Intrapartum use of oxytocin

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Abstract

Oxytocin is the most common medication used to induce or to accelerate labor and in the third-stage management of labor. Since 2007, oxytocin has been classified as a high-alert medication. It is well known that oxytocin exerts a large range of central and peripheral effects, from the modulation of neuroendocrine reflexes to the establishment of complex social and bonding behaviors related to the reproduction and care of the offspring. However, little has been demonstrated about the intrapartum use of syntetic oxytocin and the short-term and long-term effects on the mother and foetus. The purpose of this article is to review the main maternal and fetal side effects related to the use of intrapartum oxytocin. In conclusion, oxytocin use is associated with a decrease of the number of caesarean delivery and with an increase of vaginal delivery. Although it is the most common pharmacologic agent used during labour, there is still a debate about the optimum dose regimen use. Adverse maternal and neonatal outcomes of oxytocin induction and augmentation of labour are rare, but severe. The use of a clear protocol for the administration and early recognition of side effects may prevent adverse maternal and fetal complications.

Keywords: *oxytocin, labor, side effects*

Rezumat

Ocitocina este cel mai utilizat medicament pentru inducerea travaliului, creşterea contracţiilor şi pentru managementul delivrenţei. În 2007, ocitocina a fost clasificată ca medicaţie de alertă mare. Efectele ocitocinei sunt bine cunoscute, atât cele centrale, cât şi cele periferice, de la modularea reflexelor neuroendocrine la stabilirea unor comportamente sociale şi de legătură complexe legate de reproducerea şi îngrijirea nou-născutului. Cu toate acestea, există puţine dovezi privind utilizarea ocitocinei sintetice intrapartum şi efectele pe termen scurt şi lung asupra mamei şi fătului. Scopul acestui articol este de a revizui principalele efecte secundare materne şi fetale legate de utilizarea ocitocinei intrapartum. În concluzie, utilizarea ei este asociată cu o scădere a numărului de naşteri prin cezariană şi cu o creştere a numărului de naşteri vaginale. Deşi este cel mai frecvent agent farmacologic utilizat în timpul travaliului, regimul de doză optimală este un subiect încă dezbătut. Efectele adverse materne şi neonatale ale inducţiei travaliului şi creşterea numărului de contracţii folosind ocitocina sunt rare, dar severe. Utilizarea unui protocol clar pentru administrare şi recunoaşterea timpurie a efectelor secundare pot preveni complicaţiile adverse materne şi fetale.

Cuvinte-cheie: *ocitocină, travaliu, efecte adverse*

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Introduction

Since 2007, oxytocin has been classified as a high-alert medication (Simpson et al, 2007). Oxytocin is a neuropeptide hormone produced in the hypothalamus neurons and released into circulation by the posterior pituitary gland. It is well known that oxytocin exerts a wide spectrum of central and peripheral effects. The actions of oxytocin range from the modulation of neuroendocrine reflexes to the establishment of complex social and bonding behaviors related to the reproduction and care of the offspring. Endogenous oxytocin is released during labor as a response to the stretching of the cervix and uterus and during breastfeedind as a response to nipple stimulation. Due to its uterotonic effect, oxytocin is a term derived from the Greek word for "quick birth".

Oxytocin was first discovered in 1906 by Henry Dale, who demonstrated that a component of the pituitary gland caused the contraction of the uterine muscle in mammalian females. Five years later, Scott Ott discovered that a component of pituitary also caused milk secretion. The molecular structure was determinated in 1952 by the Nobel Prize laureate Vincent Du Vigneaud (Corey et al., 2012). The first use of intravenous oxytocin to initiate or augment labour and to reduce bleeding after birth was in 1960 (Uvnäs et al., 2019). The incidence of labor induction to shorten the duration of pregnancy has continued to rise over the past years. Unpublished data from the World Health Organization Global Survey on Maternal and Perinatal Health, which included 373 healthcare facilities in 24 countries and nearly 300,000 deliveries, showed that 9.6% of the deliveries involved labor induction (World Health Organization, 2011). The oxytocin receptor that mediates oxytocin-linked effects is a unique typical G protein-coupled receptor that is primarily coupled via G(q) proteins to phospholipase C-beta (Gimpl, Fahrenholz, 2001), which are associated with different effects. The oxytocin receptor gene is differently expressed in various tissues. In the uterus or hypothalamus, the oxytocin receptor regulation correlates with the pattern of sex steroids, in particular estradiol. Oxytocin also plays an important role in many other reproduction-related functions, it influences behaviour and controls the estrous cycle length, follicle luteinization in the ovary and ovarian steroidogenesis.

Before the onset of labor, uterine sensitivity to oxytocin increases concomitant with a strong upregulation of oxytocin receptors in the myometrium and, to a lesser extent,

in the decidua, where oxytocin stimulates the release of PGF2 alpha. Experiments with transgenic mice suggest that oxytocin acts as a luteotrophic hormone opposing the luteolytic action of PGF2 alpha. Thus, to initiate labor, it might be essential to generate sufficient PGF2 alpha to overcome the luteotrophic action of oxytocin in late gestation. Intravenous oxytocin is one of the most common pharmacologic agents used in labor induction and labor augmentation (Alfirevic et al., 2009). This agent increases the contractile effort of myometrium and corrects dystocia, helping to achieve a normal vaginal delivery. For labor induction, oxytocin infussion may be associated with amniotomy or used after cervical ripening. The uterine response to oxytocin increases from 20 to 30 weeks of gestation and rises rapidly at term (Caldeyro-Barcia et al., 1959). Intravenous oxytocin is less effective for labor induction in the second trimester of pregnancy.

Labor induction

There are two regimens recommended by The American College of Obstetricians and Gynecologists (ACOG) – high-dose protocol and low-dose protocol –, but there is still a debate about the optimal dose regimen to lower caesarean section rate, to shorten the length of labour or to decrease obstetrical complications. During labor, oxytocin infusion must be increased just until adequate uterine response is obtained to achieve active labor (Bor et al.,2016). Some studies compare early use versus delayed augmentation of oxytocin to treat disfunctional labor (Hinshaw et al., 2008). High-dose regimen is defined as an initial dose of ≥4 milliunits per minute (mU/min) with dose increments of at least 4 mU/min, and the low-dose regimen is defined as an initial dose between 1 and 4 mU/min with increments of 1-2 mU/min or 12 millilitres per hour (ml/h) for the first 30 minutes and increased by 2 mU/min (12 ml/h) every 30 minutes thereafter, until delivery.

The incorrect administration of oxytocin infusion without a clear protocol, and the lack of timely recognition and of appropriate treatment of excessive uterine activity can be responsible for maternal and fetal complications.

In a recent study on 4485 labor induction with oxytocin for nulliparous women, in a tertiary maternity, the low-dose regimen was compared with the high-dose regimen. Ten units of oxytocin were diluted in one litre of normal saline. The low-dose regimen commenced at 2 milliunits per minute or 12 millilitres per hour for the first 30 minutes and increased by 2 mU/min (12 ml/h) every 30 minutes thereafter, until delivery. A maximum reccomended dose delivery in the low-dose regimen was 32 mU/min (192 ml/h). The high-dose protocol commenced at 6.67 mU/min (40 ml/h) for the first 30 minutes, increasing by 6.67 mU/min (40 ml/h) every 30 minutes thereafter. The maximal dose delivery in the high-dose regimen was 40 mU/min (240 ml/h). The authors demonstrated a comparable rate of caesarean sections using low-dose or high-dose regimen. The low-dose regimen used was associated with more instrumental delivery rates for non-reassuring fetal status and with higher numbers of postpartum hemorrhage (Prichard et al., 2019). A Cochrane review comparing high-dose to low-dose oxytocin regimens demonstrated that the high dose of oxytocin was associated with uterine tachysystole (uterus contracting more than four times in 10 minutes) or to uterine hyperstimulation (tachysystole associated with suspicious cardiotocography), fetal distress, and uterine rupture (Budden et al., 2014; Cochrane). Shu-Qin Wei et al. found that high-dose oxytocin augmentation was associated with a significant reduction in caesarean delivery and with an increase in spontaneous vaginal deliveries and shortened labour; no evidence of an increase in adverse maternal or neonatal outcomes was found (Wei et al., 2010). Joan M.G. Crane et al. reported benefits using low-dose protocol, as fewer episodes of tachysistole, fewer operative vaginal deliveries, a higher rate of spontaneous vaginal delivery and a lower rate of caesarean delivery, lower rates of postpartum maternal infection and postpartum haemorrhage occured (Crane et Young, 1998). In all studies, the indications for caesarean delivery are similar between the two regimens (Budden et al., 2014) .

Maternal and neonatal side effects

The maternal main adverse effects of oxytocin during labor are hypotension, tachysistole and tachycardia, arrhythmias, intrapartum fever, nausea, vomiting, headache and flushing (Dansereau et al., 1999). This is more common in cases when high-dose oxytocin regimens are used. Tachysistole deprives the fetus of oxygen and the most serious long-term outcomes for the baby include hypoxic-ischemic encephalopathy, cerebral palsy and seizure disorders. Tachysistole can also cause uterine rupture. Oxyton induction and augmentation are associated with uterine rupture (Thisted et al., 2015). Oxytocin has significant antidiuretic action due to amino acid homology similar to arginine vasopressin. The large volume of fluids infused along with oxytocin can cause water intoxication and lead to convulsions, coma and even death. The concentration of oxytocin should be increased rather than raising the flow rate of a more diluted solution. Rarely, large doses of oxytocin may cause water retention, hyponatraemia, myocardial ischaemia, seizures and coma in mothers (Begum et al., 2009).

Conclusions

Oxytocin use is associated with the decrease in the number of caesarean delivery and with the increase in vaginal delivery. Although it is the most common pharmacologic agent used during labour, there is still a debate about the optimum dose regimen use, about the lenght of time until we get active labor. Adverse maternal and neonatal outcomes of oxytocin induction and augmentation of labour are rare, but severe. The use of a clear protocol for the administration and the early recognition of side effects may prevent adverse maternal and fetal complications. In our practice, oxytocin perfusion consisted of a dilution of five units of oxytocin in 500 ml of saline. The perfusion started with the use of 6 ml/h, which was doubled every 30 minutes up to a maximum of 96 ml/h, until achieving adequate contractions. It is used in women with spontaneous labor onset, in situations in which there is low frequency and/or intensity of uterine contractions, or when the expansion process has failed and not progressed, although it is used in other cases to increase uterine activity and thus accelerate the delivery process. ■

Conflicts of interests: The authors declare no conflict of interests.

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