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Pauline Blanc-Petitjean, H el ene Legardeur, G eraldine Meunier, Laurent Mandelbrot, Camille Le Ray, Gilles Kayem

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## **Title page**

### **Title**

Evaluation of the implementation of a protocol for the restrictive use of oxytocin during spontaneous labor

### **Short title**

Oxytocin restrictive use and spontaneous labor

### **Authors**

Pauline Blanc-Petitjean<sup>a,b</sup>, H el ene Legardeur<sup>b</sup>, G eraldine Meunier<sup>a,b</sup>, Laurent Mandelbrot<sup>b</sup>,  
Camille Le Ray<sup>a,c</sup>, Gilles Kayem<sup>a,d</sup>

### **Affiliations**

<sup>a</sup> Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOP e), Centre for Epidemiology and Statistics Sorbonne Paris Cit e (CRESS), DHU Risks in pregnancy, 75014, Paris, France

<sup>b</sup> Assistance Publique-H opitaux de Paris, Louis Mourier Hospital, Department of Obstetrics and Gynecology, DHU Risks in pregnancy, 92700, Colombes, France

<sup>c</sup> Assistance Publique-H opitaux de Paris, Cochin Hospital, Port Royal Maternity Unit, DHU Risks in Pregnancy, 75014, Paris, France

<sup>d</sup> Assistance Publique-H opitaux de Paris, Trousseau Hospital, Department of Obstetrics and Gynecology, 75012, Paris, France

**Corresponding author:** Pauline Blanc-Petitjean

Inserm UMR1153, EPOP e team

Port-Royal Maternity– 6<sup>th</sup> floor

53 avenue de l'Observatoire, 75014 Paris, France

Tel: +33-1-42-01-55-70 / +33-6-63-23-28-63 - Fax: +33-1-43-26-89-79

E-mail: pauline.blanc-petitjean@inserm.fr

1 Evaluation of the implementation of a protocol for the restrictive use of oxytocin during spontaneous  
2 labor

### 3 **Abstract**

4 **Introduction:** Use of oxytocin is associated with uterine hyperstimulation and postpartum  
5 hemorrhage with a dose-dependent effect. We aimed to evaluate the effect of the  
6 implementation of a protocol for the restrictive use of oxytocin during spontaneous labor on  
7 obstetric and neonatal outcomes.

8 **Material and methods:** We performed an observational before-and-after study among 2174  
9 women in spontaneous labor with a term singleton cephalic fetus. Obstetric and neonatal  
10 outcomes were compared according to the period, before (period A) and after (period B) the  
11 implementation of a protocol for the restrictive use of oxytocin.

12 **Results:** 1235 women were included in period A and 939 in period B. Compared to period A,  
13 the use of oxytocin during period B was significantly lower (45.5 vs. 35.1%,  $p < 0.001$ ) in  
14 both nulliparous (61.2 vs 54.6%,  $p = 0.04$ ) and multiparous women (34.0 vs. 21.1%,  $p < 0.001$ ).  
15 Labor was significantly longer in period B, both in nulliparous (6.7 vs. 7.9 h,  $p < 0.01$ ) and  
16 multiparous women (4.1 vs. 4.5 h,  $p < 0.01$ ). A lower frequency of uterine hyperstimulation  
17 (6.6 vs. 2.7%,  $p = 0.01$ ) was observed in period B. The odds of instrumental and cesarean  
18 delivery were not different between the periods (respectively adjusted odds ratio (AOR), 95%  
19 confidence interval (CI), 1.1(0.8-1.4); 1.2(0.8-1.8)) including for nulliparous women  
20 (respectively, 1.3(0.9-1.7); 1.3(0.8-1.9)).

21 **Discussion:** Reducing the use of oxytocin during spontaneous labor through the  
22 implementation of a protocol may reduce the iatrogenic effects without increasing the risk of  
23 caesarean section but this implies longer duration of labor.

24 **Key words:** Oxytocin, spontaneous labor, augmentation of labor, prolonged labor, cesarean,  
25 monitoring protocol.

26 **Main text**

## 27 **Introduction**

28 Synthetic oxytocin has been used in obstetrics since the 1950s to stimulate uterine  
29 contractility for induction or augmentation of labor [1]. Its use for augmentation of labor has  
30 spread through Friedman's work on the curves of normal dilation of labor, with wide  
31 variations between 20% and 70% of women in spontaneous labor [2, 3]. In France, oxytocin  
32 was used for 58% of women in spontaneous labor in 2010 and 71% of women in spontaneous  
33 labor with epidural analgesia at low obstetrical risk [4]. These rates may be excessive since  
34 they are higher than reported in other European countries such as the United Kingdom, the  
35 Netherlands, Denmark or Sweden, where the rates are between 20 and 30% [5-8].  
36 In case of spontaneous labor, the use of oxytocin reduces significantly the length of labor, but  
37 its systematic use has not been shown to reduce the rates of cesarean sections [9-11]. In  
38 addition, recent studies have shown an association with a dose-dependent effect between the  
39 use of oxytocin and tachysystole, ie. the occurrence of uterine hyperstimulation causing fetal  
40 heart rate (FHR) abnormalities [11-14] and of postpartum hemorrhage (PPH) [15-17].  
41 Oxytocin has thus been added to the list of potentially high-risk medication by the Institute for  
42 Safe Medication Practices, requiring precautions and a standardization of practices to reduce  
43 its use and limit iatrogenic effects [18].  
44 Failure to progress is also the most frequent indication of cesarean during labor and the  
45 increase in cesarean sections over the past 20 years, particularly in nulliparous women, is a  
46 major public health problem [19-21]. Currently recommended labor dilatation curves consider  
47 longer normal durations of first stage and also second stage of labor than previously [22-25].  
48 Given these findings, the management of spontaneous labor should be optimized based on  
49 reasonable intervention thresholds which could reduce the use of oxytocin without increasing  
50 rates of cesarean sections for labor arrest. The objective of this study was to evaluate the

51 effect of the implementation of a protocol for restrictive use of oxytocin during spontaneous  
52 labor on obstetric and neonatal outcomes.

### 53 **Material and methods**

54 We performed a comparative, before and after, single center observational study. The study  
55 was carried out in a type III university maternity hospital in the Assistance Publique-Hôpitaux  
56 de Paris, performing approximately 3,300 deliveries per year. We included in the study all  
57 women in spontaneous labor without a history of cesarean section and with a singleton live  
58 term cephalic fetus. The protocol restricting the use of oxytocin was introduced on 1st May  
59 2012 and we compared two periods, period A, before the protocol was established, from 1st  
60 November 2010 to 1st November 2011, and period B, after the protocol was put in place,  
61 from 1st May 2012 to 31st December 2012.

62 The protocol was established by a multidisciplinary working group, as routine care in the  
63 department after discussion of the available literature on the use of oxytocin. Prior to this, no  
64 protocol existed, and the administration of oxytocin was left to the practitioner's discretion.

65 The protocol recommended oxytocin infusion in the first stage of labor in case of arrested  
66 dilation for over 1 hour with ruptured membranes, with artificial rupture of the membranes to  
67 be performed before starting oxytocin, or in the second stage of labor for failure to progress  
68 over 1 hour. Oxytocin could be stopped or the doses halved in case of satisfactory  
69 progression. It should be noted that a slow progression (less than 1 cm / h) was not considered  
70 as an indication for the use of oxytocin. Beyond the latency phase (cervical dilatation greater  
71 than or equal to 5 cm at the time of our study), cesarean section was considered during the  
72 first stage after 2 hours of non-progression after obtaining four uterine contractions per 10  
73 minutes, of which at least 1 hour under oxytocin. A maximum of 4 hours of arrested dilatation  
74 was tolerated. In the second stage, pushing was to be started at the latest after 3 hours of  
75 which 1 hour under oxytocin. When women were already receiving oxytocin, pushing had to

76 start 2 hours after the diagnosis of complete dilatation. There was no differential treatment  
77 depending on whether the women were nulliparous or multiparous or whether they had an  
78 epidural.

79 The majority of data were entered prospectively by midwives in the computerized patient  
80 charts at the time of delivery. When not recorded, doses and indication of oxytocin during  
81 labor were extracted from women's medical records. Cardiotocographic records were also  
82 systematically checked to analyze FHR and uterine contractility.

83 The effect of setting up the restrictive oxytocin use protocol was assessed by comparing  
84 population characteristics between period A and period B. The primary outcome measure was  
85 the mode of delivery (spontaneous, instrumental or cesarean delivery).

86 The administration of oxytocin, its indication, dilatation at the beginning of the infusion, the  
87 total dose, the maximum flow and the cessation of the infusion were compared before and  
88 after the implementation of the protocol. Oxytocin indications which were accepted in the  
89 protocol were labor arrest in first stage, lack of engagement of the vertex after complete  
90 dilatation, or occiput posterior position. All the other reasons given, in particular insufficient  
91 uterine activity without any failure to progress, were classified as not being an indication for  
92 the use of oxytocin. The following obstetric outcomes were also evaluated according to the  
93 period: duration of labor, epidural anesthesia, uterine hyperstimulation during labor,  
94 tachysystole, ie hypertonia and / or uterine hyperkinesia associated with abnormal FHR,  
95 indication of cesarean section (failure to progress, abnormal FHR, other), postpartum  
96 hemorrhage (total blood loss greater than 500 mL), severe postpartum hemorrhage (total  
97 blood loss greater than 1000 mL) and transfusion of blood products. For neonatal  
98 characteristics, birthweight, cord pH <7.10, Apgar score at 5 minutes of life <7, and neonatal  
99 hospitalization were compared between the two periods.

100 We calculated the sample size to achieve a power of 90% with an alpha risk of 0.05, assuming  
101 a 10% to 6% reduction in uterine hyperstimulation rate from period A to period B. Under  
102 these assumptions, the calculated total sample size was 2028 women (ratio=1/1).  
103 Population characteristics, oxytocin administration, and obstetric and neonatal outcomes were  
104 compared between the two periods in univariate analysis with Chi2 tests for categorical  
105 variables and Student or Mann Whitney (non normal distribution) test for continuous  
106 variables. A category of missing data has been created if they exceeded 5%. The association  
107 between protocol implementation and the risk of instrumental delivery and cesarean section  
108 was assessed using a multivariate logistic regression model. The analysis was adjusted for  
109 potential confounders such as parity, geographical origin, body mass index (BMI), maternal  
110 age, gestational age, and birtheight. The log-linearity was acceptable for all continuous  
111 variables. No interaction was founded. Analyses were stratified on parity (primiparous,  
112 multiparous). Statistical significance was set at 0.05. The statistical analyses were performed  
113 with the Stata software (version 12.1 SE, Stata Corporation, College Station, TX).

## 114 **Results**

115 A total of 2174 women were included, including 1235 in period A (before the implementation  
116 of the protocol) and 939 in period B (after the implementation of the protocol). Of these, 42%  
117 were nulliparous. The characteristics of women and newborns were comparable between the  
118 two periods (Table 1).

119 The modalities of oxytocin use by period are shown in Table 2. Compared to period A, the  
120 use of oxytocin during period B was significantly lower (45.5 vs. 35.1%,  $p < 0.001$ ) in both  
121 nulliparous (61.2 vs 54.6%,  $p = 0.04$ ) and multiparous (34.0 vs. 21.1%,  $p < 0.001$ ). Among  
122 women who received oxytocin, the main indication was labor arrest in first stage in both  
123 periods, and the proportion of women who received oxytocin in the absence of a medical  
124 indication was lower in period B (26.7 vs. 16.7%,  $p < 0.01$ ). The total dose of oxytocin

125 received during labor was lower in period B in nulliparous (1016 vs. 708 mIU,  $p = 0.01$ ) as  
126 the maximum infusion rate (6.7 vs. 5.0 mIU / min,  $p < 0.001$ ). In period B, oxytocin infusion  
127 was more often stopped during labor (19.8 vs. 37.9%) and when discontinued, it was less  
128 often for FHR abnormality (87.4 vs. 43.2%) and more often for improved progression of labor  
129 (11.7 vs. 54.4%), ( $p < 0.01$ ).

130 The comparison of outcomes by period is shown in Table 3. Labor was significantly longer in  
131 period B, both in nulliparous (6.7 vs. 7.9 h,  $p < 0.01$ ) and in multiparous women (4.1 vs. 4.5 h,  
132  $p < 0.01$ ). The rates of instrumental delivery were not different between the two periods (19.7  
133 vs 21.1%,  $p = 0.4$ ), except for nulliparous women (39.5 vs. 46.5%,  $p = 0.04$ ). The rates of  
134 cesarean delivery were not different between the periods (5.2 vs. 6.7%,  $p = 0.1$ ) including for  
135 nulliparous women (10.0 vs. 13.7 %,  $p = 0.08$ ). Cesarean section in period B was more often  
136 indicated for labor arrest (46.0 vs. 68.3%) than for abnormal FHR (49.2 vs. 30.2%,  $p = 0.04$ ).  
137 During labor, a lower frequency of uterine hyperstimulation was observed in period B (6.6 vs.  
138 2.7%,  $p = 0.01$ ). The incidence of arterial cord pH lower than 7.10 was lower in period B than  
139 in period A (6.2 vs. 3.1%, respectively,  $p < 0.001$ ), but no difference was observed on 5-min  
140 apgar score  $< 7$  and neonatal hospitalization. There was no difference by period in PPH.

141 In multivariate analysis, no significant association was found between the mode of delivery  
142 and the period, including for nulliparous women (adjusted odds ratio (AOR), 95% confidence  
143 interval (95% CI) respectively for instrumental and cesarean delivery, 1.3 (0.9-1.7) and 1.3  
144 (0.8-1.9)).

## 145 **Discussion**

146 After the implementation of the protocol for the restrictive use of oxytocin during  
147 spontaneous labor, oxytocin administration and doses significantly decreased. There were also  
148 less uterine hyperstimulation and cesarean delivery for FHR abnormalities. Longer labor were

149 observed especially in nulliparous women, without an increase in instrumental or cesarean  
150 deliveries.

151 Our study has a number of limitations. The retrospective nature and the before-after design of  
152 our study do not make it possible to establish a direct causal link between the evaluated  
153 protocol and the differences observed between the two periods. Being a single-study can be  
154 considered as a limit, but also as a strength because it ensures practices that are homogeneous  
155 over each of the study periods. Another limit was the time necessary for the team to adopt the  
156 protocol after its implementation. Indeed, 16.7% of women still received oxytocin without  
157 indication during the second period.

158 The main strength of the study was the quality of the data, with the precise oxytocin doses  
159 and rates prospectively collected by the midwife in charge of the parturient and careful review  
160 of each medical record by a single investigator. Furthermore, all cases of labor induction were  
161 excluded, allowing for the specific study of augmentation of labor with oxytocin.

162 Our study is part of a current reflection on the use of oxytocin during spontaneous labor,  
163 whose very wide administration has for many years been guided by the standards of dilatation  
164 curves set by Friedman in the 1950s [3]. These historically imposed demands for labor  
165 progression no longer seem appropriate as the characteristics of women, BMI and maternal  
166 age in particular, and medical practices, including the use of epidural analgesia, have evolved  
167 [22-25].

168 The definition of the stages of labor and the use of oxytocin during spontaneous labor has  
169 been the subject of recent recommendations for the prevention of the first cesarean section  
170 [19, 26]. These advocate that the latency phase cannot be subjected to a maximum duration  
171 and that the diagnosis of failure to progress and the use of oxytocin should not occur before 5-  
172 6 cm dilatation (i.e. beginning of the active phase of labor). They also consider that slow  
173 progression of the first stage of labor does not constitute an indication for cesarean section. In

174 our study, for almost 60% of women, oxytocin was started before 6 cm of cervical dilation in  
175 both study periods, but data were collected before the publication of these recommendations.  
176 Our study showed a significant decrease in uterine hyperstimulation with restricted use of  
177 oxytocin. This result was expected since the use of low doses of oxytocin, the increasing of  
178 durations between two levels of flow rates and the possibility of stopping the perfusion in case  
179 of good progression have been shown to be associated with a lower occurrence of uterine  
180 hyperstimulation [11, 27-29].

181 Neonatal outcomes also appeared better with fewer pH below 7.10. However, this result  
182 should be interpreted with caution due to a large number of missing pH data and possible  
183 information bias. Indeed, according to changes in local protocols, in period A, cord pH was  
184 indicated only in case of FHR abnormalities or situations at increased risk of fetal acidosis,  
185 whereas in period B it was to be performed systematically. However, the chosen pH threshold  
186 (<7.10) is particularly low. So it is unlikely that many cases of acidosis would have remained  
187 undiagnosed in period A. For the others adverse neonatal outcomes, our study probably  
188 lacked the power to show significant differences.

189 Regarding the risk of PPH, no difference was found following the restriction of the use of  
190 oxytocin. The rate of moderate PPH was similar to that of 6.4% observed in the French  
191 multicentre study Pithagore 6 in 2005 [30]. In addition, the doses administered during the two  
192 periods of the study were much lower than those reported by Belghiti et al. [16] in their case-  
193 control study which showed an increased risk of severe PPH at higher maximum doses of  
194 4000 mIU and flow rates above 15 mIU/ min. These results may seem contradictory but  
195 prolonged labor is also a risk factor for PPH and our results clearly show that limiting the use  
196 of oxytocin results in prolonged labor.

197 The issue of reducing the use of oxytocin is part of the complex debate on the physiological  
198 duration of labor. Restricting the use of oxytocin without increasing the rate of cesarean

199 section means accepting longer phases of stagnation and longer labor. Evaluation of the  
200 impact of recent recommendations on labor management and use of oxytocin will be needed  
201 to assess maternal and neonatal benefits and risks. Our findings that restrictive use of oxytocin  
202 during labor seemed to decrease iatrogenic effects without increasing the risk of cesarean  
203 delivery should encourage other teams to establish local protocols to limit the use of oxytocin  
204 and to evaluate their results.

205

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214 **Contribution to authorship:** All authors have made substantial contributions to the  
215 conception and design of the study, or acquisition of data, or analysis and interpretation of  
216 data; drafting the article or revising it critically for important intellectual content; final  
217 approval of the version to be submitted.

218

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**Table 1: Comparison of women and neonatal characteristics by period**

<b>Period<sup>a</sup></b>	<b>Period A (n=1235)</b>	<b>Period B (n=939)</b>	<b><i>p</i></b>
<b>Maternal age (y)</b>			0.6
<20	21(1.7)	18(1.9)	
20-34.9	952(77.1)	701(74.7)	
≥ 35	234(19.0)	189(20.1)	
<b>Geographic origin</b>			0.7
Europe	464(37.6)	332(35.4)	
North Africa	479(38.8)	379(40.4)	
Subsaharian Africa	139(11.3)	114(12.1)	
Other	131(10.6)	97(10.3)	
<b>BMI, kg/m<sup>2</sup></b>			0.08
<18.5	33(2.7)	21(2.2)	
18.5-24.9	769(62.3)	578(61.6)	
25-29.9	287(23.2)	252(26.8)	
≥30	121(9.8)	69(7.4)	
<b>Nulliparous</b>	521 (42.2)	394 (42.0)	0.9
<b>Gestational age at delivery (WG)</b>			0.09
37 - 38	231(18.7)	142(15.1)	
39-40	807(65.3)	642(68.4)	
≥ 41	197(16.0)	155(16.5)	
<b>Birthweight (g)</b>	3372.6 (± 420.8)	3397.4 (± 425.7)	0.2

Data are reported as n(%) or mean(±standard deviation); <sup>a</sup> Period A: before the implementation of the protocol, Period B: after the implementation of the protocol; BMI, body mass index; WG, weeks of gestation

**Table 2: Comparison of modes of use of oxytocin according to the period**

<b>Period<sup>a</sup></b>	<b>Period A (n=1235)</b>	<b>Period B (n=939)</b>	<b><i>p</i></b>
<b>Oxytocin during labor</b>	562 (45.5)	330 (35 .1)	< 0.001
Nulliparous	319(61.2)	215(54.6)	0.04
Multiparous	243(34.0)	115(21.1)	<0.001
<b>Indication<sup>b</sup></b>			<0.001
Labor arrest in first stage	176(31.3)	188(57.0)	
Lack of engagement of the vertex in second stage	31(5.5)	17(5.2)	
Occiput posterior position	16(2.9)	10(3.0)	
No indication	150(26.7)	55(16.7)	
<i>missing</i>	<i>189(33.6)</i>	<i>60(18.2)</i>	
<b>Dilatation at the onset of oxytocin (cm)<sup>b</sup></b>	5(4 -7)	5(4-8)	0.9
Oxytocin started before 6 cm	320(56.9)	186(57.1)	1.0
<b>Total dose (mIU)<sup>b</sup></b>	638(250-1471)	600(250-1317)	0.2
Nulliparous	1016(412-2070)	708(300-1600)	0.01
Multiparous	350(187-805)	350(160-760)	0.9
<b>Maximum flow (mIU/min)<sup>b</sup></b>	5.0(3.3-8.3)	5.0(3.3-6.7)	<0.001
Nulliparous	6.7(5-10)	5.0(3.3-6.7)	<0.001
Multiparous	5.0(3.3-6.7)	5.0(1.7-8.3)	<0.001
<b>Interruption of the oxytocin infusion<sup>b</sup></b>	111(19.8)	125(37.9)	<0.01
Cause of the interruption			<0.01
Improved progression of labor	13(11.7)	68(54.4)	
Abnormal FHR	97(87.4)	54(43.2)	

Data are reported as n(%) or median(25<sup>th</sup>-75<sup>th</sup> percentile); <sup>a</sup> Period A: before the implementation of the protocol, Period B: after the implementation of the protocol; <sup>b</sup> For women who received oxytocin infusion (n=892); FHR; Fetal heart rate

**Table 3: Comparison of labor characteristics and obstetric and neonatal outcomes according to the period**

<b>Period<sup>a</sup></b>	<b>Period A (n=1235)</b>	<b>Period B (n=939)</b>	<b><i>p</i></b>
<b>Length of labor (h)<sup>b</sup></b>	5.1 (± 2.7)	5.9 (± 3.5)	<0.001
Nulliparous	6.7 (± 2.7)	7.9 (± 3.1)	<0.01
Multiparous	4.1 (± 2.1)	4.5 (± 2.5)	<0.01
<b>Length of labor ≥ 12 h</b>	33 (2.7)	60 (6.4)	<0.01
<b>Epidural analgesia</b>	1027 (83.2)	787 (83.8)	0.7
<b>Instrumental delivery<sup>b</sup></b>	231 (19.7)	185 (21.1)	0.4
Nulliparous	185 (39.5)	158 (46.5)	0.04
Multiparous	46 (6.6)	27 (5.0)	0.3
<b>Cesarean delivery</b>	64 (5.2)	63 (6.7)	0.1
Nulliparous	52 (10.0)	54 (13.7)	0.08
Multiparous	12 (1.7)	9 (1.7)	0.9
<b>Indication for cesarean<sup>c</sup></b>			0.04
Failure to progress	29 (46.0)	43 (68.3)	
FHR abnormalities	31 (49.2)	19 (30.2)	
Other	4 (6.3)	1 (1.6)	
<b>Uterine hyperstimulation<sup>d</sup></b>	37 (6.6)	9 (2.7)	0.01
<b>5-min Apgar score &lt; 7</b>	8 (0.7)	11 (1.2)	0.2
<b>pH &lt; 7.10<sup>e</sup></b>	45 (6.3)	27 (3.1)	<0.001
<i>missing</i>	519 (42.0)	69 (7.4)	
<b>Neonatal hospitalization</b>	12 (1.0)	13 (1.4)	0.4
<b>Postpartum hemorrhage (PPH)</b>			
PPH ≥ 500 ml	89 (7.2)	60 (6.4)	0.5
Severe PPH ≥ 1000 ml	35 (2.8)	31 (3.3)	0.5
Transfusion	4 (0.3)	1 (0.1)	0.3

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Data are reported as n(%) or mean( $\pm$ standard deviation); <sup>a</sup> Period A: before the implementation of the protocol, Period B: after the implementation of the protocol; <sup>b</sup> For women with vaginal delivery, N=1171 in period A and N=876 in period B; <sup>c</sup> For women with cesarean delivery, <sup>d</sup> i.e. uterine hypertonia or hyperkynesia with fetal heart rate abnormalities; <sup>e</sup> For women who had neonatal cord pH.

**Table 4: Association between the implementation of the protocol for the use of oxytocin and the risk of instrumental and cesarean delivery, multivariable model stratified on parity**

Period <sup>a</sup>	Whole population		Nulliparous		Multiparous	
	AOR <sup>b</sup> (IC95%)	<i>p</i>	AOR <sup>c</sup> (95%CI)	<i>p</i>	AOR <sup>c</sup> (95%CI)	<i>p</i>
Spontaneous vaginal delivery	ref		ref		ref	
Instrumental delivery	1.1 (0.8-1.4)	0.6	1.3 (0.9-1.7)	0.09	0.6 (0.4-1.1)	0.09
Vaginal delivery	ref		ref		ref	
Cesarean delivery	1.2 (0.8-1.8)	0.4	1.3 (0.8-1.9)	0.3	1.1 (0.4-2.6)	0.9

<sup>a</sup>Period A: before the implementation of the protocol, as reference, <sup>b</sup>Logistic regression model, adjusted on parity, geographic origin, body mass index, maternal age, gestational age, birthweight. <sup>c</sup>Logistic regression model, adjusted on geographic origin, body mass index, maternal age, gestational age, birthweight. AOR: adjusted odds ratio, CI: confidence interval.