

## Cytotec Induction and Off-Label Use

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Illustrations by Jennifer Rosenberg

Without adequate testing of Cytotec (misoprostol) for labor induction, obstetricians simply began to use it on their birthing women. They were taking advantage of a huge loophole in our drug regulatory system. Once a drug is approved by the FDA for a specific medical indication and put on the market, there is absolutely nothing to prevent any doctor from using that drug for any indication, in any dose, for any patient he or she chooses. Since the label of the drug contains the indications approved by the FDA, this is called "off-label" use of a drug.

When obstetricians using Cytotec induction are confronted about their willingness to use a drug "off-label," they inevitably answer: "We use drugs off-label all the time." There are several serious problems with this answer. First, in reality, using Cytotec for induction is not "off-label" at all—it is "on-label contraindicated." On the Cytotec label it is explicitly written that this drug is contraindicated for use on pregnant women. Contraindication would not be on the label unless data exist suggesting possible serious risks from such use. "On-label contraindicated" is a whole different level of risk-taking than a use that is not mentioned one way or the other on the label.

A second reason to be concerned with the offhand answer of some obstetricians is that all off-label use is lumped together as though there were equal risks involved. During a case I was involved in, I asked the obstetrician about the off-label use of Cytotec for labor induction. He replied with the same answer that I have heard from so many clinicians: "We use Cytotec off-label for induction just like we use other drugs off-label all the time." Compare this to someone involved in a fatal car accident who is asked why he did not follow traffic laws and drove 100 miles an hour in a 25 mile an hour zone. The driver answers: "Traffic laws are disobeyed all the time. Why just last week there were dozens of parking tickets given out in this city." You can't compare the risks of excessive speeding with the risks of illegal parking. And you can't compare the risks of Cytotec induction with the risk involved in giving other drugs to pregnant women off-label. A survey of 731 pregnant women revealed they had been given 10 drugs while pregnant (1). But of the 10 drugs given off-label, the use of nine of them on pregnant women carried very little risk while the use of the tenth drug, the prostaglandins (including Cytotec), have proven serious risks including uterine rupture, following which one in four babies die.

Another problem with the excuse "we give drugs off-label all the time" is that the doctors using it are taking matters into their own hands when it comes to the use of drugs on their patients. They are unwilling to wait for the scientific evidence that shows whether this use of the drug is safe. This represents both a cavalier disregard for the safety of women and babies and a total lack of faith in the drug regulatory system.

Those doctors and midwives using Cytotec for induction of labor off-label need to understand that they are taking very big chances with the safety of the women and babies they serve. Just about everyone in the world, after taking a careful look at the scientific evidence, has concluded we don't yet know enough about the risks to be willing to use it. This is illustrated in the following list of organizations that do and do not recommend Cytotec (misoprostol) for labor induction:

## Recommends

1 American College of Obstetricians and Gynecologists (ACOG)

## Does not recommend

1 U.S. Food and Drug Administration

2 Best scientific opinion—Cochrane Database

3 Searle (manufacturer of Cytotec)

4 Society of Obstetricians and Gynecologists of Canada

5 British Royal College of Obstetricians and Gynecologists

6 All obstetric organizations in Scandinavia

7 FIGO (International Federation of Gynecology and Obstetrics)

8 World Health Organization

9 Obstetric organizations and drug regulatory agencies in many other countries

How can ACOG possibly be willing to stand alone in opposition to the best scientific opinion in the world? Because so many of ACOG's members already use Cytotec induction off-label for its incredible convenience, the organization needs to support its members by recommending this practice. This means ACOG must find a paper published in a prominent U.S. journal supporting Cytotec induction. In ACOG's recommendation on Cytotec induction, the organization leans heavily on a paper by A.B. Goldberg and other authors published in the *New England Journal of Medicine* (2). Let's take a careful look at the contents of this paper, as it is a superb example of torturing the data until it confesses to what the authors want it to say:

"Prescribing a medication for an off-label indication is common in the treatment of pregnant women." This argument has no justification. Common usage of something does not prove it is a good idea. Experience in medical practice can often mean gaining more and more confidence in a mistake. Furthermore, as we have seen, some drugs have no serious risks involved while others carry very serious risks. And such widespread off-label prescribing is not found in other fields of medical practice.

Next, off-label use "is not considered experimental if based on sound scientific evidence." The whole purpose of on-label use is to guarantee the consumer that there is sound scientific evidence. With the off-label use of Cytotec for labor induction there are several problems:

First, no one can disagree that for a number of years in the early 1990s Cytotec was in widespread use *before* there was any sound scientific evidence. No one even knew what the proper dose should be and everyone was *experimenting* with dosage and protocol. I find no concern from ACOG or many individual obstetricians with this indisputable fact. Thousands of women were given Cytotec without knowing that it was off-label and experimental, thus giving them no opportunity for informed consent. Proof of the danger of such nonevidence-based practice came in 1999, when there was enough evidence showing the danger of Cytotec use in VBAC that even ACOG came out against it. How many women with VBAC were given Cytotec induction between 1990 and 1999? Almost certainly thousands. How many ruptured uteri? Almost certainly hundreds. How many babies died? Almost certainly dozens. How many women died? We know there were at least several. But today, rather than using this experience to push for more evidence before use, ACOG and some individual obstetricians are pushing for more use of Cytotec when its safety is still in serious doubt.

Second, who decides when there is "sound scientific evidence"? Here there is no agreement.

ACOG says there is good data to support Cytotec induction. But ACOG is not a scientific body; it is an organization of professionals—a trade union trying to protect the interests of its members. The paper's authors agree with ACOG, but a careful look at their own review shows a very flimsy database on risks. They never directly say that Cytotec induction is "safe," nor do they say that we know enough about its risks. In fact, they say the opposite.

The authors greatly confuse the reader by lumping together all uses of Cytotec during pregnancy: first trimester medical abortion, induction of labor, postpartum hemorrhage. Each of these indications has very different data and should never be combined. "Two hundred studies involving a total of more than 16,000 women" is falsely inflating the data and is most misleading. The number of studies on Cytotec labor induction is far fewer. Most of them are not randomized experimental trials, and all of them, trials included, are too small to have sufficient statistical power for the less common but catastrophic risks such as uterine rupture, perinatal mortality and maternal mortality.

The paper has a section titled "Misoprostol in the Third Trimester of Pregnancy." The first part of this section is devoted to efficacy (not risk); no one is debating the effectiveness of this drug. The debate is with the risks and here the authors admit there is more "uterine hyperstimulation with associated changes in fetal heart rate" and more "meconium-stained fluid." The authors also write, *"because there were so few serious adverse effects, the relative risk of rare adverse outcomes with the use of misoprostol for labor induction remains unknown."* (Italics mine.) So these authors never say this drug is safe for induction and admit that with regard to risks, we don't know enough! The last paragraph in this section is a review of studies trying to find the correct dosage for Cytotec induction. Here, the authors point out that only recently has there been any kind of idea about dosage amount. This was because researchers were trying to lower one of the documented risks—uterine hyperstimulation. In this nine-page paper, there were only a few sentences about the risks of Cytotec induction. These sentences admit that the risk of adverse outcomes remains unknown. This is a very weak evidence base and can in no way be considered "sound scientific evidence."

In the section titled "Induction of Labor in Women with Previous Cesarean Section," the authors review the research showing the huge increase in risk of uterine rupture in VBAC if Cytotec induction is used and correctly conclude that it should not be used in this way. They never mention that the paper showing the risk of uterine rupture with Cytotec induction in VBAC was published in 1999, a decade after Cytotec induction had been used on large numbers of VBAC women.

In fact, because the number of cases of uterine rupture being reported was on the increase in the 1990s, ACOG responded with a recommendation that VBAC be done only in the hospital with an obstetrician and anesthesiologist at the ready. This recommendation made the organization's obstetrician members happy but was a disaster for birthing women, midwives, family physicians and small hospitals. ACOG, instead of recommending stopping Cytotec induction, recommended surrounding women having VBAC with experts to deal with the rupture when it happens. This would be like children drowning in a lake at summer camp and, instead of teaching the children to swim, the counselors put a couple of life preservers in the lake. ACOG has yet to do the obvious and demand research to monitor uterine ruptures to determine the reason for the increase and the likely relationship to Cytotec and other forms of induction.

While one paper quoted by ACOG clearly shows the increased risk of uterine rupture if prostaglandin gels are used in VBAC (3), I have been unable to find any research which looks at

the contribution that Cytotec induction makes to this increase. We know that the incidence of uterine rupture has increased overall, but we do not know how Cytotec specifically factors in to this increase. The risk of uterine rupture after VBAC is 1 in 200 births, while the risk of uterine rupture with VBAC using Cytotec induction is 1 in 20 births—a tenfold increase. Because we know that the rate of induction of labor in the U.S. doubled in the 1990s, resulting in a convenient and significant increase in the rate of births Monday through Friday (4), it is quite likely that the increase in uterine rupture reported was related to the increase in induction, especially with Cytotec. Therefore, the ACOG recommendation on VBAC is not justified.

Goldberg and the other authors conclude in their paper that there is strong and consistent evidence to support the use of misoprostol for induction in the third trimester. This opinion is most inconsistent with the little data they present on the serious adverse effects (risks) of Cytotec induction. Their opinion is nevertheless used by ACOG. Because of the enormous advantages of Cytotec induction to the practicing obstetrician, the opinion is suspect. As the previous list shows, there is a large group of experts that disagrees with this opinion, believing the evidence is still insufficient to support Cytotec's use in labor induction when existing evidence gives strong indications of several serious risks. When there is disagreement on the evidence among the experts, the most conservative and safest course for the clinician to follow is the fundamental principle of medical practice: first do no harm.

Doctors find it difficult to admit mistakes. Here we have a big mistake—Cytotec induction with VBAC—that went on for years. Yet, there is no discussion of the error or what to do so it won't happen again.

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### Notes

- 1 Rayburn, W. and Farmer, K. (1997). Off-Label Prescribing during Pregnancy. *Obstetrics and Gynecology Clinics of North America* 24 (3): 471–8.
- 2 Goldberg, A.B., Greenberg, M.B. and Darney, P.D. (2001). Drug Therapy: Misoprostol and Pregnancy. *NEJM* 344 (1): 38–47.
- 3 Lydon-Rochelle, M., Holt, V., Easterling, T. and Martin, D. (2001). Risk of Uterine Rupture during Labor among Women with a Prior Cesarean Delivery. *NEJM* 345 (1): 3–8.
- 4 For detailed data on childbirth in the U.S. collected by the federal government, including intervention rates and birth by the day of the week, go to [www.cdc.gov/nchs/birth](http://www.cdc.gov/nchs/birth).

### Related Information:

- Midwifery Today's gateway page about cytotec.