

## OBSTETRICS

## Oxytocin: new perspectives on an old drug

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Oxytocin is a synthetic octapeptide currently used in a majority of all births in the United States.<sup>1</sup> In the past 2 decades, the near-universal use of controlled infusion devices and electronic fetal heart rate and uterine contraction monitoring instruments has made oxytocin safer than it once was.<sup>2</sup> Nevertheless, oxytocin remains the drug most commonly associated with preventable adverse events during childbirth.<sup>3</sup>

Oxytocin is also frequently implicated in professional liability claims and thus poses a dual concern for individual clinicians and the organizations in which they practice.<sup>4</sup> Approximately half of all paid obstetric litigation claims involve allegations of oxytocin misuse.<sup>3</sup>

Recently, oxytocin was added to the list of high-alert medications designated by the Institute for Safe Medication Practices (ISMP), a distinction reserved to only 11 other specific drugs. Such drugs are defined as those “bearing a heightened risk of harm when they are used in error” and that may “require special safeguards to reduce the risk of error.”<sup>5</sup> The ISMP is an independent, nonprofit organization whose recommendations are utilized by groups such as the Joint Commission in evaluating medication safety.

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Oxytocin is the drug most commonly associated with preventable adverse perinatal outcomes and was recently added by the Institute for Safe Medication Practices to a small list of medications “bearing a heightened risk of harm,” which may “require special safeguards to reduce the risk of error.” Current recommendations for the administration of this drug are vague with respect to indications, timing, dosage, and monitoring of maternal and fetal effects. A review of available clinical and pharmacologic data suggests that specific, evidence-based guidelines for the intrapartum administration of oxytocin may be derived from available data. If implemented, such practices may reduce the likelihood of patient harm. These suggested guidelines focus on limited elective administration of oxytocin, consideration of strategies that have been shown to decrease the need for indicated oxytocin use, reliance on low-dose oxytocin regimens, adherence to specific semiquantitative definitions of adequate and inadequate labor, and an acceptance that once adequate uterine activity has been achieved, more time rather than more oxytocin is generally preferable. The use of conservative, specific protocols for monitoring the effects of oxytocin on mother and fetus is likely not only to improve outcomes but also reduce conflict between members of the obstetric team. Implementation of these guidelines would seem appropriate in a culture increasingly focused on patient safety.

**Key words:** adverse perinatal outcomes, evidence-based guidelines, labor, monitoring protocols, oxytocin

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The designation by ISMP highlights the inability of technological safeguards, as currently utilized in the United States, to consistently prevent patient harm from oxytocin. Administration of other high alert medications (eg, insulin, methotrexate, and nitroprusside) generally involves the use of well-defined protocols that eliminate dangerous variations and minimize risk of inadvertent human error.

The purpose of this Clinical Opinion is to suggest a reevaluation of current practice patterns leading to change in how oxytocin is administered, with increased patient safety the result. Our observations and suggestions for safer administration of oxytocin are based on the available scientific studies as well as many years of both individual clinical practice and quality improvement work in large health care delivery systems.

The widespread use and utility of oxytocin in modern obstetric practice is undeniable; it is used beneficially in mil-

lions of pregnancies annually without ill effect.<sup>6</sup> That said, many of the recommendations guiding current administration of oxytocin reflect habits derived from an era when means to objectively monitor its uterine or fetal effects did not exist, cesarean delivery was labeled an “obstetrical failure” because it posed a significant health and future reproductive hazard to the mother, and rigorous clinical and pharmacological evidence had not yet accumulated.

This world no longer exists. In many instances, the apparent efficacy and safety of the various anecdotally derived means of administration (“the way we have always done it”) owe their success primarily to the resiliency of maternal-fetal biology rather than carefully considered scientific evidence. Recognition of the danger posed by other than rigorous, standardized, and scientifically based administration of oxytocin is at the heart of the ISMP high alert recommendation.

### Pharmacologic considerations

The physiologic effects and pharmacokinetics of oxytocin have been thoroughly described elsewhere.<sup>7-9</sup> Three unique characteristics of oxytocin are of special note.

First, the onset of action of a given dose of dilute oxytocin solution is relatively slow, compared with, for example, intravenously administered insulin or nitroprusside. Seitchek et al<sup>7</sup> showed that steady-state plasma levels of intravenously administered oxytocin are reached only after 40 minutes. It follows that any dosing regimen that increases the infusion rate significantly faster than this will, by definition, be a blind procedure in which additional drug is given before the full effects of the previous dose can be known.

Second, few drugs in the entire medical armamentarium have such an unpredictable therapeutic index: whereas most women requiring oxytocin achieve adequate contractions and deliver with an infusion at no more than 11-13 m/U per minute,<sup>10</sup> the effects of any given dose of oxytocin in a specific woman may range from sustained hypertonic contractions and fetal asphyxia to no discernible effect on uterine contractility. This suggests 2 things. First, the drug should be started at a relatively low dose. Second, regimens involving predetermined, lock-step increases in oxytocin infusion rate without regard to uterine response are inappropriate; any increase in dosage must be predicated upon a determination that a lower dose is insufficient in achieving normal, physiologic rates of labor progress for latent or active-phase, first-stage or second-stage labor.

Finally, with rare exception, detrimental effects of this drug are exclusively mediated through its dose-related effects on uterine activity.<sup>1,10</sup> Bakker et al<sup>11</sup> recently demonstrated an inverse relationship between number of contractions and fetal pH. Johnson et al,<sup>12</sup> using data derived from fetal pulse oximetry, demonstrated incomplete recovery of fetal oxygen saturation (SaO<sub>2</sub>) to previous baseline levels when contractions were occurring every 2 minutes or more.

Simpson and James<sup>13</sup> showed a progressive decline in fetal SaO<sub>2</sub> with persistent contraction frequencies of 5 or more in 10 minutes; no such desaturation was seen with persistent contraction frequencies of less than 5 in 10 minutes, confirming observations on fetal cerebral oxygen saturation studied by near infrared spectroscopy by Peebles et al.<sup>14</sup> Whereas the clinical significance of such declines in fetal SaO<sub>2</sub> remains to be determined, it would seem clear that if 2 administration protocols achieve equivalent clinical results (vaginal birth rate and maternal/neonatal outcome), the protocol that utilizes a lower rate of oxytocin infusion is preferable.<sup>10</sup>

### The problem with monitoring

One aspect of oxytocin use that contributes to the management dilemmas surrounding its administration is the fact that there exist only inexact technical means of measuring the effects of oxytocin on the uterus. In terms of evidence-based clinical outcomes, the superiority of internal vs external monitoring techniques has never been demonstrated in any specific clinical situation, and both of these techniques leave much to be desired.<sup>15</sup>

In early labor with an unengaged fetal head, elective artificial rupture of membranes may be contraindicated, and with minimal dilatation and/or a high cervix, placement of an internal pressure catheter may not be technically possible in spite of membrane rupture.

Even when such internal monitoring techniques are utilized later in labor, assessment of uterine activity with Montevideo units (MVUs) is far from exact. Clearly, the maternal and fetal effects of contractions lasting 45 seconds are significantly different from those of a pattern of otherwise identical contractions, each lasting 90 seconds, yet any management approach based on internal pressure catheter waveforms and MVUs must consider this difference completely irrelevant. On the other hand, management based on external tocodynamometry relies on a completely subjective, qualitative assessment of contraction strength.

Given such uncertainties in our ability to evaluate the actual nature of uterine activity, all management schemes based on uterine contraction patterns essentially represent conclusions drawn from inexact data. The fact that no significant advances in assessment of uterine activity have been made in more than half a century suggests an important area of future research that is vitally needed.<sup>16</sup> Investigations into newer techniques, such as myoelectronic monitoring, are desperately needed and could well revolutionize our understanding of the process of normal and abnormal labor and of the proper role of oxytocin in labor management.

### What is physiologic?

Comparison of oxytocin administration to nitroprusside, another drug on the short list of high-alert medications, is instructive. Nitroprusside causes relaxation of vascular smooth muscle and is given to reduce blood pressure in cases of hypertensive crisis. Administration is carefully titrated using the lowest dose possible to achieve a quantifiably verifiable blood pressure goal.

Ideally, oxytocin administration would be approached in a similar manner. Unfortunately, such quantitative titration is not possible, given the technological limitations previously discussed. However, pending the development of techniques that allow actual quantification of uterine activity, we believe that patients receiving oxytocin would be well served with the use of either of 2 definitions of acceptable uterine contractions: the consistent achievement of 200-220 MVUs or a consistent pattern of 1 contraction every 2-3 minutes lasting 80-90 seconds and palpating strong by an experienced labor nurse.<sup>12,13,15,17,18</sup>

Once these levels of uterine activity have been achieved, we see no justification for additional increases in oxytocin dose: as with nitroprusside, oxytocin should be aggressively titrated to the lowest dose compatible with sustained levels of appropriate uterine activity, as defined in previous text. There is no place in modern obstetric practice for "pitting to distress," "pitting through" a pattern of excessive uterine activity, or

continuing to blindly increase the oxytocin dose until the 1-minute Apgar score is recorded. In fact, a recent randomized trial suggests fewer operative deliveries in women whose labor is induced when oxytocin is discontinued at the onset of the active phase (5 cm).<sup>19</sup>

If the objective achievement of these defined levels of uterine activity does not result in suitable progress, cesarean delivery, rather than achievement of supra-physiological levels of uterine activity, is indicated. Once these levels have been achieved, more time, not more oxytocin, is usually the better choice.<sup>15,20,21</sup> Given the relative safety of cesarean delivery in the United States today, there is no justification for significantly exceeding established physiological levels of uterine activity in an effort to force a vaginal birth.<sup>22</sup>

### Unfortunate realities

In our experience, the underlying force driving much of the misuse of oxytocin today is the administration of this agent for provider or patient convenience. We know of no other area of medicine in which a potentially dangerous drug is administered to hasten the completion of a physiologic process that would, if left to its own devices, usually complete itself without incurring the risk of drug administration. Yet the administration of oxytocin is often undertaken under precisely these circumstances when labor is electively induced or Braxton-Hicks contractions are electively augmented.

Given the absence of outcomes-based evidence demonstrating clinical benefit of such practice, together with the cascade of potential increased risk incurred with induction of labor, the use of a high-alert medication “bearing a heightened risk of harm” seems difficult to justify under elective circumstances. Elective induction in a woman with an unripe cervix or prior to 39 completed weeks of gestation, or the use of aggressive high-dose regimens at odds with the above pharmacologic principles under elective circumstances seems especially inappropriate. The use of prostaglandin-based agents to assist in this elective process adds additional risks to a procedure that

by definition has no medical benefits and also seems unwise.<sup>23,24</sup>

In a similar manner, for a woman already in labor, the time of day or night may dictate the initiation or pace of oxytocin administration as often as true prolonged latent phase, arrest of active phase dilatation, or arrest of descent with documented inadequate contractions. Convenience as a driver of labor augmentation seems counter to a culture focused on patient safety.

The authors approach this issue with a deep personal appreciation of the toll obstetric practice takes on the life of an obstetrician and her/his family as well as the very real dangers of sleep deprivation on cognitive performance in subsequent patient encounters.<sup>25,26</sup> Our concern should not be seen in any way as a criticism of the practicing obstetrician; rather, it is an indictment of a flawed system within which most obstetricians do their best to give good care. We know of no process in medicine quite as inefficient as that exemplified by 5 board-certified obstetricians sitting in the doctors’ lounge at 2:00 AM, each waiting for a single patient to deliver.

The detrimental effects of this approach to obstetrics on the quality of life of the obstetrician is well known to all readers; the fact that such a situation ensures inescapable cognitive degradation of the care received the subsequent day by many dozens of additional clinic, obstetric, or surgical patient is less well appreciated.<sup>25,26</sup> Avoidance of such sleep deprivation by scheduled induction of labor in some women is a common, sometimes justified, but ultimately sub-optimal response to this dilemma.

Absent widespread adoption and patient acceptance of a more rational, hospitalist model of labor and delivery care in which criteria for induction, augmentation, and cesarean delivery for labor arrest are uniformly applied, and the timing of delivery is completely irrelevant to the provider, elective use of and timing of oxytocin administration will continue. Under these circumstances, both over- and underuse of the drug and an inordinately high cesarean delivery rate seem inevitable. Given these realities, the development of a uniform, safe ap-

proach to oxytocin administration seems even more critical.

### Normalization of deviance

Another factor contributing to the misuse of oxytocin is the normalization of deviance, a term used to describe degradation of professional or technical standards based on individual experience and the fact that nonadherence to the standard only uncommonly results in an adverse outcome.<sup>27,28</sup>

In obstetrics, such practice is encouraged by the ability of many fetuses to tolerate hyperstimulation without becoming seriously hypoxic or acidotic.<sup>29</sup> Thus, the recollection of a physician that “I’ve never had a problem” with a specific practice of oxytocin administration holds little weight when viewed in light of either large-scale outcomes-based evidence or basic physiologic considerations to the contrary.

From a nursing perspective, normalization of deviance may also lead to abandonment of recommended staffing ratios for women receiving oxytocin or acquiescence of nursing staff to practices they deem unsafe.<sup>30</sup>

### A team approach

Our experience in assessing and improving obstetric practices in many hundreds of different institutions has led all the authors to 1 identical conclusion: the most common cause of discord between obstetrician and labor nurse is the tendency of a physician not at the patient’s bedside to urge the use of oxytocin in a manner deemed unsafe by the bedside labor nurse.<sup>31</sup>

In this regard, we believe 3 central facts should be self-evident. First, given the disagreement between 2 individuals of equal intelligence, the person with the greatest actual experience with the object of discussion will generally be correct. Second, an experienced labor nurse has more hours of hands-on experience than most obstetricians. And third, no one, regardless of experience, can render a credible opinion regarding a fetal heart rate or uterine contraction pattern without a personal evaluation of the tracing in question.

Our combined experience in reviewing literally thousands of cases involving adverse outcomes or litigation tells us that with rare exception, in disagreements between nurse and obstetrician regarding the aggressiveness of oxytocin administration, the experienced nurse is generally correct. Ideally, the use of uniform, unambiguous, and preestablished criteria for oxytocin initiation, administration, and monitoring, agreed on in advance by both nursing and medical staff, can largely eliminate such disagreements, to the benefit of our patients.<sup>10,30</sup>

### Problems with ambiguity

Current guidelines for the administration of oxytocin are vague and allow for initial infusion rates that vary by more than an order of magnitude and dosing intervals varying by 200-300%.<sup>15</sup> Such variation has been largely driven by extrapolation from the results of highly controlled and specific protocols involving nulliparous women who present in early labor.

Although such tightly run protocols have been carried out without increased morbidity and possibly with shorter labors, no evidence exists that perinatal outcomes are improved with protocols using the aggressive active management infusion regimens, compared with more physiologic, low-dose techniques.<sup>15</sup>

In addition, a metaanalysis of randomized clinical trials demonstrated no reduction in the cesarean rate using these protocols.<sup>32</sup> Especially concerning, however, has been the tendency to extract and implement the aggressive oxytocin regimens that represent only 1 part of active management of labor protocols, without including the other components (including multiple levels of safeguards) used by the designers of these protocols. In 1 report using a protocol in which oxytocin was increased at a rate of 6 mU/min every 20 minutes labor was shortened, compared with a low-dose protocol. However, hyperstimulation was seen in half of patients, and cesarean delivery for fetal distress occurred at twice the rate seen with a low-dose regimen.<sup>29</sup>

Although no increase in short-term adverse neonatal effects was demonstrable in patients experiencing hyperstimu-

lation and undergoing cesarean delivery for fetal distress in this academic center, the avoidance of close calls is also an integral part of current patient safety-based practice; such data suggest this high-dose approach should be avoided.

A metaanalysis of 11 randomized clinical trials demonstrated that low-dose protocols in which doses were not increased more frequently than every 30 minutes resulted in fewer episodes of hyperstimulation, a higher rate of spontaneous vaginal birth, less postpartum maternal infection, and less postpartum hemorrhage, compared with more aggressive regimens.<sup>33</sup> Thus, the preponderance of data suggest not only an absence of improved perinatal outcomes with the use of high-dose protocols but also an increase in adverse events associated with the selective use of such protocols outside the strict boundaries of complete active management of labor protocols.

Given the facts that all significant adverse effects of oxytocin are dose related and that there exists no evidence of clinical benefit with the use of higher doses, an approach to oxytocin administration based on patient safety would suggest use of a low-dose approach.

Furthermore, in virtually any aspect of human endeavor, uniformity of approach per se is associated with improved performance or outcomes.<sup>2,10,34,35</sup> These considerations suggest the need for a more uniform approach to oxytocin administration, particularly within a single institution. As a reasonable addition to uniform low-dose standardization, recent evidence suggests that standard, highly specific, checklist-driven protocols focusing on the uterine and fetal response to oxytocin may improve neonatal outcomes.<sup>2,10</sup>

### But what about the cesarean rate?

As outlined in previous text, available data refute the concept that low-dose protocols result in an increased rate of cesarean delivery. Fewer elective inductions against an unripe cervix, especially in nulliparas, and fewer abnormal fetal heart rate patterns caused by hyperstimulation would tend to reduce the primary cesarean rate: indeed, existing data suggest this to be the case.<sup>10</sup> In any

event, we believe the time is long past when cesarean delivery rate can be considered a primary outcome of any importance. Furthermore, forces much larger than the aggressive or conservative use of oxytocin will continue to drive this rate.<sup>35-37</sup>

Given the safety of cesarean delivery today, any increase in neonatal morbidity cannot be justified by attempts to achieve an arbitrary rate of cesarean delivery. To quote Dr Roger Freeman, "Every woman deserves an easy vaginal delivery or an easy cesarean delivery."

### Alternative measures

The use of amniotomy as an alternative to oxytocin to accelerate established labor remains controversial, as evidenced by 2 Cochrane reviews in successive years that reached opposite conclusions.<sup>38,39</sup> However, rupture of the membranes with resultant release of endogenous prostaglandins is in fact a normal part of physiologic labor. Thus, although amniotomy may be justifiably avoided early in the course of labor, its use might be considered as an alternative or adjunct to oxytocin in cases of active-phase or second-stage arrest.<sup>15</sup>

Inadequate hydration may also lead to dysfunctional labor; conversely, aggressive hydration has been shown to shorten labor and reduce the need for oxytocin administration.<sup>15,40,41</sup> Recent evidence also suggests a similar beneficial effect of increased glucose administration on the progress of labor.<sup>42</sup> By using higher levels of intravenous fluid, well beyond the 125 mL/hour commonly administered and by including fluids containing glucose, data suggest that both shorter labors and avoidance of oxytocin use can be achieved and cesarean delivery sometimes avoided.

Continuous support (one-on-one nursing care) during labor has been shown in a randomized clinical trial of nulliparous women to reduce the need for oxytocin stimulation with no increase in cesarean deliveries or adverse outcomes.<sup>15,43</sup> A metaanalysis of 15 similar studies demonstrated that such support reduced both operative vaginal and cesarean deliveries and was associated with improved 5-minute Apgar scores.<sup>44</sup>

## TABLE

**Labor augmentation and the diagnosis of inadequate uterine activity****Criteria for labor augmentation**

Latent phase labor exceeding 20 hours in a primiparous patient or exceeding 14 hours in a parous patient

Active phase labor with arrest of dilatation exceeding 2 hours with inadequate uterine activity, as defined in below

Second-stage arrest of descent with inadequate uterine activity, as defined in below

**Criteria for the diagnosis of inadequate uterine activity**

A contraction pattern demonstrating less than 220 MVU in the presence of inadequate labor progress, as defined in above

A contraction pattern with less than a contraction every 2-3 minutes, lasting less than 80-90 seconds, and not palpating strong to an experienced labor nurse

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**Conclusions**

Although realizing the current imperfections in our ability both to monitor uterine activity and define abnormal labor progress, we suggest that the following guidelines for oxytocin administration would be appropriate for most women who receive this agent. In cases in which the medical condition of the mother has been shown to be improved by more rapid delivery, thus justifying an increased degree of fetal risk (for example severe preeclampsia with HELLP [hemolysis, elevated liver enzymes, and low platelet count] syndrome), these recommendations may not apply.

1. Elective induction of labor should be undertaken only after a thorough discussion with the patient and documentation of the risks of this procedure as opposed to awaiting natural labor. Elective induction prior to 39 completed weeks of gestation, elective induction in women with an unfavorable cervix, and elective induction with the use of prostaglandins increases risk without evidence of ben-

efit and is inappropriate. Elective induction of nulliparous women should be approached with particular caution.

- Oxytocin use should be governed by highly specific, standardized protocols, ideally focusing on uterine and fetal response rather than arbitrary dosing regulations. However, infusion protocols that increase the rates of infusion at intervals less than 30 minutes ignore the known pharmacokinetic properties of this drug and are inappropriate in most situations.
- The professional at the bedside administering and monitoring the oxytocin infusion should have authority and responsibility for assuring this is done safely. It is inappropriate to override the recommendation of a labor nurse at the bedside regarding oxytocin infusion without actual examination of the tracing.
- In the absence of a complicating condition in which expedited delivery has been shown to improve maternal or fetal outcome, oxytocin augmentation of labor should be instituted only after a patient clearly meets both longstanding, well-defined criteria for latent-phase labor prolongation or active-phase/second-stage arrest disorders and hypotonic uterine dysfunction (Table).<sup>45</sup> Once these contraction parameters have been achieved, failure of subsequent labor progression over an appropriate time period should lead to operative delivery rather than more oxytocin.
- Oxytocin should be continuously titrated to the lowest dose compatible with a physiologic rate of labor progress. In most cases of induction, this will involve a reduction or discontinuation of oxytocin after rupture of membranes and in the active phase of labor.

Despite its risks, oxytocin will continue to be a drug with great potential benefits to mother and baby. The authors feel that the application of these principles will enhance the safety of this commonly used medication.<sup>16</sup> ■

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