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

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1 **Impact of discontinuing oxytocin in active labor on neonatal morbidity: an open-label**
2 **multicenter randomized trial**
3

4 Aude Girault^{1,2}, PhD; Loïc Sentilhes³, PhD; Raoul Desbrière⁴, PhD ; Paul Berveiller⁵, PhD;
5 Diane Korb⁶, PhD; Charline Bertholdt⁷, MD; Julie Carrara⁸, MD; Norbert Winer⁹, PhD; Eric
6 Verspyck¹⁰, PhD; Eric Boudier¹¹, MD; Tiphaine Barjat¹², PhD; Gilles Levy¹³, MD; Georges
7 Emmanuel Roth¹⁴, RM; Gilles Kayem^{1,15}, PhD; Mona Massoud¹⁶, PhD; Caroline Bohec¹⁷, PhD;
8 Paul Guerby¹⁸, PhD; Elie Azria^{1,19}, PhD; Julie Blanc²⁰, PhD; H el ene Heckenroth²¹, PhD; Jessica
9 Rousseau²², MS; Charles Garabedian^{23,24}, PhD; and Camille Le Ray^{1,2}, PhD; on behalf of the
10 collaborators of the STOPOXY trial and the Groupe de Recherche en Obst etricque et
11 Gyn ecologie (GROG)

12 ¹Universit  Paris Cit , INSERM UMR 1153, Equipe EPOP , 75014 Paris, France

13 ² Department of Obstetrics and Gynecology, Port-Royal Maternity Hospital, AP-HP, Cochin Hospital, FHU
14 PREMA, F-75014 Paris, France

15 ³Department of Obstetrics and Gynecology, Bordeaux University Hospital, Bordeaux, France

16 ⁴Department of Obstetrics and Gynecology, H pital Saint Joseph, Marseille, France.

17 ⁵ Department of Obstetrics and Gynecology, Centre Hospitalier Intercommunal de Poissy/Saint- Germain-en-
18 Laye, Rue du Champ Gaillard, 78303 Poissy Cedex, France

19 ⁶Department of Obstetrics and Gynecology, Robert Debr  Hospital, AP-HP, Paris, France

20 ⁷ University of Lorraine, CHRU NANCY, Obstetrics and Gynecology Department, F-54000 NANCY, France

21 ⁸ Department of Obstetrics and Gynecology, Antoine B cl re Hospital, AP-HP, Paris, France, Paris Saclay
22 University, France

23 ⁹ Department of Obstetrics and Gynecology, University Hospital of Nantes, 44093 Nantes, France.

24 ¹⁰ Department of Obstetrics and Gynecology, Centre Hospitalier Universitaire de Rouen, Rouen, France.

25 ¹¹ Department of Obstetrics and Gynecology, Les H pitaux Universitaires de Strasbourg, Ave. Moliere 6700,
26 Strasbourg, France.

27 ¹² Department of Obstetrics and Gynecology, Saint Etienne University Hospital, Saint Etienne, France

28 ¹³ Department of Obstetrics and Gynecology, H pital Nord Franche Comt , Site Belfort

29 ¹⁴ CHU de Strasbourg, P le de Gyn cologie-Obst trique et Fertilit , Universit  de Strasbourg-SFC

30 ¹⁵ Department of Obstetrics and Gynecology, Trousseau Hospital, Sorbonne University, APHP, Paris France

31 ¹⁶ Hospices Civils de Lyon, Department of Obstetrics and Gynecology, Universit  Claude Bernard Lyon 1, Centre
32 Hospitalier Lyon Sud, Pierre B nite, France

33 ¹⁷Department of Obstetrics and Gynecology, Fran ois Mitterrand Hospital, Pau, France.

34 ¹⁸ Department of Obstetrics and Gynecology, Infinity CNRS Inserm UMR 1291, CHU Toulouse, Toulouse, France.

35 ¹⁹ Maternity Unit, Groupe Hospitalier Paris Saint Joseph, FHU PREMA, Paris, France

36 ²⁰Department of Obstetrics and Gynecology, Nord Hospital, APHM, chemin des Bourrely, 13015 Marseille,
37 France

38 ²¹Department of Gynaecology and Obstetrics, Gyn pole, Assistance Publique-H pitaux de Marseille, AMU, Aix-
39 Marseille Universit , Marseille, France

40 ²²Clinical Research Unit, Center for Clinical Investigation P1419, AP-HP, Paris, France.

41 ²³CHU Lille, Department of obstetrics, F59000 Lille, France

42 ²⁴Univ Lille, ULR 2694-METRICS, F59000 Lille, France

43
44 **Corresponding author:**

45 Aude Girault

46 Maternit  Port Royal, **123 boulevard Port Royal,**

47 **75014 Paris**

48 aude.girault@aphp.fr +331 58 41 37 71

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51

52 **Abstract**

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

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

66 **Results:** Out of the 2459 participants randomized between January 13, 2020, and January
67 24, 2022, 2170 were eligible to receive the intervention and were analyzed. The primary
68 outcome occurred in 102 of 1067 women (9.6%, 95%CI(7.9 to 11.5)) in the discontinuous
69 oxytocin group and in 101 of 1103 women (9.2%, 95%CI(7.6 to 11.0)) in the control group,
70 absolute difference 0.004, 95%CI(-0.021 to 0.029); RR 1.0, 95%CI(0.8 to 1.4). There were no
71 clinically significant differences in adverse events between the two groups of the safety
72 population.

73 **Interpretation:** Among participants receiving oxytocin in early labor, discontinuing oxytocin
74 when active phase is reached does not clinically or statistically significantly reduce neonatal
75 morbidity compared to continuous oxytocin.

76 **Trial Registration:** NCT03991091

77 **Funding:** French Ministry of Health

78

79

80 **Key words:** oxytocin, augmentation of labor, induction of labor, neonatal morbidity,
81 cesarean delivery, labor duration, birth experience

82

83 **Research in context**

84 **Evidence before study:** Previous studies have demonstrated the effectiveness of oxytocin in
85 reducing labor duration by increasing uterine contractions. However, oxytocin is also
86 associated with uterine tachysystole which can lead to abnormal fetal heart rate patterns
87 and neonatal acidosis. Despite the routine use of oxytocin in maternity settings, with over
88 80% of induced women and 15% to 40% of women in spontaneous labor receiving this
89 treatment on a daily basis, the optimal duration of oxytocin administration and its potential
90 effects on neonatal and maternal outcomes remain areas of uncertainty. We conducted a
91 comprehensive literature review to assess the existing evidence on the use of oxytocin
92 during labor and the potential benefits of discontinuing its administration during the active
93 phase. A systematic search was performed in PubMed from inception to June 1st, 2023, using
94 relevant keyword related to "oxytocin", "labor", "discontinuation", "uterine
95 hyperstimulation", "neonatal morbidity", "neonatal acidosis" and "cesarean delivery". No
96 language restrictions were applied. The search included randomized controlled trials,
97 observational studies, systematic reviews, and meta-analyses. The quality of the retrieved
98 evidence varied, considering factors such as study design, sample size, methodological rigor,
99 and risk of bias.

100 We did not identify any clinical trials specifically investigating the impact of discontinuing
101 oxytocin during the active phase of labor with neonatal morbidity as the primary outcome.
102 Most studies and all meta-analyses have indicated that discontinuing oxytocin during the
103 active phase of labor might be associated with a reduced risk of uterine tachysystole,
104 neonatal acidosis, adverse neonatal outcomes, and cesarean delivery. However, a recent
105 large trial conducted in 2021, found contrasting findings compared to those of previous
106 literature. This trial revealed a slight increase in cesarean deliveries when oxytocin was
107 discontinued, but the difference was neither clinically nor statistically significant. It is
108 noteworthy that this trial focused solely on neonatal outcomes as secondary endpoints and
109 found no significant differences in low pH, low Apgar scores, and NICU admission rates
110 between the discontinuous and continuous oxytocin groups. Nonetheless, all these studies
111 were underpowered to detect differences in neonatal morbidity rates. The available
112 evidence, including previous studies and systematic reviews, has provided some insights into
113 the potential benefits and risks of discontinuing oxytocin during labor. However, there is a
114 lack of robust evidence specifically addressing the discontinuation of oxytocin during the
115 active phase of labor and its impact on neonatal morbidity and maternal complications.

116 **Added value of the study:** The current study addresses this research gap by conducting a
117 large, multicenter, randomized controlled trial specifically powered to evaluate neonatal
118 morbidity. Our study adds to the existing evidence by specifically examining the impact of
119 discontinuing oxytocin during the active phase of labor on neonatal morbidity and other
120 important outcomes. The findings of our study, which did not demonstrate a significant
121 reduction in neonatal morbidity with discontinuous oxytocin compared to continuous
122 oxytocin, provide important insights for clinical practice, and highlight the need for
123 individualized care and consideration of patient-specific factors. By assessing the effects of
124 discontinuing oxytocin during the active phase of labor on a comprehensive range of
125 outcomes, including neonatal morbidity, mode of delivery, course of labor, maternal
126 complications, and birth experience, our study aims to contribute significant insights to the
127 existing evidence base and provide valuable guidance for clinical practice and future
128 research. Furthermore, our study emphasizes the need for updated meta-analyses as it

129 reinforces the finding that discontinuous oxytocin does not reduce the risk of cesarean
130 delivery.

131 **Implication of all the available evidence:** The results suggest that discontinuing oxytocin
132 when active phase is reached does not significantly reduce neonatal morbidity compared to
133 continuous oxytocin in participants receiving oxytocin before 4 cm of cervical dilation.
134 Furthermore, we did not find any lower risk of cesarean delivery with discontinuous oxytocin
135 use. These findings have important implications for obstetric practice, highlighting the need
136 to carefully consider the individualized management of oxytocin use during labor. As our
137 study and a recent large trial by Boie et al. (2021) showed, the discontinuation of oxytocin
138 might not offer significant benefits in reducing the risk of cesarean delivery. Given the
139 complexities of labor management and the potential variability in individual responses to
140 oxytocin, further research is warranted to optimize oxytocin administration protocols.
141

142 **Introduction**

143 Oxytocin is one of the most commonly used drugs worldwide, and is used either as
144 part of induction of labor or for augmentation of labor.¹⁻⁵ It is indeed effective in increasing
145 frequency and intensity of uterine contractions and therefore in reducing labor duration.^{6,7}
146 Obstetric situations requiring oxytocin administration before 4cm of dilation are induction of
147 labor, with or without previous cervical ripening and labor dystocia, i.e. non-progression of
148 the cervical dilation^{2,8,9}. With the current trend of increased rates of induction of labor,
149 particularly for nulliparous women at 39 weeks without medical indication,¹⁰ it is essential to
150 evaluate the use of medication such as oxytocin cautiously and consider the importance of
151 reducing unnecessary interventions.

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

161 One assumption is that, once women requiring oxytocin during the latent phase
162 enter the active phase, natural oxytocin takes over from synthetic oxytocin.¹⁹ Thus, in the
163 active phase, oxytocin could be discontinued, reducing exposure duration, and therefore
164 reducing the risk of complications, in particular neonatal complications such as hypoxia,
165 without compromising the chances of vaginal delivery. It can therefore be hypothesized that

166 discontinuation of oxytocin in the active phase of labor (from 6cm) in women who received
167 oxytocin in the latent phase or for an induction of labor could reduce neonatal morbidity but
168 also severe maternal complications such as postpartum hemorrhage. Previous studies
169 evaluating discontinuation of oxytocin in the active phase of labor have been underpowered
170 to detect a significant difference in neonatal morbidity rates, highlighting the need for
171 further research.^{20,21}

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

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

181

182 **Methods**

183 ***Study Design***

184 STOPOXY was a multicenter, randomized, open label, controlled, superiority trial
185 conducted in 21 maternity hospitals across France (List of centers and number randomized
186 per center-Table S1). The trial design was published,²² and trial protocol (Supplement 1) was
187 approved by the national agency for drug safety; the Committee for protection of persons
188 involved in biomedical research, and the French data protection authority, registration
189 number MR001.

190 ***Participants***

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

199 In all centers, oxytocin was administered according to national guidelines, i.e. low dose
200 oxytocin infusion of less than 4 mUI/min with increments every 30 min, without exceeding a
201 20 mUI/min flow rate.⁸

202 ***Randomization***

203 Before a cervical dilation of 6cm, participants were randomly assigned using a 4-size
204 permuted block randomization with a 1:1 ratio to either discontinuous oxytocin or
205 continuous with the use of a computer-generated randomization sequence. Randomization

206 was stratified on the center and parity (nullipara/multipara). The randomization procedure
207 was carried out in the labor ward by either the midwife or the obstetrician which were
208 certified in Good Clinical Practice (GCP) for research, online via the CleanWeb® interface
209 accessible 24 hours online.

210 ***Procedures***

211 The trial information was initially delivered to participants before labor during their
212 last prenatal visits, as well as during outpatient clinic visits and birth preparation classes.
213 Additionally, posters were displayed in waiting rooms, emergency rooms, and the outpatient
214 clinic to disseminate information. Further screening and informed consent took place during
215 labor induction or the onset of spontaneous labor in the labor ward. The informed consent
216 was signed before inclusion, typically after the onset of oxytocin perfusion.

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

221 After randomization, in the discontinuous group, oxytocin infusion was stopped
222 beyond a cervical dilation equal to or greater than 6cm. If necessary, caregivers were
223 instructed that oxytocin could be re-started after 2 hours of labor arrest (no progression of
224 the cervical dilation and/or no progression of the fetal head). In the control group, oxytocin
225 was continued during the active phase and during the 2nd stage. If necessary, it could be
226 stopped because of an abnormal FHR or uterine tachysystole.

227 To prevent any cross-contamination between the groups and ensure adherence to
228 the allocated treatment, we prospectively monitored the total dose and duration of oxytocin

229 administration for every 20 included participants in each participating center. This
230 monitoring process was conducted by an independent trial monitoring team.

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

233 **Outcomes**

234 The primary outcome was neonatal morbidity assessed at birth using a composite variable
235 defined by an umbilical arterial pH at birth <7.10 and/or a base excess $>10\text{mmol/L}$ and/or
236 umbilical arterial lactates $>7\text{ mmol/L}$ and/or a 5-minute Apgar score <7 and/or admission in
237 neonatal intensive care unit (NICU). This composite outcome allowed for the evaluation of
238 neonatal morbidity potentially associated with uterine tachysystole induced by oxytocin,
239 which may lead to respiratory, metabolic, or mixed acidosis and clinical implications
240 necessitating NICU admission. Each criterion represents neonatal morbidity and is
241 recognized as an indicator of adverse outcomes. The chosen thresholds are commonly
242 reported in the literature for assessing neonatal acidosis at birth.²³⁻²⁵ No specific cord
243 clamping recommendations were specified in the trial protocol.

244 Secondary outcomes included neonatal pre-acidosis, acidosis and its severity (defined
245 as umbilical arterial cord pH at birth <7.20 , < 7.10 and 7.00 and need for hypothermia for
246 neuroprotection), other neonatal complications (need for resuscitation at birth, admission to
247 NICU and length of hospital stay in NICU) mode of delivery (spontaneous delivery,
248 instrumental vaginal or cesarean delivery) and indication (rates for cesarean delivery and
249 instrumental delivery for abnormal fetal heart rate), course of labor characteristics (such as
250 median active phase duration, defined as duration from 6cm to full dilation, second stage
251 and active phase to delivery duration, defined as duration from 6cm to delivery; occiput-
252 posterior presentation at delivery, and occurrence uterine tachysystole defined by periods

253 with more than five uterine contractions in 10 minutes or hypertonus requiring medical
254 treatment), maternal fever during labor (defined as a maternal temperature $>38^{\circ}\text{C}$), and
255 post-partum hemorrhage (defined as an estimated blood loss >500 mL regardless of the
256 mode of delivery). The assessment of uterine tachysystole, as well as the monitoring of
257 oxytocin doses and the reasons for treatment discontinuation or resumption, were
258 documented using a specific sheet designed for this purpose.

259 Women's birth experience was evaluated at day 2 postpartum using the Labor
260 Agency Scale (LAS), where higher scores indicate a greater sense of control during the
261 birthing process.²⁶ Additionally, at 2 months postpartum, women's well-being was assessed
262 using the Edinburgh Postnatal Depression Scale (EPDS)²⁷. These assessments were
263 conducted through email. A rate of score >12 on the EPDS is indicative of a higher likelihood
264 of experiencing depressive symptoms of varying severity.²⁷

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

272 ***Sample size calculation***

273 Sample size calculations were based on estimated effect of discontinuous oxytocin on
274 neonatal morbidity. In a prospective population-based cohort study conducted in France in
275 2015, among women receiving oxytocin under standard care, 8% of neonates had at least

276 one criterion of the primary endpoint of the current trial.²⁸ We hypothesized a clinically
277 relevant decrease from 8% in the control group (i.e. standard care) to 5% in the
278 discontinuous oxytocin group, representing a 3% absolute difference in the neonatal
279 morbidity rate (RR = 0.62, 95%CI[0.45–0.86]). To calculate the required sample size, we used
280 a two-sided test with a power of 80% and a significance level of 0.05, along with Yates'
281 continuity correction. We considered an allocation ratio of 1:1 between the discontinuous
282 oxytocin group and the control group. Thus, the total sample size required was 2250
283 participants (1125 in each group). To ensure adequate power and account for potential
284 dropouts due to cesarean deliveries before reaching 6 cm dilation (preventing participants
285 from receiving the studied intervention), the protocol provided for an increase the required
286 sample size by 10% in each group (225 participant in total), bringing the total required
287 sample size for inclusion in the study to 2475 women.

288 Statistical analysis

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

299 Despite the intervention aiming to reduce medicalization of labor, we defined a safety
300 population as reducing an intervention may also have adverse effects. This safety population
301 included all participants from the mITT population, with participants divided into
302 discontinuous and control groups based on their actual experience during active phase of
303 labor. Participants who had a discontinuation of oxytocin and a restart during labor were
304 considered in the discontinuous group to assess any potential adverse outcomes related to
305 the reduction of oxytocin usage.

306 The baseline maternal and pregnancy characteristics of the trial participants were
307 described with qualitative variables expressed as proportions and quantitative variables as
308 medians with interquartile ranges (IQR). The two-sided 95% confidence intervals (CIs) for the
309 primary outcome were computed using the Wilson method. The comparison of the primary
310 and secondary outcomes between the randomized groups was performed using the relative
311 risk (RR) for binary variable, or the median difference for quantitative variables, along with
312 their 95%CI. The two-sided 95% CIs for the RR were computed using the log-binomial
313 regression model, and bootstrapping was employed for the median difference. Additionally,
314 for the primary outcome the absolute difference between the two groups was calculated,
315 and its 95% CI was also determined.

316 Two preplanned subgroup analyses were performed: according to the mode of onset of
317 labor (induced or spontaneous), and according to parity (nullipara or multipara). For these
318 subgroup analyses, we used the same statistical methods as the main analysis and compared
319 primary and secondary outcomes. The same analyses were also repeated in the ITT
320 population and per-protocol population. For the safety analysis we reported the proportions
321 of occurrence of the severe and unexpected adverse events and compared them between
322 the two groups using the risk difference with its 95%CI using Wilson's method.

323 Our statistical analysis plan did not include a plan to adjust for multiple comparisons
324 of secondary outcomes or subgroup. Across the entire trial population, missing data were
325 observed in less than 1% of cases. Given the negligible amount of missing data and its
326 distribution across both study arms we did not conduct the planned sensitivity analyses to
327 explore the effects of missing data.

328 All tests were bilateral with a significance level of 5%. All analyses were performed using SAS
329 software, V9.4.2 and R software (version 3.5).

330 ***Role of the funding source***

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

333 **Results**

334 Between January 13, 2020, and January 24, 2022, a total of 2493 participants were
335 included, 34 participants were not randomized due to eligibility criteria errors or other
336 reasons (n=33) or because they declined to participate (n=1) and 2459 were randomly
337 assigned to discontinuous or continuous oxytocin in the active phase of labor. A total of 92
338 (3.7%) randomized participants were excluded because they did not meet randomization
339 criteria. Of the remaining 2364, 194 (7.9%) underwent cesarean delivery before reaching a
340 cervical dilation of 6cm which resulted in a modified intention-to-treat population of 2173
341 participants (1067 in the discontinuous oxytocin group and 1103 in the control group)
342 (Figure1).

343 The two groups were well balanced with respect to baseline characteristics, with a
344 good contrast in terms of total duration of oxytocin use and total dose received (Table 1 and
345 2). According to study protocol, in the discontinuous oxytocin group, oxytocin was restarted
346 in 40.5% of the cases, and in the control group, oxytocin was stopped in 5.3% of the cases
347 (Table 2).

348 There was no clinical or statistical difference between the two groups of the mITT for
349 the primary outcome. The observed percentage of neonatal morbidity was 9.6%,
350 95%CI(7.9;11.5) in the discontinuous oxytocin group and 9.2%, 95%CI(7.6;11.0) in the control
351 group, absolute difference 0.004, 95%CI(-0.021;0.029), RR = 1.0, 95%CI(0.8 to 1.4) (Table 3).
352 Apgar score and admission to NICU were available for all participants, and cord pH was
353 available for 98% of participants. Base excess and lactate levels were not measured in all
354 centers; when the variable was not available, it was considered a missing data item.

355 There were no statistically significant differences between the two groups for the
356 rates of neonatal secondary outcomes (Table 3). No statistically significant differences were

357 observed in the mode of delivery, with a cesarean delivery rate of 10.7% (114/1067) in the
358 discontinuous oxytocin group and 9.9% (109/1103) in the control group, RR= 1.1 95%CI(0.8
359 to 1.3). Participants in the discontinuous oxytocin group had a statistically significant longer
360 median active phase, median second stage and median active phase to delivery durations
361 than participants in the control group, respectively for active phase, second stage and active
362 phase to delivery durations, 100 minutes (50 to 208) vs 90 minutes (45 to 150), median
363 difference 10.0 (0.0 to 16.0); 120 minutes (33 to 184) vs 83 minutes (23 to 166), median
364 difference 37.0 (21.0 to 51.0) and 244 minutes (122 to 386) vs 197 (93 to 317), median
365 difference 47.0 (24.0 to 65.5). Uterine tachysystole was statistically significantly less
366 frequent in the discontinuous oxytocin group compared to the control group (6.3% (62/978)
367 vs 10.4% (106/1019), RR 0.6 (0.4 to 0.8)) (Table 3).

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

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

378 The results of the analyses in the ITT population and the per-protocol population
379 yield similar results and are presented in Table S6 to S11.

380 The safety analysis showed no significant differences between the groups in serious adverse
381 events and unexpected adverse events (Table 4).

382 **Discussion**

383 Discontinuous oxytocin in the active phase of labor did not demonstrate a statistically
384 significant impact on neonatal morbidity, mode of delivery or postpartum hemorrhage.
385 However, participants in the discontinuous oxytocin group did experience longer active
386 phase, second stage and active phase to delivery durations .

387 Previous studies have suggested a potential benefit of discontinuous oxytocin in
388 reducing the risk of neonatal morbidity and acidosis, but none were powered specifically for
389 these outcomes.^{20,21,29-31} In contrast, our study was specifically designed to evaluate these
390 outcomes. Most previous studies focused on labor duration or mode of delivery and had
391 relatively small sample sizes ranging from 100 to 342 participants. These studies were
392 included in a meta-analysis which reported statistically significantly lower cesarean delivery
393 rates with discontinuous oxytocin compared to continuous oxytocin (n=1784, OR 0.69;
394 95%CI(0.56;0.86)), but longer active phase durations (n=1336, mean difference 25.57
395 minutes; 95%CI(5.28;45.87)).²⁰ Our study showed conflicting results regarding the effect of
396 oxytocin regimen on cesarean delivery rates, with a non-statistically significant higher rate of
397 cesarean delivery among participants included in the discontinuous oxytocin group.
398 However, our findings are consistent with a recent Danish trial including 1198 induced
399 women, that was not included in the meta-analysis cited above, which found no significant
400 differences between continuous and discontinuous oxytocin on the cesarean delivery rates
401 OR 1.17; 95%CI[0.90,1.53].³¹ These recent results, along with our own, contribute to the
402 growing body of literature indicating that discontinuous oxytocin may not decrease the risk
403 of cesarean delivery.

404 The reduction of uterine tachysystole in the discontinuous oxytocin group of our trial
405 is consistent with previous published studies but, interestingly does not translate in a
406 reduction of neonatal acidosis.^{20,31} This finding suggests that the relationship between
407 uterine tachysystole and adverse neonatal outcomes may not be straightforward, and that
408 other factors may play a role in determining neonatal outcomes. It is important to highlight
409 that personalized medicine approaches are already being implemented, where oxytocin flow
410 rate is adjusted based on uterine tachysystole and/or abnormal FHR patterns. However, in
411 multiparous women, despite comparable rates of uterine tachysystole between the groups
412 of discontinuous and continuous oxytocin, discontinuation of oxytocin was associated with a
413 statistically significant increase in neonatal morbidity, albeit not clinically significant. This
414 highlights the need for individualized care and consideration of patient-specific factors in
415 obstetric practice.

416 This trial is the largest trial comparing discontinuous and continuous oxytocin and
417 was specifically powered to evaluate neonatal morbidity. It involved participants from 21
418 different centers, increasing its external validity especially since French guidelines regarding
419 oxytocin infusion are similar to most international guidelines.^{4,8,9,32} The study was conducted
420 using strict inclusion and exclusion criteria.

421 This trial has some limitations. The decision to opt for an open-label design was
422 driven by practicality, as frequent un-blinding could have posed challenges during active
423 labor when timely decisions were crucial. Previous studies showed that during the active
424 phase of labor, 30 to 40% of the women with a discontinued administration of oxytocin
425 required a re-start of oxytocin.^{21,33} In situation with non-reassuring FHR (up to 8% of the
426 women in Saccones' metanalysis¹⁹), knowing the treatment group is important for the

427 obstetrician to make informed decisions regarding oxytocin infusion to reduce uterine
428 contractility. However, the open-label design might have influenced health care provider's
429 management decisions during labor, inadvertently introducing bias into the study outcomes.
430 This bias could potentially manifest in various directions, as healthcare providers who were
431 aware of the treatment allocation might have altered their clinical practices based on this
432 knowledge. For instance, in the discontinuous group, the obstetric team might have
433 resumed the treatment if they perceived inadequate progress, even though the labor was
434 indeed advancing, albeit slowly. Conversely, in the continuous oxytocin group, a lack of
435 escalation in oxytocin dosage might have been more frequent due to the obstetric team's
436 increased attention to contraction frequency, thereby also reducing the contrast between
437 the two groups and increasing the risk of not detecting a statistically significant difference
438 between the groups. However, rigorous data collection and monitoring procedures were
439 implemented, and protocol reminders were carried out to mitigate this risk. Thus, the
440 contrast between the two groups remained observable, preserving the interpretability of our
441 findings.

442 The fact that oxytocin was restarted in a significant proportion of cases in the discontinuous
443 oxytocin group could have contributed to the lack of outcome differences between the two
444 groups. The rate of restarting oxytocin in the discontinuous group aligns with findings from
445 previous studies,^{20,21,31} and further investigation is needed to better understand its
446 implications in clinical practice.

447 Although compliance rates were generally high (93.4% in the discontinuous group and 99.2%
448 in the control group), the lack of blinding might have influenced compliance rates to some
449 extent. Non-compliance, reflecting real-life situations, may have reduced the intervention's

450 contrast. However, the per-protocol analysis refutes this hypothesis, demonstrating no
451 difference between the groups for primary and secondary outcomes.

452 The study did not reach the initially targeted sample size of 2250 participants, and
453 instead, analyzed 2170 participants. While the smaller sample size could have affected the
454 study's statistical power to detect smaller effect sizes, it is essential to emphasize that the
455 observed effect size and the corresponding confidence intervals provide robust evidence for
456 the lack of a clinically significant difference in neonatal morbidity between the discontinuous
457 oxytocin and control groups. Our study remains the largest and most comprehensive
458 investigation on the impact of discontinuous oxytocin on neonatal morbidity.

459 Our study focused on neonatal outcomes as the primary endpoint, but we recognize
460 the interdependence between neonatal and maternal outcomes when discontinuing
461 oxytocin during the active phase of labor. The well-being of both the newborn and the
462 mother is intricately linked during the labor and delivery process. Therefore, it is essential to
463 also consider the impact of our intervention on maternal outcomes, such as the duration of
464 the active phase and mode of delivery, as these factors may indirectly influence neonatal
465 health.

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

471 Further research should explore the heterogeneity of responses to oxytocin among
472 women. It is plausible that individual variations, encompassing genetic predispositions,

473 hormonal profiles, and obstetric and medical history, contribute to divergent outcomes.
474 Identifying these factors could pave the way for targeted interventions, where
475 discontinuation of oxytocin is strategically implemented for specific groups of women who
476 are more likely to benefit. Moreover, investigating patient-centered outcomes such as
477 maternal satisfaction, and long-term neonatal development in the context of these
478 personalized approaches could provide a more comprehensive understanding of the impact
479 of discontinuing oxytocin.

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

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

491 **Declarations**

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497 interpretation of data and in writing the manuscript.

498

499 **Authors' contributions**

500 AG: conceived the study and participated in the project design, obtained the funding,
501 drafted the manuscript, and approved the final manuscript

502 CLR: conceived the study and participated in the project design, obtained the funding, read,
503 edited, and approved the final manuscript.

504 JR: performed the statistical analyses, edited and approved the final manuscript

505 LS, RD, PB, DK, CB, JC, NW, EV, EB, TB, GL, GER, GK, MM, CB, PG, EA, JB, HH, JR, CG: read,
506 edited and approved the final manuscript.

507

508 **Declaration of interests:**

509 - Loïc Sentilhes has carried out consultancy work and been a lecturer for Ferring
510 Laboratories, GlaxoSmithKline and Bayer, and been a lecturer for Norgine in the
511 previous 3 years.

512 - Paul Berveiller has acted as consultant for Ferring, General Electric Medical System,
513 Norgine, Becton Dickinson.

514 - Charles Garabedian has carried out consultancy work for Bioserinity, and been a
515 lecturer for General Electrics and Bayer in the previous 3 years.

516 - Norbert Winer has been a lecturer for Roche Diagnostic.

517 The other authors do not report any potential conflicts of interest.

518

519 **Data sharing**

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

523

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621 [women-and-babies-pdf-35109866447557](https://www.nice.org.uk/guidance/cg190/resources/intrapartum-care-for-healthy-women-and-babies-pdf-35109866447557)
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