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Oxytocin augmentation and neurotransmitters in prolonged delivery: An experimental appraisal

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ABSTRACT

The uterus is a highly innervated organ, and during labor, this innervation is at its highest level. Oxytocinergic fibers play an important role in labor and delivery and, in particular, the Lower Uterine Segment, cervix, and fundus are all controlled by motor neurofibers. Oxytocin is a neurohormone that acts on receptors located on the membrane of the smooth cells of the myometrium. During the stages of labor and delivery, its binding causes myofibers to contract, which enables the fundus of the uterus to act as a mediator. The aim of this study was to investigate the presence of oxytocinergic fibers in prolonged and non-prolonged dystocic delivery in a cohort of 90 patients, evaluated during the first and second stages of labor. Myometrial tissue samples were collected and evaluated by electron microscopy, in order to quantify differences in neurofibers concentrations between the investigated and control cohorts of patients. The authors of this experiment showed that the concentration of oxytocinergic fibers differs between non-prolonged and prolonged dystocic delivery. In particular, in prolonged dystocic delivery, compared to non-prolonged dystocic delivery, there is a lower amount of oxytocin fiber. The increase in oxytocin appeared to be ineffective in patients who experienced prolonged dystocic delivery, since the dystocic labor ended as a result of the altered presence of oxytocinergic fibers detected in this group of patients.

1. Introduction

The Gravid Uterus (GU) represents an organ richly innerved by neurofibers (Ncs) and during labor and delivery, this innervation is at its highest level. The uterine innervation is by Ncs and Neurotransmitters (Nts) in the fundus, body and cervix with different anatomical distributions of NCS in these three anatomical areas. In fact, Di Tommaso et al. demonstrated in non-pregnant uterus that the cervix shows a wide innervation, with a large amount of Ncs than the corpus of the uterus [1]. Furthermore, this study revealed in the cervix, a high rate of enkephalinergic and oxytocinergic fibers and a smaller amount of adrenergic, dopaminergic, serotoninergic, SP-positive, CIP-positive, prolactinergic and polypeptide growth protein fibers. Although Di Tommaso et al. detected a greater amount of enkephalinergic and

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oxytocinergic fibers, they were unable to show that these peacemakers existed in non-pregnant uteruses. However, these authors showed the high concentration of Ncs enkephalinergic and OXT fibers in correspondence of internal uterine orifice (IUO). The isthmus of the uterus is an upper third of the cervix of the uterus and it is the portion that separates the cervix from the uterine body [2]. The uterine isthmus is a canal that in non-pregnant uterus has a length of 5–7 mm. The upper limit of the isthmus is a narrowing, called the anatomical orifice of Aschoff, the upper limit that cannot be circumscribed and called the histological IUO. In pregnant uterus, isthmus plays a very important role because it participates in the lower uterine segment (LUS) formation. The LUS is an anatomical entity developing during pregnancy and reaching the maximum size during childbirth. It disappears after the placental delivery. The LUS was anatomically described as the thin lower part of the uterus at full term of pregnancy, located between the body and the cervix of the uterus. The shape of the LUS is similar to a cap opened in the top and, in the lower part, LUS is connected to the cervix. The LUS at term of pregnancy has a posterior wall, two lateral walls and a wider and more convex anterior wall of 9–10 cm.

1.1. The upper and lower uterine segment anatomy and innervation

The upper limit is not clearly delimited because of the size of the LUS, which is subject to variation for the parity, for the size of the fetus, placenta, amniotic fluid, and abnormal labor. Some authors considered a transient and positionally variable ring of muscle contraction, as the upper limit of the LUS. When this muscular ring becomes pathological, it is called Bandl's ring. Between the lower uterine segment (LUS) and the upper uterine segment (UUS), the Bandl's ring demonstrates a shift in the uterine wall's thickness. The Bandl's ring in dystocic and prolonged dystocic labor (PDL) can be associated to LUS overdistension, called uterine "sacculation" or "marsupialization", showing an "hourglass uterus" appearance. Some studies, performed by Scanner Electron microscopy (SEM) and Fluorescence Microscopy (FM), revealed in the Post Cesarean Uterine Scar (PCUS) e presence of SP, VIP neurofibers. Presence of Nts and of Ncs in **PCUS** demonstrated the LUS innervation [3]. The LUS contains many Ncs, as showed by Malvasi et al. [4]. They demonstrated that in prolonged dystocic delivery (PDD), the LUS over-distension caused important anatomical changes in the myometrial innervation, with LUS and UUS modifications [4]. The LUS structural modifications during labor, especially in PDL, included different anatomical elements, as collagen, muscles, and vessels [5]. The impact of dystocia and the tensile characteristics and changes of the LUS in previous caesarean scars were documented by Buhimschi et al. [6]. Malvasi et al. revealed that in the PDD there is a morphometric reduction of adrenergic fibers, evaluated by SEM and FM [7], and of enkephalinergic neurofibers in comparison to non-progressive dystocic labor (NPDD) [8]. This study investigated, by SEM and FM, the presence of oxytocinergic Nfc in NPDD and PDD during cesarean section (CS). Two groups performed a labor without induction by prostaglandin, but by oxytocin, because the PG could alter the quantification of oxytocin (OXT) fibers. The OXT neurofibers are the parasympatic and orthosympatic sensitive and motor (afferent and efferent) postganglionic neurofibers.

1.2. The uterine innervation

The uterus is richly innervated by parasympatic and orthosympatic fibers. The parasympatic component is mediated by the pelvic nerve, the orthosympatic innervation is represented by mesenteric inferior and hypogastric ganglions [9]. The preganglior fibers that start form uterus go through the pelvic, hypogastric and aortic plexus and end in the spinal ganglions T10–11-12 [10]. The fibers start from vagina, cervix and LUS following the pudendal nerve and pelvic nerve, ending in the S2-S3-S4 ganglions. Uterus innervations are organized in the uterus-vaginal plexus in two peduncles: the cervix-isthmic peduncle and the uterine corpus peduncle. The motor fibers of uterine corpus belong to the orthosympatic system [11]. The motor fibers of the LUS and those of the superior portion of vagina belong to the parasympatic system [12]. During the labor, the uterine fundus plays a pacemaker role, with contractions involving LUS and cervix [13]. The oxytocinergic fibers play an important role in labor and delivery, particularly with motor-neurofibers that from UPS caused contractions also in LUS and in cervix (Fig. 1).

The aim of this study was to investigate the presence of oxytocinergic fibers in prolonged and non-prolonged dystocic labor, in a cohort of pregnants evaluated during the first and second stages of labor. This study did not investigate OXT neurotransmitters and OXT receptors, but focused on the OXT neurofibers detection and their quantification, by morphometric OXT neurofibers evaluation in the LUS.

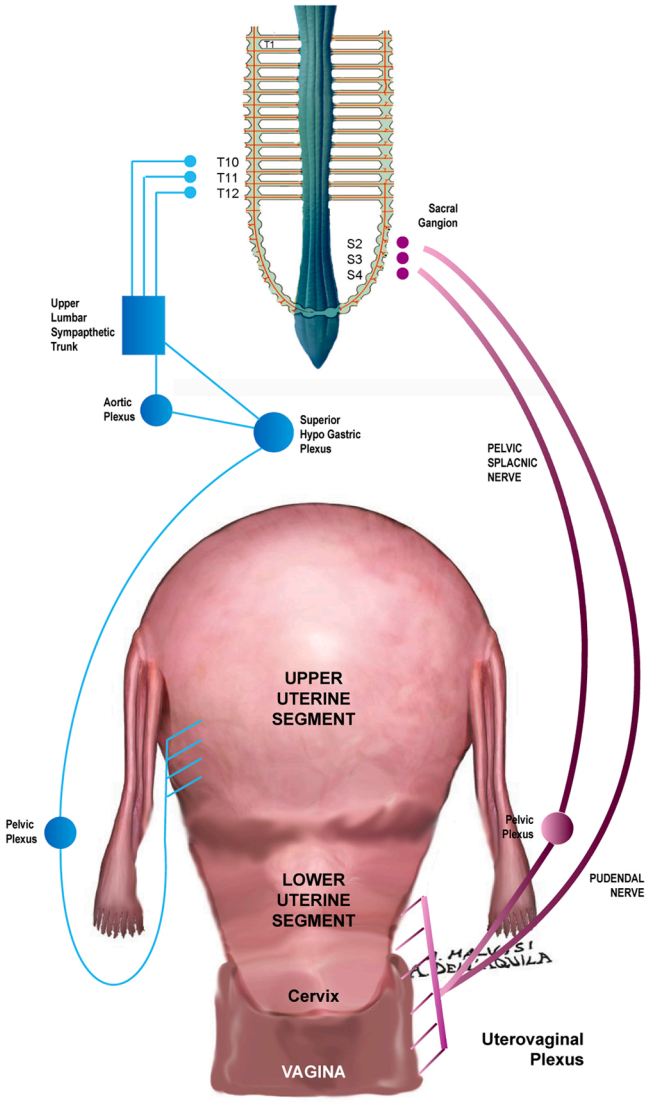

Fig. 1. Gravid uterine innervation representation. In the drawing the pregnant uterus in labor is divided into three parts: UUS, LUS and cervix. The usual ring of muscle contraction is situated between UUS and LUS (perhaps a pacemaker site). The preganglior fibers that start form uterus, go through the pelvic, hypogastric, and aortic plexus and end in the spinal ganglions T10–11-12 (blue light line). The fibers start from vagina, cervix and LUS, and follow the pudendal nerve, pelvic nerve and end in the S2-S3-S4 ganglions (purple lines). The peduncle of the cervico-isthmic nerve receives fibers from the hypogastric ganglion and forms the Lee-Frankenauser ganglion on the posterior portion of the cervix and LUS, which regulates sensory and motor innervation especially of the lower part of the uterus.

2. Results

A total of 136 patients enrolled, only 90 completed this study. The remaining 46 women were lost during the study for different reason: 20 refused to undergo LUS biopsy, 17 patients underwent urgent CS at night (there was no histology laboratory available) and 9 pregnant women subsequently refused to continue the study. The patients were homogenously subdivided in two groups as follows: 44 NPDD group 1 as women scheduled for CS in dystocic labor and 46 women in group 2, as submitted to CS for PDD. The mean age of the pregnant patients was similar in both groups, so no statistical differences were found for the mean BMI, gestational age of delivery, and birthweight for both groups (Table 1). The histologic samples examined to quantify the distribution of OXT nerve fibers demonstrated a different concentration of OXT fibers between NPDD and PDD delivery. In particular, a significant and notable reduction concentration of OXT fibers in LUS of patient with PDD (10 + - 2.4) in comparison with patients of CS in NPDD (17 + −5.7) where identify by FM evaluations. All these results are reported in Table 2 and Fig. 2.

3. Discussion

OXT was the first neurohormone and neuropeptide biochemically described and synthesized [14]. OXT has effects on the central [15] and autonomic nervous system [16,17]. The OXT is a neurohormone and neurotransmitter that plays an important role in delivery. The OXT and the vasopressin neuropeptides have a similar biochemical structure and represent an integrated neurohormone system [18].

Estradiol and progesterone have an impact in the oxytocin receptor's function [19]. These steroids receptors, as OXT receptors, act on the myometrial contractility at term of pregnancy [20,21]. There is a correlation between OXT and endogenous prostaglandin F2 alpha in labor [22], particularly this prostaglandin acts on the Upper Uterine Segment (UPS) and the LUS [23].

The literature reports several studies about the relationship with synthetic OXT augmentation and normal and abnormal labor duration. Many studies have been published on dystocic labor and oxytocin augmentation. The PDD and oxytocin augmentation have been less investigated [24,25].

The myometrium, frequently containing blood vessels, is where the post-ganglionic sympathetic and parasympathetic nerve fibers terminate. These fibers have varicosities at their extremities (containing synaptic vesicle) from which they produce Nts and a significant amount of OXT during labor and delivery. The functions of the **UPS** and of the LUS are coordinated during pregnancy and particularly during labor and in normal delivery. The uterus may take on the shape and size necessary to hold and move the fetus thanks to the smooth muscle's structure, which allows for contractions.

Myometrial muscle cells communicate with gap junctions, which synchronize myometrial function through conduction of electrophysiological signals during labor, as a single smooth unit. Several electrophysiological behaviors were observed in uterine smooth muscle cells, such as action potentials (spikes with a smooth plateau, spikes with an oscillatory plateau, and bursts of spikes). The action potential with oscillatory plateau resembles the electrophysiological response recorded in hair cell [26,27]. Recently, a model approach was used to understand the ionic currents dynamic during the excitability of uterine smooth muscle by using Huxley and Hodgkin models that is able to understand the role of ion channels [28]. Further, by using modeling the effects of the estradiol (via reduction in calcium and potassium selective channel conductance), oxytocin (via an increase in intracellular calcium release) and the tocolytic nifedipine (via a block of L-type calcium channels currents) on action potentials and contractions are also reproduced [29], indicating the pivotal role of ion channel in labor and delivery. Oxytocin acts by binding to specific receptors present on the membrane of smooth myocytes, activating a cascade of intracellular signals that prolong cytosolic calcium and modifies the ion channel activity [30].

Smith et al. reported that in order to improve the synchronous contractions for labor, the uterine muscle works as voltage oscillator that becomes increasingly coupled by gap junctions till the end of pregnancy [31]. These muscle junctions increase in number prior to labor. This is regulated by estrogen, progesterone, and prostaglandin. Many studies in animals and humans show that a single action potential does not travel distances greater than a few centimeters [32]. The contractions of the smooth cells through myosin and actine machinery are regulated by a pathway that involves voltage-gated Ca2 + channels [33]. The depolarizations determine an activation of voltage-gated Ca2 + channels and trigger the vesicles exocytosis with releases OXT and OXT-receptor activation on the smooth cells (Fig. 3).

The OXT-receptors belong to the G-protein coupled receptor family; the binding of oxytocin to receptors of uterine smooth cells determines the uterine contractions by starting the phospholipase C pathway that results in the production of 1,2-diacylglicerol and inositol 1,4,5-triphosphate, which activates calcium from intracellular stock [34].

Although there are many studies about the uterine pacemaker, interactions between the uterine environment and ion channel activity are not still clear [35,36].

During labor, the simultaneous contractions of uterine muscle cells increase intrauterine pressure for the cervix dilatation. The contraction of the larger area results in a raised intrauterine pressure. This process causes myocyte depolarization in other parts of the uterus, generating synchronous activity and more force in triggered recruited into the contraction [31]. Conversely, Andersen et al. demonstrated that abnormal uterine contractions may result from pacemaker in unusual locations (mid-uterus), but further studies must be necessary to clarify the mechanism [37]. It is suggestive to think that the absence of coordination between UPS and LUS in the prolonged and obstructed labor could determine the presence of the Bandl's ring [38]. The second stage of labor is characterized by the full cervical dilatation until the childbirth [39]. However, there is not a unanimous consensus for the prolonged labor definition and duration.

In fact, Zipori et al. report that increasing the second stage more than an hour in nulliparous and multiparous, decreased the CS and increased maternal and fetal complications [40].

The ACOG guidelines define a prolonged second stage as more than 2 h without or 3 h with epidural analgesia or neuraxial labor analgesia (NLA) in nulliparous women, and 1 h without, or 2 h with epidural in multiparous women [41]. The second stage is defined as the stage when

Table 1
Demographic characteristics of two groups.

Demographic characteristics of two groups		
	CS in patients with non-prolonged labor	CS in patients with prolonged labor > 3 h
COHORTS	GROUP − 1 = 44	GROUP-2 = 46
AGE (YEARS)	32.6 ± 4.5	33.2 ± 3.7
BMI (kg/m*2)	26.5 ± 6.1	27.3 ± 58
GESTATIONAL AGE (WEEKS + DAY)	40 ± 3.4	40 ± 2.6
BIRTH WEIGHT (gr)	3890 ± 278	3920 ± 239

Table 2
Evaluation of OXT nerve fibers in the LUS of NPDD and PDD of pregnant patients.

EVALUATION OF OXYTOCIN (OXT) NERVE FIBERS IN LUS IN PATIENTS WITH NON-PROLONGED LABOR (<3 h) AND IN PATIENTS WITH PROLONGED LABOR (>3 h) OF SECOND LABOR STAGE	
GROUP-1 = 44	GROUP-2 = 46
NERVE FIBER DENSITY CONTAINIG OXYTOCIN IN IMMUNOREACTIVITY WITHIN SPECIMENS OF HUMAN LOWER UTERINE SEGMENT (LUS)	
17 ± 5.7	10 ± 2.4

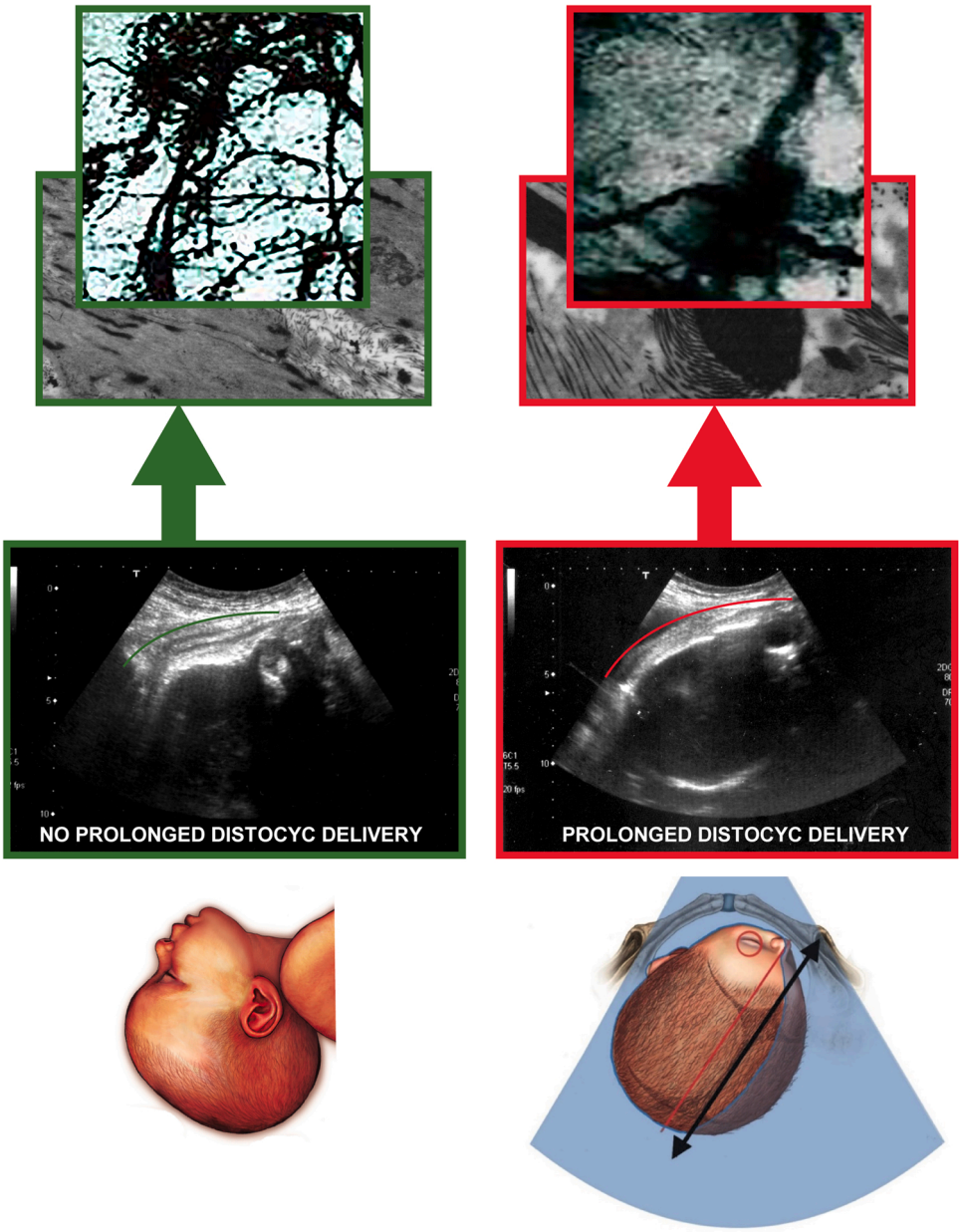

Fig. 2. The image shows a drawing and a ultrasonographic sectional photo of the LUS and FH in dystocic delivery. On the left, non-prolonged dystocic delivery is showed by transabdominal longitudinal ultrasonographic section of fetal head in OPP (the green curve indicates the LUS). On the right, prolonged dystocic delivery is showed by the transabdominal longitudinal scan of FH in OPP and posterior asynclitism (the red line represents the LUS in overdistension). At the top of the photo, there is the corresponding SEM of the LUS in NPDD (at the top of the left) and of PDD (at the top of the right) taken with the SEM. Over the SEM image, there are the photos of oxytocinergic fibers of the same LUS section, respectively, on the left in the NPDD (green arrow and the green line of the box) and on the right in PDD (red arrow and red line of the box) obtained by FM. One can see the oxytocinergic fibers examined in the specimens of LUS in PDD are less than those in NPDD.

the cervical dilatation is full. However, the second stage diagnosis must include the fetal head position at ischial spine at level zero according the ACOG classification. The diagnosis of fetal head (FH) position in the birth canal is performed by traditional vaginal digital examination (VE) and recently by intrapartum ultrasound (IU) also. The diagnosis of second stage based only on cervical dilatation is incomplete and requires the diagnosis of FH in the birth canal. Moreover, the IU improves the diagnosis of FH malposition and malrotation in comparison to VE. The diagnosis of FH position is possible by the application of the angle of progression (AOP): an angle of at least 120 degrees measured during the second stage of labor was associated with subsequent possible spontaneous vaginal delivery [42]. In fact, Dupuis et al. demonstrated that with VE, errors occurred in 50% to 88% of cases for residents and in 36% to 80% of cases for attending physicians, depending on the position [43].

The NLA is another condition that modifies the second labor stage duration in comparison to labor without NLA and it has an impact on delivery outcome [44]. During NLA, cervical dilatation occurs before the descent of FH due to the effects of analgesic drugs. The employed analgesic drugs, determine a fast full cervical dilatation, but the descent and the internal rotation of FH happened later [45]. During the PDD, after following ACOG [46] and NICE guidelines, it is advisable to stop the analgesic drugs administration and proceed with the delivery to avoid medical-legal problems [47]. In the last year, the application of IU in delivery ward and in delivery room have changed the dystocia diagnosis in comparison to the traditional vaginal digital examination, especially in delivery with fetal malposition and malrotation [48]. The PDD can request the operative vaginal delivery (OVD) [49].

The IU improves the diagnosis of the FH malposition and

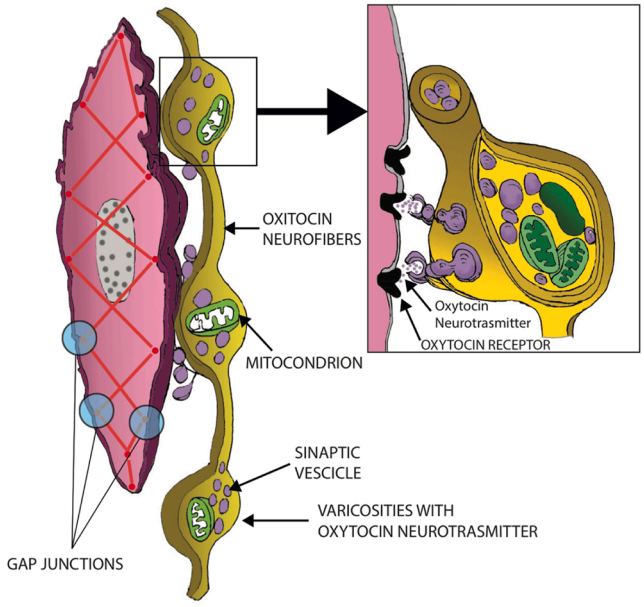

Fig. 3. The figure shows the OXT innervation mechanism of the smooth cell (in red color on the left). The smooth cell receives from the varicosities of post-ganglionic fibers (yellow color on the right). The OXT is produced by exocytosis of synaptic vesicles that contain OXT neurotransmitters in purple. OXT reaches the receptors on the membrane of smooth cells and stimulates the contraction of myofibers red grid, located in the smooth cells.

malrotation, therefore it is used before the application of VE to avoid vacuum failure [50] and reduce complications. The OXT augmentation in PDD can cause complications, especially fetal distress.

Verspyck et al. showed that early amniotomy and high doses of OXT may both increase the risk of fetal heart rate abnormalities [51]. Drummond et al. reported that OXT is the most commonly drug used in labor, and it has been associated with claim of malpractice outcome complicated by induction of augmentation of OXT [52]. The absence of international criteria of dystocia does not permit the confirmation of OXT augmentation and dystocia and it represents an open question in fetal and maternal complications [24].

In fact, Selin et al. affirmed that OXT augmentation is one of the consequence of dystocia [53]. Bernitz et al. supported the use of protocol of OXT augmentation in low-risk nulliparous without dystocia to reduce CS and OVD [54]. Haggsgard claimed that the OXT infusion has a role in the dystocia and in the delivery [55] and Ekelin argues the ambiguity of OXT use [56]. Gaudernack recommended that the caution use of synthetic OXT augmentation avoids the dystocia [57], Rossen et al. affirmed that the judicious use of OXT augmentation reduces the emergency CS [58] and Steer et al. claimed that the OXT should not be used, since the risks are more than the benefits [59].

Another problem with the use of OXT in labor is the correlation with NLA and, especially, the CSE that could determine the bradycardia and uterine hypertonus. In fact, during CSE for pain management the rapid onset may produce a transient unbalance of maternal catecholamine level, leading to uterine hyperactivity and fetal heart rate (FHR) abnormalities [60]. In fact, Abrado et al. reported that CSE is associated with significantly greater rate of FHR abnormalities, related to the hypertonus of the uterus compared to epidural analgesia [61]. Furthermore, Van de Velde et al. connected the FHR with CSE [62] at dosage of analgesia drugs, observing that FHR abnormalities are frequent after administration of 7.5 μg. of intrathecal sufentanyl compared to other NLA [63]. Besides, in some cases, OXT augmentation determines maternal hypotension and consequent FHR abnormalities [64].

Another controversial issue is the inappropriate OXT augmentation in labor, that although infrequent, it can cause uterine rupture (UR) in scarred and rarely non scarred uterus [65]. Nabhan and Boulvain recommended the appropriate OXT augmentation use in PDD [66]. Zhang et al. reported the risk of UR in TOLAC with OXT augmentation [67], while Dekker et al. shown a similar risk in repeated CS after OXT induction of labor [68]. Nevertheless, Weimar et al. claimed that the risk of UR is associated with a low Bishop score and the onset of OXT administration [69]. On the other hand, OXT alone presents a low risk of UR in repeated CS in comparison to the association with PG [70] and several authors observed that the endogenous and exogenous PG modified biochemistry of the scar and increased the UR risk in repeated CS compared to the augmentation of OXT [71].

Although rare, the primary UR is possible, and it shows high morbidity [72]. Iqbal et al. showed that the sequential use of PG and OXT augmentation in labor are important risk factors of UR in scarred but also in non-scarred uterus [73]. Other authors underlined the importance of careful uterine contraction monitoring and judicious control of OXT infusion rate of unscarred uterus to present the UR [74]. Also reported cases of UR in primigravida with non-scarred uterus during obstructed labor (OL) represent an obstetric condition of UR risk, especially in multiparous women [75]. Walsh et al. discussed the importance of surveillance in primiparous, to avoid complications in rare but catastrophic unscarred uterus [76].

The administration of synthetic OXT in labor and the controversial use in case of maternal-fetal complications have increased the ligation, the liability and consequent claims [77]. Miller et al. proposed the standardization of exogenous OXT administration to prevent litigation in case of excessive uterine contractility, fetal oxygenation alterations and adverse outcomes [78]. Moreover, Vitner et al. reported a purpose of checklist OXT administration use in labor [79]. Stalnaker et al. discussed the importance of synthetic OXT inappropriate use and the risk factor, fetal complications and claim [80] and other researchers reported the same aspects about synthetic OXT augmentation, complications and litigation, liability and claim [81].

To reduce abnormalities, the obstetric literature suggests low OXT doses or OXT discontinue administration. In fact, Saccone G. et al. reported that the discontinue use of OXT reduces the HFR distress [82].

The literature reports the alterations of collagen and Nc in the in patients with dystocic labor and CS [83,84]. In PDD, as recommended by ACOG guidelines, it is advisable after the diagnosis of dystocia to suspend PDD and carry out the delivery [85]. In this study, the patients were not induced with prostaglandin but with OXT. In patients with PDD the OXT augmentation appears useless, since the dystocic labor did not proceed. In PDL and even more in obstructed labor (OL), the OXT augmentation can cause fetal distress and if neglected can determine UR.

Based on the results of our study and the literature, it is possible to speculate the results in current obstetrical practice. After having confirmed that the diagnosis of dystocia by IU caused by malposition and malrotation of FH and after waiting for the second stage of labor according to ACOG guidelines, it is advisable, in our opinion, to proceed with the delivery. Otherwise, the delay in the dystocic labor could be determined fetal and maternal complications and possible litigation, liability and claim [86]. The management of labor shared decision-making regarding to proceed with expectant management or OVD or CS after weighing risks and benefits of each chance. Moreover, the decision to extend the duration of labor is currently personalized for each patient and fetus and should be agreed, depending on the individual circumstance. In fact, the term “judicious” is often used in some studies of OXT administration in absence of international guidelines indicating a personalized use of OXT augmentation.

The reduced number of patients evaluated in our trial for the high cost of FM antibodies was the limit of this study. Further studies are being necessary to evaluate the alterations of LUS innervation in the PDD and in particularly OXT-neurofibers alterations and the possible consequences in the successive delivery. There are some guidelines about the use of OXT in labor, for example the European Guidelines

[87], but there are not international guidelines for OXT augmentation in dystocic and prolonged labor. The OXT may cause possible maternal complications, among these last one the pelvic floor hematoma [88] during OXT augmentation, according for Alòs-Pereñíguez [89] require an informed consent for OXT administration. Other studies are required to determine the alterations of OXT innervation in the uterus with OXT administration in PDD, therefore it is advisable a judicious use of OXT infusion in PDD, especially in scarred uterus [26,90] to avoid complications and medico-legal litigation [91–93].

4. Materials and methods

A total of 960 nulliparous patients of the Department of Obstetrics and Gynecology of two University-affiliated Hospitals were evaluated, from December 2020 to December 2021. The inclusion criteria for pregnant women at initial labor were patients with a single pregnancy at term, fetus in cephalic presentation, and no complications in pregnancy. The exclusion enrolment criteria were pregnant women with any previous gynecologic surgery and any of the following problems experienced during pregnancy: macrosomia, infections, anticoagulation therapy, pre-eclampsia, HELLP syndrome, ruptured membranes for more than 36 h, placenta previa, and other placental pathologies. A total of 158 women were assessed and declared eligible to participate in the study. Among them, 136 women provided informed consent and were enrolled, after an ultrasound evaluation on initial labor. All enrolled patients signed informed consent before inclusion in this study, as approved by the local institutional research board committee. All of these patients underwent evaluations involving membrane rupture and oxytocin administration without the use of active labor management. Starting from 3 to 4 cm of cervical dilatation and fetal head at ischial spine station − 1 or lower, patients were assessed by ultrasonography (Aloka instrument SSD 2000 MultiView, Tokyo, Japan and GE Healthcare instrument, Voluson 730 Expert, Chalfont St. Giles, United Kingdom), both equipped by a multifrequency convex transabdominal transducer. All women were also examined by digital examinations (DE), at intervals of 45–90 min in the first, and of 15–30 min in the second stage. All women were followed until delivery. These pregnant women were submitted to intrapartum transabdominal sonography (ITAS) assessment for detection of head position in the first and second stage of labor, to detect either the persistent occiput posterior position (POPP) or the translation from anterior to posterior fetal head position. The fetal US landmark to detect the occiput posterior position (OPP) was the single fetal orbit, with “face to pubes” opposed on the presented fetal head side. All pregnant women with PDL were patients in spontaneous labor and in neuraxial labor analgesia (LNA). The LNA was administered with a low dose of combined spinal-epidural (CSE) analgesia. The CSE technique consisted of the needle-through-needle technique in intervertebral space (L3-L4) (Espocan®-, B. Braun, Italia). The spinal needle “Spinocan” 27 G was used through the Tuohy needle of 18 G. After that cerebrospinal fluid exited from the needle, a mixture of ropivacaine 0.02% with 0.25 μg·mL− 1 of Sufentanil (5 mL) was administered in the spinal space. The mixture of ropivacaine 0.07–0.15% (dilution of drugs depends on the stage, position, and station of the head) with 0.3 μg·mL− 1 of Sufentanil (10–15 mL) was administered in epidural space. Top-ups were repeated every two hours and when the pain started again until full dilatation was reached. Starting from 5 cm of cervical dilatation, an oxytocin infusion was administered by 20 UI synthetic oxytocin (Syntocinon ®) in 500 mL Hydrosaline solution, at 4 mUI/min. The oxytocin augmentation was monitored in continuous cardiotocography (CTG) to detect the normal or abnormal fetal heart rate (FHR). A group with 44 patients showed dystocia, FHR alterations and not reassuring CTG; therefore, it has been suspended OXT augmentation and the CS was performed. A group with PDD did not present CTG abnormalities that permits prolonged labor over three hours following ACOG guidelines, but the persistence of FH malposition-malrotation, diagnosed by intrapartum ultrasound (IU), was the indication for CS. According to American College Obstetrics and Gynecology (ACOG) guidelines, labor is defined as prolonged labor when it lasts more than 4 h with neuraxial labor analgesia (NLA). The PDL was recorded when the duration of the second stage exceeded 4 h, according to International Guidelines, and showed an angle of progression $\leq 97^{\circ}$. The PL for the occiput posterior position (OPP), the asynclitism, or the occiput transverse position (OTP) was diagnosed through vaginal examination (VE) and IU. The OPP was diagnosed by the face-to-pubis sign and orbit-to-pubis sign. The asynclitism was diagnosed by the squint sign with TAU with translabial ultrasound (TLU) and asymmetric midline sign. All patients showing a PDL underwent a CS, according to traditional obstetric criteria. The control group was composed of patients set to undergo CS for dystocia and non-reassuring CTG, under LNA, by CSE. These patients of the control group, undergoing non-urgent CS, were pregnant women with a singleton fetus in a cephalic presentation to undergo CS, for previous at-term CS, scheduled after an ultrasonographic diagnosis of breech or transverse presentation, multiple pregnancies, and women wishing to have a CS for personal reasons. All patients, before CS, received a prophylactic antibiotic administration of 2 gr of Cefazolin intravenously. The surgical technique was a modified Stark’ CS. The uterine incision was transversally on the LUS after bladder flap detachment. After fetus extraction, the placenta was delivered spontaneously, and the uterus was exteriorized. The surgeons sampled four serial consecutive full-thickness sections of 5 mm depth (with the inclusion of the myometrial layer) on the LUS, with the scissors for morphological analysis. Samples included the full thickness of the cervical wall, taken from each LUS using sterile scissors: two samples of approximately 5 mm depth were obtained from the upper and two from the lower edge. The specimens were immediately transferred, in a container filled with dry ice, to the laboratory, where samples were washed by immersion in cold Krebs–Ringer’s solution and assayed with immunofluorescent techniques to detect OXT-positive nerve fibers. All data were collected and recorded in a database, successively analyzed by an independent reviewer.

5. Conclusions

This study shows an altered presence of oxytocin fibers in PDD over four hours, which represent an experimental proof of the LUS innervation and modification. In fact, during PDD the mechanical overdistension of LUS by FH can determine vascular alterations, ischemia and inflammation. It suggests that in PDD, OXT does not have the same effects on the LUS compared to NPDD, being oxytocinergic fibers modified and reduced in number. They will need further studies on the innervation and functionality of smooth cells in the PDL to establish whether oxytocin augmentation determines more advantages or more disadvantages.

Institutional review board statement

The local Institutional Review Board Statement approved the study with the following number CER 0120. The study was conducted in accordance with the Declaration of Helsinki.

Informed consent statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

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CRediT authorship contribution statement

Conceptualization, A.M., B.F. and A.T.; methodology, A.M; software, B.F.; validation, A.B. and Z.Z.; formal analysis, M.D.; investigation, E.C. (Eliano Cascardi) and A.V.; resources, E.C. (Ettore Cicinelli).; data curation, G.R.D. and M.B.; writing—original draft preparation, A.M., E. C. (Eliano Cascardi), M.D. and A.T.; writing—review and editing, E.G., M.B., A.B., G.M.B., A.V., E.C. (Ettore Cicinelli); visualization, A.B.; supervision, A.M., A.T., B.F.; project administration, A.M. critical revision of the manuscript for important intellectual content and final approval: A.M. and A.B. Finally, A.M. and A.B. equally contributed as co-first authors. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

All the authors declare that they have not conflicts of interest.

References

[1] Di Tommaso S, Cavallotti C, Malvasi A, Vergara D, Rizzello A, De Nuccio F, et al. A qualitative and quantitative study of the innervation of the human Non Pregnant Uterus. Curr Protein Pept Sci 2017;18:140–8. https://doi.org/10.2174/1389203717666160330105341.

[2] Malvasi A, Tinelli A, Cavallotti C, Stark M. Anatomische Aspekte von Schwangerschaft und Kaiserschnitt. Der Kaiserschnitt. Elsevier; 2009. p. 39–66.

[3] Malvasi A, Cavallotti C, Gustapane S, Giacci F, Di Tommaso S, Vergara D, et al. Neurotransmitters and neuropeptides expression in the uterine scar after cesarean section. Curr Protein Pept Sci 2017;18:175–80. https://doi.org/10.2174/1389203717666160322150034.

[4] Adams Waldorf KM, Singh N, Mohan AR, Young RC, Ngo L, Das A, et al. Uterine overdistention induces preterm labor mediated by inflammation: observations in pregnant women and nonhuman primates. 830 e831-830 e819 Am J Obstet Gynecol 2015;213. https://doi.org/10.1016/j.ajog.2015.08.028.

[5] Konovalov PV, Mitrofanova LB, Gorshkov AN, Ovsyannikov FA. Morphological features of the myometrium in connective tissue dysplasia in women with uterine inertia. Arkh Patol 2015;77:18–25. https://doi.org/10.17116/patol201577518-25.

[6] Buhimschi CS, Buhimschi IA, Yu C, Wang H, Sharer DJ, Diamond MP, et al. The effect of dystocia and previous cesarean uterine scar on the tensile properties of the lower uterine segment. Am J Obstet Gynecol 2006;194:873–83. https://doi.org/10.1016/j.ajog.2005.09.004.

[7] Malvasi A, Vimercati A, Ricci I, Picardi N, Cicinelli E, Kosmas I, et al. Dystocic labor and adrenergic and noradrenergic neurotransmitters: a morphological experimental study. Int J Mol Sci 2022;23. https://doi.org/10.3390/ijms231911379.

[8] Malvasi A, Cicinelli E, Baldini GM, Vimercati A, Beck R, Dellino M, et al. Prolonged dystocic labor in neuraxial analgesia and the role of enkephalin neurotransmitters: an experimental study. Int J Mol Sci 2023;24. https://doi.org/10.3390/ijms24043767.

[9] Gabbe, S.G., Niebyl, J.R., Simpson, J.L., Landon, M.B., Galan, H.L., Jauniaux, E.R., Driscoll, D.A., Berghella, V., Grobman, W.A. Obstetrics: normal and problem pregnancies e-book; Elsevier Health Sciences: 2016.

[10] Liu B, Tong C, Eisenach JC. Pregnancy increases excitability of mechanosensitive afferents innervating the uterine cervix. Anesthesiology 2008;108:1087–92. https://doi.org/10.1097/ALN.0b013e31817302e0.

[11] Atwal G, du Plessis D, Armstrong G, Slade R, Quinn M. Uterine innervation after hysterectomy for chronic pelvic pain with, and without, endometriosis. Am J Obstet Gynecol 2005;193:1650–5. https://doi.org/10.1016/j.ajog.2005.05.035.

[12] Pinsard M, Mouchet N, Dion L, Bessede T, Bertrand M, Darai E, et al. Anatomic and functional mapping of human uterine innervation. Fertil Steril 2022;117:1279–88. https://doi.org/10.1016/j.fertnstert.2022.02.013.

[13] Giovannetti O, Tomalty D, Velikonja L, Jurkus C, Adams MA. The human cervix: comprehensive review of innervation and clinical significance. Clin Anat 2023;36:118–27. https://doi.org/10.1002/ca.23960.

[14] Jurek B, Neumann ID. The oxytocin receptor: from intracellular signaling to behavior. Physiol Rev 2018;98:1805–908. https://doi.org/10.1152/physrev.00031.2017.

[15] Carter CS, Kenkel WM, MacLean EL, Wilson SR, Perkeybile AM, Yee JR, et al. Is Oxytocin "Nature's Medicine"? Pharm Rev 2020;72:829–61. https://doi.org/10.1124/pr.120.019398.

[16] Domes G, Steiner A, Porges SW, Heinrichs M. Oxytocin differentially modulates eye gaze to naturalistic social signals of happiness and anger. Psychoneuroendocrinology 2013;38:1198–202. https://doi.org/10.1016/j.psyneuen.2012.10.002.

[17] Quintana DS, Rokicki J, van der Meer D, Alnaes D, Kaufmann T, Cordova-Palomera A, et al. Oxytocin pathway gene networks in the human brain. Nat Commun 2019;10:668. https://doi.org/10.1038/s41467-019-08503-8.

[18] Gainer H. Cell-type specific expression of oxytocin and vasopressin genes: an experimental odyssey. J Neuroendocr 2012;24:528–38. https://doi.org/10.1111/j.1365-2826.2011.02236.x.

[19] Fuchs AR, Fuchs F, Husslein P, Soloff MS. Oxytocin receptors in the human uterus during pregnancy and parturition. Am J Obstet Gynecol 1984;150:734–41. https://doi.org/10.1016/0002-9378(84)90677-x.

[20] Hild-Petito S, Verhage HG, Fazleabas AT. Immunocytochemical localization of estrogen and progestin receptors in the baboon (Papio anubis) uterus during implantation and pregnancy. Endocrinology 1992;130:2343–53.

[21] Perrot-Applanat M, Groyer-Picard M, Garcia E, Lorenzo F, Milgrom E. Immunocytochemical demonstration of estrogen and progesterone receptors in muscle cells of uterine arteries in rabbits and humans. Endocrinology 1988;123:1511–9.

[22] Nagata I, Sunaga H, Furuya K, Makimura N, Kato K. Changes in the plasma prostaglandin F2 alpha metabolite before and during spontaneous labor and labor induced by amniotomy, oxytocin and prostaglandin E2. Endocrinol Jpn 1987;34:153–9. https://doi.org/10.1507/endocrj1954.34.153.

[23] Xu C, Long A, Fang X, Wood SL, Slater DM, Ni X, et al. Effects of PGF2alpha on the expression of uterine activation proteins in pregnant human myometrial cells from upper and lower segment. J Clin Endocrinol Metab 2013;98:2975–83. https://doi.org/10.1210/jc.2012-2829.

[24] Kujabi ML, Mikkelsen E, Housseine N, Obel J, D'Mello BS, Meyrowitsch DW, et al. Labor augmentation with oxytocin in low- and lower-middle-income countries: a systematic review and meta-analysis. AJOG Glob Rep 2022;2:100123. https://doi.org/10.1016/j.xagr.2022.100123.

[25] Costley PL, East CE. Oxytocin augmentation of labour in women with epidural analgesia for reducing operative deliveries. Cochrane Database Syst Rev 2013;2013:CD009241. https://doi.org/10.1002/14651858.CD009241.pub3.

[26] Catacuzzeno L, Fioretti B, Perin P, Franciolini F. Spontaneous low-frequency voltage oscillations in frog saccular hair cells. J Physiol 2004;561:685–701. https://doi.org/10.1113/jphysiol.2004.072652.

[27] Catacuzzeno L, Fioretti B, Franciolini F. Voltage-gated outward K currents in frog saccular hair cells. J Neurophysiol 2003;90:3688–701. https://doi.org/10.1152/jn.00308.2003.

[28] Rihana S, Terrien J, Germain G, Marque C. Mathematical modeling of electrical activity of uterine muscle cells. Med Biol Eng Comput 2009;47:665–75. https://doi.org/10.1007/s11517-009-0433-4.

[29] Testrow CP, Holden AV, Shmygol A, Zhang H. A computational model of excitation and contraction in uterine myocytes from the pregnant rat. Sci Rep 2018;8:9159. https://doi.org/10.1038/s41598-018-27069-x.

[30] Zak M, Kestler B, Cornwell T, Taylor MS. Augmented K(Ca)2.3 channel feedback regulation of oxytocin stimulated uterine strips from nonpregnant mice. Int J Mol Sci 2021;22. https://doi.org/10.3390/ijms222413585.

[31] Smith R, Imtiaz M, Banney D, Paul JW, Young RC. Why the heart is like an orchestra and the uterus is like a soccer crowd. Am J Obstet Gynecol 2015;213:181–5. https://doi.org/10.1016/j.ajog.2015.06.040.

[32] Young RC. Mechanotransduction mechanisms for coordinating uterine contractions in human labor. Reproduction 2016;152:R51–61. https://doi.org/10.1530/REP-16-0156.

[33] Wray S, Prendergast C. The myometrium: from excitation to contractions and labour. Adv Exp Med Biol 2019;1124:233–63. https://doi.org/10.1007/978-981-13-5895-1_10.

[34] Phaneuf S, Rodriguez Linares B, TambyRaja RL, MacKenzie IZ, Lopez Bernal A. Loss of myometrial oxytocin receptors during oxytocin-induced and oxytocin-augmented labour. J Reprod Fertil 2000;120:91–7. https://doi.org/10.1530/jrf.0.1200091.

[35] Young RC. The uterine pacemaker of labor. Best Pr Res Clin Obstet Gynaecol 2018;52:68–87. https://doi.org/10.1016/j.bpobgyn.2018.04.002.

[36] Wray S, Burdyga T, Noble D, Noble K, Borysova L, Arrowsmith S. Progress in understanding electro-mechanical signalling in the myometrium. Acta Physiol 2015;213:417–31. https://doi.org/10.1111/apha.12431.

[37] Andersen HF, Barclay ML. A computer model of uterine contractions based on discrete contractile elements. Obstet Gynecol 1995;86:108–11. https://doi.org/10.1016/0029-7844(95)00111-4.

[38] Tinelli A, Di Renzo GC, Malvasi A. The intrapartum ultrasonographic detection of the Bandl ring as a marker of dystocia. Int J Gynaecol Obstet 2015;131:310–1. https://doi.org/10.1016/j.ijgo.2015.06.030.

[39] Gimovsky AC. Defining arrest in the first and second stages of labor. Minerva Obstet Gynecol 2021;73:6–18. https://doi.org/10.23736/S2724-606X.20.04644-4.

[40] Zipori Y, Grunwald O, Ginsberg Y, Beloosesky R, Weiner Z. The impact of extending the second stage of labor to prevent primary cesarean delivery on maternal and neonatal outcomes. 191 e191-191 e197 Am J Obstet Gynecol 2019;220. https://doi.org/10.1016/j.ajog.2018.10.028.

[41] Cheng YW, Caughey AB. Defining and managing normal and abnormal second stage of labor. Obstet Gynecol Clin North Am 2017;44:547–66. https://doi.org/10.1016/j.ogc.2017.08.009.

[42] Barbera AF, Pombar X, Perugino G, Lezotte DC, Hobbins JC. A new method to assess fetal head descent in labor with transperineal ultrasound. Ultrasound Obstet Gynecol 2009;33:313–9. https://doi.org/10.1002/uog.6329.

[43] Dupuis O, Silveira R, Zentner A, Dittmar A, Gaucherand P, Cucherat M, et al. Birth simulator: reliability of transvaginal assessment of fetal head station as defined by the American College of Obstetricians and Gynecologists classification. Am J Obstet Gynecol 2005;192:868–74. https://doi.org/10.1016/j.ajog.2004.09.028.

[44] Zhang J, Yancey MK, Klebanoff MA, Schwarz J, Schweitzer D. Does epidural analgesia prolong labor and increase risk of cesarean delivery? A natural experiment. Am J Obstet Gynecol 2001;185:128–34. https://doi.org/10.1067/mob.2001.113874.

[45] Malvasi A, Raimondo P, Beck R, Tinelli A, Kuczkowski KM. Intrapartum ultrasound monitoring of malposition and malrotation during labor neuraxial analgesia:

maternal outcomes. J Matern Fetal Neonatal Med 2020;33:3584–90. https://doi.org/10.1080/14767058.2019.1579193.
[46] ACOG Practice Bulletin No. 107: Induction of labor Obstet Gynecol 114 2009 386 397 doi: 10.1097/AOG.0b013e3181b48ef5.
[47] Beck R, Malvasi A, Kuczkowski KM, Marinelli E, Zaami S. Intrapartum sonography of fetal head in second stage of labor with neuraxial analgesia: a literature review and possible medicolegal aftermath. Eur Rev Med Pharm Sci 2019;23:3159–66. https://doi.org/10.26355/eurrev_201904_17673.
[48] Rizzo G, Ghi T, Henrich W, Tutschek B, Kamel R, Lees CC, et al. Ultrasound in labor: clinical practice guideline and recommendation by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine Foundation. J Perinat Med 2022;50:1007–29. https://doi.org/10.1515/jpm-2022-0160.
[49] Skinner SM, Giles-Clark HJ, Higgins C, Mol BW, Rolnik DL. Prognostic accuracy of ultrasound measures of fetal head descent to predict outcome of operative vaginal birth: a comparative systematic review and meta-analysis. Am J Obstet Gynecol 2022. https://doi.org/10.1016/j.ajog.2022.11.1294.
[50] Sainz JA, Borrero C, Aquise A, Serrano R, Gutierrez L, Fernandez-Palacin A. Utility of intrapartum transperineal ultrasound to predict cases of failure in vacuum extraction attempt and need of cesarean section to complete delivery. J Matern Fetal Neonatal Med 2016;29:1348–52. https://doi.org/10.3109/14767058.2015.1048680.
[51] Verspyck E, Sentilhes L. Abnormal fetal heart rate patterns associated with different labour managements and intrauterine resuscitation techniques. J Gynecol Obstet Biol Reprod 2008;37(*Suppl 1*):S56–64. https://doi.org/10.1016/j.jgyn.2007.11.011.
[52] Drummond S. Oxytocin use in labor: legal implications. J Perinat Neonatal Nurs 2018;32:34–42. https://doi.org/10.1097/JPN.0000000000000300.
[53] Selin L, Almstrom E, Wallin G, Berg M. Use and abuse of oxytocin for augmentation of labor. Acta Obstet Gynecol Scand 2009;88:1352–7. https://doi.org/10.3109/00016340903358812.
[54] Buerengen T, Bernitz S, Oian P, Dalbye R. Association between one-to-one midwifery care in the active phase of labour and use of pain relief and birth outcomes: a cohort of nulliparous women. Midwifery 2022;110:103341. https://doi.org/10.1016/j.midw.2022.103341.
[55] Haggsgard C, Persson EK. Management of oxytocin for labour augmentation in relation to mode of birth in Robson group 1. Midwifery 2020;90:102822. https://doi.org/10.1016/j.midw.2020.102822.
[56] Ekelin M, Kvist LJ, Persson EK. Midwifery competence: content in midwifery students' daily written reflections on clinical practice. Midwifery 2016;32:7–13. https://doi.org/10.1016/j.midw.2015.10.004.
[57] Gaudernack LC, Froslie KF, Michelsen TM, Voldner N, Lukasse M. De-medicalization of birth by reducing the use of oxytocin for augmentation among first-time mothers - a prospective intervention study. BMC Pregnancy Childbirth 2018;18:76. https://doi.org/10.1186/s12884-018-1706-4.
[58] Rossen J, Ostborg TB, Lindtjorn E, Schulz J, Eggebo TM. Judicious use of oxytocin augmentation for the management of prolonged labor. Acta Obstet Gynecol Scand 2016;95:355–61. https://doi.org/10.1111/aogs.12821.
[59] Steer PJ. Oxytocin should not be used to augment labour: FOR: there is too much risk for too little benefit. BJOG 2015;122:1543. https://doi.org/10.1111/1471-0528.13571.
[60] Yang L, Wan L, Huang H, Qi X. Uterine hypertonus and fetal bradycardia occurred after combined spinal-epidural analgesia during induction of labor with oxytocin infusion: a case report. Med (Baltim) 2019;98:e16282. https://doi.org/10.1097/MD.0000000000016282.
[61] Abrao KC, Francisco RP, Zugaib M. Changes in cardiotochography following combined spinal-epidural labor analgesia. Rev Bras Ginecol Obstet 2009;31:51–3. https://doi.org/10.1590/s0100-72032009000200001.
[62] Van de Velde M, Teunkens A, Hanssens M, Vandermeersch E, Verhaeghe J. Intrathecal sufentanil and fetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. Anesth Analg 2004;98:1153–9. https://doi.org/10.1213/01.ANE.0000101980.34587.66.
[63] Lee JS. Does intrathecal sufentanil really cause more episodes of fetal bradycardia? Anesth Analg 2004;99:1267. https://doi.org/10.1213/01.ANE.0000133948.71761.F8.
[64] Anim-Somuah M, Smyth RM, Cyna AM, Cuthbert A. Epidural versus non-epidural or no analgesia for pain management in labour. Cochrane Database Syst Rev 2018.
[65] Ophir E, Odeh M, Hirsch Y, Bornstein J. Uterine rupture during trial of labor: controversy of induction's methods. Obstet Gynecol Surv 2012;67:734–45. https://doi.org/10.1097/OGX.0b013e318273feeb.
[66] Nabhan A, Boulvain M. Augmentation of labour. Best Pr Res Clin Obstet Gynaecol 2020;67:80–9. https://doi.org/10.1016/j.bpobgyn.2020.03.011.
[67] Zhang H, Liu H, Luo S, Gu W. Oxytocin use in trial of labor after cesarean and its relationship with risk of uterine rupture in women with one previous cesarean section: a meta-analysis of observational studies. BMC Pregnancy Childbirth 2021;21:11. https://doi.org/10.1186/s12884-020-03440-7.
[68] Dekker GA, Chan A, Luke CG, Priest K, Riley M, Halliday J, et al. Risk of uterine rupture in Australian women attempting vaginal birth after one prior caesarean section: a retrospective population-based cohort study. BJOG 2010;117:1358–65. https://doi.org/10.1111/j.1471-0528.2010.02688.x.
[69] Weimar CH, Lim AC, Bots ML, Bruinse HW, Kwee A. Risk factors for uterine rupture during a vaginal birth after one previous caesarean section: a case-control study. Eur J Obstet Gynecol Reprod Biol 2010;151:41–5. https://doi.org/10.1016/j.ejogrb.2010.03.023.
[70] Ogbonmwan SE, Miller V, Ogbonmwan DE, Akinsola AA. Review of vaginal birth after primary caesarean section without prostaglandin induction and or syntocinon augmentation in labour. J Matern Fetal Neonatal Med 2010;23:281–5. https://doi.org/10.3109/14767050903067394.
[71] Buhimschi CS, Buhimschi IA, Patel S, Malinow AM, Weiner CP. Rupture of the uterine scar during term labour: contractility or biochemistry? BJOG 2005;112:38–42. https://doi.org/10.1111/j.1471-0528.2004.00300.x.
[72] Gibbins KJ, Weber T, Holmgren CM, Porter TF, Varner MW, Manuck TA. Maternal and fetal morbidity associated with uterine rupture of the unscarred uterus. 382 e381-386 Am J Obstet Gynecol 2015;213. https://doi.org/10.1016/j.ajog.2015.05.048.
[73] Al-Zirqi I, Daltveit AK, Forsen L, Stray-Pedersen B, Vangen S. Risk factors for complete uterine rupture. 165 e161-165 e168 Am J Obstet Gynecol 2017;216. https://doi.org/10.1016/j.ajog.2016.10.017.
[74] Catanzarite V, Cousins L, Dowling D, Daneshmand S. Oxytocin-associated rupture of an unscarred uterus in a primigravida. Obstet Gynecol 2006;108:723–5. https://doi.org/10.1097/01.AOG.0000215559.21051.dc.
[75] Chigbu B, Onwere S, Kamanu C, Aluka C, Adibe E, Onichakwe C. Rupture of the uterus in a primigravida: a case report. Niger J Clin Pract 2010:*13*.
[76] Walsh CA, Baxi LV. Rupture of the primigravid uterus: a review of the literature. quiz 353-324 Obstet Gynecol Surv 2007;62:327–34. https://doi.org/10.1097/01.ogx.0000261643.11301.56.
[77] Page K, McCool WF, Guidera M. Examination of the pharmacology of oxytocin and clinical guidelines for use in labor. J Midwifery Women's Health 2017;62:425–33. https://doi.org/10.1111/jmwh.12610.
[78] Miller LA. Oxytocin, excessive uterine activity, and patient safety: time for a collaborative approach. J Perinat Neonatal Nurs 2009;23:52–8. https://doi.org/10.1097/JPN.0b013e3181961506.
[79] Vitner D, Lipworth H, Weiner E, Bas Lnado M, Page A, Melamed N, et al. The effect of the implementation of institutional checklist on expert opinion of oxytocin use in labor. Arch Gynecol Obstet 2020;302:127–31. https://doi.org/10.1007/s00404-020-05590-7.
[80] Stalnaker BL, Maher JE, Kleinman GE, Macksey JM, Fishman LA, Bernard JM. Characteristics of successful claims for payment by the Florida Neurologic Injury Compensation Association Fund. discussion 271-263 Am J Obstet Gynecol 1997;177:268–71. https://doi.org/10.1016/s0002-9378(97)70186-8.
[81] Studdert DM, Fritz LA, Brennan TA. The jury is still in: Florida's Birth-Related Neurological Injury Compensation Plan after a decade. J Health Polit Policy Law 2000;25:499–526. https://doi.org/10.1215/03616878-25-3-499.
[82] Saccone G, Ciardulli A, Baxter JK, Quinones JN, Diven LC, Pinar B, et al. Discontinuing oxytocin infusion in the active phase of labor: a systematic review and meta-analysis. Obstet Gynecol 2017;130:1090–6. https://doi.org/10.1097/AOG.0000000000002325.
[83] Malvasi A, Cavallotti C, Resta L, Mynbaev OA, Di Tommaso S, Vergara D, et al. Laminin and collagen IV: two polypeptides as marker of dystocic labor. Curr Protein Pept Sci 2017;18:149–54. https://doi.org/10.2174/1389203717666160322150125.
[84] Malvasi A, Tinelli A, Cavallotti C, Morroni M, Tsin DA, Nezhat C, et al. Distribution of substance P (SP) and vasoactive intestinal peptide (VIP) in pseudocapsules of uterine fibroids. Peptides 2011;32:327–32. https://doi.org/10.1016/j.peptides.2010.10.034.
[85] Malvasi A, Vinciguerra M, Lamanna B, Cascardi E, Damiani GR, Muzzupapa G, et al. Asynclitism and its ultrasonographic rediscovery in labor room to date: a systematic review. Diagnostics 2022;12. https://doi.org/10.3390/diagnostics12122998.
[86] Berglund S, Grunewald C, Pettersson H, Cnattingius S. Severe asphyxia due to delivery-related malpractice in Sweden 1990-2005. BJOG 2008;115:316–23. https://doi.org/10.1111/j.1471-0528.2007.01602.x.
[87] Writing G, Nunes I, Dupont C, Timonen S, Guideline P, Ayres de Campos D, et al. European Guidelines on Perinatal Care - Oxytocin for induction and augmentation of labor[Formula: see text]. J Matern Fetal Neonatal Med 2022;35:7166–72. https://doi.org/10.1080/14767058.2021.1945577.
[88] Denson LE, Terrell DR, Vesely SK, Peck JD, Quiroz LH, Shobeiri SA. The prevalence of pelvic floor hematoma after vaginal delivery. Female Pelvic Med Reconstr Surg 2021;27:393–7. https://doi.org/10.1097/SPV.0000000000000895.
[89] Alos-Pereniguez S, O'Malley D, Daly D. Women's views and experiences of augmentation of labour with synthetic oxytocin infusion: a qualitative evidence synthesis. Midwifery 2023;116:103512. https://doi.org/10.1016/j.midw.2022.103512.
[90] Zizza A, Tinelli A, Malvasi A, Barbone E, Stark M, De Donno A, et al. Caesarean section in the world: a new ecological approach. J Prev Med Hyg 2011;52:161–73.
[91] Shwayder JM. Waiting for the tide to change: reducing risk in the turbulent sea of liability. Obstet Gynecol 2010;116:8–15. https://doi.org/10.1097/AOG.0b013e3181e5e2ec.
[92] Clark SL, Belfort MA, Dildy GA, Meyers JA. Reducing obstetric litigation through alterations in practice patterns. Obstet Gynecol 2008;112:1279–83. https://doi.org/10.1097/AOG.0b013e31818da2c7.
[93] Malvasi A, Loco B, Malvasi VM, Loverro M, Hatirnaz S, Beck R. Intrapartum sonography and devices used in obstetric practice: current trends and future perspectives. Intrapartum Ultrason Labor Manag: Labor Deliv Puerperium 2021:751–65.