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Review

Examination of the Pharmacology of Oxytocin and Clinical Guidelines for Use in Labor

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Katie Page, CNM, MSN, William F. McCool, CNM, PhD, Mamie Guidera, CNM, MSN

The use of exogenous oxytocin to induce or augment labor has increased in recent years. This literature-informed review examines the action of this medication and the potential associated complications, with an evaluation of current professional practice guidelines. A brief history of the use of exogenous oxytocin for labor induction or augmentation is presented. In addition, risk management strategies for the prevention of oxytocin-related adverse outcomes and subsequent litigation are identified.

Keywords: augmentation of labor, fetal heart rate monitoring, high-alert medication, induction of labor, intrapartum care, oxytocin, Pitocin, risk management, tachysystole

A related patient education handout can be found at the end of this issue and at www.sharewithwomen.org

INTRODUCTION

Oxytocin has been used exogenously for managing labor dystocia in various forms and dosages since the early 20th century. Despite its widespread use, oxytocin is one of 12 drugs designated as a "high-alert medication" by the Institute for Safe Medication Practices.[1] This is because current technology that controls the dose and frequency of dosing does not consistently prevent patient harm when this drug is used.[1] Indeed, oxytocin is the drug most commonly associated with preventable adverse events during childbirth.[1] The US Food and Drug Administration (FDA) has approved oxytocin for use in medically indicated induction, labor augmentation, adjunctive therapy in abortion management, and for treating postpartum hemorrhage. The use of oxytocin for elective induction is considered off-label.[2] The purpose of this review is to examine the pharmacokinetics of synthetic oxytocin during the labor process and associated maternal and neonatal risks in relationship to current guidelines. A discussion of litigation associated with the use of oxytocin and risk management strategies for clinicians are presented.

In the United States, the rate of labor induction for women who are at or beyond 37 weeks' gestation increased from 9.6% to 23.2% between 1990 and 2014.[3,4] According to the *Listening to Mothers III*[5] survey, 31% of women giving birth in 2012 to 2013 received oxytocin to "speed up" labor. International organizations recommend oxytocin as first line for the prevention and treatment of postpartum hemorrhage.[6] However, there continues to be wide variation in practice patterns and clinical guidelines, despite a substantial amount of research over the past decade on the use of oxytocin in labor and postpartum. Guidelines from professional organizations related to the use of oxytocin include recommendations based on expert opinion and have not universally embraced recommendations consistent with known pharmacokinetic properties of oxytocin.[7–12] Medication administration errors can result in significant harm to women and newborns and can result in litigation involving midwives, nurses, and physicians. Clearly, this is an important area for continued research and evaluation to guide best practices.

Address correspondence to Katie Page, CNM, MSN, CMG Women's Center, 2007 Graves Mill Road, Forest, VA 24551. E-mail: kapage@live.com

HISTORICAL USE OF METHODS TO STIMULATE LABOR

The use of synthetic preparations of oxytocin (Pitocin, Syntocinon) in caring for pregnant women, particularly as an agent for induction of labor, is a relatively new practice in women's health. For centuries, midwives and physicians have tried a variety of herbs, medicinal preparations, and mechanical efforts, to assist the progress of labor or hasten the end of postpartum uterine bleeding. In ancient Greece, Hippocrates recommended mammary stimulation and mechanical dilation of the cervix.[13] The use of enemas and folk medicines were described in 16th-century Europe for augmenting labor or controlling postpartum hemorrhage.[14] In the 19th century, a medicinal precursor to oxytocin, ergot, a fungus that grows on grains, was being used orally to stimulate the uterus during labor. It caused strong and uncontrollable contractions, resulting in severe, constant pain and, potentially, uterine rupture.[15] Thus, its use became limited to the postpartum period for the control of hemorrhage. Ergot continues to be used today in synthetic form as methylergometrine maleate (Methergine).

It was not until the early part of the 20th century that the endogenous hormone oxytocin was identified and put to use during labor and birth or postpartum.[16] The hormone's ability to contract the uterus was first described by Dale in 1906.[17] It was then given its name using the Greek words for "quick birth."[17,18] In 1909, Bell was reported to be the first obstetrician to use a pituitary extract that contained oxytocin, known as pituitrin, for treating postpartum hemorrhage. However, inaccuracies in the measurement of extracts and the mixture's accompanying vasopressin properties

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Quick Points

- Oxytocin, a high-alert medication, contributes to adverse outcomes and should not be used without a medical indication.
- It is recommended that institutions have practice guidelines or protocols for oxytocin use during labor that are consistent with the pharmacokinetic properties.
- Shared decision making about use of oxytocin for labor augmentation includes discussion of the primary benefit of reduced time to birth, in addition to known risks of oxytocin exposure.
- If oxytocin is used for labor induction or augmentation, discontinuing the infusion when active labor is achieved can be considered.
- Standardized order sets and administration checklists may reduce risk of harm to women and fetuses, and risk of litigation for clinicians.

caused deleterious side effects, such as hypertension and uterine rupture.[13,19] Theobald et al[16] argued in 1948 that its use for inducing labor was unreliable, and subsequently pituitrin was mostly relegated to preventing or controlling postpartum hemorrhage.

The significant increase in the use of oxytocin for augmenting or inducing labor did not occur until the 1950s when du Vigneaud and colleagues developed a synthetic version, thus enabling better control of the hormone during administration.[20] Oxytocin is currently manufactured in the United States most commonly under the trade name of Pitocin. Obstetricians in the 1960s and 1970s experimented with different dosages and timing of administration to induce or augment labor, as well as control postpartum hemorrhage. By the 1980s, following FDA approval, oxytocin became widely used in the United States for inducing and augmenting labor.[21] By the turn of the century, 20% of pregnancies in the United States were being induced, a majority involving the use of oxytocin, and by 2012, approximately 50% of laboring women in the United States were undergoing either an induction or augmentation of labor using oxytocin.[4,5] Experimentation with dosages and timing of oxytocin administration has continued in efforts to improve its desired effects and to curtail potential adverse effects.

THE EFFECT OF ENDOGENOUS OXYTOCIN ON LABOR

The exact role that oxytocin plays in the initiation and continuation of labor is unclear. Endogenous oxytocin is primarily produced in the hypothalamus and secreted from the posterior pituitary gland, where it interacts with receptors in the brain and in the myometrium.[22,23] In parts of the brain stem, midbrain, cortex, and spinal column, animal studies have shown an increase in oxytocin receptor expression and binding as pregnancy progresses.[23] Within these areas, oxytocin acts on neuroreceptors to release or inhibit other hormones and modulators involved in mood, stress reactivity, maternal attachment behavior, and pain that may influence labor progress.[23] Oxytocin is also produced locally in the decidua via estrogen-mediated production, where it has a paracrine function promoting prostaglandin formation in reproductive tissue. This action may contribute indirectly to initiating labor.[22]

The concentration of oxytocin that can be measured in maternal circulation at the onset of labor is not significantly different from concentrations measured antepartum in the late-term gestation period.[22] In animal studies, oxytocin receptor expression and sensitization in the uterine myometrium and decidua is increased dramatically near term.[22,23] This up-regulation of oxytocin receptors continues throughout labor and may be the key to labor onset and perpetuation.[22,23] The increased up-regulation of oxytocin receptors, as suggested by this work, appears to be more important than increased blood concentrations of oxytocin in labor initiation and continuation. The concentration of oxytocin receptors and signaling across gap junctions in the uterine myometrium is not uniform, however.[24] Thus, contractions may be dyssynchronous and variable in frequency and intensity at labor onset. During physiologic active labor, the frequency of contractions averages 4 in a 10-minute period.[25]

PHYSIOLOGIC EFFECTS OF EXOGENOUS OXYTOCIN

Synthetic oxytocin is structurally identical to the oxytocin secreted by the pituitary gland and peripheral reproductive tissues. Pharmacokinetic studies have shown an onset of action within 3 to 5 minutes and a half-life of 10 to 12 minutes.[1] Steady state for each dose is not achieved until 30 to 60 minutes, which corresponds to 3 to 5 half-lives.[1]

When synthetic oxytocin is used to stimulate contractions in labor, the pattern that results can often be indistinguishable from spontaneous labor, although the intensity of individual contractions may be increased.[22,26] Measurements of uterine blood flow during an oxytocin-induced contraction in active labor have shown significantly increased uterine artery velocity resistance when compared to spontaneous uterine contractions.[26] The response is dose dependent and widely variable, based on the oxytocinase activity, oxytocin receptor expression, and post receptor metabolism within each uterus.[22] These processes are influenced by a woman's age, gestational age, parity, and cervical dilatation. Some women will need a relatively low amount of oxytocin to have the therapeutic effect of physiologic labor progression, while others will require larger doses over a longer period of time to achieve the same outcome. Maternal and fetal complications related to

oxytocin use also appear to be dose dependent and may be influenced by duration of exposure.[1]

Uterine Blood Flow and Fetal Oxygenation

Blood flow through the uterus into and out of the intervillous space in the placenta decreases with each contraction event. In 1994, Peebles et al[25] observed that contractions occurring at intervals of less than 2 minutes were associated with a decrease in fetal cerebral oxygenation as detected via near infrared spectroscopy. If contractions occur too often, fetal exchange of gases and lactic acid across the intervillous space may not have time to equilibrate, and fetal hypoxia or acidemia may ensue. Variant fetal heart rate (FHR) changes may be observed.[25]

In 2008, Simpson and James[10] analyzed oxytocin-induced contraction patterns of 56 women undergoing elective induction of labor and concomitant changes in FHR with regard to fetal oxygen saturation using pulse oximetry. Normal uterine activity was defined as less than 5 contractions per 10-minute period.[10] The investigators found a 20% decline in fetal oxygen saturation after 30 minutes of 5 or more contractions ($P < .001$).[10] A 29% decrease was noted when there were 6 or more contractions per 10 minutes after 30 minutes ($P < .001$).[10] Fetal heart rate changes did not manifest until 20 minutes of excessive uterine activity despite desaturation beginning within the first 5 minutes.[10] Contraction frequency, independent of FHR changes on a fetal monitor, warrants close scrutiny when oxytocin is being used during labor.

Neonatal Outcomes Associated With Excessive Uterine Activity

In 2007, Bakker et al[11] found that excessive uterine activity correlated with lower umbilical artery pH at birth even in the absence of FHR changes. In this sample (N = 1433), an umbilical cord artery pH of less than 7.11, or mild acidosis, was associated with a contraction frequency average of 5 per 10 minutes in the last hour of the first stage of labor ($P = .006$) and 5.5 per 10 minutes in the second stage ($P = .002$). The umbilical cord artery pH was always greater than 7.12 when contraction frequency was 4.8 in 10 minutes in the first stage of labor, and 5.2 in 10 minutes in the second stage.[11] Oxytocin was administered for induction or augmentation to 75% of the women whose labor tracings were evaluated. Even though these results demonstrate mild declines in pH associated with increased frequency of uterine contractions, this does show an increase in the number of newborns with potential for significant acidemia at birth when contraction activity during labor is too frequent.

A large (N = 51,519), cohort study by Yeh et al,[27] demonstrated this relationship between pH and neonatal outcome. The highest risk for adverse neonatal outcomes of encephalopathy with seizures and/or death within the first 4 weeks of life (relative risk [RR], 18.2; 95% confidence interval [CI], 10.50-31.70), intensive care unit admission (RR, 6.38; 95% CI, 5.72-7.10), and 5-minute Apgar less than 7 (RR, 49.05; 95% CI, 33.98-70.79) was not until pH was below 7.0. When the umbilical artery pH was 7.06 to 7.10, the RR of neonatal encephalopathy with seizures and/or death was 2.22 (95% CI, 1.12-5.98), slightly higher than at pH 7.11 to 7.15 (RR, 1.76; 95% CI, 0.87-4.07).[27] Neonates exposed to frequent uterine contractions (5 or more per 10 minutes) during labor could be particularly vulnerable to newborn acidemia if there are maternal or fetal conditions that adversely affect fetal oxygenation during labor, or in the event of terminal bradycardia or other sentinel event at birth, which will exacerbate acidemia.

Oxytocin Receptor Desensitization

Prolonged activation of the oxytocin receptor results in a process of receptor desensitization.[24] Robinson et al[24] treated cultured myometrial tissue with a high-dose concentration of oxytocin and found that after 4 hours, approximately 50% of cells failed to respond to oxytocin with the anticipated rise in intracellular calcium that is necessary to stimulate the uterine muscles to contract. No increase in intracellular calcium was detected in any cell after 6 hours; however, post receptor signaling continued. This indicates that receptors internalize at the cell wall and continue to function in other, less understood, processes despite loss of contractility.[24] Based on the concentration of available receptors in different regions of the myometrium, synchronicity and strength of contractions may be adversely affected as these receptors are internalized or down-regulated.[24] This may manifest clinically as labor dystocia or postpartum hemorrhage. Some women will spontaneously express fewer oxytocin receptors prior to and during labor that will further predispose them to similar outcomes if exposed to exogenous oxytocin. These findings emphasize the variability of dose-response to exogenous oxytocin.

Clinical evidence supports the findings of in vitro studies of oxytocin on myometrial preparations. Known risk factors for postpartum hemorrhage include infection, prolonged labor in the second stage, and augmentation of labor with exogenous oxytocin administration.[28] In a 2011[28] investigation examining the relationship between severe postpartum hemorrhage (PPH) (requiring blood transfusion) and oxytocin exposure, 50% (n = 109) of cases of severe PPH were attributed to uterine atony. Severe PPH was more likely when oxytocin was infused for a longer duration prior to birth (684 vs 330 mins, $P < .001$) and with a higher maximum dose (16.6 vs 7.0 milliunits/min, $P < .001$). Exposure to 20 milliunits/min of oxytocin for 4.2 hours or more increased the odds of severe PPH by 1.62 (95% CI, 1.05-2.57), after confounding variables were controlled.[28] Thus, administering oxytocin at the lowest effective dose for the shortest duration possible to achieve the desired effect on labor may help reduce clinically significant PPH.

Effects of Exogenous Oxytocin on Other Organ Systems

Oxytocin has been shown to have an effect on the cardiovascular, renal, and central nervous systems of humans.[23,29,30] In the peripheral vasculature it causes relaxation of the smooth muscle, which can result in decreased blood pressure and reflex tachycardia.[29] This effect is most documented when oxytocin is given postpartum by intravenous (IV) bolus to prevent postpartum hemorrhage following cesarean birth. Bolus doses of 3 to 10 units can result in significant hypotension,

tachycardia, and electrocardiographic changes within the first 30 to 60 seconds following injection.[29,31] These changes, in addition to symptoms of chest pain, palpitations, dyspnea, and nausea, mimic those seen with myocardial ischemia.[29,31] The effects appear to be transient, lasting for 5 to 10 minutes.[29,31] It is unclear if these changes are clinically significant in low-risk women, but they could present additional risks for women with underlying cardiovascular complications in pregnancy and childbirth, especially following cesarean birth.[29,31] The World Health Organization guideline on the prevention of PPH recommends administration of 10 units of oxytocin during the third stage of labor and cautions against rapid IV infusion to reduce cardiovascular effects.[6] The amount of time used to define rapid infusion versus bolus is not distinguished in the literature. Recent studies have evaluated the effectiveness of lower doses than 10 units to stimulate adequate uterine tone to prevent hemorrhage and have found fewer cardiovascular effects for women having elective cesarean birth.[31] Additional research will be needed to evaluate if these lower doses of oxytocin are also effective when women have labored prior to cesarean birth.

Oxytocin also has antidiuretic effects by mimicking vasopressin action in the kidneys to increase water retention.[30] In a study examining this antidiuretic effect in rats, synthetic oxytocin was found to interact with vasopressin receptors stimulating an increase in proteins that decreased urine production and increased urine osmolality.[30] As a result, for some women in labor, higher doses or longer duration of oxytocin can cause symptomatic hyponatremia.[30]

Animal studies have also shown that very low amounts of synthetic oxytocin are able to penetrate the blood-brain barrier; however, it is unclear how this affects the central neuronal actions that influence maternal-infant bonding, mood, and the breastfeeding dyad.[23] For an in-depth review on the influence of synthetic oxytocin on central nervous system pathways that may affect maternal-newborn bonding and maternal stress, readers are referred to the article by Bell et al[23] published in this journal.

EVIDENCE-BASED USE OF OXYTOCIN IN CLINICAL PRACTICE

With respect to the known adverse effects of oxytocin and the variability of response, midwives, physicians, and nurses must reserve its use for when labor falls outside of physiologic parameters or when other maternal or fetal indications for intervention present. Appreciation of the normal physiology of uterine contractions and the time it may take for labor to progress is essential. Titration of oxytocin could then be aimed to mimic physiologic labor and may minimize harm.

Zhang et al[32] have provided modern standards for defining active labor following an investigation of 62,415 women in spontaneous labor. These investigators reported that in most women, acceleration of cervical dilation representing the onset of the active phase of labor does not occur until after 6 centimeters, regardless of parity. They also recognized that some women, particularly nulliparous women, may experience even slower rates of dilation throughout labor and still achieve spontaneous vaginal birth.[32] The Zhang findings have challenged decades of understanding regarding the phases of the first stage of labor and when augmentation of labor using oxytocin should be implemented.

Oxytocin Administration for Labor Induction

For labor that is induced, the latent phase of the first stage of labor may also be significantly longer than previously believed. A 2012 study[29] (N = 5388) examined labor records of women who gave birth from 2004 to 2008 and found that prior to a cervical dilatation of 6 centimeters, labor was longer if it was induced or augmented with oxytocin compared to women whose labor was spontaneous. Specifically, the duration of time for each centimeter of dilatation between 3 and 6 centimeters, regardless of parity, was significantly longer during induced labor, than the time for this amount of cervical change in women whose labor was spontaneous ($P < .01$).[29] However, the active phase of the first stage of labor was similar for women of any parity after cervical dilatation of 6 to 7 centimeters.[29] The total duration of labor was longer for nulliparous women who were induced (median [95th percentile], 5.5 h [16.8 h]), compared to nulliparous women in spontaneous labor (3.8 h [11.8 h]) ($P < .01$).[29] Similarly, multiparous women with induced labor had a longer total duration of labor (4.4 h [16.2 h]), versus multiparous women who labored spontaneously (2.4 h [8.8 h]) ($P < .01$).[29]

A longer-than-conventional latent phase is important to consider when assessing if a woman's labor is protracted or arrested. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) recommend that labor protraction or arrest disorders not be diagnosed before 6 centimeters of dilatation, and a "failed induction" should be reserved for no progress beyond at least 24 hours, with oxytocin administered for at least 12 to 18 hours after membranes have ruptured.[34]

Some clinicians question if oxytocin can be discontinued in the active phase of induced labor without increasing the length of labor or the incidence of cesarean. Diven et al[35] conducted a small (N = 252), single-center randomized controlled trial in the United States and found no difference in the rate of cesarean birth when oxytocin was discontinued after active labor (> 4 cm), compared to continuing oxytocin infusion until birth. Women who had oxytocin discontinued experienced a longer duration of active labor by a median of 1.2 hours ($P = .004$).[35] In adjusted analysis, chorioamnionitis was not significantly associated with oxytocin discontinuation (adjusted relative risk ratio, 0.90; 95% CI, 0.23-3.44).[35] Chorioamnionitis was attributed to the use of intrauterine pressure catheters (IUPCs) and a longer duration of membrane rupture.[35] In this population, 46% of women randomized to discontinuation had oxytocin restarted for either a decreased frequency of contractions or a lack of cervical change, but there was no increase in the incidence of cesarean compared to the group that had oxytocin continued until birth.[35] Discontinuing the use of exogenous oxytocin once active labor is achieved can be considered for women undergoing labor induction. This practice could be protective against risks associated with prolonged oxytocin exposure by reducing the extent of oxytocin receptor desensitization but needs to be balanced against possible increased

risks for chorioamnionitis if IUPCs are used to monitor labor progress.

Oxytocin for Treatment of Labor Dystocia

Guidelines based on the data from the Consortium of Safe Labor[32] aim to define normal labor progress for modern intrapartum care. Making the diagnosis of dystocia and augmenting labor with oxytocin before cervical dilatation of 6 centimeters may be over treatment. This practice then exposes women and fetuses to unnecessary risk of adverse effects of oxytocin administration.

Several studies have investigated the optimal timing of oxytocin initiation following a diagnosis of dystocia and the impact on vaginal birth rates and risks to the woman and fetus. According to an analysis from the Cochrane Collaboration,[36] when oxytocin is administered immediately at the time of diagnosis of slow labor progress, the duration of labor is reduced by a mean of 2.2 hours (95% CI, –3.29 to –1.10). This could be significant from a cost perspective. However, immediate initiation of oxytocin compared to expectant management for an additional one to 4 hours prior to oxytocin augmentation does not increase the incidence of spontaneous vaginal birth, rendering no difference in the rates of cesarean (RR, 0.88; 95% CI, 0.66-1.19) or operative vaginal birth (RR, 1.17; 95% CI, 0.72-1.88).[36] Tachysystole accompanied by variant FHR patterns was observed more frequently with immediate or early oxytocin use.[36] There was no significant difference in Apgar score (RR, 1.02; 95% CI, 0.46-2.28) or neonatal intensive care unit admission (RR, 0.95; 95% CI, 0.60-1.50) based on the timing of oxytocin initiation.[36] Maternal satisfaction scores did not improve, and pain perception was rated higher when oxytocin was initiated early.[36] The authors concluded that the decision to augment labor could be decided by the woman based on a reduced time to birth, rather than emphasis on mode of birth or morbidity.[36] There was significant heterogeneity among the studies analyzed. However, the authors concluded that the results likely represent a true effect because the outcomes were in the same direction after a random-effects meta-analysis.[36] In summary, when labor dystocia is identified, a period of expectant management prior to oxytocin initiation does not increase risks for the woman or fetus. Shared decision-making and informed consent discussions that support the unique labor process of each woman and that emphasize the primary benefit of reduced length of labor would be most consistent with this evidence.

Dosing Protocol: High Dose Versus Low Dose

The dosing protocols for the use of oxytocin to induce or augment labor differ widely as a result of variable study design and fall into 2 categories: high dose or low dose. High-dose protocols have a starting dose of 6 milliunits/min, with an incremental increase of 1 to 6 milliunits/min every 15 to 40 minutes, and a maximum dose of 40 milliunits/min.[8,9] Low-dose protocols have starting doses of 0.5 to 1 milliunits/min, with an incremental increase of 1 to 2 milliunits/min every 15 to 40 minutes, and a maximum dose 20 to 40 milliunits/min.[8,9] Although ACOG[8,9] states that either high-dose or low-dose oxytocin administration at dosage intervals of 15 to 40 minutes is appropriate for use in labor, this recommendation is inconsistent with the known pharmacokinetics of oxytocin metabolism and contrary to the principle of using the lowest dose of a drug in order to achieve a desired effect.

Table 1. Guidelines From ACOG and AWHONN for Low-Dose Oxytocin Infusion in Labor

Organization	AWHONN	ACOG
Starting dose	1 milliunits/min	0.5-2 milliunits/min
Increment dose	1-2 milliunits/min	1-2 milliunits/min
Frequency	Every 30-60 minutes	Every 15-40 minutes

Abbreviations: ACOG, the American College of Obstetricians and Gynecologists; AWHONN, the Association of Women's Health, Obstetric, and Neonatal Nurses. Adapted from: ACOG[8]; AWHONN.[38]

Baseline plasma concentrations of endogenous oxytocin during labor compare to a rate of approximately 5 to 7 milliunits/min of continuous IV oxytocin.[37] Any addition of exogenous oxytocin will have a cumulative effect.[37] A majority of women receiving exogenous oxytocin during labor give birth vaginally with a maximum infusion of approximately 11 to 13 milliunits/min.[1] Higher doses of oxytocin are associated with increased fetal and neonatal risks related to tachysystole and variant FHR patterns. High-infusion doses are also associated with uterine rupture in rare cases. A definitive maximum dose has not been established,[8,37] but based on current evidence, a maximum dose of 20 milliunits/min may be reasonable. Higher doses may increase maternal and fetal risks as presented, particularly if higher doses are maintained for prolonged periods of time. Increased time rather than increased dose may be safer and still effective.

According to a 2013 Cochrane review,[12] high-dose oxytocin (starting dose and an increment $\geq$ 4 milliunits/min) was associated with a statistically significant reduction in the length of labor (mean difference of 3.5 h; 95% CI, –6.38 to –0.62). High-dose oxytocin also was associated with a decreased cesarean birth rate and increased vaginal birth rate. Neither of these outcomes, however, was statistically significant when the largest study was removed due to a high risk of allocation bias ($I^2 = 58\%$ with inclusion, $I^2 = 0\%$ when excluded).[12] High-dose regimens were more often associated with tachysystole, but there was no significant difference in neonatal outcomes.[12] There was also no significant difference in rates of chorioamnionitis.[12] Current data are not sufficient to recommend routine use of high-dose oxytocin.[12] Guidelines from ACOG[8,9] and the Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN)[38] for low-dose infusion of oxytocin are presented in Table 1.

Assessing Uterine Activity and Fetal Heart Rate During Oxytocin Administration

Adequate assessment of uterine activity and the presence or absence of variant FHR patterns is a critical component of safe administration of oxytocin.[8,11,39] There is no evidence that one method of fetal cardiotocography (internal vs external) is more effective during labor when exogenous oxytocin is administered.[39] Recommendations for standard use of internal tocodynamometry during induced or augmented labors are based on expert opinion.[39] Neonatal outcomes

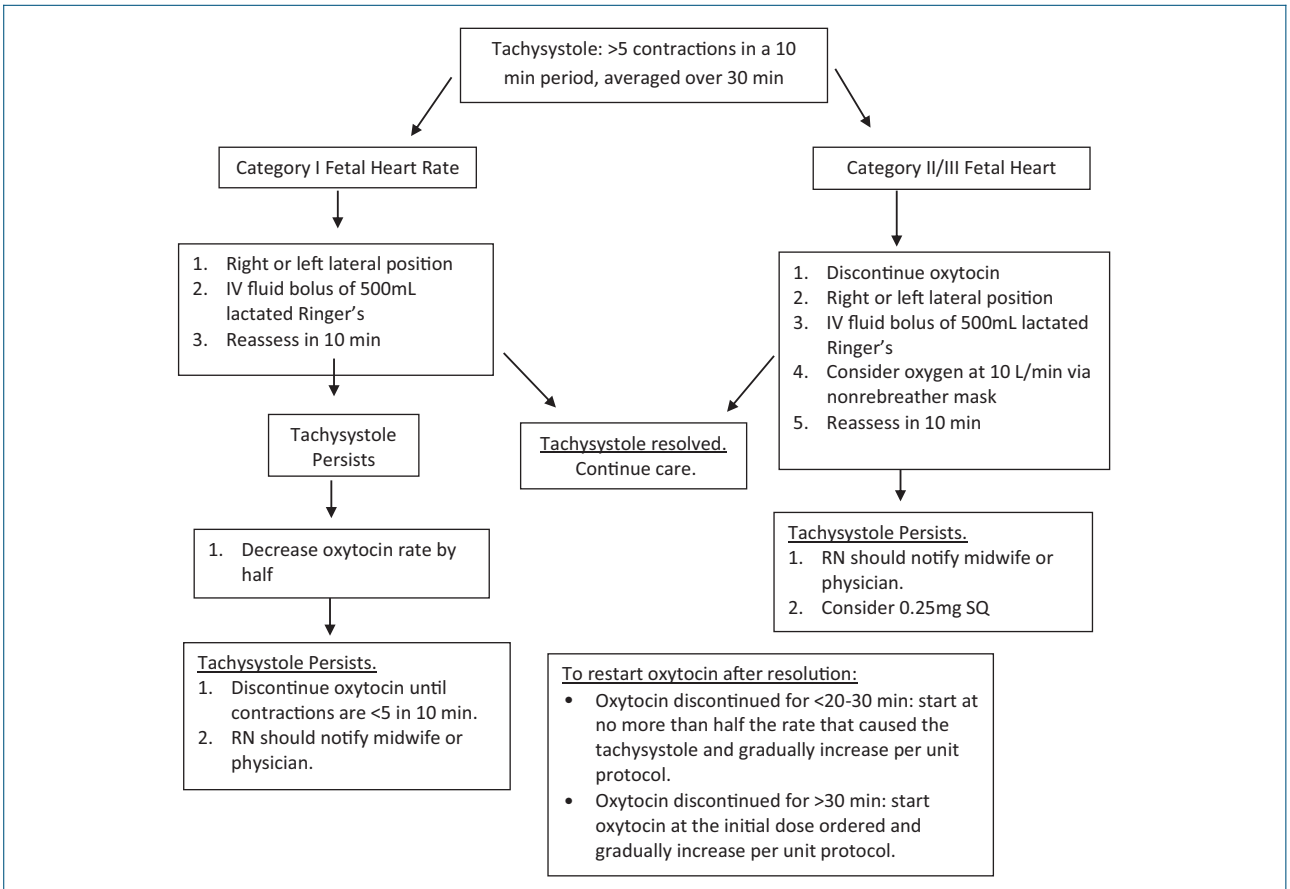

Figure 1. Treatment Algorithm for Oxytocin-induced Uterine Tachysystole and Fetal Heart Rate Abnormalities

are not significantly different with either method, and there is no reduction in operative birth associated with internal tocodynamometry.[39] Any method of assessment should include palpation of the uterus between contractions to evaluate resting tone.

The 2008 National Institute of Child and Human Development workshop on electronic fetal monitoring produced updated guidelines on nomenclature for fetal monitoring interpretation and included guidelines for assessing uterine contractions.[7] In this guideline, uterine contractions were quantified and categorized as representing normal frequency at a rate of less than or equal to 5 contractions in 10 minutes, averaged over 30 minutes.[7] Tachysystole was defined as more than 5 contractions in 10 minutes, averaged over 30 minutes.[7] This recommendation is based on expert opinion. As previously discussed, for some fetuses, contractions that occur at this "normal" rate of 5 per 10-minute period may cause oxygen desaturation and mild hypoxemia.[10,11] Particularly when oxytocin is administered, a contraction frequency of less than 5 per 10-minute period, may be more consistent with physiologic labor and could reduce adverse neonatal outcomes that may be attributed to decreased fetal oxygenation.

Treatment of Tachysystole and Abnormal Fetal Heart Rate

For tachysystole that occurs with or without FHR abnormalities, there are several methods for treatment, including decreasing or discontinuing the oxytocin, administering an IV fluid bolus of 500 mL of lactated Ringer's, and maternal repositioning to a lateral position.[10] Simpson and James[10] evaluated the effectiveness of these methods for intrauterine resuscitation. Tachysystole resolved in a mean (standard deviation [SD]) of 6 minutes (1.9 min) when all methods were combined; 10 minutes (3.1 min) following oxytocin discontinuation and fluid bolus; and 14 minutes (2.6 min) following discontinuation of oxytocin alone ($P < .001$).[10] It is recommended that tachysystole be treated even when the FHR pattern remains normal.[10]

ADVERSE OUTCOMES AND LITIGATION ASSOCIATED WITH OXYTOCIN USE

The pharmacotherapy most frequently associated with adverse perinatal outcomes is oxytocin.[1] Malpractice case excerpts have demonstrated a lack of timely recognition and treatment to resolve tachysystole, incorrectly interpreting fetal monitoring, or failure to perform a timely cesarean as contributing to adverse outcomes associated with oxytocin use.[1,40] Inappropriate increases of oxytocin, lack of palpation to assess uterine activity, and failure to address uterine tachysystole have also been associated with malpractice.[41]

RISK MANAGEMENT STRATEGIES FOR SAFE OXYTOCIN USE

There are several risk management strategies that have been proposed in recent years to promote evidence-based use of this high-risk medication while minimizing adverse

effects to the woman and fetus.[37,41,42] Institutions that take a collaborative approach to the use of oxytocin in maternity care involve all stakeholders—midwives, physicians, nurses, administrators, pharmacists, and risk managers—who can be critical in policy change and process improvement. Processes that aim to prevent harm include identifying appropriate candidates for whom oxytocin may be beneficial, counseling women on risks and benefits and documentation of the discussion, adopting a standard order set that is based on pharmacokinetic and pharmacodynamic evidence, and having a standard definition of tachysystole that requires treatment independent of FHR pattern or the woman's perception of pain.[1,37,41]

The American College of Nurse-Midwives (ACNM) advocates for no induction or augmentation of labor without an evidence-based clinical indication.[43] The ACOG Practice Bulletin on induction of labor[8] lists examples of accepted indications for labor induction. A low-dose protocol for oxytocin initiation and titration beginning at 1 milliunit/min and allowing for increase of 1 to 2 milliunits/min no more frequently than every 30 to 60 minutes based on specified maternal-fetal indicators is consistent with current knowledge and pharmacokinetic principles.[37,41] Safe titration can be achieved using premixed 30 units of oxytocin in 500 mL of IV fluid because 1 milliunit of oxytocin equals 1 mL/h on a standard infusion pump.[38] Once regular contractions and adequate cervical change based on the stage of labor has been achieved, oxytocin should not be increased.[41] Decreasing the dose incrementally to the lowest dose that maintains labor progress, or discontinuing the infusion after progressive active labor has been achieved, can also be considered.[35]

Frequent assessment based on the stage of labor encourages timely identification and treatment of tachysystole, and any accompanying FHR changes.[44] A treatment algorithm that can be adapted into hospital protocols is shown in Figure 1. Policies that allow nurses to discontinue or decrease the dose of oxytocin without initially contacting the midwife or physician may hasten response time.[45] To meet these guidelines of assessment and documentation, adequate unit staffing is needed so that a registered nurse is providing care for no more than one woman during labor induced or augmented with oxytocin, although a maximum ratio of 1:2 may be appropriate.[45]

Finally, adoption and implementation of checklists for use prior to and during administration of oxytocin allow for concurrent safety monitoring and reduce variation in practice patterns (Table 2).[41,42,46] Periodic case review is also possible with these and other audit tools for ongoing peer review and quality assurance.[45] Checklists should be included in the institution's electronic medical record system for easier documentation. Outcomes of checklist utilization have included lower maximum dose of oxytocin without longer labor duration or increased operative birth.[37,41,42] Some institutions have experienced prolonged labor, increased rates of chorioamnionitis, and increased cesarean births for labor dystocia following implementation of a low-dose oxytocin checklist.[46] These outcomes could also be attributed to management practices related to timing of admission, diagnosis of labor dystocia, internal monitoring, frequency of vaginal examinations, and other influencing factors. Other reports have shown a decreased risk of cesarean birth and fewer neonatal intensive care unit admissions when the dose adjustments are predicated on maternal-fetal response rather than a specific time period.[37] Additional research in these areas would be beneficial to clinical practice.

Table 2. Items to Include in an Oxytocin Use Checklist

Documentation by ordering provider prior to initiating oxytocin
GA, EFW, vertex fetal presentation, and adequacy of the pelvis
Indication for induction or augmentation
Informed consent by the woman that indicates a discussion of indication, risks, benefits, and alternatives
Most recent cervical examination
Bishop score ≥ 6 if labor is being induced
Assessment and documentation prior to initiating oxytocin
A reactive nonstress test or negative contraction stress test
Category I FHR tracing in the previous 30 min
Frequency of contractions in a 10-minute period, averaged over 30 minutes
Assessment and documentation prior to increasing oxytocin dose
Category I FHR tracing in the previous 30 minutes
If FHR is category II: No more than one late deceleration or 2 variable decelerations
No more than 5 contractions in 10 minutes averaged over 30 minutes
Uterus is palpated and must be soft between contractions
If IUPC is in place, MVU must be less than 300 in a 10-minute period

Abbreviations: EFW, estimated fetal weight; FHR, fetal heart rate; GA, gestational age; IUPC, intrauterine pressure catheter; MVU, Montevideo units.
Adapted from: Krening et al,[41] and Clark et al.[42]

CONCLUSION

Oxytocin is a complex hormone that exerts powerful action in the body during labor and birth, and presents significant risk to the woman and fetus if not administered and monitored safely. Suggested risk management strategies for the use of oxytocin in labor include the following: utilize shared decision making and document informed consent for induction or augmentation; establish institutional guidelines and/or protocols that are consistent with its pharmacokinetic properties and pharmacodynamic effects, including a maximum dose; palpate uterine activity and document it prior to increasing the dose; discontinue its administration when active labor is established; and provide education, standardization, and support for all providers managing the administration of exogenous oxytocin.

Midwives, physicians, nurses, and administrators best serve women by providing the time and resources for the development of protocols for safety. Educational programs

can ensure that all providers who manage the administration of exogenous oxytocin understand the pharmacokinetics and potential complications of this high-alert medication. The safety of women and their newborns depends on it.

AUTHORS

Katie Page, CNM, MSN, is in full-scope practice in Lynchburg, Virginia, at Centra Medical Group Women's Center.

William F. McCool, CNM, PhD, FACNM, is the director of the Midwifery Graduate Program at the University of Pennsylvania and is in clinical practice with affiliation with the Hospital of the University of Pennsylvania.

Mamie Guidera, CNM, FACNM, is on faculty at the University of Pennsylvania teaching professional issues and works at the Hospital of the University of Pennsylvania and the Latina Women's Health Center. She is the chairperson of the professional liability section (PLS) of ACNM.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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