Sep 1, 2004
By: Gary Ventolini, MD, Ran Neiger, MD
Contemporary OB/GYN

Grand Rounds

Using and abusing oxytocin

By Gary Ventolini, MD, and Ran Neiger, MD

Both high and low doses of oxytocin can safely and effectively induce or augment labor. When do you use each approach and when do high doses constitute abuse?

The goal of labor induction (stimulation of uterine contraction before the onset of labor) and augmentation (stimulation of inadequate uterine contractions) is basically the same: achieving regular uterine activity to bring about cervical dilation and fetal descent, while avoiding hyperstimulation. Oxytocin helps accomplish this goal by instructing uterine muscle cells to contract during labor. While synthetic oxytocin is by no means the only method of inducing and augmenting labor, it's the most common medication in obstetrics. In fact, in some parts of the world, it's given to every woman following delivery, and many parturients receive it for inducing or augmenting labor.

The drug has been used in obstetrics for nearly 100 years, starting shortly after the discovery in 1906 of the uterotonic activity of extracts of the posterior pituitary gland.[1] Three years after researchers described its structure, Vincent du Vigneaud synthesized the hormone in 1953, for which he received the Nobel Prize.[2] Our goal is to review the biochemical rationale for using oxytocin and give examples of physiologic oxytocin regimens in patients at high risk for fetal distress during labor.

Oxytocin physiology

The hypothalamus produces oxytocin, which is synthesized as a prohormone (prooxyphysin) in the supraoptic and paraventricular hypothalamic nuclei. Bound to a large transport peptide called neurophysin, it's packaged and transported in granules to nerve terminals in the posterior lobe of the pituitary gland (neurohypophysis), where it's stored. From there, oxytocin prohormone is secreted into the cerebrospinal fluid and directly into the portal circulation, as it's being converted enzymatically to oxytocin during transport.[3]

Oxytocin's release from the posterior pituitary is chiefly regulated by cholinergic and noradrenergic neurotransmitters and opioid peptides, but elevated estrogen levels also increase the number of oxytocin receptors and thyrotropin-releasing hormone (TRH) stimulates oxytocin secretion. The precise physiologic role of the hormone has been difficult to pin down because of the pulsatile manner of its release, at 3- to 5-minute intervals, and because it's difficult to measure.[4] During pregnancy, oxytocin acts as a circulating hormone as well as a local mediator.[5] In addition to the oxytocin released from the posterior pituitary gland, it's also synthesized in the decidua and the placenta—and it promotes the decidua's release of prostaglandins (Figure 1).[6,7]

For the better part of pregnancy, uterine activity remains low. But then just before labor begins, the uterus begins contracting. Uterine contractile responses to oxytocin increase from 20 to 30 weeks' gestation and remain unchanged from 34 weeks until term, at which time the sensitivity rapidly increases.[8] In the mid-1980s, research suggested that as the uterus undergoes distention, especially near term, the gap junction formation between myometrial cells increases.[9] Concomitantly, the number of myometrial and decidual oxytocin receptors greatly increase as pregnancy advances, with a further increase during labor itself (Figure 1).

Researchers have recently found a dramatic increase in oxytocin receptors in reproductive-tract tissues in late pregnancy and discovered that administering drugs to inhibit those receptors delays the onset of labor.[10] Near term,

uterine contractions become more frequent, intense, and coordinated. Then during labor itself, previously weak and painless Braxton Hicks contractions (pressure of 10 to 15 mm Hg above baseline) become coordinated, frequent, regular, and painful (occurring every 2 to 4 minutes with a pressure of 30 to 50 mm Hg above resting tone and lasting 60 to 90 seconds).[11] It's thought that the initial signal to stimulate a contraction is located in a pacemaker region near the uterotubal junctions. The cells in this area do not differ anatomically from other myometrial cells, but their numbers are greater.

The contractions are thought to propagate through gap junctions, which are clusters of intercellular channels between adjacent cells. The channels are formed by the direct apposition of oligomeric transmembrane proteins, permitting the direct exchange of ions and small molecules between cells without involvement of the extracellular space. Gap junction channels are composed of oligomers of connexins, an enlarging family of proteins consisting of more than 20 members.[12]

Although we know that oxytocin stimulates myometrial contractions during labor, it doesn't seem to directly *initiate* spontaneous labor in women. Decidual oxytocin receptors, which increase throughout labor and peak at delivery, stimulate the formation of prostaglandin F_2 alpha (PGF_2) receptors and PGF_2 alpha production.[13] Prostaglandin in turn potentiates and maintains oxytocin-induced contractions by regulating gap union formation.[14] We know that *maternal* plasma levels of oxytocin do not increase before and during the early stages of labor. However, the finding that oxytocin levels are higher during labor in the umbilical artery blood than in the umbilical vein or maternal blood suggests a *fetal* source for the oxytocin produced early in labor.[15] Levels of maternal plasma oxytocin *do* rise during the second stage of labor, when the fetus is expelled. Finally, during the last stage of labor, after the placenta is delivered, endogenous oxytocin assists in re-establishing hemostasis.[16]

Oxytocin's successful track record

At a time when physicians are converting to "evidenced-based" approaches, a recent review of the Cochrane database found no support for the use of oxytocin either alone or in combination with amniotomy for cervical ripening and inducing labor in patients at term.[16] Nevertheless, the drug has long been used successfully for labor induction and augmentation. In 1965, the FDA approved synthetic oxytocin for labor *augmentation*—but not for labor induction.[17] As mentioned earlier, the goal of labor induction and augmentation is basically the same: achieving regular uterine activity to bring about cervical dilation and fetal descent, while avoiding hyperstimulation. So it's not surprising that the oxytocin regimens for labor induction and augmentation are similar.

But before using this powerful medication, consider all the indications and contraindications for labor induction or augmentation. Fetal well-being and uterine activity are usually monitored for 20 to 30 minutes before oxytocin is begun —and assessed frequently thereafter. Fetal presentation should be assessed and fetal weight estimated. Oxytocin is diluted and administered intravenously via an infusion pump—with the infusion usually inserted into the "main" IV line.

How the uterus responds to synthetic oxytocin depends on gestational age, myometrial sensitivity to oxytocin, preexisting uterine activity, and cervical status. In general, patients vary widely and unpredictably in their sensitivity, regardless of gestational age. But despite individual responses to the drug, specific patterns have been seen in families that suggest a genetic predisposition.[18]

Oxytocin regimens for labor induction or augmentation are quite varied. The earliest protocols were based on the findings of invitro pharmacologic studies and indirect methods of determining the pharmacokinetics of the drug that suggested a half-life of only about 5 minutes. These protocols called for a starting dose of 2 to 6 mU/min and frequent increases, 1 to 2 mU/min every 15 to 20 minutes, until an adequate uterine contraction pattern was achieved. More sophisticated studies determined that when oxytocin is administered IV, uterine response occurs quickly, within 3 to 5 minutes, but the interval to reach a steady-state and maximal response is longer, about 40 minutes after initiating or altering the infusion rate.[19] When the dose of oxytocin is increased to intervals significantly less than 40 minutes, uterine hyperstimulation and fetal distress are more likely to occur. Studies of plasma oxytocin levels during continuous

infusion showed first-order saturation kinetics, with a progressive, linear, stepwise increase with each increase in the infusion rate.[15]

Based on newer drug and clinical data, oxytocin regimens used in the United States during the 1980s were variations of low-dose protocols. The infusion rate of oxytocin was started at 0.5 to 2 mU/min, and the dose was gradually increased by 1 or 2 mU/min every 40 to 60 minutes. A dose of more than 20 mU/min in a term pregnancy was rarely necessary (Table 1).

TABLE 1
Guidelines for "physiologic" use of oxytocin

This approach is intended for patients with maternal or fetal conditions that predispose the fetus to tolerate uterine contractions poorly.
1. Cervical ripening Continuous IV infusion of 2 to 4 mU/min for 8-12 h.
2. Induction or augmentation Start oxytocin at 0.5-1 mU/min. Increase by 1-2 mU/min every 30 to 40 min until an adequate contraction pattern is established: (3-5 contractions/10 min or 200-250 Montevideo units/10 min). Maximum dose is 20 mU/min. Reassess the patient if more than 20 mU/min is required. Once an adequate contraction pattern has been achieved, try to decrease the oxytocin dose by 1 mU/min every 30 to 40 min unless contraction pattern becomes inadequate.
3. Postpartum administration Mix 10 to 20 U of oxytocin in 1,000 mL of crystalloids and run at 200 to 250 mL/h. Decrease the rate after administering the first liter.

In 1984, O'Driscoll and colleagues reported a "high-dose" oxytocin protocol for "active management of labor."[20] Starting the drug at 6 mU/min and increasing the dose by 6 mU/min every 20 minutes until an adequate contraction pattern was achieved, they showed a lower cesarean delivery rate, with a comparable neonatal outcome. Many subsequent studies compared various "high-dose" oxytocin protocols (frequent increases of 4 to 6 mU/min) to traditional "low-dose" (slower increases by 0.5 to 2 mU/min) regimens.

In the last 10 years, most randomized clinical studies of oxytocin focused on comparing its pharmacologic properties with clinical response to different infusion doses, rate of increase, and pulsatility versus continuous infusion.[21,22] In 1992, investigators compared increasing oxytocin by 1 mU/min versus 6 mU/min every 20 minutes in a large group of women whose labor was induced or augmented—and found the high-dose protocol to be effective and safe.[23] Women in the high-dose group had significantly shorter labors and fewer failed inductions, while neonatal outcomes were similar to those in the low-dose group. Although hyperstimulation occurred in half the women in the high-dose group, it was managed by adjusting the oxytocin dose.[24]

In 1999 other researchers randomized women whose labors were induced or augmented to either low- (1.5 mU/min increases) or high-dose (4.5 mU/min increases) oxytocin.[25] Women in the high-dose group had shorter labors and fewer C/S deliveries.[25] But at the same time, another group of investigators demonstrated the effectiveness of a low-

rate protocol of oxytocin administration for inducing labor.[26] Cummiskey and Dawood reported that pulsatile administration of oxytocin was as effective and safe as continuous infusion.[27] Other investigators concluded that a continuous low-dose protocol for oxytocin could effectively induce labor in women with either ripe or unripe cervices and was associated with fewer episodes of uterine hyperstimulation.[28] Currently, the American College of Obstetricians and Gynecologists endorses both regimens as appropriate for labor stimulation.

When does high-dose oxytocin constitute abuse?

When the fetus is already compromised and has little reserve, frequent powerful uterine activity is likely to further compromise the fetus, leading to C/S delivery and a depressed newborn. Therefore, use special precautions when inducing or augmenting labor in a woman with chronic hypertension or preeclampsia, in pregnancies complicated by fetal growth restriction, and when clinical findings suggest placental abruption.

Fetal intolerance of tachysystole is also more likely in situations such as extreme prematurity, oligohydramnios, and multifetal gestation. In addition, maternal vasculopathy—either due to an autoimmune disorder such as systemic lupus erythematosus (SLE) or because of long-standing diabetes—is likely linked to intolerance of uterine hyperstimulation. In these and similar conditions, use oxytocin carefully, keeping in mind that a low-dose protocol more often leads to successful vaginal delivery. Certainly, there's no place in the practice of modern obstetrics to increase oxytocin to the point that fetal distress is evident, only to have to decrease the oxytocin level or to perform an emergency C/S. Such management may result in a lawsuit if the outcome of the laboring patient or her newborn is less than ideal.

Other abuse scenarios. Oxytocin is also abused when one attempts to induce labor, especially in patients with unfavorable uterine cervix, and "induction failure" is diagnosed shortly thereafter, before the onset of active labor. We feel that as long as the fetal condition is reassuring, cervical ripening should precede labor induction. Once labor induction has begun, don't abandon it in favor of a C/S delivery before the cervix has started changing only because a set length of time has elapsed.

Use misoprostol—not oxytocin—for early abortion. Another example of oxytocin misuse is for 1st or 2nd trimester induction of pregnancy termination (both elective and spontaneous abortions). At that early gestational age, there are just not enough oxytocin receptors present to do the job. Manage these obstetrical conditions using prostaglandin E_1 (misoprostol) instead; it's a more effective agent in these situations.

At the second stage of labor, the distention of the lower birth canal might cause oxytocin from the maternal neurohypophysis to be released into the bloodstream, increasing myometrial contractions.[29] A dose of 10 to 20 mU/min of oxytocin in the second stage of labor is considered sufficient to prevent postpartum hemorrhage. Giving more than 40 U to a postpartum patient represents oxytocin abuse, because a dose of 36 mU/min will adequately contract a postpartum uterus.[30]

Keep these main issues in mind

- Oxytocin, oxytocin receptors, and prostaglandins all have a role in human parturition; however, the mechanism of labor is still not fully understood.
- Both low- and high-dose oxytocin protocols have been found to be effective and safe for labor induction and augmentation.
- "Physiologic" doses of oxytocin may be safer in patients at high risk for hyperstimulation, fetal distress, or both.

REFERENCES

1. Dale HH. On some physiologic actions of ergot. *J Physiol (Lond).* 1906;34:163-206.

2. du Vigneaud V, Ressler C, Swan JM, et al. The synthesis of an octapeptide amide with the hormonal activity of oxytocin. *J Am Chem Soc.* 1953;75:4879-4880.

3. Gainer H, Wray S. Oxytocin and vasopressin. From genes to peptides. *Ann NY Acad Sci.* 1992;652:14-28.

4. Dawood MY, Raghavan KS, Pociask C, et al. Oxytocin in human pregnancy and parturition. *Obstet Gynecol.* 1978;51:138-143.

5. Dawood MY. Evolving concepts of oxytocin for induction of labor. *Am J Perinatol.* 1989;6:167-172.

6. Chibbar R, Miller FD, Mitchell BF. Synthesis of oxytocin in amnion, chorion, and decidua may influence the timing of human parturition. *J Clin Invest.* 1993;91:185-192.

7. Zingg HH, Rozen F, Chu K, et al. Oxytocin and oxytocin receptor gene expression in the uterus. *Recent Prog Horm Res.* 1995;50:255-273.

8. Caldeyro-Barcia R, Theobald GW. Sensitivity of the pregnant human myometrium to oxytocin. *Am J Obstet Gynecol.* 1968;102:1181.

9. Fuchs AR, Fuchs F, Husslein P, et al. Oxytocin receptors in the human uterus during pregnancy and parturition. *Am J Obstet Gynecol.* 1984;150:734-741.

10. Blanks AM, Thornton S. The role of oxytocin in parturition. *BJOG.* 2003;110(Suppl 20):46-51.

11. Fuchs AR, Romero R, Keefe D, et al. Oxytocin secretion and human parturition: pulse frequency and duration increase during spontaneous labor in women. *Am J Obstet Gynecol*. 1991;165:1515-1523.

12. Simon AM, Goodenough DA. Diverse functions of vertebrate gap junctions. *Trends Cell Biol.* 1998;8(12): 477-483.

13. Fuchs AR. Plasma, membrane receptors regulating myometrial contractility and their hormonal modulation. *Semin Perinatol.* 1995;19:15-30.

14. Garfield RE, Hayashi RH. Appearance of gap junctions in the myometrium of women during labor. *Am J Obstet Gynecol.* 1981;140:254-260.

15. Baxi LV, Petrie RH. Pharmacologic effects on labor: effects of drugs on dystocia, labor, and uterine activity. *Clin Obstet Gynecol.* 1987;30:19-32.

16. Howarth GR, Botha DJ. Amniotomy plus intravenous oxytocin for induction of labour (Cochrane Review). In: The Cochrane Library, Chichester, UK: John Wiley & Sons, Ltd, Issue 2, 2004.

17. Food and Drug Administration. NDA 18261/S11, 1965.

18. Fuchs AR, Fuchs F. Endocrinology of human parturition: a review. *Br J Obstet Gynaecol.* 1984;91:948-967.

19. Seitchik J, Amico J, Robinson AG, et al. Oxytocin augmentation of dysfunctional labor. IV. Oxytocin pharmacokinetics. *Am J Obstet Gynecol.* 1984;150:225-228.

20. O'Driscoll K, Foley M, MacDonald D. Active management of labor as an alternative to cesarean section for dystocia. *Obstet Gynecol.* 1984;63:485-490.

21. Satin AJ, Leveno KJ, Sherman ML, et al. Factors affecting the dose response to oxytocin for labor stimulation. *Am J Obstet Gynecol.* 1992;166:1260-1261.

22. Satin AJ, Leveno KJ, Sherman ML, et al. High-dose oxytocin: 20- versus 40-minute dosage interval. *Obstet Gynecol*. 1994;83:234-238.

23. Satin AJ, Leveno KJ, Sherman ML, et al. High- versus low-dose oxytocin for labor stimulation. *Obstet Gynecol.* 1992;80:111-116.

24. Muller PR, Stubbs TM, Laurent SL. A prospective randomized clinical trial comparing two oxytocin induction protocols. *Am J Obstet Gynecol.* 1992;167:373-380.

25. Merrill DC, Zlatnik FJ. Randomized, double-masked comparison of oxytocin dosage in induction and augmentation of labor. *Obstet Gynecol*. 1999;94:455-463.

26. Blakemore KJ, Qin NG, Petrie RH, et al. A prospective comparison of hourly and quarter-hourly oxytocin dose increase intervals for the induction of labor at term. *Obstet Gynecol*. 1990;75:757-761.

27. Cummiskey KC, Dawood MY. Induction of labor with pulsatile oxytocin. *Am J Obstet Gynecol.* 1990;163:1868-1874.

28. Mercer B, Pilgrim P, Sibai B. Labor induction with continuous low-dose oxytocin infusion: a randomized trial. *Obstet Gynecol.* 1991;77:659-663.

29. Giraldi A, Enevoldsen AS, Wagner G. Oxytocin and the initiation of parturition. A review. *Dan Med Bull.* 1990; 37:377-383.

30. de Geest K, Thiery M, Piron-Possuyt G, et al. Plasma oxytocin in human pregnancy and parturition. *J Perinat Med.* 1985; 13(1): 3-13.

DR. VENTOLINI is Director, Division of General Ob/Gyn, and DR. NEIGER is Clinical Professor, Division of Maternal-Fetal Medicine, Wright State University School of Medicine, Dayton, Ohio.

Take-home messages

- Before using oxytocin, consider all indications and contraindications for labor induction or augmentation. Monitor fetal well-being and uterine activity for 20 to 30 minutes before starting this powerful drug.
- To prevent compromising a fetus, use special precautions when inducing or augmenting labor in a woman with chronic hypertension or preeclampsia, in pregnancies complicated by fetal growth restriction, and when clinical findings suggest placental abruption.
- Use oxytocin carefully in patients with maternal vasculopathy (either due to an autoimmune disease like SLE or long-standing diabetes) who are unlikely to tolerate uterine hyperstimulation. Keep in mind that a low-dose protocol is more likely to result in a successful vaginal delivery.
- Don't give more than 40 units of oxytocin to a postpartum patient (36 mU/min is sufficient to contract a postpartum uterus).

Gary Ventolini, Ran Neiger. Grand Rounds: Using and abusing oxytocin. *Contemporary Ob/Gyn* Sep. 1, 2004;49:42-49.