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Impact of discontinuing oxytocin in active labor on neonatal morbidity: an open-label multicenter randomized trial

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Abstract

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

**Methods:** STOPOXY was a multicenter, randomized, open-label, controlled, superiority trial conducted in 21 maternity units in France. Participants who received oxytocin before 4cm dilation were randomly assigned, in a 1:1 ratio to either discontinuous oxytocin (oxytocin infusion stopped beyond a cervical dilation equal to or greater than 6cm) or continuous oxytocin (administration of oxytocin is continued until delivery). Randomization was stratified by center and parity. The primary outcome, neonatal morbidity, was assessed at birth using a composite variable defined by an umbilical arterial pH at birth <7.10 and/or a base excess >10mmol/L and/or umbilical arterial lactates>7 mmol/L and/or a 5-minute Apgar score <7 and/or admission in neonatal intensive care unit.

**Results:** Out of the 2459 participants randomized between January 13, 2020, and January 24, 2022, 2170 were eligible to receive the intervention and were analyzed. The primary outcome occurred in 102 of 1067 women (9.6%, 95%CI(7.9 to 11.5)) in the discontinuous oxytocin group and in 101 of 1103 women (9.2%, 95%CI(7.6 to 11.0)) in the control group, absolute difference 0.004, 95%CI(-0.021 to 0.029); RR 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 labor, discontinuing oxytocin when active phase is reached does not clinically or statistically significantly reduce neonatal morbidity compared to continuous oxytocin.

**Trial Registration:** NCT03991091

**Funding:** French Ministry of Health

**Key words:** oxytocin, augmentation of labor, induction of labor, neonatal morbidity, cesarean delivery, labor duration, birth experience
Research in context

Evidence before study: Previous studies have demonstrated the effectiveness of oxytocin in reducing labor 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 induced women and 15% to 40% of women in spontaneous labor receiving this treatment on a daily basis, 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 labor and the potential benefits of discontinuing its administration during the active phase. A systematic search was performed in PubMed from inception to June 1st, 2023, using relevant keyword related to "oxytocin", "labor", "discontinuation", "uterine hyperstimulation", "neonatal morbidity", "neonatal acidosis" and "cesarean delivery". No language restrictions were applied. The search included randomized 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 rigor, and risk of bias.

We did not identify any clinical trials specifically investigating the impact of discontinuing oxytocin during the active phase of labor with neonatal morbidity as the primary outcome. Most studies and all meta-analyses have indicated that discontinuing oxytocin during the active phase of labor might be associated with a reduced risk of uterine tachysystole, neonatal acidosis, adverse neonatal outcomes, and cesarean delivery. However, a recent large trial conducted in 2021, found contrasting findings compared to those of previous literature. This trial revealed a slight increase in cesarean 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 NICU admission rates between the discontinuous and continuous oxytocin groups. Nonetheless, all these 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 labor. However, there is a lack of robust evidence specifically addressing the discontinuation of oxytocin during the active phase of labor and its impact on neonatal morbidity and maternal complications.

Added value of the study: The current study addresses this research gap by conducting a large, multicenter, randomized controlled trial specifically powered to evaluate neonatal morbidity. Our study adds to the existing evidence by specifically examining the impact of discontinuing oxytocin during the active phase of labor 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 to continuous oxytocin, provide important insights for clinical practice, and highlight the need for individualized care and consideration of patient-specific factors. By assessing the effects of discontinuing oxytocin during the active phase of labor on a comprehensive range of outcomes, including neonatal morbidity, mode of delivery, course of labor, 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 emphasizes the need for updated meta-analyses as it
reinforces the finding that discontinuous oxytocin does not reduce the risk of cesarean delivery.

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

Oxytocin is one of the most commonly used drugs worldwide, and is used either as part of induction of labor or for augmentation of labor.\textsuperscript{1-5} It is indeed effective in increasing frequency and intensity of uterine contractions and therefore in reducing labor duration.\textsuperscript{6,7}

Obstetric situations requiring oxytocin administration before 4cm of dilation are induction of labor, with or without previous cervical ripening and labor dystocia, i.e. non-progression of the cervical dilation.\textsuperscript{2,8,9} With the current trend of increased rates of induction of labor, particularly for nulliparous women at 39 weeks without medical indication,\textsuperscript{10} it is essential to evaluate the use of medication such as oxytocin cautiously and consider the importance of reducing unnecessary interventions.

The most important side effect of oxytocin infusion is uterine tachysystole, which has been shown to occur in more than 30% of women induced with oxytocin.\textsuperscript{11-14} Oxytocin-induced tachysystole is associated with significant oxygen desaturation and non-reassuring fetal heart rate patterns (FHR), contributing to neonatal acidosis.\textsuperscript{11,15} Acidosis accounts for a significant proportion of term neonatal morbidity due to related complications such as hospitalization in neonatal intensive care units, but also cerebral palsy or neonatal death the most severe cases. In addition, the effectiveness of oxytocin in decreasing the cesarean delivery rate has not been demonstrated.\textsuperscript{16,17} Moreover, its administration is potentially associated with maternal complications, such as post-partum hemorrhage.\textsuperscript{18}

One assumption is that, once women requiring oxytocin during the latent phase enter the active phase, natural oxytocin takes over from synthetic oxytocin.\textsuperscript{19} 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 hypothesized that...
discontinuation of oxytocin in the active phase of labor (from 6cm) in women who received oxytocin in the latent phase or for an induction of labor could reduce neonatal morbidity but also severe maternal complications such as postpartum hemorrhage. Previous studies evaluating discontinuation of oxytocin in the active phase of labor have been underpowered to detect a significant difference in neonatal morbidity rates, highlighting the need for further research.\textsuperscript{20,21}

A meticulous approach to the administration of oxytocin, particularly given the increasing rates of labor induction, possesses the potential to recalibrate obstetric practices by prioritizing judicious interventions. This approach attends to the well-being of both mothers and neonates.

Thus, our main objective was to measure the impact of discontinuing oxytocin in active phase of labor on the neonatal morbidity rate. Secondary objectives included measuring the impact of discontinuing oxytocin on low pH thresholds and need for hypothermia, mode of delivery, course of labor, maternal complications, and birth experience.
Methods

Study Design

STOPOXY was a multicenter, randomized, open label, controlled, superiority trial conducted in 21 maternity hospitals across France (List of centers and number randomized per center-Table S1). The trial design was published, and trial protocol (Supplement 1) 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, registration number MR001.

Participants

Eligible participants were pregnant women aged 18 years or older, with a singleton term pregnancy (≥37 weeks), and a fetus in cephalic presentation receiving oxytocin before reaching 4cm of cervical dilation, regardless of mode of onset of labor. Women with a scarred uterus, a fetus with a fetal growth retardation <3rd percentile for gestational age or congenital abnormality, abnormal fetal heart rate at randomization, participating in another trial involving medication, who were not able to communicate fluently in the French language or have medical insurance were not eligible for this trial. Informed written consent was obtained from all participants.

In all centers, oxytocin was administered according to national guidelines, i.e. low dose oxytocin infusion of less than 4 mUI/min with increments every 30 min, without exceeding a 20 mUI/min flow rate.8

Randomization

Before a cervical dilation of 6cm, participants were randomly assigned using a 4-size permuted block randomization with a 1:1 ratio to either discontinuous oxytocin or continuous with the use of a computer-generated randomization sequence. Randomization
was stratified on the center and parity (nullipara/multipara). The randomization procedure was carried out in the labor ward by either the midwife or the obstetrician which were certified in Good Clinical Practice (GCP) for research, online via the CleanWeb® interface accessible 24 hours online.

Procedures

The trial information was initially delivered to participants before labor 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 labor induction or the onset of spontaneous labor in the labor ward. The informed consent was signed before inclusion, typically after the onset of oxytocin perfusion.

Participants were included if they received oxytocin before 4cm, subsequently, randomization took place before reaching 6cm of cervical dilation. This process ensured that some participants could be included but not randomized either because of a cesarean delivery before 6cm, or because of an abnormal fetal heart rate.

After randomization, in the discontinuous group, oxytocin infusion was stopped beyond a cervical dilation equal to or greater than 6cm. If necessary, caregivers were instructed that oxytocin could be re-started after 2 hours of labor arrest (no progression of the cervical dilation and/or no progression of the fetal head). In the control group, oxytocin was continued during the active phase and during the 2nd stage. If necessary, it could be stopped because of an abnormal FHR 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 center. This monitoring process was conducted by an independent trial monitoring team.

Although this trial took place during the COVID-19 pandemic, the recruitment, randomization, 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 <7.10 and/or a base excess >10mmol/L and/or umbilical arterial lactates>7 mmol/L and/or a 5-minute Apgar score <7 and/or admission in neonatal intensive care unit (NICU). This composite outcome allowed for the evaluation of neonatal morbidity potentially associated with uterine tachysystole induced by oxytocin, which may lead to respiratory, metabolic, or mixed acidosis and clinical implications necessitating NICU admission. Each criterion represents neonatal morbidity and is recognized as an indicator of adverse outcomes. The chosen thresholds are commonly reported in the literature for assessing neonatal acidosis at birth.\(^{23-25}\) No specific cord clamping recommendations were specified in the trial protocol.

Secondary outcomes included neonatal pre-acidosis, acidosis and its severity (defined as umbilical arterial cord pH at birth <7.20, < 7.10 and 7.00 and need for hypothermia for neuroprotection), other neonatal complications (need for resuscitation at birth, admission to NICU and length of hospital stay in NICU) mode of delivery (spontaneous delivery, instrumental vaginal or cesarean delivery) and indication (rates for cesarean delivery and instrumental delivery for abnormal fetal heart rate), course of labor characteristics (such as median active phase duration, defined as duration from 6cm to full dilation, second stage and active phase to delivery duration, defined as duration from 6cm to delivery; occiput-posterior presentation at delivery, and occurrence uterine tachysystole defined by periods}
with more than five uterine contractions in 10 minutes or hypertonus requiring medical
treatment), maternal fever during labor (defined as a maternal temperature >38°C), and
post-partum hemorrhage (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 Labor
Agency Scale (LAS), where higher scores indicate a greater sense of control during the
birthing process. Additionally, at 2 months postpartum, women's well-being was assessed
using the Edinburgh Postnatal Depression Scale (EPDS). These assessments were
conducted through email. A rate of score >12 on the EPDS is indicative of a higher likelihood
of experiencing depressive symptoms of varying severity.

During the study, the investigators promptly reported four serious adverse events:
postpartum hemorrhage, characterized 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.

Sample size calculation

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
We hypothesized a clinically relevant decrease from 8% in the control group (i.e. standard care) to 5% in the discontinuous oxytocin group, representing a 3% absolute difference in the neonatal morbidity rate (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 control 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 cesarean deliveries before reaching 6 cm dilation (preventing participants from receiving the studied intervention), the protocol provided for an increase the required sample size by 10% in each group (225 participant in total), bringing the total required sample size for inclusion in the study to 2475 women.

Statistical analysis

The main analysis of the primary and secondary outcomes was performed in the modified intention-to-treat population (mITT). The modified intention-to-treat population included participants who underwent randomization (excluding those who withdrew consent or were deemed ineligible after randomization) and had reached a cervical dilation of at least 6 cm, making them eligible for the intervention. We also analyzed two other populations: the intention-to-treat population (ITT) population which included all randomized participants, regardless of whether they reached 6 cm dilation, except for those who withdrew consent or were considered ineligible after randomization; and the perprotocol population, which included the participants from the mITT who received the allocated intervention as intended by the protocol.
Despite the intervention aiming to reduce medicalization of labor, we defined a safety population as reducing an intervention may also have adverse effects. This safety population included all participants from the mITT population, with participants divided into discontinuous and control groups based on their actual experience during active phase of labor. Participants who had a discontinuation of oxytocin and a restart during labor were considered in the discontinuous 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 interquartile ranges (IQR). The two-sided 95% confidence intervals (CIs) for the primary outcome were computed using the Wilson method. The comparison of the primary and secondary outcomes between the randomized groups was performed using the relative risk (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 labor (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 analysis 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 subgroup. 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, V9.4.2 and R software (version 3.5).

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.
Results

Between January 13, 2020, and January 24, 2022, a total of 2493 participants were included, 34 participants were not randomized due to eligibility criteria errors or other reasons (n=33) or because they declined to participate (n=1) and 2459 were randomly assigned to discontinuous or continuous oxytocin in the active phase of labor. A total of 92 (3.7%) randomized participants were excluded because they did not meet randomization criteria. Of the remaining 2364, 194 (7.9%) underwent cesarean delivery before reaching a cervical dilation of 6cm which resulted in a modified intention-to-treat population of 2173 participants (1067 in the discontinuous oxytocin group and 1103 in the control group) (Figure1). The two groups were well balanced with respect to baseline characteristics, with a good contrast in terms of total duration of oxytocin use and total dose received (Table 1 and 2). According to study protocol, in the discontinuous oxytocin group, oxytocin was restarted in 40.5% of the cases, and in the control group, oxytocin was stopped in 5.3% of the cases (Table 2).

There was no clinical or statistical difference between the two groups of the mITT for the primary outcome. The observed percentage of neonatal morbidity was 9.6%, 95%CI(7.9;11.5) in the discontinuous oxytocin group and 9.2%, 95%CI(7.6;11.0) in the control group, absolute difference 0.004, 95%CI(-0.021;0.029), RR = 1.0, 95%CI(0.8 to 1.4) (Table 3). Apgar score and admission to NICU were available for all participants, and cord pH was available for 98% of participants. Base excess and lactate levels were not measured in all centers; when the variable was not available, it was considered a missing data item. There were no statistically significant differences between the two groups for the rates of neonatal secondary outcomes (Table 3). No statistically significant differences were
observed in the mode of delivery, with a cesarean delivery rate of 10.7% (114/1067) in the discontinuous oxytocin group and 9.9% (109/1103) in the control group, RR= 1.1 95%CI(0.8 to 1.3). Participants in the discontinuous oxytocin group had a statistically significant longer median active phase, median second stage and median active phase to delivery durations than participants in the control group, respectively for active phase, second stage and active phase to delivery durations, 100 minutes (50 to 208) vs 90 minutes (45 to 150), median difference 10.0 (0.0 to 16.0); 120 minutes (33 to 184) vs 83 minutes (23 to 166), median difference 37.0 (21.0 to 51.0) and 244 minutes (122 to 386) vs 197 (93 to 317), median difference 47.0 (24.0 to 65.5). Uterine tachysystole was statistically significantly less frequent in the discontinuous oxytocin group compared to the control group (6.3% (62/978) vs 10.4% (106/1019), RR 0.6 (0.4 to 0.8)) (Table 3).

Both the completion rate of the LAS at day 2 postpartum (84.9%) and the completion rate of the EPDS at 2 months postpartum (61.4%) were comparable between the two groups. There were no statistically significant differences in the median scores of the LAS or the rate of scores >12 in the EPDS between the two groups (Table 3).

Table S2 and S3 provide baseline and oxytocin characteristics for each subgroup of the modified intention-to-treat population. The results of the subgroup analyses concerning mode of onset of labor and nulliparous women were consistent with the main analysis (Table S4 and S5). In the multiparous subgroup, the discontinuous oxytocin group had statistically significant higher rates of neonatal morbidity 5.2% (27/521) vs 2.5% (13/521), RR= 2.1, 95%CI(1.1 to 4.0) (Table S5).

The results of the analyses in the ITT population and the per-protocol population yield similar results and are presented in Table S6 to S11.
The safety analysis showed no significant differences between the groups in serious adverse events and unexpected adverse events (Table 4).
Discussion

Discontinuous oxytocin in the active phase of labor did not demonstrate a statistically significant impact on neonatal morbidity, mode of delivery or postpartum hemorrhage. 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. In contrast, our study was specifically designed to evaluate these outcomes. Most previous studies focused on labor 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 statistically significantly lower cesarean delivery rates with discontinuous oxytocin compared to continuous oxytocin (n=1784, OR 0.69; 95%CI(0.56;0.86)), but longer active phase durations (n=1336, mean difference 25.57 minutes; 95%CI(5.28;45.87)). Our study showed conflicting results regarding the effect of oxytocin regimen on cesarean delivery rates, with a non-statistically significant higher rate of cesarean delivery among participants included in the discontinuous oxytocin group. However, our findings are consistent with a recent Danish trial including 1198 induced women, that was not included in the meta-analysis cited above, which found no significant differences between continuous and discontinuous oxytocin on the cesarean delivery rates OR 1.17; 95%CI[0.90,1.53]. These recent results, along with our own, contribute to the growing body of literature indicating that discontinuous oxytocin may not decrease the risk of cesarean delivery.
The reduction of uterine tachysystole in the discontinuous oxytocin group of our trial is consistent with previous published studies but, interestingly does not translate in a reduction of neonatal acidosis.\textsuperscript{20,31} This finding suggests that the relationship between uterine tachysystole and adverse neonatal outcomes may not be straightforward, and that other factors may play a role in determining neonatal outcomes. It is important to highlight that personalized medicine approaches are already being implemented, where oxytocin flow rate is adjusted based on uterine tachysystole and/or abnormal FHR patterns. However, in multiparous women, despite comparable rates of uterine tachysystole between the 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 individualized care and consideration of patient-specific factors in obstetric practice.

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 centers, increasing its external validity especially since French guidelines regarding oxytocin infusion are similar to most international guidelines.\textsuperscript{4,8,9,32} 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 labor when timely decisions were crucial. Previous studies showed that during the active phase of labor, 30 to 40% of the women with a discontinued administration of oxytocin required a re-start of oxytocin.\textsuperscript{21,13} In situation with non-reassuring FHR (up to 8% of the women in Saccones’ metanalysis\textsuperscript{19}), 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 provider’s management decisions during labor, inadvertently introducing bias into the study outcomes. This bias could potentially manifest in various directions, as healthcare 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 labor was indeed advancing, albeit slowly. Conversely, in the continuous oxytocin group, a lack of 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 between the two groups remained observable, preserving the interpretability of our findings.

The fact that oxytocin was restarted in a significant proportion of cases 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 group aligns with findings from previous studies, and further investigation is needed to better understand its implications in clinical practice.

Although compliance rates were generally high (93.4% in the discontinuous group and 99.2% in the control group), the lack of blinding might have influenced compliance rates to some extent. Non-compliance, reflecting real-life situations, may 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, analyzed 2170 participants. While the smaller sample size could have affected the study's statistical power to detect smaller effect sizes, it is essential to emphasize that the observed effect size and the corresponding confidence intervals provide robust evidence for the lack of a clinically significant difference in neonatal morbidity between the discontinuous oxytocin and control 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 recognize the interdependence between neonatal and maternal outcomes when discontinuing oxytocin during the active phase of labor. The well-being of both the newborn and the mother is intricately linked during the labor 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 may indirectly influence neonatal health.

Furthermore, while our primary outcome assessment was limited to neonatal morbidity at birth, it is important to note that certain adverse neonatal events or complications may 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 may 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 pave the way for targeted interventions, where discontinuation of oxytocin is strategically implemented for specific groups of women who are more likely to benefit. Moreover, investigating patient-centered outcomes such as maternal satisfaction, and long-term neonatal development in the context of these personalized approaches could provide a more comprehensive understanding of the impact of discontinuing oxytocin.

In the current obstetrical landscape, there has been a notable increase in the rates of labor 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 induced women, providing valuable insights for optimizing obstetric care and guiding clinical decision-making in the context of increasing induction rates.

In conclusion, among participants receiving oxytocin before 4cm of cervical dilation, discontinuing oxytocin when 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 individualized care and patient-specific factors in obstetric practice.
Declarations

Funding
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Authors’ contributions
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

Declaration of interests:
- Loïc Sentilhes has carried out consultancy work and been a lecturer for Ferring Laboratories, GlaxoSmithKline and Bayer, and been a lecturer for Norgine in the previous 3 years.
- Paul Berveiller has acted as consultant for Ferring, General Electric Medical System, Norgine, Becton Dickinson.
- Charles Garabedian has carried out consultancy work for Bioserinity, and been a lecturer for General Electrics and Bayer in the previous 3 years.
- Norbert Winer has been a lecturer for Roche Diagnostic.
The other authors do not report any potential conflicts of interest.

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

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References


