Original Article: Oxytocin During Elective Caesarean Section and Risk of Severe Postpartum Haemorrhage

Ramesh Baradaran Bagheri
Assistant Professor of Infertility & IVF, Department of Obstetrics and Gynecology, School of Medicine, Alborz University of Medical Sciences, Alborz, Iran. (Corresponding author ORCID: 0000-0002-9853-6799)

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ABSTRACT

Introduction: The common perception that this treatment has no serious side effects is probably influenced by this flawed evidence. In this large population-based study, our goals were to determine whether there was an independent relationship between the amount of oxytocin exposed during labor and the risk of developing severe PPH and to determine whether the prophylactic use of oxytocin after delivery affected this relationship. **Material and Methods:** women who had straightforward pregnancies and delivered term singletons vaginally. Cases were 1483 women with severe PPH, which was indicated by peripartum hemoglobin changes of less than 4 g/dl or the requirement for blood transfusions. 90 women from a randomly selected group of expectant mothers without PPH served as the controls. Using two-level multivariable logistic regression modeling, the independent relationship between the oxytocin level during labor and the risk of developing severe PPH was examined and quantified with ORs. **Results:** After adjusting for all possible confounders, oxytocin exposure during labor was linked to a higher risk of severe PPH when prophylactic oxytocin was not given after delivery. With more oxytocin injected, the association became stronger. The risk of severe PPH was approximately three times higher for total doses between 2 and 4 IU and six times higher for total doses over 4 IU. **Conclusion:** A separate risk factor for severe PPH appears to be oxytocin during labor. Our findings add to the body of evidence highlighting the need for precautions to reduce maternal complications when oxytocin is used to speed up labor, including strict indications, the use of the lowest effective dose, and careful efficacy evaluation.

Introduction

Obstetric hemorrhage continues to be one of the main causes of maternal mortality in developed nations, accounting for 10% to 30% of direct maternal deaths in nations that conduct maternal death investigations. It plays a significant role in severe maternal morbidity as well [1-3].

Postpartum hemorrhage (PPH) prevalence has recently increased, according to reports from a number of developed nations. When the temporal trends in known risk factors are taken into account, this rise [4-6], which is only seen in immediate/atonic PPH in Australia, Canada, and

Corresponding Author: Ramesh Baradaran Bagheri (R_Baradaran@yahoo.com)

the USA, is still significant. This emphasizes the need for additional research into potential PPH risk factors [7-9].

We concentrated on aspects of labor care because they may influence uterine tone, have changed over time, and can be altered. Oxytocin administration, which is frequently used to initiate or speed up labor, is a strong candidate.

Despite the lack of available data, it appears that oxytocin infusion during labor has become a standard practice in developed nations, which may worry a sizable percentage of expectant mothers—at times even the majority—of the time. This evolution is cause for concern because it suggests that the use of oxytocin has been expanded from narrow to broader but ill-defined indications without a solid evidence-base13 14 or a thorough assessment of its safety, particularly for the risk of PPH [10-12].

This endogenous hormone plays a physiological role in preserving uterine contractility throughout labor and reinforcing it after delivery to stop postpartum bleeding. However, its pharmacological use for triggering or enhancing labor may desensitize receptors, impairing oxytocin's post-delivery effects on uterine contractility and raising the risk of atonic PPH [13-15]. Women who receive exogenous oxytocin after delivery to prevent PPH, an intervention that is now advised in routine practice, may experience different effects from oxytocin given during labor depending on whether they do or do not [16].

Clinical studies on the impact of oxytocin administration during labor on the risk of PPH have produced conflicting results, and their conclusions are hampered by methodological flaws, particularly the failure to account for the indication bias associated with prolonged labour, the amount of oxytocin infused, or the possibility of a differential impact depending on whether the woman received prophylactic oxytocin after birth or not [17-19].

The common perception that this treatment has no serious side effects is probably influenced by this flawed evidence [20-22]. In this large population-based study, our goals were to determine whether there was an independent relationship between the amount of oxytocin exposed during labor and the risk of developing severe PPH and to determine whether the prophylactic use of oxytocin after delivery affected this relationship [23-25].

Material and Methods

Women who were chosen for the study were participants in the cluster randomised controlled Pithagore6 trial, which was carried out in 106 French maternity units that functioned as six perinatal networks [26-28].

There was no discernible difference in the rate of severe PPH between the two groups of hospitals, which was its main goal in evaluating a multifaceted educational intervention to lower the rate of the condition (details available elsewhere). 20% of deliveries in France were made at the 106 Pithagore6 maternity units, which made up 17% of all French maternity units [29-31].

From December 2019 to November 2020, data were gathered for a full year in each unit. PPH was determined by peripartum hemoglobin (Hb) delta of >2 g/dl (considered equivalent to the loss of >500 ml of blood) or was clinically determined by obstetricians or midwives [32].

A routine prenatal checkup near the end of the pregnancy allowed for the measurement of prepartum Hb; postpartum Hb was only measured three days after delivery and was the lowest reading. Each unit's birth attendants noted any deliveries that had PPH and reported them to the research team. Each month, a research assistant reviewed the delivery suite logbooks for each unit as well as any available computerized patient charts [33-35].

The patient's obstetrics file was further checked to confirm the PPH diagnosis for each delivery

where PPH was mentioned, the uterine cavity was examined, or the placenta was manually removed [36-38]. In the 106 care units, there were 146 deliveries during the 1-year data collection period, accounting for 9365 cases of PPH (defined either by estimated blood loss or by drop in Hb), for a total PPH incidence of 6.4 percent. By randomly choosing 1/60 of all other deliveries, a representative sample of women without PPH in the same units during the same time period was created [39-41].

We chose the study population from the population by excluding subgroups of women who were likely to introduce bias due to selection or major confounding by indication or other factors: women with pre-existing conditions, previous uterine surgery, including caesarean delivery, multiple pregnancies, obstetric disease, fetal death, preterm delivery (before 37 weeks of gestation), and c-section deliveries [42-44].

Finally, the study population included women who had an uncomplicated pregnancy and had a vaginal delivery of a term (at least 37 weeks) singleton. For our case-control analysis, the 1487 cases were women with severe PPH defined by a peripartum Hb delta of 4 g/dl or more (considered equivalent to the loss of 1000 ml or more of blood) or by the need for blood transfusion; the delay between the prenatal Hb measurement and the delivery was (mean ± SE (25th, 75th percentile)) (in days) 11±0.7 (0, 14); a total of 1758 parturients without PPH served as controls [45-47].

Shortly after delivery, information from the patient's chart was used to record the woman's characteristics, her pregnancy, labor, and delivery. Maternal age, body mass index (BMI) prior to pregnancy, prior uterine curettage, prior PPH, primiparity, induction of labor, fever (>38°C), epidural analgesia, duration of active phase of labor (in minutes) [48-50], oxytocin during labor, duration of expulsive efforts (in minutes, categorised according to the 50th, 75th, and 90th percentiles of distribution in the control group), and gestational age at The study of oxytocin exposure during labor included three quantitative variables: total dose (in international units), maximum infusion rate (in milli international units per minute), and total duration of infusion (in minutes) [51].

These quantitative variables were categorized using the 50th, 75th, and 90th percentiles of their distribution in the control group, rounded to the nearest whole number An important confounding factor in the association under investigation is labor duration, particularly during its active phase, so its assessment has received special attention. When cervical dilation reaches 3 cm, the active stage of the first stage of labor begins . We used a number of rules to avoid bias caused by the truncation of this record for women who went into labor before arriving at the hospital [52].

For women admitted with a cervical dilation of 3 cm or less, the active phase lasted for the amount of time that was measured between 3 cm and full dilation. The total duration of the active phase of labor was calculated using each woman's mean cervical dilation rate (derived from the time of dilation measurement at admission to full dilation), which was based on the 12 percent of cases and 27 percent of controls who were admitted with cervical dilation >3 cm. The duration of their active labor was deemed to be missing in 0 point 7 percent (n=10) of cases and 1 point 3 percent (n=23) of controls because the mean cervical dilation speed could not be accurately estimated for women whose cervix was fully dilated at admission [53-55].

Using a two-level multivariable logistic regression with a random intercept to account for the data's hierarchical structure and the clustering of the women in maternity units, the independent impact of oxytocin treatment during labor on the risk of severe PPH was evaluated and quantified. In bivariate analyses, we made adjustments for covariables that had

previously been identified as risk factors for severe PPH. The effects of oxytocin for labor augmentation on parity, labor induction, and prophylactic oxytocin after delivery were tested for clinically significant interactions.

Ethical Considerations: This study has been approved by the committee of Alborz University of Medical Sciences(Ethic No: IR.ABZUMS.REC.1401.146)

Results

In 32 (37%) women, uterine atony was the cause of severe PPH. In 42 (17%) women, partial or complete placenta retention was the cause, and in 36 (22%) women, cervical, vaginal, or perineal wounds were the cause. 359 women, or 24% of all cases, had no known cause(Fig 1).

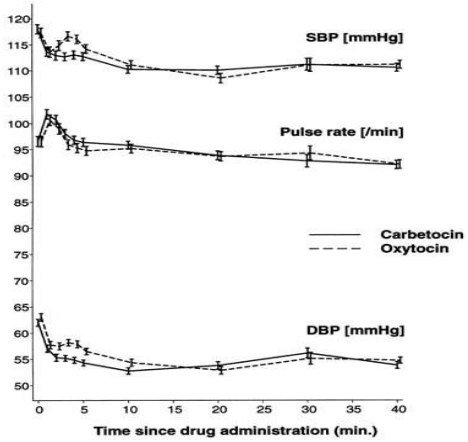

Figure 1: intervention results in blood loss

In total, 31 (21%) women underwent blood transfusions, 24 (5%) underwent arterial embolization, 2 (2%) underwent vascular ligation, and 1 (2%) underwent hysterectomy; 99 (7%) were transferred to intensive care. In comparison to controls, women with severe PPH were older, more frequently primiparous, and more likely to have experienced severe PPH in the past. Post-term delivery, induction of labor, epidural analgesia, longer labor, surgical delivery, episiotomy, or perineal tears were also more common in cases. In comparison to controls, women with severe PPH received oxytocin significantly more frequently (73%) during labor. The crude OR for hemorrhage increased from 1 to 4 depending on the oxytocin infusion rate, duration, and total duration at a maximal rate(Fig 2).

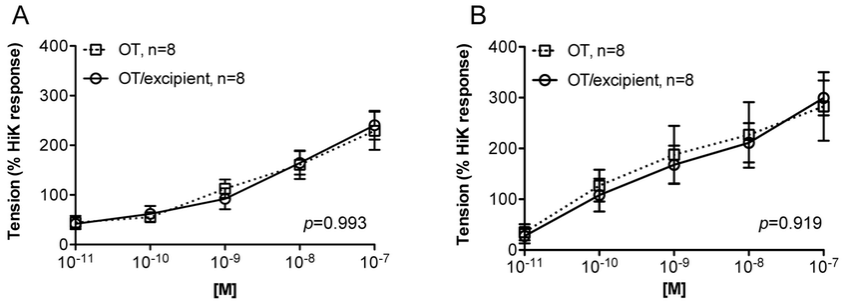

Figure 2: tension between tow groups

For the risk of severe PPH, there was a significant quantitative interaction between oxytocin during labor and its prophylactic use after birth (p=0.004 for the Wald test of interaction). For women who did not receive prophylactic oxytocin after delivery , the crude OR for severe PPH associated with oxytocin during labor was 2.3, and for those who did. To

further explore its role, we then stratified our multivariate analyses based on the prophylactic use of oxytocin following delivery [56-58].

After adjusting for all possible confounders, oxytocin exposure during labor was linked to a higher risk of severe PPH when prophylactic oxytocin was not given after delivery. With more oxytocin injected, the association became stronger. The risk of severe PPH was approximately three times higher for total doses between 2 and 4 IU and six times higher for total doses over 4 IU. Similarly, the association between severe PPH and the maximum infusion rate of oxytocin appeared dose-related: the adjusted OR was 2 point 2 for a maximal rate between 10 and 15 mIU/min and 3 point 2 for a maximal rate of >15 mIU/min(Figure 3).

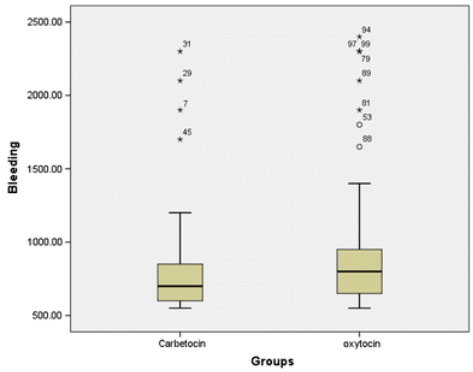

Figure 3: Hb changes after intervention

When the level of oxytocin exposure was taken into account, the risk of severe PPH appeared significantly higher for women in the most exposed categories. The adjusted OR was 2.1 for a total dose of >4 IU and 1.7 for a maximal infusion rate of >15 mIU/ml in the group of women who received prophylactic oxytocin after delivery. Sensitivity analyses revealed that the various hypotheses regarding the distribution of missing values for BMI and the length of expulsive efforts had no effect on the outcomes. Similar outcomes were obtained from a secondary analysis of cases limited to females with severe atonic PPH (n=4) and the same control group.

Discussion

When women who did not receive prophylactic oxytocin after delivery received oxytocin infusion during labor, we discovered an independent dose-related association between this and severe PPH. Only for the highest category of exposure was there a significant correlation between oxytocin during labor and severe PPH in women who received prophylactic oxytocin after delivery. We paid close attention to removing any potential confounders, but we were unable to completely eliminate the possibility that there was still some residual confounding at play.

However, given our careful adjustment for labor duration, a residual confounder associated with uterine tone that would both increase the need for oxytocin and the risk of PPH is unlikely. Our study's design had a number of advantages.

Since the study was population-based, the similarity between the Pithagore6 source population and the general population in terms of the traits of women and units strengthens the external validity of our findings. The sample size offered sufficient statistical power to investigate the relationship between severe PPH and rare exposures, such as the highest oxytocin dose categories. The comparability of these two groups is guaranteed by the choice of cases and controls from the same cohort of people [59].

We chose an objective criterion of severity (peripartum drop in Hb) because it is more likely to be determined consistently than estimated blood loss and, more importantly, because it is independent of medical practices in light of the debate over the definition of severe PPH. Information on oxytocin administration, such as dosage, timing, and infusion rates, as well as information on other aspects of labor, such as cervical dilation at admission and labor duration, was directly extracted from medical records [60-62].

The precise characterization of the exposure of interest and the effective control of confounders

were both made possible by the detailed data. Finally, we minimized the biases that weakened the findings of earlier studies investigating this association in the design of our analysis strategy. To prevent residual confounding, it is crucial to control for labor duration adequately. Our estimation of the actual total duration of the active phase, which accounts for the cervical dilation at arrival, probably accurately captures the dynamics of labor. In contrast to earlier studies that examined labor length as a binary variable (prolonged labor), which increased their risk of residual confounding, we also considered this estimated duration as a continuous variable [63-65].

This finding of an independent dose-related association between oxytocin infusion and PPH in women not receiving prophylactic oxytocin during the third stage of labor is consistent with earlier studies showing desensitization of the oxytocin receptor following prolonged or high-dose oxytocin exposure.

Similarly, a recent study using rat myometrial strips found that pre-exposure to supraphysiologic oxytocin concentrations decreased the oxytocin-induced contractile response. Our findings imply that these research results are clinically applicable and have implications for the use of exogenous oxytocin during labor. Although they had limitations, earlier clinical studies had found a link between labor induction and PPH. Women with PPH were exposed to higher levels of oxytocin during labor, according to a small case-control study of 108 women.

Two other studies found similar ORs, with a risk of hemorrhage 1 point 6 times higher in women receiving oxytocin during labor. Sheiner et al. reported a significant association between labour augmentation with oxytocin and PPH in a population-based study including 153 women. However, because these studies did not account for a number of confounding factors, such as individual and obstetrical risk factors for PPH, the nature of the association reported in these studies was questioned. The most important finding is that two of these studies did not account for labor duration, a significant confounding variable linked to both oxytocin use and PPH [66].

In contrast, Sosa et al recently came to the conclusion that oxytocin during labour is not associated with severe PPH. Their study involved 123 women who gave birth vaginally, 211 of whom had the condition. The incidence of severe PPH was higher, though not statistically significant, in women who received oxytocin during labor (2 point 4 percent) than in women who did not (1 point 9 percent); similarly, a higher, but not statistically significant, risk of blood transfusion was associated with oxytocin use during labor [67].

As a result, their inability to detect an association of the magnitude we report here cannot be explained. Only the highest category of total dose of oxytocin was associated with severe PPH in postpartum women who received prophylactic oxytocin.

Given the volume of comparisons made, we cannot rule out the possibility that this result was discovered by chance. One conceivable theory is that the pharmacologic dose of oxytocin administered during that phase counteracts the effects of oxytocin received during labor and restores uterine contractility by compensating for receptor desensitization.

An experimental study that found that oxytocin-pre-exposed myocytes' ability to contract after a supraphysiologic stimulus supports this theory. In accordance with two additional studies, women who received oxytocin for at least two hours of labor required nine times more of the hormone than non-laboring women to achieve adequate uterine retraction after delivery.

The risk of experiencing severe PPH and the dose-related relationship between oxytocin infusion during labor and that risk have implications for clinical practice. By increasing

uterine contractility while being administered during labor, oxytocin may help avoid needing a caesarean section for labor arrest. It is unlikely that its current use during labor will strictly adhere to its evidence-based indications and modalities of use, though.

In fact, the fact that it was used by 60% of the women who gave birth vaginally in our study and that similar percentages have been reported in other developed nations suggests that it is now a standard component of obstetric management and frequently given in circumstances where there is no evidence that it improves clinically relevant outcomes.

It is alarming that there is a discrepancy between the widespread use of this medication and the scant availability of reliable scientific data on its safety. Our findings suggest that oxytocin during labor increases the risk of severe PPH and provide more proof of these risks. Even at moderate doses, this effect seems to be dose-dependent and noticeable.

Conclusion

A separate risk factor for severe PPH appears to be oxytocin during labor. Our findings add to the body of evidence highlighting the need for precautions to reduce maternal complications when oxytocin is used to speed up labor, including strict indications, the use of the lowest effective dose, and careful efficacy evaluation. To support the use of this antiquated medication in a current and secure procedure, large-scale studies examining these three critical points should be conducted in the future.

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