



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

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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

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

Abstract

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

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

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

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

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

Main text

Introduction

Synthetic oxytocin has been used in obstetrics since the 1950s to stimulate uterine contractility for induction or augmentation of labor [1]. Its use for augmentation of labor has spread through Friedman's work on the curves of normal dilation of labor, with wide variations between 20% and 70% of women in spontaneous labor [2, 3]. In France, oxytocin was used for 58% of women in spontaneous labor in 2010 and 71% of women in spontaneous labor with epidural analgesia at low obstetrical risk [4]. These rates may be excessive since they are higher than reported in other European countries such as the United Kingdom, the Netherlands, Denmark or Sweden, where the rates are between 20 and 30% [5-8].

In case of spontaneous labor, the use of oxytocin reduces significantly the length of labor, but its systematic use has not been shown to reduce the rates of cesarean sections [9-11]. In addition, recent studies have shown an association with a dose-dependent effect between the use of oxytocin and tachysystole, ie. the occurrence of uterine hyperstimulation causing fetal heart rate (FHR) abnormalities [11-14] and of postpartum hemorrhage (PPH) [15-17].

Oxytocin has thus been added to the list of potentially high-risk medication by the Institute for Safe Medication Practices, requiring precautions and a standardization of practices to reduce its use and limit iatrogenic effects [18].

Failure to progress is also the most frequent indication of cesarean during labor and the increase in cesarean sections over the past 20 years, particularly in nulliparous women, is a major public health problem [19-21]. Currently recommended labor dilatation curves consider longer normal durations of first stage and also second stage of labor than previously [22-25].

Given these findings, the management of spontaneous labor should be optimized based on reasonable intervention thresholds which could reduce the use of oxytocin without increasing rates of cesarean sections for labor arrest. The objective of this study was to evaluate the

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

Material and methods

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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Table 1: Comparison of women and neonatal characteristics by period

Period^a	Period A (n=1235)	Period B (n=939)	<i>p</i>
Maternal age (y)			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)	
Geographic origin			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)	
BMI, kg/m²			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)	
Nulliparous	521 (42.2)	394 (42.0)	0.9
Gestational age at delivery (WG)			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)	
Birthweight (g)	3372.6 (± 420.8)	3397.4 (± 425.7)	0.2

Data are reported as n(%) or mean(±standard deviation); ^a 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

Period^a	Period A (n=1235)	Period B (n=939)	<i>p</i>
Oxytocin during labor	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
Indication^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>	
Dilatation at the onset of oxytocin (cm)^b	5(4 -7)	5(4-8)	0.9
Oxytocin started before 6 cm	320(56.9)	186(57.1)	1.0
Total dose (mIU)^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
Maximum flow (mIU/min)^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
Interruption of the oxytocin infusion^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(25th-75th percentile); ^a Period A: before the implementation of the protocol, Period B: after the implementation of the protocol; ^b 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

Period^a	Period A (n=1235)	Period B (n=939)	<i>p</i>
Lenght of labor (h)^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
Lenght of labor ≥ 12 h	33 (2.7)	60 (6.4)	<0.01
Epidural analgesia	1027 (83.2)	787 (83.8)	0.7
Instrumental delivery^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
Cesarean delivery	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
Indication for cesarean^c			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)	
Uterine hyperstimulation^d	37 (6.6)	9 (2.7)	0.01
5-min Apgar score < 7	8 (0.7)	11 (1.2)	0.2
pH < 7.10^e	45 (6.3)	27 (3.1)	<0.001
<i>missing</i>	519 (42.0)	69 (7.4)	
Neonatal hospitalization	12 (1.0)	13 (1.4)	0.4
Postpartum hemorrhage (PPH)			
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

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

	Whole population		Nulliparous		Multiparous	
Period ^a	AOR ^b (IC95%)	<i>p</i>	AOR ^c (95%CI)	<i>p</i>	AOR ^c (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

^aPeriod A: before the implementation of the protocol, as reference, ^bLogistic regression model, adjusted on parity, geographic origin, body mass index, maternal age, gestational age, birthweight. ^cLogistic regression model, adjusted on geographic origin, body mass index, maternal age, gestational age, birthweight. AOR: adjusted odds ratio, CI: confidence interval.