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Review

How to reduce synthetic oxytocin administration and stimulate the production of endogenous oxytocin in childbirth

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From the womb to the adult
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Abstract

The purpose of this review is to examine synthetic and natural oxytocin use in pregnancy and post-partum.

We distinguished synthetic oxytocin (Syntocinon®) use in labor as a uterine contraction stimulant in two parts: the first is for induction or augmentation of labor; the second for prevention of post-partum hemorrhage (PPH).

Oxytocin, key hormone in the process of childbirth and lactation, is a strong smooth muscle stimulant. For this reason it is widely used to induce/augment labor and to prevent and cure PPH.

However, Syntocinon® can penetrate the placenta and reach fetal circulation, thus causing various systemic effects on mother and fetus. Oxytocin plays an important role as a neurotransmitter in the central nervous system, affecting numerous neuro-behavioral functions and it is involved in many types of parental behavior in humans and animals. It is, in fact, involved in a wide variety of physiological and pathological functions such as sexual activity, penile erection, ejaculation, pregnancy, uterus contractions, milk ejection, maternal behavior, social bonding, and stress. Oxytocin has a decisive role in the process of "bonding" between mother and child and in that of social affiliation.

We therefore explored the opportunity to reduce the use of Syntocinon® in labor ward as a precautionary measure.

Finally, we place the emphasis on some techniques that will probably increase the production of endogenous oxytocin.

Keywords

Oxytocin, pregnancy, augmentation, post-partum hemorrhage, neuro-behavioral.

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Oxytocin structure and function

Oxytocin is a pituitary neuropeptide hormone composed of nine amino acids. It has a molecular mass of 1,007 daltons. Oxitocyn is produced by both mother and fetus and is produced as a primary site from magnocellular neurons of the paraventricular nucleus and the suprachiasmatic nucleus of the hypothalamus, and it is also synthesized peripherally in non-neural sources such as ovary [1, 2] testis [3] adrenal gland [4], thymus [5], and pancreas [6]. Some studies found increased oxytocin levels at the onset of labor and during labor compared to one or two weeks before labor, reaching a peak when the fetal head is delivered. However, there is a wide variation of results reported in literature because plasma oxytocin levels are difficult to measure, because oxytocin has a half-life of a few minutes and a plasma concentration lower than other hormones, and because it is released in a pulsatile pattern. Moreover, there are many differences in experimental methods of study and in dosage evaluation [7, 8]. Oxytocin is transported through axons of the hypothalamic nuclei neurons that end in the posterior lobe of the pituitary gland (neurohypophysis) where it is processed from pro-peptide into mature peptide. From neurohypophysis, oxytocin is released into the bloodstream by exocytosis, in response to a variety of stimuli. This process takes place in the pituitary gland during labor, lactation, uterine expansion, stress, sexual stimulation and during different kinds of social interactions. Oxytocin is involved in the development and maintenance of attachment between individuals, in bonding between mother and child, in romantic love as well as in filial love; in fact, maternal and romantic love share the evolutionary purpose to maintain species, also sharing a common nucleus of neural mechanism [9]. All vertebrates have an oxytocin-like nonapeptide hormone that supports reproductive functions. Its genes are believed to result from a gene duplication event; the ancestral gene is estimated to be about 500 million years old and it is also found in cyclostomata, modern members of the Agnatha [10]. While the structure of oxytocin is highly conserved in placental mammals, a novel structure of oxytocin was recently reported in marmosets, tamarins, and other new world primates [11]. Much of the phenomena occurring during labor and childbirth take place mainly in the archaic structures of the brain, affected by systems entirely involuntary, unconscious, instinctive and genetically programmed, whose action is intended to our survival. The network more interested is the limbic system which is the archaic brain interposed between rational brain mechanisms and output of the nervous system. The instinctive behaviors determined by it are subjected to judgements culturally determined and introduced by the neocortex, very developed in our species, whose activity generates many inhibitions, as well as during any sexual experience, particularly influenced by environmental stimuli. As a result, the activation of oxytocin production can be both cortical and subcortical as shown by studies by Zeki et al. [12]. Oxytocin mRNA is increased during labor in amnion, chorion, and principally in the decidua [13]. Syntocinon® is catabolized in the gastrointestinal tract, so it must be administered by injection or as a nasal spray. Its half-life is about three to ten minutes in the blood when given intravenously. When administered via nasal spray, Syntocinon® crosses the blood-brain barrier and shows psychoactive effects in humans [14]. Unlike intravenous administration, intranasal Syntocinon® has a duration of at least 2.2 hours and as long as 4 hours [15]. Syntocinon® probably crosses the placenta in both directions by simple diffusion. Concentrations are usually higher in umbilical than in maternal blood. In addition, umbilical artery oxytocin concentrations at term (15-40 pg/ml) are higher than umbilical vein (4-12 pg/ml) and maternal (1-10 pg/ml) concentrations. The umbilical A-V difference suggests that oxytocin diffusion is mostly from fetal towards maternal circulation [16]. When administered during labor, Syntocinon® can quickly reach fetal

circulation. The permeability is probably higher in the maternal-to-fetal direction than in the reverse. However, there are only a few studies on this topic, sometimes with conflicting results, therefore not allowing to draw definitive conclusions. Moreover, we are aware that Syntocinon® administration induces the desensitization of oxytocin receptors [17-20]. Syntocinon® is a strong smooth muscles stimulant; it increases muscle cells sodium permeability by depolarizing them, with a consequent lowering of the excitability threshold. In any case, we shouldn't consider this single effect of Syntocinon® in such a significant moment as childbirth; we should indeed take into account its other systemic effects on mother and fetus in the risk/benefits ratio of Syntocinon® administration.

Part one: oxytocin for augmentation of labor

A reasonable approach based on Syntocinon® pharmacokinetics for augmentation of labor considers a starting dose of 2 mU/min, increased by 2 mU/min every 40-45 minutes until regular contractions are achieved, or for a maximum dose of 20-30 mU/min. Syntocinon® administration should consider its half-life (about 3-10 minutes) and the time needed to reach a steady-state (about 4-5 plasma half-lives) [21]. Approximately 30-40 minutes are required for any particular dose of Syntocinon® to reach a steady-state and the maximal uterine contractile response. Increasing the Syntocinon® dose earlier than 30-40 minutes can be dangerous since steady-state has not been reached yet and the entire effect of the previous administration has not been fully achieved. All this seems reasonable, although waiting to reach a steady state before considering the dose inadequate is not proven by prospective trials [22]. Note that each patient's response to the same Syntocinon® concentration is unique and both uterine contractility and progress of labor should be carefully monitored. That's why epidemiologic studies, evaluating just the mean and the median, could draw approximate conclusions about the optimal dosage for each single patient. This is also the reason why the studies reach conflicting results, with some suggesting a low-dose Syntocinon® infusion regimen, and some others a high-dose one [23], whereas other papers recommend an intermediate-dose Syntocinon® regimen [24]. In conclusion, we can say that there isn't an ideal dose for each single woman, and, therefore, the administration of Syntocinon® must be personalized as per each single case. Uterine activity evaluation is often inaccurate, therefore any regimen based only on uterine contractile pattern is not correct. Syntocinon® administration is based also on the correct definition of uterine contractions, such as:

1. the achievement of contractions of 200-220 Montevideo units (MVUs) of intensity;
2. one contraction every 2-3 minutes, lasting 80-90 seconds, judged as strong on abdominal palpation performed by an experienced midwife.

Once this kind of uterine activity is obtained, there is no need to increase Syntocinon® administration. If labor is not progressing, a more accurate diagnosis or even a caesarean section is indicated rather than a further increase in the Syntocinon® dosage, that would determine excessive and not physiological increase in uterine contractions.

Quoting Steven Clark, "*three unique characteristics of oxytocin are of special note. First, the onset of action of a given dose of dilute oxytocin solution is relatively slow… Second, few drugs in the entire medical armamentarium have such an unpredictable therapeutic index… Finally, with rare exception, the detrimental effects of this drug are exclusively mediated through its dose-related effects on uterine activity*" [22]. Since the high variability in individual response to Syntocinon® it would be extremely useful to adopt a specific check list for its administration. This could be a rather long and complex process in an obstetric division and could take even more than a year to be implemented, because introducing a shared protocol requires different clinical organizational steps [25]. If such a multifaceted strategy is adopted, involving the entire obstetric staff, Syntocinon® use could be improved, according to clinical international guidelines. In the Obstetric Division where I work, Syntocinon® use is monitored by a specific check list: the midwife in charge should fill out this written check list, put on cardiotocography (CTG) every 30 minutes.

This checklist is composed of six items:

- at least one acceleration (15 beats per minute x 15 seconds) in 30 minutes or an adequate variability in the absence of accelerations;
- no more than one late deceleration in 30 minutes;
- no more than two variable decelerations in 30 minutes;
- no more than four contractions in 10 minutes;
- no contraction lasting more than 120 seconds on abdominal palpation;

- the uterus should be relaxed between contractions.

If even a single item on the checklist can't be ticked by the midwife, the doctor will be consulted. Audits regarding the correct use of this procedure should be carried out at least once a year. In this first year of use of this new checklist, we had no reports of any side effects imputable to Syntocinon® use in 1,700 deliveries. We shouldn't forget that oxytocin has been added to the list of 11 high-alert medications designated by the Institute for Safe Medication Practices (ISMP). Those drugs are defined as those "*bearing a heightened risk of harm when they are used in error*" and may require special safeguards to reduce these risks of error [22]. Most allegations in obstetric lawsuits relate in some manner to the management of labor and delivery, and many of those involve Syntocinon® misuse. A common problem frequently reported in obstetric malpractice claims is the inappropriate use of Syntocinon®, with subsequent uterine hyper-stimulation, non-reassuring fetal status, depressed newborns at birth, long-term sequelae or even neonatal death [26]. Syntocinon® induced uterine hyper-stimulation could have a strong impact on fetal oxygen status. In fact, fetal oxygen saturation ($FSpO_2$) decreases during contractions reaching the lowest level about 92 seconds after the peak of the contraction, with approximately 90 seconds required for $FSpO_2$ to return to previous levels. When contractions are occurring every 2 minutes or even more frequently, $FSpO_2$ recovery to previous baseline levels is incomplete [27]. The association between the use of Syntocinon®, hyper-stimulation, and fetal distress is well known and documented, and the association between Syntocinon® and acidemia has been quite thoroughly investigated. Syntocinon® is an independent risk factor for acidemia at birth even after correcting the confusing variables [28]. In this study of 472 cases of suspected malpractice, 177 babies (38%) were born with severe asphyxia, due to non-recognition of signs of asphyxia in 98% of cases and to an incautious use of Syntocinon® in 71% of cases. In particular, Syntocinon® was given without signs of uterine inertia to 49 women, 19 of whom were hyper-stimulated and 44 received Syntocinon® despite severely pathological heart tracings. Different studies reported an association between acidemia at birth and Syntocinon® administration [29].

Given the widespread and liberal use of Syntocinon® during labor, this concept is of great importance in the definition of obstetric care.

Studies in rats suggest that maternal administration of Syntocinon® might adversely affect central nervous system metabolic response to hypoxia at birth [30]. In particular, intravenous Syntocinon® injections to pregnant rats before birth worsened the acute central nervous system metabolic response to anoxia at birth, as assessed by brain lactate and ATP levels in their neonatal offspring. The results of this study appear to run counter to in-vitro experiment results by Tyzio et al. [31]. These authors demonstrated, using brain slices, that maternal oxytocin exerts a neuro-protective action on fetal neurons during parturition. In conflict with this in-vitro experiment, the study of Patricia Boksa et al. used a model of birth anoxia in-vivo, with the advantage of involving a whole body response to global anoxia, affecting multiple organ systems. This systemic involvement, determined by Syntocinon® administration, could be responsible for the negative response to hypoxia documented in this study. Probably, these different results are due to the difference between endogenous oxytocin and Syntocinon® administration.

The doctoral thesis of Maria Jonsson describes four illuminating studies on the quality and amount of Syntocinon® use in the delivery room [32]. We will now focus on the first three studies, leaving for a moment the fourth study, which refers to the use of oxytocin prophylaxis of excessive blood loss during Caesarean sections, which will be the topic of the second part of our paper. We can briefly draw some conclusions from these three studies.

First of all, convictions for negligence are, with few exceptions, related to incorrect CTG interpretation. In most cases, the inappropriate management was correlated with a questionable use of Syntocinon®. The lack of action, due to the misreading of CTG and/or to misuse of Syntocinon® or failure to suspend it are, in most cases, the decisive causes of ominous outcomes.

There is a strong association between acidosis at birth and uterine hyperkinesia in the two hours before birth. Syntocinon® was administered in most cases of uterine hyperkinesia. This, together with the incorrect CTG interpretation, contributed significantly to determine acidosis at birth.

The duration of the second stage of labor is less important and is not related to acidosis if operators take into account the frequency of contractions. Metabolic acidosis at birth is associated with sub-optimal care during childbirth in half of the cases. The high rate of suboptimal care, related to CTG

interpretation and Syntocinon® use, proves a great difference between guidelines and clinical practice. Metabolic acidosis and subsequent neonatal morbidity, could probably be avoided in 40-50% of cases. For this reason, respect and adherence to guidelines should be monitored continuously [33-35]. We should abandon the concept that increasing forces in labor is always the solution to labor dystocia. After all, there is little evidence regarding the general impact of Syntocinon® on a slowly progressing labor, except that it shortens labor, but we have known for a long time that "*shortening labor by force does not improve clinical outcome*" [36]. However, prolonged labor is an important cause of maternal and perinatal mortality and morbidity *per se*, irrespective of the way we try to correct it. In the study of Laughon et al., the composite maternal morbidity is higher in nulliparous women who give birth in epidural after a prolonged second stage of labor. Specific morbidity is increased in this group of women with a rate approximately three times higher of chorioamnionitis, as well as an increased risk of episiotomy, third- and fourth-degree perineal tears and longer duration of hospitalization (median one day longer). Multiparous women who delivered after a prolonged second stage regardless of epidural use had higher rates of chorioamnionitis, higher odds of postpartum hemorrhage and third- or fourth-degree perineal tears after adjustment. However, the study didn't show significantly increased risks for other serious maternal complications, including need for blood transfusions, cesarean hysterectomy, or intensive care unit admission. The rate of neonatal morbidity is increased by 11% for nulliparous and 9% for multiparous, with a prolonged second stage, which is about 2-3% higher than in delivery with a normal second stage [37].

Thus, "failure of labor to progress" has become one of the leading indications for primary caesarean section all over the world, particularly in first-time mothers since a significant proportion of caesarean sections is performed for dystocia [38]. Dystocia appears to be associated with a significantly increased maternal and neonatal mortality and morbidity, and that is a major problem both in terms of finances and public health [38]. There is growing concern that caesarean sections are performed too soon in many cases, without exploring less invasive interventions that could lead to vaginal birth. Adverse maternal and neonatal outcomes seem to be related more to the cause of dystocia or to augmentation of labor than to prolonged labor *per se*. To identify the exact cause of the slowness or non-progression of labor in clinical practice can be difficult. However, the evaluation of the progression of labor can not take into account only cervical dilation, but should also consider other factors, such as the descent and rotation of the presenting part, the duration and frequency of contractions, as well as hydration and nutritional and psychological needs of the mother. The uterine cervix that dilates slowly or the slow descent of the fetal head are just warning signs, that can properly be considered as screening tests. The cause of this abnormality should then be searched both in maternal and fetal conditions such as stress, fasting, fetal trunk and head malpositions, fetal distress, etc. [39]. If we use cervical dilation curves as screening, and not as diagnostic tests, we can try other therapeutic strategies and not just augmentation with Syntocinon®. It is demonstrated that encouraging women to walk in the setting of a prolonged labor can be helpful [40]. This randomized clinical trial enrolled 57 women (nulliparous and multiparous). In the ambulatory group, only 50% of women received oxytocin, conversely in the second group every woman had oxytocin administered. Statistically significant differences between the two groups are: the average duration of the second stage, which is lower in the ambulatory group, stronger contractions in the oxytocin group before the start of the active phase of the second stage and a more positive experience in the walking group. The test sample was too small to estimate the effects on the health of infants but women in the ambulatory group also had lower use of analgesia in the first stage, less operative deliveries, more normo-reactive CTG before the active phase of the second stage, and fewer complications recorded in the post-natal period. The practice to ambulate women with consequent possible postponement of Syntocinon® infusion, allows a better selection of those patients needing Syntocinon® and therefore prevents the administration of Syntocinon® to women who would still have normal and effective contractions later. Although the results of other studies are not in complete agreement with the study of Hemminki et al., certainly walking not impaired active labor and is not harmful to the mothers or their infants [39]. As evidenced by the study of Cluett et al., laboring in water under midwifery care may be an option for slow progress in labor, reducing the need for obstetric intervention, and offering an

alternative pain management strategy [41, 42]. In the case of occiput posterior position, asynclitism or deflected presentations, the woman should be encouraged to change her posture in order to try to correct fetal malposition [43]. If the change of maternal posture cannot modify fetal position, manual rotation of the fetal head is also possible [44]. Another technique that can be used in case of slow cervical dilation or slow descent of fetal head is massage [45]. Indeed, massage has been proven to increase oxytocin production and to decrease ACTH blood concentration [46]. Moreover, giving the patient the possibility of laboring in a "pleasant" environment can probably also increase the endogenous production of oxytocin [47]. In this way, we can reduce Syntocinon® administration, facilitating endogenous oxytocin production.

In our work group, we applied a protocol called "Comprehensive Management", using cervimetric curves as a screening test. When cervical dilation or presenting part progression were slow, we tried to carry out a presumptive diagnosis of the cause of dystocia (**Fig. 1**), followed by the above-mentioned alternative correction techniques. Applying our Comprehensive Management protocol, in the first six months of its implementation, the rate of

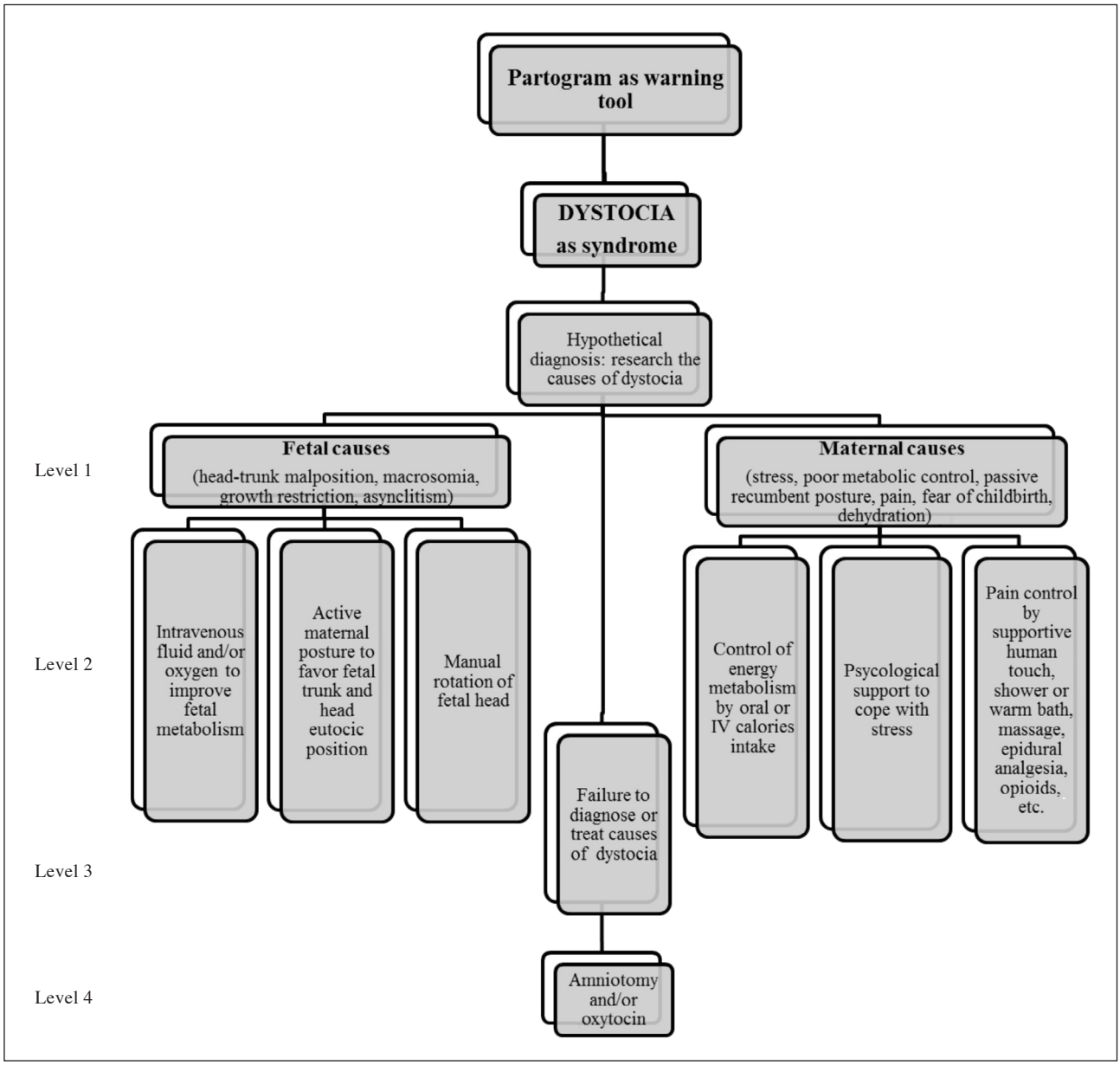

Figure 1. The Comprehensive Management of dystocia in labor.

The first level shows the attempt to find a cause of dystocia. The second level shows the possible areas of treatment. The third and fourth levels show the standard treatment of dystocia, which is adopted only in the event of failure of the first and second levels.

oxytocin use for augmentation of labor decreased significantly from 28.1% (72/256 patients; 95% CI: 22.7-34.1) to 14.2% after intervention (47/332 patients; 95% CI: 10.6-18.4) (Fisher's exact test: $p < 0.0001$) [48]. Later, in another Obstetric Unit, improving further our Comprehensive Management, we were able to reduce oxytocin use in all deliveries from 19.8 % to 13.1% ($p < 0.0008$), also decreasing amniotomy from 19.8 % to 11,19.2 % ($p < 0.0001$) [49].

After all what is the need of using Syntocinon® so often in labor if there are no differences between Syntocinon® administration versus no treatment in terms of caesarean section rate, operative vaginal deliveries and both maternal and neonatal outcomes [50]?

Moreover, in first-time mothers on epidural there are no significant differences between patients augmented with Syntocinon® and non-augmented patients in the primary outcomes of cesarean section (RR 0.95 95% CI 0.42 to 2.12) or instrumental delivery (RR 0.88, 95% CI 0.72 to 1.08). Similarly, there were no statistically significant differences between the two groups in any of the secondary outcomes for which data were available [51]. However, Syntocinon® is not free from important biological effects also on the mother [52]; the review of Al-Zirqi et al. [51] evaluates uterine rupture trends over a period of 40 years in Norway. The authors showed that incidence rates per 10,000 deliveries in the first, second, third, and fourth decades were 1.2, 0.9, 1.7, and 6.1, respectively. Significant contributing factors to this increase were higher rates of labor augmentation with Syntocinon®, scarred uteri from previous caesarean sections and labor induction with prostaglandins or prostaglandins combined with Syntocinon®. The authors concluded by arguing that uterine rupture incidence was increased and that obstetric interventions contributed to this increase.

Moreover, is it proven that the amount of intrapartum Syntocinon® administered in labor predicts plasma oxytocin levels two months postpartum; these levels are lower in patients treated with Syntocinon®, suggesting a possible long-term effect of this routine intervention, the consequences of which are largely unknown [52, 53].

An interesting review was carried out to identify the primary and secondary outcome measures in randomized trials and systematic reviews that measured the effectiveness of Syntocinon® to treat the extension of the first or second stage of labor. The authors also identified any positive health outcome in this field. They included 33 publications, 28 RCTs in which at least one of the two groups in the study received Syntocinon® augmentation for delay in spontaneous labor (slow progress) and five systematic reviews. Almost none of the studies included references to women-centered outcomes (e.g. maternal experience of pain, maternal perception of duration of labor) or to positive health outcomes (for example intact perineum or maternal self-esteem). Thus, the literature demonstrates the urgent need for studies on this topic [53].

Perinatal Syntocinon® administration was associated with a 2.4 times increased odds of bipolar disorders later in life. Syntocinon® was also associated with decreased performances on the Raven Matrices, but not on the Peabody Picture Vocabulary Test. Childhood cognition was not associated with later bipolar disorders. The study has some limitations, for example the childhood cognitive battery did not include tests related to multiple domains of cognition which have been associated with later bipolar disorder and the sample size of children exposed to Syntocinon® was quite modest. However, the study provides evidence for a potentially important perinatal risk factor for bipolar disorder and cognitive impairment in childhood [54]. Additional preliminary data suggest caution in Syntocinon® administration in labor [55]. Gregory et al. performed an epidemiological analysis using multi-variable logistic regression modeling involving the North Carolina Detailed Birth Record and Education Research databases [55]. The study featured 625,042 live births linked with school records, including more than 5,500 children with a documented exceptionality designation for autism. This work suggests that induction/augmentation during childbirth is associated with increased odds of autism diagnosis in childhood. However, great caution is needed before changing completely our clinical practice in the delivery room. It is known that association doesn't mean causality, therefore SMFM (Society for Maternal-Fetal Medicine) on Labor Induction or Augmentation and Autism Spectrum Disorders (ASD) stated: "*SMFM has reviewed the evidence and feels that the recent publication is far from definitive, uses methodology that cannot prove causality and does not indicate a causal relationship between labor induction/augmentation and ASD. Therefore, this single study should not be viewed as an incentive*

or provide justification for any change in practice regarding labor induction and management" [56].

Studies from Europe and the United States report that up to 50% of primiparas and 20% of multiparas received Syntocinon® augmentation during labor [57-60].

In mammals, the prevalence of dystocia is generally not as high as we could expect from a complex mechanism undergoing a huge evolutionary selective pressure such as childbirth. Childbirth is the final event determining species preservation. In horses, for example, dystocia occurred in 10.1% of all births and the most common causes of dystocia were abnormalities of fetal position [61].

In dogs, dystocia is infrequently due to a lack of force, conversely it is due to maternal causes in 37.9% of cases, to fetal reasons in 21.5% and in 34.7% of cases for a combination of both [62].

We should consider a slow cervical dilation or a slow descent of fetal head as warning signs, and we could properly include them in the category of screening tests. We should apply to human labor the paradigm that we always apply when we try to carry out good medical practices: diagnosis before therapy. The cause of dystocia should then be searched both in maternal and fetal conditions, such as stress, fasting, fetal trunk and head malpositions, fetal distress, macrosomia, fear of childbirth, growth restriction, dehydration. Dystocia in labor is a syndrome not a disease (**Fig. 2**). A syndrome is a set of medical signs and symptoms that are correlated with each other and, sometimes, with a specific disease and it can be caused by various factors. Before increasing forces using Syntocinon® we should consider first if the lack of force is the reason for dystocia. A greater attention to the evidence and the analysis of each clinical case lead to a reduction of the intervention in labor [63]. The study by Chaillet and colleagues [63] was performed to determine whether a multifaceted 1.5-year intervention to improve professional onsite training with audits and feedback would reduce the rate of cesarean delivery. Of 184,952 participants enrolled from 32 hospitals in Quebec, 53,086 gave birth in the year preceding the intervention and 52,265 gave birth in the year after the intervention. The

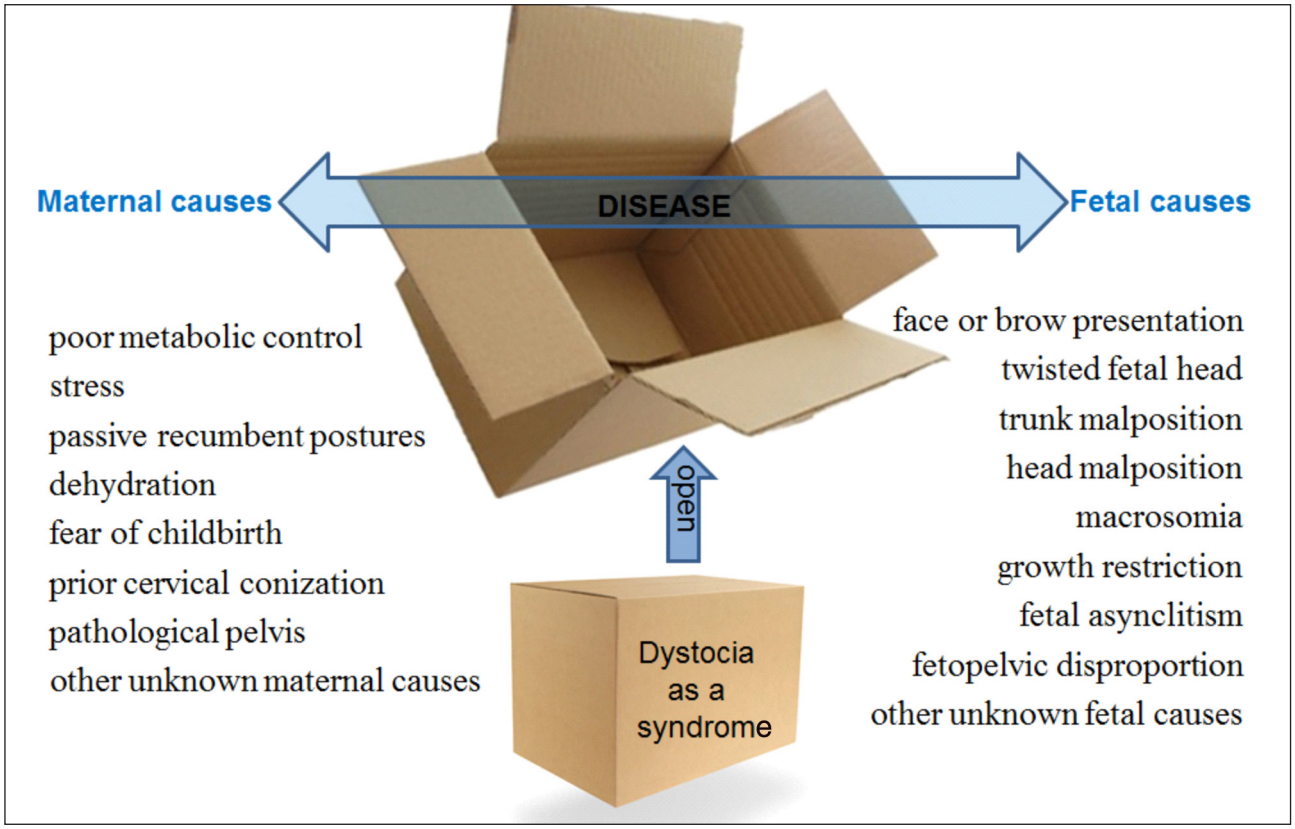

Figure 2. Dystocia in labor as a syndrome.

In this figure dystocia is represented as a closed box that, when it's opened, by identifying a presumptive etiology, allows to make the diagnosis and consequently to act on the probable causes.

intervention consisted of initial onsite training by instructors from the Society of Obstetricians and Gynecologists of Canada regarding evidence-based management of labor and delivery, clinical audits of indications for cesarean delivery, feedback to clinicians, and implementation of best practices. Women with low-risk pregnancies had a significant reduction in cesarean delivery rate, whereas those with high-risk pregnancies did not (adjusted risk difference, -1.7%; 95% CI, -3.0% to -0.3%; p = .03 vs. p = .35; p = .03 for interaction). Also oxytocin use during labor decreased in both groups, the decrease was greater in the control hospitals (adjusted OR, 1.16; 95% CI, 1.09 to 1.23; p < .001; adjusted risk difference, 3.2%; 95% CI, 1.9% to 4.6%). The lower rates of cesarean delivery associated with this intervention were not accompanied by adverse maternal or neonatal effects, based on findings of this cluster-randomized controlled trial.

In conclusion, it is proven that mothers who received Syntocinon® infusion during labor show a significant negative correlation between the amount of Syntocinon® and their endogenous oxytocin levels two days later (p = 0.019), so the higher the dose of Syntocinon® administered during labor, the lower their endogenous oxytocin levels will be two days later [52, 64]. This could have huge epigenetic consequences and probable effects on neuro-behavioral development in some sensitive individuals. Blood oxytocin concentrations are highly heritable within families; its level is a strong predictor of social functioning in autism spectrum disorder children, in their unaffected siblings, and healthy control children [65]; this study indicates that dysregulated oxytocin biology is not uniquely associated with ASD social phenotypes as widely theorized, but instead variation in oxytocin biology contributes to important individual differences in human social functioning, including the severe social impairments which characterize ASD. In this study a change in oxytocin receptor polymorphisms such as carriers of the "G" allele of rs53576, showed impaired affect recognition performance, while carriers of the "A" allele of rs2254298 exhibited greater global social impairments in all groups. Currently we are not able to understand what fetuses may be adversely affected by the administration of Syntocinon® and which may not. Once we have discovered this, we would get closer to having the so called "tailored medicine" in the delivery room too.

Syntocinon® hasn't been demonstrated to be always an effective cure for dystocia during labor, and must be used with caution, not only in those patients we are reasonably sure that the cause of dystocia has to be found in reduced or ineffective uterine activity. In patients who have not a disorder of uterine activity it is urgent to look for other causes and hence other treatments for dystocia. Syntocinon® remains a valuable strategy in Obstetrics but, before we get to know more, we should administer this drug cautiously and in an attentive and adequate way. Furthermore, we should learn to better select a population of patients in which the increase in the strength of uterine contractility is useful.

Part two: oxytocin for prevention of postpartum hemorrhage

Postpartum hemorrhage (PPH) means a blood loss of 500 ml or more after a vaginal delivery. Hemorrhage is defined as severe if it is greater than 1,000 ml. A blood loss of 1,000 ml or more after a cesarean section can be defined as abnormal [66]. Primary PPH is used to describe a loss of blood within 24 hours from delivery while secondary PPH occurs between 24 hours and 12 weeks postpartum [67].

PPH is one of the most frequent causes of mortality and morbidity in obstetric population worldwide, causing about 25% of maternal deaths each year [68]. In Italy PPH is the most important cause of direct death during childbirth [69].

Most deaths take place 24-48 hours from delivery [70]. 66% of deaths due to PPH are still due to "substandard care" [71]. Moreover, PPH is also cause of 73% of all serious morbidity during pregnancy and is the most frequent obstetrical cause of admission to intensive care units [72].

The possibility of an effective prevention for this pathology must therefore be considered a clinical priority.

However, important distinctions must be taken into consideration with regards to where delivery takes place, as well as between countries with low income and limited health resources, and those with high income and good healthcare resources.

Active treatment during third stage of labor seems to be the chosen treatment to prevent PPH, which reduces maternal blood loss and the risk of PPH. A systematic review, including seven studies concerning 8,247 women, showed that active treatment during third stage of labor reduces the

prevalence of PPH by about 60% [73]. The active treatment of the third stage of labor is made up of three elements:

1. early clamping of the umbilical cord;
2. controlled cord traction;
3. prophylactic oxytocic drug as the anterior shoulder is delivered.

Out of these three elements, only the administration of uterotonic prior to shoulder delivery continues to have an unanimously recognized effective role. In the past, early clamping of the umbilical cord was considered an important element of the active treatment of the third stage, with clamping defined as early if carried out 16 seconds after delivery, and late if carried out one to two minutes after delivery. Over time, no evidence has been found to show that failure to carry out early clamping increases the number of cases of PPH, both minor and severe. On the other hand, late clamping, placing the newborn on the mother's abdomen, has many advantages, as it improves haematological state, reducing the risk of anemia, as well as promoting cardiovascular and respiratory adaptation [74] and bonding. Late clamping results in only a slight increase in phototherapy treatment (+2%). The other component of the treatment of the third stage is the controlled cord traction, the validity of which has been disproven by a randomized controlled trial published by Gülmezoglu and colleagues [75]. The authors demonstrated that out of 581 women managed without controlled cord traction, only one had a blood loss of 1,000 ml or higher. If carried out by untrained operators, controlled cord traction increases the risk of uterine inversion by from 1 to 7 times. In Gülmezoglu's study, the main factor that contained the overall rate of PPH at just over 10%, in both groups, was the administration of an injection of uterotonic at birth. The uterotonic with the best cost/benefits ratio is Syntocinon®; an intramuscular dosage of 10 IU seems to be the best treatment for the prevention of PPH. At present, the only action deemed to be really important in the reduction of PPH prevalence is the administration of 10 IU of Syntocinon®. For women without risk factors of PPH who deliver vaginally, intramuscular administration of Syntocinon® (10 IU) is the chosen treatment, while for women who have delivered by cesarean section, slow intravenous infusion of 5 IU of Syntocinon® promotes uterine contraction decreasing blood loss [76]. The administration of Syntocinon® may, however, be inappropriate in women with important cardiovascular disorders, suggesting that for these patients we need to consider a different kind of prevention without cardiovascular effects. In these cases, tranexamic acid (TA) could be an alternative medication [77]. The results of a controlled double-blind vs. placebo study demonstrated the effectiveness of TA in reducing haemorrhages during and after cesarean sections [78]. Another randomized double-blind vs. placebo study carried out on 454 patients showed that intravenous administration of 1 g of tranexamic acid 5 minutes after the disengagement of the shoulder, in addition to the active management of the third stage of labor, reduces the amount of blood loss in vaginal deliveries. In fact, in this study, the percentage of PPH was lower in the experimental group (1.8%) compared to control group (6.8%). This advantage was not seen in cases of a blood loss greater than 1,000 ml. No thrombotic events were seen [79]. Moreover, as reported in part one, Syntocinon® has numerous systemic effects since receptors for oxytocin have been found in different tissues, such as blood vessels, kidneys, ovaries, testicles, the thymus gland, heart, pancreas and adipose tissue [80]. Syntocinon® is responsible not only of uterine contractions, but it is also involved in milk ejection, in maternal behavior, in social bonding, in the process of "bonding" between mother and child, in stress and social affiliation [9].

In the prevention or treatment of haemorrhage, Syntocinon® reacts quickly, with a latency period of less than one minute after an intravenous injection, its half-life is 3 minutes and 2 to 4 minutes after an intramuscular injection. The response of oxytocin lasts 30 to 60 minutes after intramuscular/intravenous administration (less for intravenous). Metabolic clearance speed is about 20 ml/kg per minute [81].

It is well known that Syntocinon® has serious adverse maternal cardiovascular effects, including hypotension, myocardial ischemia, arhythmia, nausea, sickness, headache and hot flashes. Due to structural similarities with vasopressin, it has a moderate antidiuretic effect, and spill over effect on the ADH receptor at high concentrations. An excessive dosage of Syntocinon® can cause water retention, hyponatremia, convulsions and coma, specially if administered via intravenous with a glucose solution [83, 84]. Moreover, Syntocinon® can cause the release of Brain Natriuretic Peptide, resulting in a clinical presentation of peripheral vasodilatation, hypotension and increased cardiac output, all mediated by an increase in the systolic

range heart rate. Pulmonary artery pressure increases considerably for at least 10 minutes after a bolus of 10 IU of Syntocinon® during general anesthesia. These effects can be poorly tolerated in case of abnormal ventricular function, aortic or mitral stenosis, and hypovolemia [82]. Syntocinon® must be administered with caution to patients with susceptibility to myocardial ischemia due to pre-existing cardiovascular pathology, such as hypertrophic cardiomyopathy, valvular and/or ischemic heart disease, including coronary vasospasm, so it's important to avoid significant changes in blood pressure and in heart rate in these patients. Syntocinon® must be administered with caution to patients with "Long QT syndrome" and to patients taking medication influencing the length of the QTc interval. In rare circumstances (incidence rate < 0.0006), pharmacological induction of labor with uterotonics, including Syntocinon®, increases the risk of postpartum disseminated intravascular coagulation (DIC) and the effect is independent from the type of substance used. This risk is increased particularly if the woman has further risk factors for DIC, such as age over 35 and gestational age of more than 40 weeks. Syntocinon® seems to have side effects on bleeding, on coagulation and on fibrinogen level. The frequency and mechanism with which these interactions take place is relatively unknown [83]. The study of Golparvar et al. assessed the effects on the forming of the clot and on circulation after the administration of Syntocinon® according to two different infusion regimens, 15 units/hours and 30 units/hours respectively, in healthy women who had given birth, by means of the analysis of thromboelastography. The authors concluded that Syntocinon® has a modest effect of hypercoagulability on maternal blood, which is increased as per the dosages administered [84]. Syntocinon® is considered an uncommon cause of severe allergic reaction during delivery. It was recently demonstrated that sensitization to latex could be an important predisposing factor to anaphylaxis after Syntocinon® infusion during delivery [85]. With any method of administration, Syntocinon® can cause the following side effects: frequent effects (> 1/100) such as headache, tachycardia, bradycardia, nausea, sickness; uncommon effects (> 1/1,000) such as arrhythmia [86]; rare effects (> 1/10,000) such as anaphylactoid reaction associated with dyspnoea, hypotension or shock, rash.

Many detailed guidelines can be found in literature regarding the best use of uterotonic substances and obstetrical interventions to carry out in order to prevent PPH. However, changes in the hemostatic mechanisms, considered consequences to an uncontrolled bleeding, are not taken into consideration as causes and, consequently, as prevention of PPH. Interest towards the coagulation pattern of a woman giving birth was reassessed after the results of a prospective study carried out in France from 2002 to 2004 were released. This study aimed to assess if changes to the hemostasis markers are predictors of the severity of PPH, and demonstrated a possible relationship between the reduction of fibrinogen levels and outcomes (PPH), with an increased risk of severe haemorrhage of 2.63 (IC 95%) each 1 g/L of decrease in fibrinogen. However, the study did not provide explanations regarding the cause of fibrinogen reduction, and, therefore, at present, we do not know if the reduction of fibrinogen levels is a cause or a consequence of PPH [87]. Current knowledge indicates that fibrinogen levels are higher in pregnant women compared not pregnant ones, and fibrinogen increase considerably in the third trimester of pregnancy, in relation to the levels of estrogens [88]. Conversely after delivery a decrease in the levels of haematic estrogens can be seen, with the consequent reduction of the concentration of plasma fibrinogen, that continues during the first periods of postpartum [89]. This, together with the intravascular deposition of fibrin during postpartum, that leads to an increase in the use of fibrinogen, enables to assign a rational to the use of TA in the prevention of PPH. Studies of placental biopsies, using an electronic microscope show that after a normal delivery, a fibrin extravascular network is formed immediately on the endometrial surface [90]; the absence or lack of formation of this network could be a cause of PPH that has still not been studied. In fact, some studies demonstrated the effectiveness of TA in reducing haemorrhages during cesarean sections and vaginal deliveries [78, 79]. Last but not least, as a recent review suggests, TA remains stable for at least 12 weeks in a great variety of different conditions and does not require refrigeration. Therefore, considering the low rate of complications, the possibility of oral administration, TA is an ideal medication to reduce maternal mortality caused by PPH specially in low income countries such as Sub-Saharan Africa, where about 50% of deliveries take place at home, and where the availability of

this medication could reduce maternal mortality caused by PPH by 30% (about 22,000 deaths per year), thanking also to its low cost [91].

Syntocinon® showed great effectiveness in the prevention of PPH so the other two components of active management are not longer recommended. Syntocinon® is the treatment of choice (grade A) and can be used either after the shoulders expulsion or rapidly after the placental delivery (grade B). A dose of 5 or 10 IU must be administrated intravenously over at least 1 minute or directly by an intramuscular injection (professional agreement) except in women with documented cardiovascular disease in which the duration of intravenous perfusion should be over at least 5 minutes (professional agreement). 5 or 10 IU can be injected intravenously over 1 minute, and over 5 minutes in women with cardiovascular disease in patients undergoing cesarean section (professional agreement) [76]. However, this medication can also have serious secondary effects, some of which are still being studied, therefore it is important to study the possibility of alternative medication such as TA, which has lower systemic effects compared with Syntocinon®, can be administered orally and is affordable. Furthermore TA could be the best prevention where the healthcare system is not available or efficient.

However, we should consider that in countries with high income, the situation differs greatly. In these countries, with a good healthcare system, healthy women with normal levels of hemoglobin do not suffer any negative effects from a blood loss of 500 ml, which is just a little higher than the amount lost during a routine blood donation. Looking in details at all maternal deaths in the United Kingdom from 2006 to 2008, we can see that out of 2.3 million women who gave birth, only five deaths were due to PPH:

- three of the five women died due to insufficient observation during the post-operative phase;
- one of the women had a level of hemoglobin of 7.5 before the cesarean section, had a blood loss of 1-2 L during the operation, and died some months later of pneumonia;
- the fifth woman died alone at home after unrecognized pregnancy and labor [92].

None of these women can be considered a "healthy woman with normal levels of hemoglobin and at low risk of haemorrhage". It would be correct to say that PPH is not one of the main causes of maternal death in low-risk women, in a place with expert doctors and midwives and in high income countries. Therefore we could assist these patients with an attitude that better respects physiology. If a woman starts bleeding excessively after delivery, it is obvious that an uterotonic treatment is needed as soon as possible.

The attention of the personnel assisting patients during childbirth and in the first hours postpartum, along with a prompt medical therapy in case of PPH, could be the best and most affordable prevention strategy for low-risk patients where the healthcare system can guarantee a complete and prompt assistance.

In conclusion we can decide to do PPH prophylaxis or not but we should do our best to guarantee the best strategy for every single patient or group of patients, without going on with the policy of "one size fits all".

Declaration of interest

The Author declares that there is no conflict of interest.

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