2.3%) of 1005 participants in the discontinuous oxytocin group and 41 (3.5%) of 1165 participants in the continuous oxytocin group, and suspicion of maternal infection which was present in 21 (2.1%) of 1005 participants in the discontinuous oxytocin group and 21 (1.8%) of 1165 participants in the continuous oxytocin group (table 4).

## Discussion

Discontinuous oxytocin in the active phase of labour did not demonstrate a significant effect on neonatal morbidity, mode of delivery, or postpartum haemorrhage. However, participants in the discontinuous oxytocin group did experience longer active phase, second stage, and active phase to delivery durations.

Previous studies have suggested a potential benefit of discontinuous oxytocin in reducing the risk of neonatal morbidity and acidosis, but none were powered specifically for these outcomes.<sup>20,21,29–31</sup> In contrast, our study was specifically designed to evaluate these outcomes. Most previous studies focused on labour duration or mode of delivery and had relatively small sample sizes ranging from 100 to 342 participants. These studies were included in a meta-analysis which reported significantly lower caesarean delivery rates with discontinuous oxytocin compared with continuous oxytocin (n=1784, RR 0.69 [95% CI 0.56–0.86]), but longer active phase durations (n=1336, mean difference 25.57 min [5.28–45.87]).<sup>20</sup> Our study showed conflicting results regarding the effect of oxytocin regimen on caesarean delivery rates, with a non-significantly higher rate of caesarean delivery among participants included in the discontinuous oxytocin group. However, our findings are consistent with a Danish trial which included 1198 women who were induced, that was not included in the meta-analysis cited previously, which found no significant differences between continuous and discontinuous oxytocin on the caesarean delivery rates (RR 1.17 [0.90–1.53]).<sup>31</sup> These previous results along with our own contribute to the growing body of literature indicating that discontinuous oxytocin might not decrease the risk of caesarean delivery.

The reduction of uterine tachysystole in the discontinuous oxytocin group in our trial is consistent with previous published studies but does not translate to a reduction of neonatal acidosis.<sup>20,31</sup> This finding suggests that the relationship between uterine tachysystole and adverse neonatal outcomes might not be straightforward, and that other factors might have a role in determining neonatal outcomes. It is important to highlight that personalised medicine approaches are already being implemented, where oxytocin flow rate is adjusted based on uterine tachysystole or abnormal fetal heart rate patterns. However, in multiparous women, despite comparable rates of uterine tachysystole between the

	Discontinuous oxytocin group (n=1067)	Continuous oxytocin group (n=1103)
Cervical dilation at oxytocin onset, cm	2 (2–3)*	2 (2–3)*
Cervical dilation at inclusion, cm	2 (2–3)	2 (2–3)†
Total duration of oxytocin infusion, min	345 (221–541)	424 (290–630)‡
Total dose of oxytocin received during labour, mUI	1921 (990–3965)	2599 (1405–4814)§
Oxytocin restarted after 6 cm dilation	432/1067 (40.5%)	NA
Oxytocin stopped after 6 cm dilation for abnormal fetal heart rate or hypertonus	NA	58/1102 (5.3%)
Duration from oxytocin onset to active labour, min	260 (170–396)¶	262 (168–395)¶

Data are n/N (%) or median (IQR). NA=not applicable. \*Data on cervical dilation at oxytocin onset were missing for two participants in the discontinuous oxytocin group and four participants of the continuous oxytocin group. †Data on cervical dilation at inclusion were missing for one participant of the discontinuous oxytocin group. ‡Data on total duration of oxytocin infusion were missing for one participant of the continuous oxytocin group. §Data on total dose of oxytocin received during labour was missing for one participant of the continuous oxytocin group. ¶Data on duration from oxytocin onset to active labour were missing for 44 participants of the discontinuous oxytocin group and one participant of the continuous oxytocin group.

**Table 2: Characteristics of oxytocin infusion in the modified intention-to-treat population**

groups of discontinuous and continuous oxytocin, discontinuation of oxytocin was associated with a statistically significant increase in neonatal morbidity, albeit not clinically significant. This highlights the need for individualised care and consideration of patient-specific factors in obstetric practice.

To our knowledge, this trial is the largest trial comparing discontinuous and continuous oxytocin and was specifically powered to evaluate neonatal morbidity. It involved participants from 21 different centres, increasing its external validity especially since French guidelines regarding oxytocin infusion are similar to most international guidelines.<sup>4,8,9,32</sup> The study was conducted using strict inclusion and exclusion criteria.

This trial has some limitations. The decision to opt for an open-label design was driven by practicality, as frequent un-blinding could have posed challenges during active labour when timely decisions were crucial. Previous studies showed that during the active phase of labour, 30–40% of the women with a discontinued administration of oxytocin required a restart of oxytocin.<sup>21,33</sup> In situations with non-reassuring fetal heart rate patterns (estimated in up to 8% of women in a previous meta-analysis<sup>19</sup>), knowing the treatment group is important for the obstetrician to make informed decisions regarding oxytocin infusion to reduce uterine contractility. However, the open-label design might have influenced health-care providers' management decisions during labour, inadvertently introducing bias into the study outcomes. This bias could have potentially manifested in various directions, as health-care providers who were aware of the treatment allocation might have altered their clinical practices based on this knowledge. For instance, in the discontinuous group, the obstetric team might have resumed the treatment if they perceived inadequate progress, even though the labour was indeed advancing, albeit slowly. Conversely, in the continuous oxytocin group, a lack of

	Discontinuous oxytocin group (n=1067)	Continuous oxytocin group (n=1103)	Relative risk or median difference (95% CI)
Primary outcome, neonatal morbidity at birth*	102/1067 (9.6%)	101/1103 (9.2%)	1.0 (0.8 to 1.4)
Secondary outcomes			
Severity of neonatal acidosis			
Umbilical arterial pH <7.20	178/1002 (17.8%)	192/1013 (18.9%)	0.9 (0.8 to 1.1)
Umbilical arterial pH <7.10	31/1002 (3.1%)	32/1013 (3.2%)	1.0 (0.6 to 1.6)
Umbilical arterial pH <7.00	0/1002	5/1013 (0.5%)	..
Need for hypothermia	2/1067 (0.2%)	0/1103	..
Other neonatal complications			
Need of resuscitation at birth	91/1067 (8.5%)	83/1103 (7.5%)	1.1 (0.8 to 1.5)
NICU admission	28/1067 (2.6%)	24/1103 (2.2%)	1.2 (0.7 to 2.1)
Length of stay, days	4 (2–7.5)	2 (1–3)	2.0 (–1.0 to 5.0)
Mode of delivery			
Spontaneous	734/1067 (68.8%)	782/1103 (70.9%)	1.0 (0.9 to 1.0)
Instrumental vaginal delivery	219/1067 (20.5%)	212/1103 (19.2%)	1.1 (0.9 to 1.2)
Caesarean delivery	114/1067 (10.7%)	109/1103 (9.9%)	1.1 (0.8 to 1.3)
Caesarean for abnormal fetal heart rate	26/1067 (2.4%)	39/1103 (3.5%)	0.7 (0.4 to 1.1)
Instrumental delivery for abnormal fetal heart rate	80/1067 (7.5%)	97/1103 (8.8%)	0.8 (0.6 to 1.1)
Course of labour			
Active first stage of labour duration†, min	100 (50–208)‡	90 (45–150)‡	10.0 (0.0 to 16.0)
Second stage duration, min	120 (33–184)§	83 (23–166)§	37.0 (21.0 to 51.0)
Active first stage to delivery duration¶, min	244 (122–386)	197 (93–317)	47.0 (24.0 to 65.5)
Occiput-posterior presentation at delivery	37/1016 (3.6%)	41/1038 (3.9%)	0.9 (0.6 to 1.4)
Uterine tachysystole	62/978 (6.3%)	106/1019 (10.4%)	0.6 (0.4 to 0.8)
Maternal fever during labour	112/993 (11.3%)	117/1027 (11.4%)	1.0 (0.8 to 1.3)
Post-partum haemorrhage	111/960 (11.6%)	119/993 (12.0%)	1.0 (0.8 to 1.2)
Labour Agency Scale, score	163 (143–177)**	164 (145–177)**	–1.0 (–5.2 to 1.0)
Edinburgh Postnatal Depression Scale score >12	139/655 (21.2%)	141/680 (20.7%)	1.0 (0.8 to 1.3)

Data are n/N (%) or median [IQR], and relative risk or median difference with 95% CI. One planned secondary outcome, fetal scalp blood sampling during labour, was not reported as it was not available in every centre. NICU=neonatal intensive care unit. \*Neonatal morbidity at birth was assessed using a composite variable defined by an umbilical arterial pH at birth <7.10, a base excess greater than 10 mmol/L, umbilical arterial lactates less than 7 mmol/L, a 5-min Apgar score less than 7, or admission to neonatal intensive care unit. †Duration from 6 cm cervical dilation to full dilation. ‡Data for active first stage of labour duration were missing for 120 participants in the discontinuous oxytocin group and 113 participants of the continuous oxytocin group. §Data for second stage duration were missing for 83 participants of the discontinuous oxytocin group and 82 participants of the continuous oxytocin group. ¶Duration from 6 cm cervical dilation to delivery. ||Data for active first stage to delivery duration were missing for 44 participants of the discontinuous oxytocin group and one participant of the continuous oxytocin group. \*\*Data for Labour Agency Scale were missing for 149 participants of the discontinuous oxytocin group and 176 participants of the continuous oxytocin group.

**Table 3: Primary and secondary outcomes in the modified intention-to-treat population**

escalation in oxytocin dosage might have been more frequent due to the obstetric team’s increased attention to contraction frequency, thereby also reducing the contrast between the two groups and increasing the risk of not detecting a statistically significant difference between the groups. However, rigorous data collection and monitoring procedures were implemented, and protocol reminders were carried out to mitigate this risk. Thus, the contrast

	Discontinuous oxytocin group (n=1005)	Continuous oxytocin group (n=1165)
<b>Serious adverse events</b>		
Neonatal death	1* (0.1%)	0
Maternal death	0	0
Severe PPH	32 (3.2%)	35 (3.0%)
Neonatal hypothermia	2 (0.2%)	0
<b>Maternal unexpected adverse events</b>		
Moderate PPH	23 (2.3%)	41 (3.5%)
Suspicion of infection	21 (2.1%)	21 (1.8%)
Maternal anaemia	11 (1.1%)	8 (0.7%)
Headache	5 (0.5%)	3 (0.3%)
Hypotension	4 (0.4%)	4 (0.3%)
Transient motor deficit	4 (0.4%)	1 (0.1%)
High blood pressure	2 (0.2%)	2 (0.2%)
Obstetric anal sphincter injuries	2 (0.2%)	1 (0.1%)
Epidural analgesia complications	0	4 (0.3%)
<b>Neonatal unexpected adverse events</b>		
Birth trauma	2 (0.2%)	2 (0.2%)
Congenital anomaly	1 (0.1%)	1 (0.1%)
Jaundice	8 (0.8%)	8 (0.7%)
Neonatal hypoglycaemia	1 (0.1%)	1 (0.1%)

Data are n (%). Severe PPH was defined as an estimated blood loss greater than 1000 mL. Moderate PPH was defined as an estimated blood loss greater than 500 mL. PPH= postpartum haemorrhage. \*The death was due to severe hypoxic-ischaemic encephalopathy. The newborn was transferred to the intensive care unit immediately after delivery, and in hypothermia. Additional examinations revealed severe brain lesions, and a decision was ultimately made to discontinue medical treatment.

**Table 4: Adverse events in the safety population**

between the two groups remained observable, preserving the interpretability of our findings.

The fact that oxytocin was restarted in a substantial proportion of participants in the discontinuous oxytocin group could have contributed to the lack of outcome differences between the two groups. The rate of restarting oxytocin in the discontinuous oxytocin group aligns with findings from previous studies,<sup>20,21,31</sup> and further investigation is needed to better understand its implications in clinical practice.

Although adherence rates were generally high (93.4% in the discontinuous oxytocin group and 99.2% in the continuous oxytocin group), the absence of blinding might have influenced adherence rates to some extent. Non-adherence, reflecting real-life situations, might have reduced the intervention’s contrast. However, the per protocol analysis refutes this hypothesis, demonstrating no difference between the groups for primary and secondary outcomes.

The study did not reach the initially targeted sample size of 2250 participants, and instead only included 2170 participants in the mITT population. Although the smaller sample size could have affected the study’s statistical power to detect smaller effect sizes, it is



essential to emphasise that the observed effect size and the corresponding CIs provide robust evidence for the absence of a clinically significant difference in neonatal morbidity between the discontinuous oxytocin and continuous oxytocin groups. Our study remains the largest and most comprehensive investigation on the impact of discontinuous oxytocin on neonatal morbidity.

Our study focused on neonatal outcomes as the primary endpoint, but we recognise the interdependence between neonatal and maternal outcomes when discontinuing oxytocin during the active phase of labour. The wellbeing of both the newborn and the mother is intricately linked during the labour and delivery process. Therefore, it is essential to also consider the impact of our intervention on maternal outcomes, such as the duration of the active phase and mode of delivery, as these factors could indirectly influence neonatal health.

Furthermore, although our primary outcome assessment was limited to neonatal morbidity at birth, it is important to note that certain adverse neonatal events or complications might not manifest immediately and could potentially occur within the first 7 days or even up to 28 days of life. As a result, our study might not provide a comprehensive assessment of the long-term neonatal outcomes associated with this intervention.

Further research should explore the heterogeneity of responses to oxytocin among women. It is plausible that individual variations, encompassing genetic predispositions, hormonal profiles, and obstetric and medical history, contribute to divergent outcomes. Identifying these factors could aid the development of targeted interventions, where discontinuation of oxytocin is strategically implemented for specific groups of women who are more likely to benefit. Moreover, investigating patient-centred outcomes such as maternal satisfaction, and long-term neonatal development in the context of these personalised approaches could provide a more comprehensive understanding of the impact of discontinuing oxytocin.

In the current obstetric landscape, there has been a notable increase in the rates of labour induction, particularly among nulliparous women at 39 weeks without medical indication. This trend highlights the need to carefully approach the use of interventions such as oxytocin and strive to reduce unnecessary treatments. Our trial is particularly relevant as it included a significant proportion of women who were induced, providing valuable insights for optimising obstetric care and guiding clinical decision making in the context of increasing induction rates.

In conclusion, among participants receiving oxytocin before 4 cm of cervical dilation, discontinuing oxytocin when the active phase is reached did not show a reduction in neonatal morbidity compared to continuous oxytocin. This study highlights the need for future research on individualised care and patient-specific factors in obstetric practice.

#### Contributors

AG conceived the study and participated in the project design, obtained the funding, drafted the manuscript, and approved the final manuscript. CLR conceived the study and participated in the project design, obtained the funding, read, edited, and approved the final manuscript. JR performed the statistical analyses, edited, and approved the final manuscript. LS, RD, PB, DK, CBe, JC, NW, EV, EB, TB, GL, GER, GK, MM, CBo, PG, EA, JB, HH, JR, and CG read, edited, and approved the final manuscript. AG, CLR, CG, and JR had access to all the raw data and verified it. AG, CLR, and LS were responsible for the decision to submit the manuscript.

#### Declaration of interests

LS has carried out consultancy work and been a lecturer for Ferring Laboratories, GlaxoSmithKline, and Bayer, and has been a lecturer for Norgine. PB has acted as a consultant for Ferring, General Electric Medical System, Norgine, and Becton Dickinson. CG has carried out consultancy work for Bioserinity, and been a lecturer for General Electric and Bayer. NW has been a lecturer for Roche Diagnostics. All other authors declare no competing interests.

#### Data sharing

Data sharing requests will be considered by the management group upon written request to the corresponding author. De-identified participant data or other prespecified data will be available subject to a written proposal and a signed data sharing agreement.

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