OXYTOCIN: THE NEW "HIGH ALERT" MEDICATION

A. Oxytocin Becomes a High Alert Drug

On August 9, 2007, the Institute for Safe Medication Practices named oxytocin to its list of High-Alert Medications.[1] Institute surveys had shown that well over "half of all respondents" and "73% of nurses believed that oxytocin should be a high-alert medication."[2] The "high-alert" warning is a rare distinction reserved for only 11 drugs. Though mistakes with these medications "may or may not be more common…the consequences of … error[s] are clearly more devastating to patients."[3]

B. The AJOG Takes a New Look at an Old Drug

In January 2009, citing the Institute High-Alert, the American Journal of Obstetrics and Gynecology issued a new Clinical Opinion addressing the safety of oxytocin and "suggesting the need for greater caution with the

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[1] The Institute for Safe Medication Practices, "ISMP 2007 Survey on High-Alert Medications" defining high-alert medications as "those that bear a heightened risk of causing significant harm when they are used in error." *See also* http://www.ismp.org/Tools/highalertmedications.pdf

[2] The Institute for Safe Medication Practices, "ISMP 2007 Survey on High-Alert Medications." *See also* http://www.ismp.org/Tools/highalertmedications.pdf

[3] The Institute for Safe Medication Practices, "ISMP 2007 Survey on High-Alert Medications" defining high-alert medications as "those that bear a heightened risk of causing significant harm when they are used in error." *See also* http://www.ismp.org/Tools/highalertmedications.pdf

intrapartum use of the drug."[4] The Opinion recommends a "re-evaluation of current practice patterns" and "change in how oxytocin is administered" in order to promote patient safety.[5]

"Historically, early regimens of oxytocin administration were highly individualized by physician preference, ranging from relatively low doses to extremely high doses."[6] Dating back to the 1940s, controversy existed over "the best and most appropriate regimen for oxytocin use."[7] Since oxytocin was known to be patient dependent rather than drug dependent,[8] the effect of the drug on any given patient was unpredictable.[9] Even when guidelines were first established, there were no reliable methods for monitoring the effects of oxytocin on the uterus and fetus. Moreover, cesarean delivery, in early times, was considered an "obstetrical failure," given the high maternal

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[4] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug". American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[5] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug". American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[6] Danforth's, Obstetrics and Gynecology, 9th edition, pp. 410 (2003).

[7] Danforth's, Obstetrics and Gynecology, 9th edition, pp. 410 (2003); Freeman, R. et al., "A protocol for use of oxytocin." American Journal of Obstetrics & Gynecology, Vol. 197, Issue 5 (2007) states "there is less than consensus regarding the best nursing and physician practices with respect to the safe use and efficacy of this potentially dangerous drug."

[8] Hayes, E. et al., "Improving patient safety and uniformity of care by a standardized regiment for the use of oxytocin" American Journal of Obstetrics and Gynecology, Vol. 198, Issue 6 (June 2008) states "It is important to appreciate variation within a patient population when setting a standardized dosing regimen …."

[9] Danforth's, Obstetrics and Gynecology, 9th edition, pp. 410 (2003) states "[w]ith intravenous administration, there is a concentration-dependent increase in its serum levels but with wide individual variation in responsiveness to the drug."

risk.[10] Many obstetricians used unnecessary high doses of oxytocin causing excessive uterine activity and believed that intervention was not needed "until resultant nonreassuring changes in the fetal heart rate (FHR) pattern" were seen.[11] Nurses were trained to "pit to distress."

The Opinion highlighted the need to change management protocols given the dangerous propensities of oxytocin. Moreover, it acknowledged characteristics of oxytocin, and the variable effects it could have on patients.[12] For example, "the effects of any given dose of oxytocin in a specific woman m[ight] range from sustained hypertonic contractions and fetal asphyxia to no discernible effect on uterine contractility."[13] Moreover, since oxytocin had a slow dilution rate, dosing regimens that increased too quickly could have unpredictable and unsafe results.[14] The Opinion recommended a "uniform, unambiguous, and pre-established" approach to

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[10] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[11] Simpson, K. et al., "Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns." American Journal of Obstetrics and Gynecology, pp. 34 (July 2008) states, "Potentially adverse effects on the fetus may be avoided by minimizing periods of hyperstimulation and treating it in a timely manner rather than waiting until the FHR pattern is nonreassuring….Fetal well-being may be in jeopardy when oxytocin-induced hyperstimulation occurs during labor."

[12] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[13] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[14] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

oxytocin administration to avoid 'close calls' in "patient safety-based practice."[15]

Contrary to previous specific administration recommendations,[16] the Clinical Opinion stated that oxytocin should be started at "relative low doses."[17] Regimens involving pre-determined, automatic increases in oxytocin rates, without regard to uterine response, were no longer appropriate.[18] Thus, if there are two oxytocin protocols that achieved the same clinical results, the protocol with the lower rate of infusion was "clearly preferable."[19] Moreover, low doses were preferred to high doses since the latter could cause hyperstimulation which was "seen in up to half of patients," and c-section for fetal distress seen at "twice the rate seen with a low-dose regimen."[20] This was particularly true since there was "no evidence of clinical benefit" in using higher doses of oxytocin.[21]

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[15] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug". American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

[16] Creasy & Resnick, Maternal-Fetal Medicine, 5th edition, pp. 674 (2004) states "Oxytocin infusion is begun at 4 mU/minute and is increased by 6 mU/minute every 15 minutes until there are seven contractions per 15 minutes. The oxytocin infusion rate does not exceed 40 mU/minute."

[17] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[18] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[19] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[20] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

The Opinion stated that fetal monitoring was a necessity during oxytocin administration as a means to document "uterine activity and fetal heart rate."[22] However, since internal and external monitoring "le[ft] much to be desired," in terms of measuring the effects of oxytocin on the uterine activity, the Clinical Opinion set out two acceptable methods for quantification:

> We believe that patients receiving oxytocin would be well served with the use of either of two definitions of acceptable definitions of uterine contractions: the consistent achievement of 200-300 MVUs or a consistent pattern of 1 contraction every 2-3 minutes lasting 80-90 seconds and palpating strong by an experienced labor nurse.[23]

Once the levels mentioned were achieved, there was "no justification for additional increases in oxytocin dose."[24] Moreover, oxytocin needed to be "aggressively titrated" to the "lowest dose compatible with sustained

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[21] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

[22] Sanchez-Ramos, L. "Induction of Labor." Obstetrics & Gynecology Clinics, Vol. 32, Issue 2, (June 2005), "[s]trong consideration should be given to the use of internal monitoring when high doses of oxytocin are required or when satisfactory progress in labor is not being made."

[23] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[24] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

levels of appropriate uterine activity."[25] Finally, the Opinion made clear that c-section delivery was indicated where oxytocin use did not achieve adequate results:

> If objective achievement of these levels does not result in suitable progress, cesarean delivery, rather than achievement of supraphysiologic levels of uterine activity, is indicated….Given the relative safety of cesarean delivery in the United States today, [26] there is no justification for significantly exceeding established physiologic levels of uterine activity in an effort to force a vaginal birth.[27]

The forces driving misuse of oxytocin included: "provider or patient convenience," and "normalization of deviance" (caregivers anecdotally concluding that many fetuses tolerated hyperstimulation without becoming injured).[28] These misconceptions regarding oxytocin use seemed "counter to

[25] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 35 (January 2009).

[26] Clark, S., et al, "Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery." American Journal of Obstetrics & Gynecology, Vol. 199, p. 38 (July 2008) states "Universal perioperative use of pneumatic compression devices for all women undergoing cesarean delivery would largely eliminate the statistical difference in death related to cesarean delivery vs. vaginal birth."

[27] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, pp. 35, 37 (January 2009).

[28] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

a culture focused on patient safety."[29] Therefore, a "team approach" during oxytocin induction was the preferred method.[30]

Interestingly, the Opinion's authors observed that with rare exception, labor nurses had "more hours of hands-on experience" than obstetricians and were therefore "generally correct" in disputes as to the aggressiveness of oxytocin administration.[31] In fact, the care provider with "greatest actual experience" with oxytocin would "generally be correct."[32] However, regardless of experience, no one could provide a "credible opinion" regarding fetal heart rate monitoring, or contraction patterns, "without personal evaluation of the tracing in question."[33]

C. Oxytocin Has Long Been Recognized as Dangerous

Long before the American Journal of Obstetrics and Gynecology recognized the need for greater caution with oxytocin, evidence suggested

[29] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

[30] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

[31] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

[32] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

[33] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200, p. 36 (January 2009).

that the drug posed significant risks.[34] Oxytocin augmentation had been associated with neonatal seizures,[35] low apgar scores,[36] fetal distress,[37] hyperstimulation,[38] uterine rupture,[39] higher incidence of cesarean section deliveries,[40] postpartum hemorrhage,[41] neonatal jaundice,[42] hyperbilirubinemia,[43] and retinal hemorrhages.[44] The effects of oxytocin on

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[34] Gabbe, S. et al., Obstetrics, 4th edition, p. 379 (2002) describes "a number of complications" including uterine hyperstimulation, water intoxication, hypotension, and uterine rupture.

[35] Minchom, P. et al., "Antecedents and outcome of very early neonatal seizures in infants born at or after term." Br J Obstet Gynaecol, Vol. 94, pp. 431-9 (May 1987); Saliba, R. et al., "Risk Factors for Neonatal Seizures: A Population-based Study, Harris county, Texas." American Journal of Epidemiology, Vol. 154, No. 1, pp. 14-20 (2001); Schwartz, R. et al., "Transplacental hyponatremia due to oxytocin," Br Med J, Vol. 1, pp. 152-153 (1978).

[36] Herbst A, et al., "Risk factors for acidemia at birth". Obstet Gynecol, Vol. 90, Issue 1, pp. 125-30 (1997).

[37] Goer H., The Thinking Woman's Guide to a Better Birth. (1999); Simpson, K. et al., "Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns" American Journal of Obstetrics & Gynecology, Vol. 199 (July 2008) states "Hyperstimulation is associated with negative effects on fetal status. The more contractions in 30 minutes, the more pronounced the effect."

[38] Crane, J. et al., "Excessive uterine activity accompanying induced labor." Amerian Journal Obstetrics & Gynecology, Vol. 97, pp. 926-31 (2001).

[39] Catanzarite, V. et al., "Oxytocin-associated rupture of the unscarred uterus in a primigravida." Obstetrics and Gynecology, Vol. 108, part 2, pp. 723-25 (2006); Locatelli, A. et al., "Induction of labor: Comparison of a cohort with uterine scar from previous cesarean section vs. a cohort with intact uterus." The Journal of Maternal-Fetal and Neonatal Medicine, Vol. 19, pp. 471-75 (2006).

[40] Kaul, B et al., "Induction of labor with oxytocin increases cesarean section rate as compared with oxytocin for augmentation of spontaneous labor in nulliparous parturients controlled for lumbar epidural analgesia" Journal of Clinical Anesthesia, Vol. 16, Issue 6 (Sept 2004) states "Patients who have their labor induced request analgesia sooner and are at higher risk of cesarean section than are patients who go into labor spontaneously."; Yudkin, P. et al., "A retrospective study of induction of labour." Br J Obstet Gynaecol, Vol. 86, pp. 257-65 (April 1979).

[41] Jacobs, A. et al., "Causes and treatment of postpartum hemorrhage." www.uptodate.com

[42] Chalmers I, et al., "Use of oxytocin and incidence of neonatal jaundice." Br Med J, Vol. 2, pp. 116-8 (1975); D'Souza SW et al., "The effect of oxytocin in induced labour on neonatal jaundice." Br J Obstet Gynaecol, Vol. 86, pp. 133-8 (1979).

[43] Buchan, PC. "Pathogenesis of neonatal hyperbilirubinaemia after induction of labor with oxytocin." Br Med J 1979;2:1255-7; Beazley, J. et al., "Neonatal hyperbilirubinemia following the use of oxytocin in labour." Br J Obstet Gynecol. Vol. 82, pp 265-271 (1975).

uterine activity and fetal oxygen desaturation were seen where contraction patterns had a "frequency of every 2 minutes or less."[45] Incorrect dosing could result in violent contractions "as to kill the fetus, rupture [the uterus], or both."[46] In third world countries, oxytocin was associated with encephalopathy, intrapartum fetal death, and other intrapartum complications.[47] Reports of adverse results from oxytocin use had lead the Food and Drug Administration to issue a black box warning that oxytocin should be restricted to medically indicated inductions and augmentations and not elective ones.[48]

In more recent studies, oxytocin use has been shown to be an important risk factor for fetal acidemia at birth.[49] The mechanism occurs

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[44] Schoenfeld, A., et al., "Retinal hemorrhages in the newborn following labor induced by oxytocin and dinoprostone." Arch Ophthalmol, Vol. 103, pp. 932-934 (1985).

[45] Clark, S., et al., Clinical Opinion, "Oxytocin: new perspectives on an old drug." American Journal of Obstetrics & Gynecology, Vol. 200 (January 2009).

[46] Williams, Obstetrics, 21st edition, p. 323 (2001).

[47] Ellis, M. et al., "Risk factors for neonatal encephalopathy in Kathmandu, Nepal, a developing country: unmatched case control study." BMJ, Vol. 320, pp. 1229-36 (May 2009); Adamson, S. et al., "Predictors of neonatal encephalopathy in full term infants." BMJ, Vol. 311, pp. 598-602 (1995).

[48] Product information: Pitocin, oxytocin injection, USP. Monarch Pharmaceuticals, IncBristol, (TN) (1998), as cited in Hayes, E., et al., "Improving patient safety and uniformity of care by a standardized regimen for the use of oxytocin," American Journal of Obstetrics and Gynecology, Vol. 198, Issue 6, pp. 1-10 (2008).

[49] Jonsson, M. et al., "Acidemia at birth, related to obstetric characteristics and to oxytocin use, during the last two hours of labor." Acta Obstet Cynecol Scand, Vol. 87, pp. 745-50 (2008) states, "A hyperactive uterine contraction pattern and oxytocin use are the most important risk factors for acidemia at birth.; Bakker, P., et al., "Elevated uterine activity increases the risk of fetal acidosis at birth," Amerian Journal Obstetrics Gynecology, Vol . 196 (2007) states, "Increased uterine activity is significantly associated with a higher incidence of an umbilical artery pH of 7.11 or less."

when an excessive amount of uterine contractions result in a decrease or interruption in blood flow between the mother and fetus, which directly impacts the oxygen exchange.

D. Drug Company and Pharmacist Warnings

According to Merck, oxytocin's adverse reactions include: "brain or CNS damage (permanent)," "neonatal seizure," "neonatal jaundice," "neonatal retinal hemorrhage," "fetal death," "low apgar score (5 minute)," "bradycardia."[50] Extreme caution must be exercised when oxytocin induction is performed.

The American Society of Health-System Pharmacists ("AHFS") indicates the following precautions should be taken when using oxytocin:

1. careful evaluation of pelvic adequacy;
2. do not induce when the benefit-to-risk ratio for the mother or child favors surgical intervention;
3. not recommended when labor is progressing normally, or when hypertonic labor patterns occur, "especially since [the] drug response may be accentuated during the second stage of labor;"
4. do not use to augment labor when vaginal delivery is contraindicated (e.g., total placenta previa);

Contraindications include:

1. Substantial cephalopelvic disproportion;
2. unfavorable fetal position or presentation;
3. obstetrical emergencies where maternal or fetal risk-to benefit ratio favors surgery;

[50] Merck Manual Professional, http://www.merck.com/mmpe/print/lexicomp/oxytocin.html

4. fetal distress when delivery is not imminent;
5. umbilical cord prolapse;
6. uterine activity fails to progress adequately;
7. hyperactive or hypertonic uterus;
8. where vaginal delivery is contraindicated;
9. uterine or cervical scarring from previous cesarean section or major cervical or uterine surgery;
10. unengaged fetal head;
11. history of hypersensitivity of oxytocin.[51]

As a general precaution, oxytocin should not be administered "when pregnancy is complicated by fetal distress, hydramnios, partial placenta previa, prematurity, borderline cephalopelvic disproportion, predisposition for uterine rupture, except in unusual circumstances requiring the clinician's judgment."[52] Further, oxytocin should be discontinued, if "prolonged uterine contractions (>90 seconds), or rising intrauterine pressure occur or if uterine motility interferes with fetal heart rate."[53]

CONCLUSION

In 2009, the American Journal of Obstetrics and Gynecology, in a Clinical Opinion, finally recognized oxytocin as a "high alert" drug and established new guidelines promoting patient safety. Caregivers are now encouraged to use lower doses of oxytocin and perform cesarean deliveries, where oxytocin is ineffective or causing distress. It is unclear why it took so

[51] AHFS Drug Information, www.ashp.org

[52] AHFS Drug Information, www.ashp.org

[53] AHFS Drug Information, www.ashp.org

long to make these new recommendations, given oxytocin's known dangerous propensities over the last several decades. However, the new opinion lays the groundwork for potentially preventing hundreds of babies from suffering intrapartum asphyxia and trauma, due to excessive use pitocin.