

Induced and Seduced: The Dangers of Cytotec

By Ina May Gaskin

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Early in her second pregnancy, Gretchen Brown (a pseudonym) decided to get care from an obstetrician. After all, she was 35, it had been 16 years since her last child was born, and an obstetrician seemed like the safest possible choice. The one she chose worked with nurse-midwives, but it was he who saw her at each of her prenatal visits. Still, Gretchen was taken aback by the way he reintroduced himself at every visit, a clear sign that he didn't remember her from one time to the next. "I felt like one of the cattle being herded in and out," she later told her sister. Despite these misgivings, Gretchen fully expected that her obstetrician would be present for the birth of her baby and never considered looking for a different doctor or going to a midwife. She felt healthy during her pregnancy; any complaints she had seemed relatively minor.

Gretchen's water bag broke at midnight on February 27, 2000, two days before her due date, and a mixture of amniotic fluid and blood gushed out. Although not in labor, she packed her bag, and her husband, Gary, drove her to the hospital. The maternity nurse who examined her did not seem concerned about the bleeding; she gave Gretchen a sleeping pill and kept her supplied with pads to soak up the blood that was still flowing during the night.

The next morning, with Gretchen still not in labor, the nurse-midwife on duty suggested that labor should be stimulated with a drug called Cytotec. Unaware that Cytotec is not approved by the Food and Drug Administration (FDA) for labor induction, Gretchen agreed to the plan.

Cytotec's manufacturer, G. D. Searle Corporation, obtained FDA approval in 1988 for its use in preventing peptic ulcers. By 1997, Cytotec had become "the predominant agent of choice" for labor induction, according to Dr. Charles Lockwood, chairman of obstetrical practices for the American College of Obstetricians and Gynecologists (ACOG). Even so, the package insert contains an explicit warning that "Cytotec may cause the uterus to rupture during pregnancy if it is used to bring on labor." The insert goes on to say that uterine rupture may lead to "severe bleeding, hospitalization, surgery, infertility, or death."

Without telling Gretchen about any of these possibilities, the midwife placed the small white tablet (or a portion of one; her notes did not specify the amount) in Gretchen's vagina and left. Very soon Gretchen was in hard labor, with intensely painful contractions coming one right after another. Refused an epidural because her cervix was not open enough, Gretchen labored on. When the midwife suggested Stadol to take the edge off the pain, Gretchen asked if the drug would have a negative effect on her baby. "You won't be having this baby until at least 6:00 tonight, and by that time, its effect will have worn off!" the midwife replied.

However, labor was no easier after the Stadol. The pain was just as strong, but now Gretchen felt as if she were floating and disconnected from what was happening to her. Still bleeding throughout her labor, she had the feeling that her contractions were abnormally hard and close together, and she wished that her obstetrician were by her side. At 6 or 7 centimeters of dilation, she was given an epidural, but it gave little relief. Suddenly, Gretchen began pushing, and the baby's head descended rapidly. She found out later that her obstetrician--who had not seen her since her arrival at the hospital--had left for home just as her baby girl was being born, shortly after noon. The baby's heart was beating, but she was limp and unable to breathe on her own. A team of nurses, joined by a pediatrician, worked intensively on her for ten minutes in the birth room.

Gretchen looked on, feeling increasingly weak. Once the baby was sufficiently stabilized to be wheeled out to the neonatal intensive care unit, attention returned to Gretchen, who was now losing blood at an alarming rate. "Your uterus is asleep," the midwife told her as she massaged Gretchen's uterus and turned up the medication in the intravenous line to her arm. The midwife and several nurses continued to work on Gretchen for almost 20 minutes, frequently paging her obstetrician on the intercom. By this time, with her blood pressure at only 68/35 (normal is 110/70), Gretchen weakly asked the nurses, "Am I going to die?" and passed out. Her cousin, who was holding a cool cloth against Gretchen's forehead, saw blood beginning to ooze from the IV site on her arm, a sign that Gretchen had lost so much blood that her blood had lost its ability to clot. This complication, called disseminated intravascular coagulation (DIC), is frequently fatal.

It was nearly two hours after the birth of Gretchen's baby before the obstetrician came back to the hospital and got Gretchen into surgery. Fifty units of whole blood and platelets were required to save her life. When she regained consciousness, she was on a ventilator with a tube

down her nose. She remained on the ventilator for five days, in intensive care for seven days, and in the hospital for ten days.

It was months before Gretchen learned--from searching the Internet--that her brush with death had been caused by the Cytotec, that the drug lacked FDA approval, and that such "off-label use" is completely legal. Once the FDA approves a drug for one purpose, it may be legally prescribed for any other indication. When drugs are prescribed in this "off-label" fashion, they are not subject to the usual FDA testing process, and women who haven't given their informed consent to taking the drug become unwitting experimental subjects of ad hoc, unorganized, informal-and usually unpublished-research.

When I first heard of Cytotec in 1999, I was surprised to learn that it had already become US obstetricians' favorite drug for labor induction and that many were using it for convenience and for "geographic and social factors."¹ A "convenience" induction is one carried out to suit a practitioner's call schedule or office hours: induce the woman at the hospital in the morning, do office visits, and finish the birth before dinnertime. Some doctors prefer this to getting up when labor occurs at night. "Geographic" inductions are those designed for women with histories of prior fast labors, who might have trouble getting to the hospital on time. "Social factor" inductions are those demanded by women who become uncomfortable in late pregnancy and believe that elective inductions are safe and medically ethical.

As I combed through the medical literature to catch up on this new obstetrical fad, I was shocked to learn that Cytotec has been connected to numerous cases of ruptured uteri, life-threatening hemorrhages, emergency hysterectomies, profoundly brain-damaged babies, stillbirths, newborn deaths, and even some maternal deaths. How, I wondered, can a drug remain popular when it carries such risks? When I found out how difficult it is to research the literature on Cytotec in a thorough way (these results have not been compiled in any single article published in US medical literature), I realized that most practitioners are unaware of the sum of reported Cytotec disasters.

Most Cytotec-induced labors, it should be noted here, do not have disastrous consequences. For a significant number of women, Cytotec seems to do just what they and their caregivers want: labor usually begins and results in a vaginal birth within 24 hours of induction. No one disputes that it is the most effective of all drugs for starting labor, including those approved by the FDA for this purpose. Besides, since

Cytotec works so efficiently for most women and can be legally prescribed without FDA approval, there is little incentive to find out why the drug sometimes has such catastrophic effects.

Another reason for Cytotec's stunning popularity is that it is less cumbersome than most other forms of labor induction. Intravenous Pitocin was the most common method of inducing and augmenting labor before doctors began using Cytotec. The problem with Pitocin is that it does not work well in women whose cervixes are "unripe"--that is, hard, thick, and closed. Many a woman with an unripe cervix has endured a four- or five-day Pitocin induction, only to end up with a cesarean. With a Cytotec induction, on the other hand, most physicians don't consider it necessary to have an intravenous line in place, so women are able to move around freely during labor.

Equally important, Cytotec is dirt cheap: a single 25-mcg dose costs less than 50 cents. All other high-tech induction methods, including Pitocin and prostaglandin gels and inserts, cost several hundred dollars each time they are used. Cytotec's cost is mentioned as often as its efficacy in the medical literature.

Cytotec is manufactured in 100-mcg tablets intended for oral use. When physicians began prescribing it for labor induction, many administered the entire tablet. Reports of uterine ruptures and other serious complications surfaced and led to smaller doses, for the most part. However, since the Cytotec tablet is unscored, pharmacists have to cut it into halves or quarters with tiny knives, an awkward and inaccurate process. No one has managed to cut a tablet into eighths without reducing it to powder.

To add to the confusion, there is no agreement about what constitutes the right dosage size or interval or even the most appropriate route of administration. Some place it inside the cervix, others behind the cervix; some give it orally, others rectally; and others place it in the mouth.

It has long been known that pharmacological agents that stimulate uterine contractions may overstimulate the uterus in labor, to the point of shearing off the placenta, rupturing the uterus, or causing the uterus to contract so hard and long that the baby is deprived of essential oxygen. Early reports revealed Cytotec's potential to cause unnaturally hard, long uterine contractions but brushed aside worries that such abnormal uterine activity could eventually result in catastrophe for some women and babies.^{2,3}

My review of 30 misoprostol [Cytotec] induction studies and reports representing 3,415 births was far less reassuring. I found 14 baby deaths, 25 uterine ruptures, 2 maternal deaths, and 2 life-threatening hemorrhages.⁴⁻¹⁴ Significantly, several of these complications occurred in women given a single 25 mcg dose—the smallest dose possible.¹⁵ According to one researcher, the author of several studies, "Some patients appear to be quite sensitive to misoprostol, demonstrating prolonged contraction responses after a dose of the agent, sometimes in excess of 20 hours after the drug."¹⁶

Still more deaths were recently reported in *Mother Jones*.¹⁷ Through a Freedom of Information Act request to the FDA, the magazine learned that in the last three years alone, the agency has received reports of 30 cases of uterine rupture (eight cases in which the fetus died in utero) and two maternal deaths. These maternal deaths, by the way, were not the two reported in the medical journals and cited above. Unfortunately, there is no way to know how much overlap might exist between outcomes reported in medical journals and those reported to the FDA. Several studies of Cytotec-induced births cite increases of meconium in the amniotic fluid, abnormal fetal heart rates, and the numbers of babies needing resuscitation and stays in the neonatal intensive care unit.

In any case, there are many other indications that the catastrophic results cited above do not represent a comprehensive tally of all of the poor outcomes associated with Cytotec. As mentioned earlier, I have learned of still more uterine ruptures and deaths (both infant and maternal), near-deaths, and damaged babies, from women, family members, nurses, midwives, and physicians with direct involvement in each case.

A recent study indicates that Cytotec labor inductions in women who have had a previous cesarean carry a 28-fold increase in the risk of uterine rupture.¹⁸ Another study was abruptly cancelled when two women out of 17 with prior cesareans and Cytotec-induced labors suffered uterine ruptures.¹⁹

In 1999, several months after these two studies were published, ACOG issued a special set of guidelines for Cytotec, specifying that it no longer be used in women with prior cesarean sections.²⁰

At the same time, ACOG was careful to sanction its use in women who haven't had previous uterine surgery, in spite of the fact that several

of the uterine ruptures reported in the medical literature occurred in such women.²¹⁻²⁴ The most respected international body of physicians and researchers, the Cochrane Collaboration, cites numerous reports of fetal distress and uterine rupture associated with Cytotec inductions, whether or not a woman had had prior uterine surgery. "It [Cytotec] cannot be recommended for routine use at this stage," the group stated.²⁵

We call it "vigilante justice" when a mob tries and executes a person suspected of a crime, bypassing the socially agreed-upon forms of administration of justice. When obstetricians bypass the agreements in place to test drug safety for pregnant women, we might call this "vigilante obstetrics." One of the most egregious aspects of US obstetricians' off-label use of misoprostol--a perfect example of vigilante obstetrics--is that there were approximately six years (1992-1998) during which physicians used the drug to induce labor in women who had had prior cesarean sections.

On August 23, 2000, spurred by a large lawsuit brought by an Oregon man whose wife died after a Cytotec induction, G. D. Searle Corporation mailed a letter to 200,000 healthcare practitioners, warning that off-label use of Cytotec has resulted in the death of mothers and infants, uterine rupture, hysterectomy, retained placenta, severe vaginal bleeding, shock, and pelvic pain. According to an informal poll cited by Mother Jones, this warning was heeded by an estimated one-third of US hospitals, which forbade further use of Cytotec for the induction of labor.

Searle's letter clearly upset some obstetricians who had come to depend upon Cytotec's efficacy in labor induction. Some angrily petitioned ACOG to take action against the impending death of their favorite induction drug. On November 1, 2000, ACOG submitted what it called a "citizen petition" to the FDA requesting that the agency require Searle to withdraw its letter warning of Cytotec's potential dangers when used for labor induction.

The FDA has yet to comply with this request.

How many women require induction of labor for valid medical reasons? Our experience at The Farm Midwifery Center, the rural Tennessee birth center of which I have been the executive director for 30 years, indicates that in healthy women the induction rate should not exceed 10 percent. Slightly more than 5 percent of women we have cared for had labors induced by such time-honored methods as castor oil or

sweeping the membranes. We also advise couples that making love without a condom can aid in ripening the cervix as the woman approaches term, since human semen contains high concentrations of prostaglandins--the very substance that Cytotec is synthesized to imitate.

Contrast The Farm's induction rate, which has remained the same for 30 years, with what has happened in the US at large, where the rate of induced labor has risen sharply over the last decade or so, largely because of Cytotec. From 9 percent in 1989, it rose to 13 percent in 1993 and to nearly 19 percent in 1997.²⁶

What protection do pregnant women have when it comes to the off-label use of obstetrical drugs? Very little, according to Laura Bradbard, spokeswoman for the FDA. "There are no safe drugs. You need to do your homework, ask a lot of questions, and speak with your physician about your case and the medications," she said. My advice is to look for midwives and physicians whose practices are more similar to those in European countries and New Zealand, where Cytotec is not used for induction and where maternal-infant outcomes are consistently better than those in the US. Elective inductions are unethical and unsafe, period.

NOTES

1. D. A. Wing and R. H. Paul, "Cervical Ripening and Labor Induction," *Contemp Ob/Gyn* (March 1999): 112-116.

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4. D. V. Surbek, H. Boesinger et al., "A Double-Blind Comparison of the Safety and Efficacy of Intravaginal Misoprostol and Prostaglandin E2 to Induce Labor," *Am J Obstet Gynecol* 177 (1997): 1018- 1023.

5. D. A. Wing, G. Ortiz-Omphroy et al., "A Comparison of Intermittent Vaginal Administration of Misoprostol with Continuous Dinoprostone for Cervical Ripening and Labor Induction," *Am J Obstet Gynecol* 177 (1997): 612-618.

6. D. A. Wing and R. H. Paul, "Induction of Labor with Misoprostol for Premature Rupture of Membranes beyond Thirty-six weeks' Gestation," *Am J Obstet Gynecol* 179 (1998): 94-99.

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12. D. A. Wing, D. Ham et al., "A Comparison of Orally Administered Misoprostol with Vaginally Administered Misoprostol for Cervical Ripening and Labor Induction," *Am J Obstet Gynecol* 180 (1999): 1155-1160.

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15. See Note 6.

16. D. A. Wing, A. Rahall et al., "Misoprostol: An Effective Agent for Cervical Ripening and Labor Induction," *Am J Obstet Gynecol* 172 (1995): 1811-1816.

17. D. Goodman, "Forced labor: Why Are Obstetricians Speeding Deliveries with an Ulcer Drug That Endangers Mothers and Their Babies?," *Mother Jones*, January/February 2001.

18. See Note 14.

19. See Note 7.

20. "Induction of Labor with Misoprostol." ACOG Committee Opinion, November 1999.

21. D. A. Merrell, M. A. T. Koch et al., "Induction of Labour with Misoprostol in the Second and Third Trimesters of Pregnancy," *S Afr Med J* 85 (1995): 1088-1090.

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For additional information about the induction of labor, see the following article in a past issue of *Mothering*: "Let the Baby Decide: The Case against Inducing Labor," no. 105.

Ina May Gaskin, MA, Certified Professional Midwife, has been a midwife for more than 30 years and is currently president of the Midwives Alliance of North America. She has three living children, all in their

20s, and two grandchildren. She is the author of Spiritual Midwifery; her next book will be published in 2002 by Bantam/Dell.