www.jpnim.com Open Access
Journal of Pediatric and Neonatal Individualized Medicine 2014;3(1):e030123
doi: 10.7363/030123
Publication: 2014 Apr 09

Invited review

Oxytocin and customization of assistance in labor

Antonio Ragusa, Alessandro Svelato

Department of Obstetrics and Gynecology, Niguarda Hospital, Milan, Italy

Abstract

Synthetic oxytocin (synOT) is a commonly used drug in labor and it can be applied in all stages of labor. SynOT has been increasingly used over the years, and is currently one of the most common drugs employed in obstetrics. The goal of synOT administration is to cause the augmentation of labor; unfortunately, guidelines for the administration of this drug are often non-specific, although synOT is the drug most commonly associated with preventable adverse perinatal outcomes. Approximately half of all paid obstetric litigation claims in the United States involve allegations of injudicious use of oxytocin, and the association between oxytocin use, hyperstimulation, fetal distress and adverse neonatal outcome are well know. Furthermore, synOT and oxytocin have some extragenital effects that should be known by obstetricians. This review will present the viewpoint of the authors on this topic.

Keywords

Synthetic oxytocin, labor, litigation, side effects, newborn, augmentation, dystocia.

Corresponding author

Antonio Ragusa, Department of Obstetrics and Gynecology, Niguarda Hospital, Milan, Italy; email: antonio.ragusa@gmail.com.

How to cite

Ragusa A, Svelato A. Oxytocin and customization of assistance in labor. J Pediatr Neonat Individual Med. 2014;3(1):e030123. doi: 10.7363/030123.

Introduction

Oxytocin was isolated and synthesized for the first time in 1953 by Vincent du Vigneaud (1901-1978) who was awarded the Nobel Prize for Chemistry for this discovery two years later.

Synthetic oxytocin (synOT) is a commonly used drug in labor and it can be applied in all stages of labor. SynOT has been increasingly used over the years, and is currently one of the most common drugs employed in obstetrics [1]. Its use in delivery rooms in the Western world has reached epidemic levels, with percentages of use of between 44.5-75% in nulliparous and between 25-40% in pluriparous [2-4]. SynOT is often used to treat dystocia, which is characterized by abnormal slow progress of labor, and is among the most common challenges in birth care, especially for primiparous women [5-7]. In a study of primiparas with spontaneous onset of labor at term, 37% were found to develop labor dystocia [8]. Swedish data has reported the use of synOT augmentation in some 70% of primiparas at term [9, 10].

The goal of synOT administration is to cause the augmentation of labor (that is, uterine activity sufficient to produce cervical change and fetal descent while avoiding uterine hyperstimulation and fetal compromise). A wide variety of synOT regimens may be used for labor augmentation provided that proper precautions are met, as clear guidelines and continuous cardiotocography (CTG).

Unfortunately, guidelines for the administration of this drug are often non-specific [11], although synOT is the drug most commonly associated with preventable adverse perinatal outcomes [12]. Approximately half of all paid obstetric litigation claims in the United States involve allegations of injudicious use of oxytocin [13].

The association between oxytocin use, hyperstimulation, fetal distress and adverse neonatal outcome are well know [14-18]. Indeed, adverse perinatal outcome, related to fetal hypoxia due to impairment of gas exchange between contractions, may occur in the presence of uterine hyperactivity [18, 19].

Nevertheless, few obstetricians are also informed about the developmental consequences that synOT has on the fetus. It is known that, in addition to the classic endocrine functions in female animals during parturition and lactation, oxytocin acts as a potent modulator of social behavior in a diverse range of species from worms and voles to humans [20]. In particular, recent evidence shows that newborns' neurobehavioral cues may be sensitive to intrapartum synOT [21].

In experiments on animals, the administration of oxytocin during labor was seen to have long term effects with regard to bonding, social behavior and on the hypothalamic-pituitary-adrenal axis, many of these effects show sexually dimorphic behavior [22].

Evidence coming from studies on humans show that the use of synOT in labor has effect on the maternal hormone balance. In a study [23], a significant negative correlation was noted in mothers who had received oxytocin infusion during labor: the higher the dose of synOT received during labor, the lower their endogenous oxytocin levels two days later. We know that the mothers' plasma oxytocin in post partum is related to the amount of affectionate parenting behaviors, including "motherese" vocalizations, the expression of positive affect, and affectionate touch, whereas paternal plasma oxytocin is correlated with the degree of stimulatory parenting behavior, including proprioceptive contact, tactile stimulation, and object presentation [24].

In consideration of the above, it is very important to assess and analyze methods to manage dystocia that reduce the use and the amounts of synOT given during labor.

Checklists and standardized protocols for the use of oxytocin have been tested and recommended by several authors in order to reduce adverse neonatal outcomes [11, 25].

In this paper, with the aim of clarifying the meaning of a new type of obstetric management, we briefly describe two particularly exemplary clinical cases.

Case 1

Mrs. B.B., 28 years old, white Caucasian, Gravidity 1, Parity 0, at 38 weeks plus 3 days of gestation, uneventful pregnancy and normal fetal growth. At 08:00 am, the patient was admitted in active labor. Obstetrical examination reported an effaced, central cervix dilated: 4 cm, membranes intact. The presenting part was cephalic, station: -3, posterior left position. At 10:00 am, after two hours of regular active labor with four contractions in 10 minutes, position and cervical dilatation were unchanged. Fetal Heart Rate (FHR) was normal. The doctor on duty prescribed and performed amniotomy. After two hours, at 12:00 am, dilation was 5 cm and high-dosage oxytocin augmentation was administered. Two hours later, at 2:00 pm, dilation was 8 cm. Fetal position was right posterior and the head was still deflexed with a palpable presenting brow at the centre of the pelvic canal, station was -2, the contractions

were six in 10 minutes, FHR showed atypical repetitive variable decelerations. An emergency caesarean section was performed. At 2:30 pm, a male fetus weighing 3,450 g was delivered surrounded by thick meconium, Apgar score was 1 and 5 at one and five minutes respectively. Umbilical artery pH was 7.04, base deficit -12. The overall duration of labor was 6 hours and 30 minutes. The newborn was discharged in good clinical health.

Case 2

Mrs. C.H., 26 years old, Algerian, Gravidity 1, Parity 0, uneventful pregnancy and normal fetal growth. At 6:00 pm, the patient was admitted in active labor. Obstetrical examination recorded: posterior cervix, 75% shortened, dilation: 3 cm, intact amniotic sac, the presenting part was cephalic, station: -4, and no information was searched for head position. The contractions were two in 10 minutes. FHR was normal.

At 7:54 pm, the cervix was posterior, 80% shortened, dilation: 4 cm, intact amniotic sac, the presenting part was cephalic, station: -4, un-assessable head position. At 10:00 pm, cervical dilatation were unchanged, position of the fetal head was right anterior occiput markedly deflected with palpable brow at the centre of the pelvic cavity. This condition was explained to the patient. Pain control was achieved by epidural analgesia. Active postures were explained to the patient in order to favor fetal head rotation and flexion. FHR showed slight typical variable decelerations, which reduced in intensity and frequency. At 1:30 am position of the fetal head was right anterior occiput well flexed, without palpable brow, and dilation was complete. At 3:10 am, a female newborn of 3,680 g was delivered. Apgar score was 10 at one and five minutes, umbilical cord pH 7.22, and base deficit -2.9. The total duration of first stage of labor was 7 hours and 30 minutes, the active second stage lasted 1 hour and 40 minutes.

Discussion

Commonly the cervimetric curve and the progression of the fetal presented part during second stage of labor have been used to diagnose labor dystocia. Using them as a screening test to looking for causes of dystocia together with a standardized protocol, which introduce the need to specify indications, reduces the use of oxytocin for augmentation of labor, without changing the length of the same. Screening and, therefore, the presumptive diagnosis made before administration of synOT enabled to use the drug in patients who needed it most. This, together with the lower dosages used, led to speed reduction of labor in augmented patients while reducing, however, the number of uterine hyperstimulations. In short, excluding fetal malposition or problems regarding maternal tolerance to pain led to a reduced, more targeted and appropriate use of synOT.

The analysis of the two above clinical cases is paradigmatic: in most delivery rooms in the Western world, these two cases would have been treated in the same way, with amniotomy and oxytocin, as for the first case with not so encouraging results.

The association between oxytocin use and acidaemia at birth has not been thoroughly investigated. In prospective studies of induced or augmented labor in which high- versus low-dose protocols for oxytocin administration have been compared, no increased risk of acidaemia has been found [34-37]. Higher doses resulted in increased rates of hyperstimulation in some studies, although none demonstrated any significant difference in neonatal outcomes [35, 37, 38].

A recent systematic review [27] showed that the system of administration of high dosage of oxytocin was associated to a reduction in the number of caesarean sections and in the duration of labor compared to an increase in episodes of uterine hypertonus. We have written we were against this uncritical and depersonalized use of meta-analysis [39]. In studies, strict protocols limited the use of oxytocin, and discontinuation or decrease of the infusion were applied in situations of hyperstimulation, resulting in improvement of the fetal status [40]. Consequently, results in studies regarding the association between oxytocin use and acidaemia are conflicting. An explanation for this may be that if strict guidelines are followed for oxytocin administration, as for controlled clinical studies, with regard to supervision of contraction frequency and FHR patterns, the risk of fetal acidosis at birth could be avoided [40]. However, this focus is not always present in real-life daily clinical situations.

There is a need of studies based on practical or pragmatic trials, which should register daily clinical practice, and provide answers to different types of questions compared to randomized controlled trials.

The need to integrate these two types of knowledge in evidence-based medicine has been recently stigmatized; fundamentally, there is no clear line that separates efficacy studies from those which assess effectiveness [41].

It is well known that there is a linear relationship between the amount of synOT administered during labor and acid base equilibrium at birth, and that hyperactive uterine contraction pattern and synOT use are the most important risk factors for acidaemia at birth [40]. Moreover, increased uterine contractility is a risk factor for hypoxic/ischemic encephalopathy in full-term newborns [42].

In addition, various studies show that the short-term behavior of human newborns is influenced by the use of synOT during labor. Fewer pre-feeding cues were observed in infants exposed to synOT versus those unexposed and differences were significant for brief and sustained hand to mouth cues [21]. In a pilot study of 20 healthy newborns exposed to intrapartum synOT and epidural, less sucking activity was observed in newborns exposed to higher versus lower intrapartum synOT dosage ($p = 0.03$) [43]. Additionally, three months after birth, there was less exclusive breastfeeding in women exposed to higher versus lower intrapartum synOT dosage [43]. An epidemiology study found that immediate postpartum administration of synOT significantly related to a 6-8% reduction in breastfeeding at 48 h postpartum [44]. In another study [21], 44% of exposed infants demonstrated a low level of pre-feeding organization, compared to none from the unexposed group. In contrast, 25% of exposed versus 64% of unexposed infants demonstrated high pre-feeding organization. After adjusting for covariates, exposed infants had 11.5 times (95% CI: 1.8-73.3) the odds of demonstrating low/medium versus high levels of pre-feeding organization compared to unexposed infants [21].

SynOT was recently added to the list of medication designated as high-alert by the USA Institute for Safe Medication [45]. High-alert medications are drugs that bear a heightened risk of causing significant patient harm when they are used in error.

The common mistakes regarding synOT use in clinical practice need to be emphasized, not least in view of the fact that the use of synOT is liberal, widespread and is on the increase. The role of synOT is a frequent issue in malpractice cases regarding labor and has been estimated to cause harm in 20-30% of such cases [46]. Violation of guidelines regarding use of synOT is probably one reason for adverse neonatal outcomes [46]. It is unlikely that there is a lack of awareness of their existence and their contents. A possible reason is that non-adherence only uncommonly results in an adverse neonatal outcome experienced by the individual midwife or physician, since many fetuses have the ability to tolerate hyperstimulation without becoming seriously affected [46], with the consequence that staff members lose their awareness of adverse side effects, such as hyper-stimulation of contractions [43]. This mechanism, really important in obstetrics and in all contexts with low prevalence of side effects, is known as the normalization of deviance [12].

In our opinion, the epidemic level of use that synOT has reached in Western countries is in part due to the fact that, in delivery rooms, a diagnosis is not usually carried out, and we tend to observe events that take place and to give them a name (slow down of cervimetric curve, secondary arrest of dilation, prolonged latent phase, arrest of progression of the presenting part, etc.). These names do not correspond to the search for an etiology and, therefore, etiological therapies are not applied.

As already said, synOT is often used to treat dystocia, but one of the real problem is that there is no universal consensus on the definition of dystocia. One way to define labor abnormalities is to divide them into protraction disorder (slower than normal) and arrest disorder (complete cessation of progress). To diagnose either of these disorders, the woman must be in the active phase of labor. The World Health Organization defines protraction disorder as less than 1 cm/h in cervical dilatation for a minimum of 4 hours [47].

The term “cervical dystocia” is just the description of a biological phenomenon, during which the uterine cervix dilates slowly or the part presented does not progress correctly into the pelvic cavity, which is a biological warning sign and can be used as a clinical screening test. The cause of this abnormality might be searched both in maternal and fetal conditions. Causes of dystocia can be cephalo-pelvic disproportion, deflection attitude, occiput posterior position and inefficient uterine contractions [48]. If we look for a causal diagnosis regarding labor arrest, we can discover that the incorrect position of the fetus is the cause in 60% of cases [49]. Other aspects may also be taken into consideration when discussing causes of dystocia, such as psychological factor, and risk factors

such as high maternal age, high body mass index, infertility, epidurals use and stress during labor [50, 51]. It should therefore be clear that therapy for dystocia cannot be the same and monotonic for all these causes. The ACOG (American College of Obstetricians and Gynecologists) bulletin on dystocia correctly claims that: "Abnormal labor or dystocia in the first or second stage of labor can be associated with one or more abnormalities of the cervix, uterus, maternal pelvis, or fetus. In addition, advanced maternal age, nulliparity, maternal anxiety, multiple gestation, and intrauterine infections have been reported to be associated with longer active labors." The ACOG committee of experts, however, do not draw the natural consequences from the assumptions, even though correct, as they do not make any further mention of these causative agents and, on the other hand, continues saying: "Dystocia is defined as abnormal labor (...) A more practical classification is to categorize labor abnormalities as slower-than-normal (protraction disorders) or complete cessation of progress (arrest disorders)"; the bulletin therefore concludes that: "Oxytocin administration should be considered when a patient has a protraction or arrest disorder" [5].

Once labor has been diagnosed [52, 53], we must understand the correct speed with which to proceed, considering that any cervimetric curve that we choose from the many suggested by literature is, once again, the macroscopic description of a biological phenomenon, and not the absolute benchmark for that particular woman, at that particular time of her labor [54]. In other word the speed at which cervical dilation continues during labor for each woman is characteristic for that particular woman and not for others as demonstrated by the elegant work of Incerti et al. [55]. Obstetricians and midwives must know and respect the individuality of each woman; deviation for the percentage is not a diagnosis, but only an alarm signal that needs a diagnosis. Unfortunately, soon after their introduction, cervical dilatation curves were named "labor curves" as a result of an uncensored "clinical rhotacism": the cervix became the totality of labor and a normal labor had to be forced into a normal dilating cervix. This is the result of what we could define as a minimalistic approach to the management of labor where cervical dilatation becomes a diagnostic test on top of which medical action is taken in a cascade of interventions, amniotomy, oxytocin infusion and caesarean section, without any attempt to understand the reason of this type of delay in dilatation (**Fig. 1**).

A more open approach should be applied during labor towards the different causes of dystocia, not confusing the causes of the dystocia, both maternal and fetal, with the consequences of the same, that are lack of progress in dilation and descent of the presenting part. We call this approach "comprehensive management" of dystocia (**Fig. 2**).

In our experience, we utilized the same paradigm of Western medicine to human labor that is applied to any deviation from normal physiology: diagnosis before therapy.

We have known, for some time now, that the therapeutic use of change of maternal posture [30, 56] or digital rotation from occipito-posterior to occipito-anterior decreases the need for caesarean sections [32, 57, 58].

There are many open questions that need to be studied further. In addition to fetal position and behavior, there are further important questions that the therapist must consider when faced with an arrest disorder in labor, such as the psychological state of the woman or the type of relationship the woman has with those assisting her during labor and birth or with her partner. The psychological state of the mother is closely connected to the duration of labor [59, 60]. In effect, taking into consideration and diagnosing the psychological state of the parturient in the case of dystocia, we can also carry out a diagnosis that includes not only the therapeutic possibility of augmentation, but also alternative possibilities such as, for example, the presence of a midwife specifically trained or the use of pain control techniques [61]. Of course, if the problem that causes the dystocia is the mother's character, the cure cannot be only or exclusively the speeding up of labor using amniotomy or oxytocin [62].

A further aspect not well studied regarding labor is the quality of the relationship that the mother has with those assisting her during labor and birth; which is closely connected with the perception of pain [63]. The relationship with the midwife can and must therefore be therapeutic [64, 65]. Some interesting explanations have been given about relationship between length of labor and stress [66]. When we prescribe synOT we must remember that oxytocin has been called "the Great Facilitator of Life" [67], it interferes with numerous human homeostatic systems (**Fig. 3**); administering it means that we must be reasonably sure that the benefits of the medication outweigh the costs. In a study [68] – in which the authors compare, one month postpartum, the childbirth experiences of primiparous women with slow labor progress who

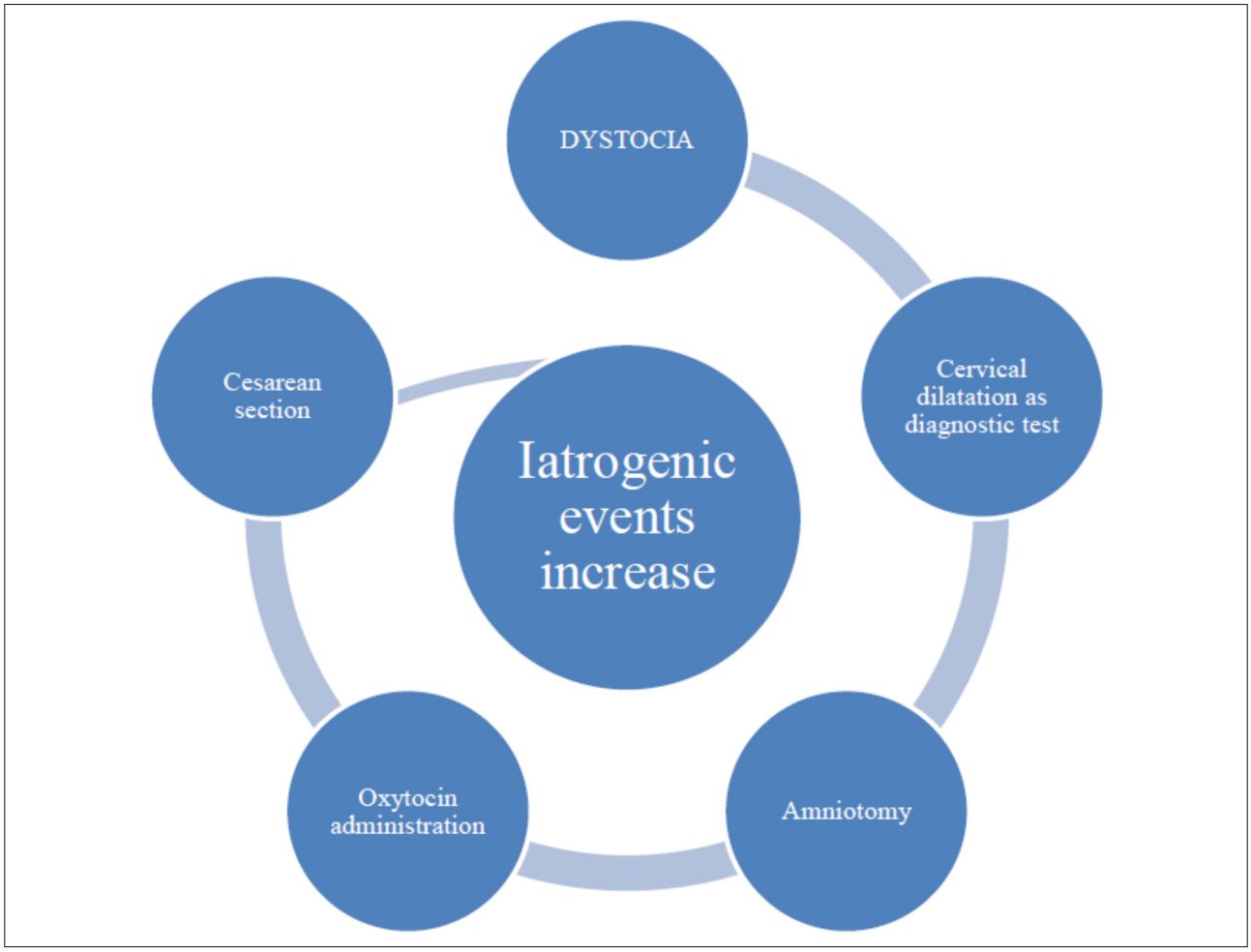

Figure 1. The vicious circle of the minimalistic approach to the management of labor. Cervical dilatation becomes a diagnostic test on top of which medical action is taken in a cascade of interventions: amniotomy, oxytocin administration and caesarean section, without any attempt to understand and treat the reason of delay in dilatation.

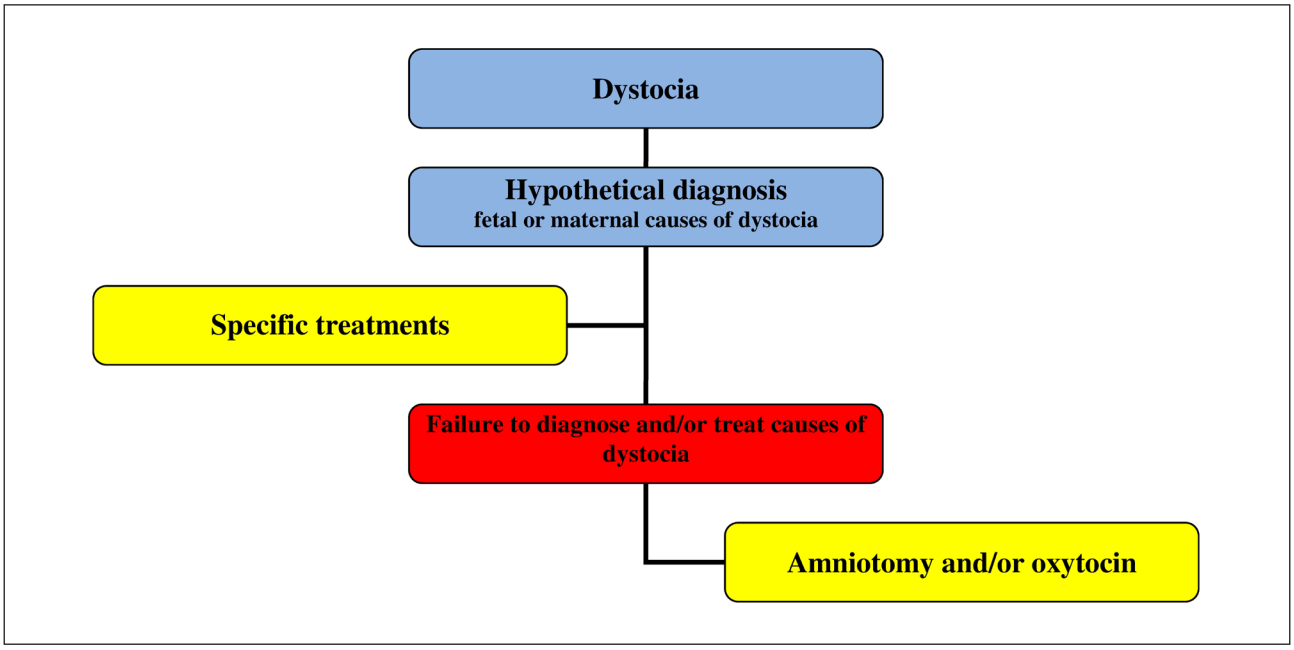

Figure 2. Comprehensive management of cervical dystocia during human labor.

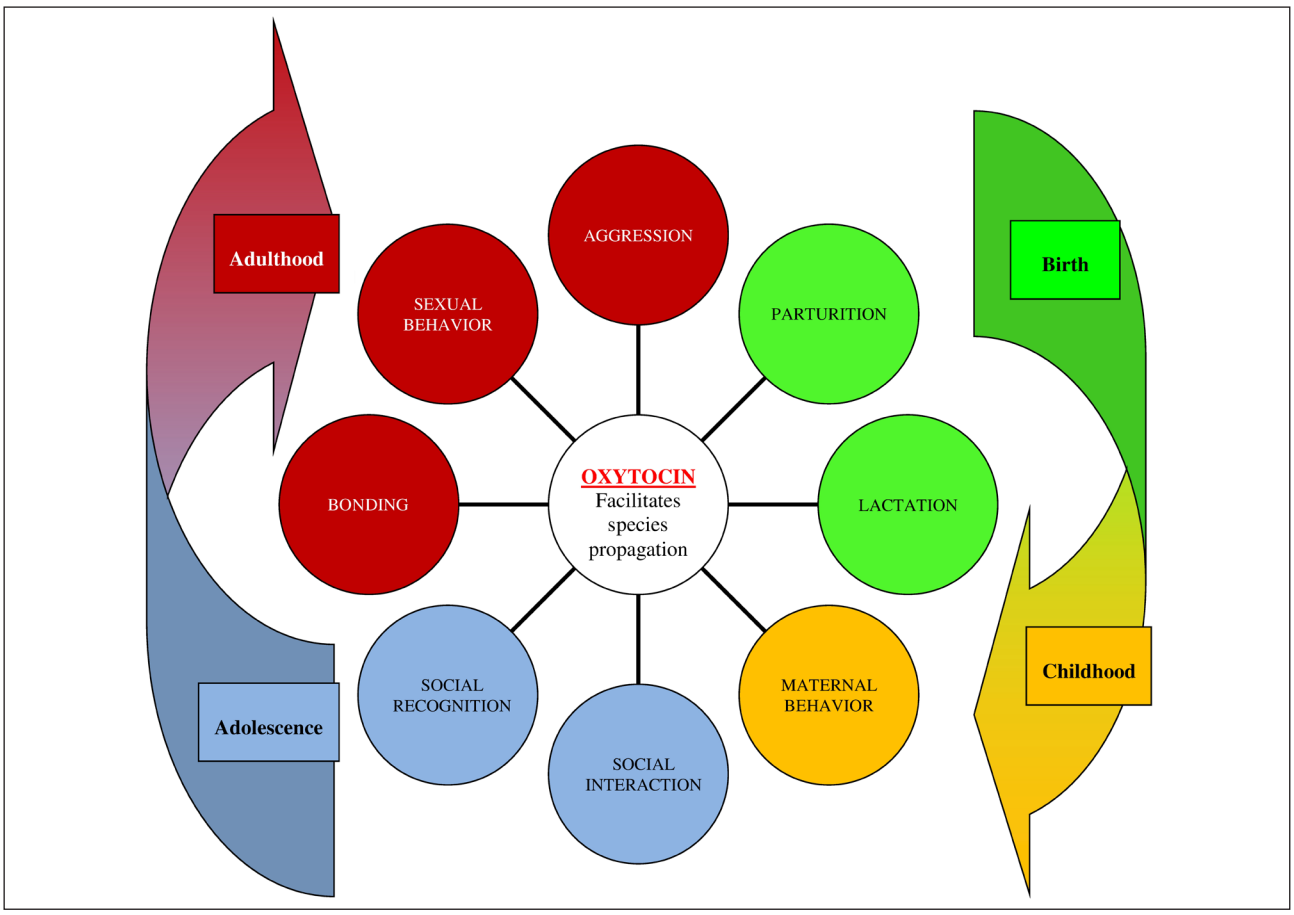

Figure 3. The spheres of life illustrate numerous areas at which oxytocin may affect behavior and physiology to facilitate the propagation of the species in different periods of life. Modified from Lee et al., 2009 [67].

had received early versus postponed oxytocin augmentation – early oxytocin augmentation for slow labor progress does not appear to be more beneficial than expectant management regarding women's perceptions of childbirth one month postpartum. The authors conclude saying: "Given the risks for the fetus associated with oxytocin treatment, prudent expectant management seems to be a safe and viable alternative" [68]. We must change our clinical habits and behavior, motivating them with therapeutic actions supported by etiological diagnosis. The administration of oxytocin must be reserved for the category of parturients who have, objectively, a reduction in the effectiveness and frequency of uterine contractility, after the exclusion of all other possible causes.

In our department, simply using the cervimetric curve as a screening tool and not as a diagnostic tool, in two years we have reduced the use of synOT from 40% to 5% on all labor and delivery. Amniotomy was reduced from 22% to 2.6%. These changes have led to a significant reduction in iatrogenic interventions on childbirth. The overall result has been the reduction in the number of caesarean sections, especially in the first four out of ten Robson's groups [26], In particular, in group one of Robson the proportion of caesarean sections was reduced from 25.6% to 6% [personal data].

Personalized labor

It is crucial to consider labor as a unique process involving not only the length of cervical dilatation and descent of the fetal presented part but also and primarily the woman with her obstetric and personal history, her feelings and behaviors. Adopting a customized approach that we name "comprehensive management" versus minimalistic management of dystocia in laboring patients belonging to the first four out of ten Robson's groups reduces the use of oxytocin and amniotomy for augmentation of labor, leading to a reduction in the number of caesarean sections performed during labor.

In probability theory, the normal (or Gaussian) distribution is a continuous probability distribution, defined by the formula:

$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

Gaussian distribution is said to be normally distributed and is called a normal deviate. If $\mu = 0$ and $\sigma = 1$, the distribution is called the *standard normal distribution* or the *unit normal distribution*, and a random variable with that distribution is a *standard normal deviate*. Since its introduction, the normal distribution has been known by many different names: the law of error, the law of facility of errors, Laplace's second law, Gaussian law, etc. However, by the end of the 19th century some authors had started using the name *normal distribution*, where the word "normal" was used as an adjective – the term now being seen as a reflection of the fact that this distribution was seen as typical, common – and thus "normal". However, as early as 1920, Person wrote: "Many years ago I called the Laplace-Gaussian curve the *normal* curve, which name, while it avoids an international question of priority, has the disadvantage of leading people to believe that all other distributions of frequency are in one sense or another *abnormal*..." [69].

In conclusion, the mean and median (indicators of central tendency) are abstract measures that are not suitable for each single case, they describe a biological phenomenon but do not, alone, enable us to carry out a diagnosis. Normality and cervimetric curves must be used as a guide to highlight the need to carry out a diagnosis and not be used as the diagnosis itself.

Personalized medicine must take the place of percentile medicine in traditional clinical approach (diagnosis and treatment). Personalized medicine uses percentile curves to give a prognosis or carry out a diagnosis and consequent treatment using a "patient-centric" approach in which the individual profile of each single person is assessed and, on the basis of this, a specific therapeutic strategy is applied. This guarantees the patient more opportunities to be informed about the individual probabilities of becoming ill or to suffer from certain complications, also iatrogenic, and, in short, means limiting to the utmost the "toxic cost" of the diagnosis/treatment, without paying a price in terms of reduction in effectiveness.

The impact of this approach is evident not only on the quality of life of the patient, but also on the optimization of the management of health care resources. In fact, we are already questioning the sustainability of Healthcare Systems (using diagnostic/treatment methods that enable to save by carrying out specific diagnosis, which also enable to give more precise prognosis and, last but not least, use types of therapy really efficient for each individual patient, resulting in savings that are not only economical, but social too).

In the Western world, more than half the women who give birth are administered oxytocin during labor [33]. From an evolutionary or phylogenetic point of view, it is unlikely that this is really needed, and is therefore a biological need. The fact that more than half of Western women need pharmaceutical help to give birth is unreasonable and, in fact, the reasons behind the widespread and strong administration of oxytocin in the Western world are not only biological, but also cultural. Nevertheless, it can be easily seen that reducing the use of oxytocin and amniotomy enables to respect longer augmented labor times and probable lead an improvement in all the other index of maternal and newborn outcomes (spontaneous or operative labor, caesarean delivery, rate of episiotomy, acid-base balance at birth). Nevertheless, we trust that personalized therapy will improve patient outcomes, finally entering in the era of personalized medicine.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Holmgren S, Silfver KG, Lind C, Nordström L. Oxytocin augmentation during labor: how to implement medical guidelines into clinical practice. Sex Reprod Healthc. 2011;2(4):149-52.
2. Tracy SK, Sullivan E, Wang YA, Black D, Tracy M. Birth outcomes associated with interventions in labour amongst low risk women: a population-based study. Women Birth. 2007;20(2): 41-8.
3. Blix E, Pettersen SH, Eriksen H, Røyset B, Pedersen EH, Øian P. Use of oxytocin augmentation after spontaneous onset of labor. Tidsskr Nor Laegeforen. 2002;122(14):1359-62.
4. Selin L, Almström E, Wallin G, Berg M. Use and abuse of oxytocin for augmentation of labor. Acta Obstet Gynecol Scand. 2009;88(12):1352-7.
5. American College of Obstetrics and Gynecology Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin Number

49, December 2003: Dystocia and augmentation of labor. Obstet Gynecol. 2003;102(6):1445-54.

6. Kjaergaard H, Olsen J, Ottesen B, Nyberg P, Dykes AK. Obstetric risk indicators for labour dystocia in nulliparous women: a multicentre cohort study. BMC Pregnancy Childbirth. 2008;8:45.
7. Bugg GJ, Stanley E, Baker PN, Taggart MJ, Johnston TA. Outcomes of labours augmented with oxytocin. Eur J Obstet Gynecol Reprod Biol. 2006;124(1):37-41.
8. Kjaergaard H, Olsen J, Ottesen B, Dykes AK. Incidence and outcomes of dystocia in the active phase of labor in term nulliparous women with spontaneous labor onset. Acta Obstet Gynecol Scand. 2009;88(4):402-7.
9. Selin L, Wallin G, Berg M. Dystocia in labour – risk factors, management and outcome: a retrospective observational study in a Swedish setting. Acta Obstet Gynecol Scand. 2008;87(2): 216-21.
10. Svärdby K, Nordström L, Sellström E. Primiparas with or without oxytocin augmentation: a prospective descriptive study. J Clin Nurs. 2007;16(1):179-84.
11. Clark S, Belfort M, Saade G, Hankins G, Miller D, Frye D, Meyers J. Implementation of a conservative checklist-based protocol for oxytocin administration: maternal and newborn outcomes. Am J Obstet Gynecol. 2007;197(5):480.e1-5.
12. Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. Am J Obstet Gynecol. 2009;200(1): 35.e1-6.
13. Clark SL, Belfort MA, Dildy GA, Meyers JA. Reducing obstetric litigation through alterations in practice patterns. Obstet Gynecol. 2008;112(6):1279-83.
14. Herbst A, Wolner-Hanssen P, Ingemarsson I. Risk factors for acidemia at birth. Obstet Gynecol. 1997;90(1):125-30.
15. Liston WA, Campbell AJ. Dangers of oxytocin-induced labour to fetuses. Br Med J. 1974;3(5931):606-7.
16. Klink F, Grosspietzsch R, Klitzing LV, Oberheuser F. Uterine contraction intervals and transcutaneous levels of fetal oxygen pressure. Obstet Gynecol. 1981;57(4):437-40.
17. Vanner T, Gardosi J. Intrapartum assessment of uterine activity. Baillieres Clin Obstet Gynaecol. 1996;10(2):243-57.
18. Johnson N, van Oudgaarden E, Montague I, McNamara H. The effect of oxytocin-induced hyperstimulation on fetal oxygen. Br J Obstet Gynaecol. 1994;101(9):805-7.
19. Simpson KR, James DC. Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns. Am J Obstet Gynecol. 2008;199(1): 34.e1-5.
20. Insel TR. The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior. Neuron. 2010;65(6):768-79.
21. Bell AF, White-Traut R, Rankin K. Fetal exposure to synthetic oxytocin and the relationship with prefeeding cues within one hour postbirth. Early Hum Dev. 2013;89(3):137-43.
22. Carter CS. Developmental consequences of oxytocin. Physiol Behav. 2003;79(3):383-97.
23. Handlin L. Human-Human and Human-Animal Interaction. Some Common Physiological and Psychological Effects. Doctoral Thesis, Swedish University of Agricultural Sciences, Skara, 2010.
24. Gordon I, Zagoory-Sharon O, Leckman JF, Feldman R. Oxytocin and the development of parenting in humans. Biol Psychiatry. 2010;68(4):377-82.
25. Hayes EJ, Weinstein L. Improving patient safety and uniformity of care by a standardized regimen for the use of oxytocin. Am J Obstet Gynecol. 2008;198(6):622.e1-7.
26. Robson M, Hartigan L, Murphy M. Methods of achieving and maintaining an appropriate caesarean section rate. Best Pract Res Clin Obstet Gynaecol. 2013;27(2):297-308.
27. Wei SQ, Luo ZC, Qi HP, Xu H, Fraser WD. High-dose vs low-dose oxytocin for labor augmentation: a systematic review. Am J Obstet Gynecol. 2010;203(4):296-304.
28. Perry RL, Satin AJ, Barth WH, Valtier S, Cody JT, Hankins GD. The pharmacokinetics of oxytocin as they apply to labor induction. Am J Obstet Gynecol. 1996;174(5):1590-3.
29. American College of Obstetricians Gynecologists. ACOG technical bulletin. Induction of labor. Number 217 – December 1995 (replaces no. 157, July 1991). Int J Gynaecol Obstet. 1996;53(1):65-72.
30. Racinet C. Maternal posture during parturition. Gynecol Obstet Fertil. 2005;33(7-8):533-8.
31. Priddis H, Dahlen H, Schmied V. What are the facilitators, inhibitors, and implications of birth positioning? A review of the literature. Women Birth. 2012;25(3):100-6.
32. Reichman O, Gdansky E, Latinsky B, Labi S, Samueloff A. Digital rotation from occipito-posterior to occipito-anterior decreases the need for cesarean section. Eur J Obstet Gynecol Reprod Biol. 2008;136(1):25-8.
33. Shields SG, Ratcliffe SD, Fontaine P, Leeman L. Dystocia in nulliparous women. Am Fam Physician. 2007;75(11):1671-8.
34. Thorp JA, Boylan PC, Parisi VM, Heslin EP. Effects of high-dose oxytocin augmentation on umbilical cord blood gas values in primigravid women. Am J Obstet Gynecol. 1988;159(3):670-5.
35. Merrill DC, Zlatnik FJ. Randomized, double-masked comparison of oxytocin dosage in induction and augmentation of labor. Obstet Gynecol. 1999;94(3):455-63.
36. Sadler LC, Davison T, McCowan LM. A randomised controlled trial and metaanalysis of active management of labour. BJOG. 2000;107(7):909-15.
37. Smith JG, Merrill DC. Oxytocin for induction of labor. Clin Obstet Gynecol. 2006;49(3):594-608.
38. Seitchik J, Castillo M. Oxytocin augmentation of dysfunctional labor. I. Clinical data. Am J Obstet Gynecol. 1982;144(8):899-905.
39. Ferrazzi E, Paganelli A, Ragusa A. Oxytocin regimen for labor augmentation, labor progression, and perinatal outcomes. Obstet Gynecol. 2012;119(2 Pt 1):380-1.
40. Jonsson M, Nordén-Lindeberg S, Ostlund I, Hanson U. Acidemia at birth, related to obstetric characteristics and to oxytocin use, during the last two hours of labor. Acta Obstet Gynecol Scand. 2008;87(7):745-50.

41. Horwitz RI, Abell JE, Christian JB, Wivel AE. Right answers, wrong questions in clinical research. Sci Transl Med. 2014;6(221):221fs5.
42. Hayes BC, McGarvey C, Mulvany S, Kennedy J, Geary MP, Matthews TG, King MD. A case-control study of hypoxic-ischemic encephalopathy in newborn infants at >36 weeks gestation. Am J Obstet Gynecol. 2013;209(1):29.e1-19.
43. Olza Fernández I, Marín Gabriel M, Malalana Martínez A, Fernández-Cañadas Morillo A, López Sánchez F, Costarelli V. Newborn feeding behaviour depressed by intrapartum oxytocin: a pilot study. Acta Paediatr. 2012;101(7):749-54.
44. Jordan S, Emery S, Watkins A, Evans JD, Storey M, Morgan G. Associations of drugs routinely given in labour with breastfeeding at 48 hours: analysis of the Cardiff Births Survey. BJOG. 2009;116(12):1622-32.
45. Institute for Safe Medical Practices. High-alert medications. Available at: www.ispm.org, last access: March 2014.
46. Jonsson M, Nordén SL, Hanson U. Analysis of malpractice claims with a focus on oxytocin use in labour. Acta Obstet Gynecol Scand. 2007;86(3):315-9.
47. World Health Organization Maternal Health and Safe Motherhood Programme. World Health Organization partograph in management of labour. Lancet. 1994;343(8910):1399-404.
48. O'Driscoll K, Meagher D, Robson M. Active Management of Labour. 4th edn. Mosby Ireland, 2004.
49. Marpeau L, Sergent F, Manson F, Verspyck E, Eurin D. [Mechanisms of the stagnation of dilatation in the active phase of labor]. [Article in French]. Gynecol Obstet Fertil. 2002;30(4):282-5.
50. Nationella Medicinska Indikationer. [National Medical Indications 2011, Indication for augmentation with oxytocin in active labour]. [Report in Swedish]. Available at: http://www.skl.se/MediaBinaryLoader.axd?MediaArchive_FileID=3ddb2190-c60b-4109-ac7f-26fe2c355854, last access: March 2014.
51. Nerum H, Halvorsen L, Oian P, Sørlie T, Straume B, Blix E. Birth outcomes in primiparous women who were raped as adults: a matched controlled study. BJOG. 2010;117(3):288-94.
52. World Health Organization. Diagnosis of Labour. http://www.who.int/surgery/publications/Obstetricsafetyprotocols.pdf, last access: March 2014.
53. Ragusa A, Mansur M, Zanini A, Musicco M, Maccario L, Borsellino G. Diagnosis of labor: a prospective study. Med Gen Med. 2005;7(3):61.
54. Zhang J, Troendle JF, Yancey MK. Reassessing the labor curve in nulliparous women. Am J Obstet Gynecol. 2002;187(4):824-8.
55. Incerti M, Locatelli A, Ghidini A, Ciriello E, Consonni S, Pezzullo JC. Variability in rate of cervical dilation in nulliparous women at term. Birth. 2011;38(1):30-5.
56. Stremler R, Hodnett E, Petryshen P, Stevens B, Weston J, Willan AR. Randomized controlled trial of hands-and-knees positioning for occipitoposterior position in labor. Birth. 2005;32(4):243-51.
57. Haddad B, Abirached F, Calvez G, Cabrol D. Manual rotation of vertex presentations in posterior occipital-iliac or transverse position. Technique and value. J Gynecol Obstet Biol Reprod (Paris). 1995;24(2):181-8.
58. Phipps H, de Vries B, Lee PN, Hyett JA. Management of occiput posterior position in the second stage of labour: a survey of obstetric practice in Australia and New Zealand. Aust N Z J Obstet Gynaecol. 2012;52(5):450-4.
59. Albers LL. The evidence for physiologic management of the active phase of the first stage of labor. J Midwifery Womens Health. 2007;52(3):207-15.
60. Lowe NK. A review of factors associated with dystocia and cesarean section in nulliparous women. J Midwifery Womens Health. 2007;52(3):216-28.
61. Cluett ER, Pickering RM, Brooking JI. An investigation into the feasibility of comparing three management options (augmentation, conservative and water) for nulliparae with dystocia in the first stage of labour. Midwifery. 2001;17(1):35-43.
62. Johnston RG, Brown AE. Maternal trait personality and childbirth: The role of extraversion and neuroticism. Midwifery. 2013;29(11):1244-50.
63. Leap N, Sandall J, Buckland S, Huber U. Journey to confidence: women's experiences of pain in labour and relational continuity of care. J Midwifery Womens Health. 2010;55(3):234-42.
64. Pascali-Bonaro D, Kroeger M. Continuous female companionship during childbirth: a crucial resource in times of stress or calm. J Midwifery Womens Health. 2004;49(4 Suppl 1):19-27.
65. Greulich B, Tarrant B. The latent phase of labor: diagnosis and management. J Midwifery Womens Health. 2007;52(3):190-8.
66. Lowe NK, Corwin EJ. Proposed biological linkages between obesity, stress, and inefficient uterine contractility during labor in humans. Med Hypotheses. 2011;76(5):755-60.
67. Lee HJ, Macbeth AH, Pagani JH, Young WS 3rd. Oxytocin: the great facilitator of life. Prog Neurobiol 2009;88(2):127-51.
68. Bergqvist L, Dencker A, Taft C, Lilja H, Ladfors L, Skaring-Thorsén L, Berg M. Women's experiences after early versus postponed oxytocin treatment of slow progress in first childbirth – a randomized controlled trial. Sex Reprod Healthc. 2012;3(2):61-5.
69. Pearson K. Notes on the History of Correlation. Biometrika. 1920;13(1):25-45.