CBCnews
THE NATIONAL

Forced Labour

Doctors have found that an ulcer medication also works to induce labour. But is it safe?

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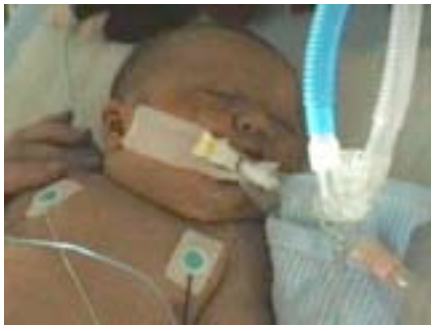
It's a little pill that helps deliver very important packages. It's called Misoprostol or its brand name Cytotec. It was originally approved by health regulators to treat stomach ulcers, but it has another use, one that hasn't been approved. It's a quick and cheap way to trigger labour in pregnant women. Many believe that Misoprostol is not safe.



Ian Malone

On the day their son Ian was born, Christine and Dylan Malone had no hint of the catastrophe to come. It had been a

healthy pregnancy and Christine was being induced with the latest drug to kick start labour.

All was calm in the birthing centre near Seattle. Midwives would deliver their baby. Christine's first two births had been easy. She'd been induced before and thought she knew what to expect.

"I remember losing all sensation in my hands to my elbows and my feet to my knees. My face was numb. I was hyperventilating," she recalls. "At a certain point I realized something was terribly wrong. I was in so much pain. I felt as if I was literally being sliced open from the inside out. My entire body was just ripping in half."

Christine Malone

Dylan Malone

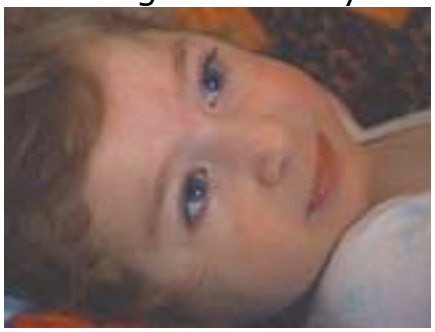
When Ian was born, he wasn't breathing.

"They pulled him out… and I can remember like it just happened yesterday that he was not blue, he was sort of grayish. He was this deathly grey colour," says Dylan.

Midwives tried to resuscitate him. When that failed, they finally called for help.

The baby's life was saved in a hospital emergency room. He had been without oxygen for 20 minutes. The brain damage was severe. For Christine, the force of the contractions had ruptured an artery.

"She was feeling her uterus go into these incredible spasms lasting two, three, four minutes," says Washington-based perinatologist Marsden Wagner, who was asked by the Malones to review what happened and give his expert opinion. "When the uterus contracts, it shuts down the blood flow from the mother to the baby, and the baby gets what we call "hypoxic" – without oxygen. And, you know, how long can you hold your breath before you pass out? Come on. If the baby goes without oxygen it damages the baby's brain permanently."



Ian Malone

Three years later, Ian will never be more advanced than he is now. He needs 12 different drugs to protect his frail body from seizures – up to 250 a day.

His lungs are filled with fluid. He's fed through a tube because it's impossible to swallow on his own.

Christine and Dylan blame the midwives for mishandling Ian's birth. But they believe the cause of the emergency was the drug Christine's obstetrician had prescribed to start her labour: Misoprostol.

"The underlying trauma was the drug," says Dylan. "People need to know that taking this drug for many people causes a very unnatural labour."

Carter Saiter

In Walton, New York, Carter Saiter was born with brain damage after a Misoprostol-induced labour. His mother Lynn died.

"This is a drug that we know can have very serious consequences," says Dr. Marsden Wagner.

The label warns it's not for pregnant women

Misoprostol, or Cytotec, is approved for stomach ulcers, *not* labour. The label clearly warns it's not for pregnant women because it has a significant side effect – it can cause contractions, triggering an abortion.

In the 1990s, doctors discovered they could harness the side effect to induce women about to give birth.

Five years ago, Dr. Gregory Davies started testing Misoprostol in clinical trials in Kingston, Ont. Eventually he began to use it routinely. This is perfectly legal, even though the drug is not approved for obstetrics. It's called "off-label" use.

"The reality is that 80 to 90 per cent of drugs that are used in pregnant women are used off-label," says Davies. "The reason for that is the manufacturers of these medications are not interested in doing studies on pregnant women to find out the true safety of their medications in pregnant women because they make up a very small market share of where they could be selling the medications."

Dr. Davies thinks Misoprostol has promise.

"It doesn't involve an intravenous and for certain there is attractiveness to the fact that labours on average are shorter when Misoprostol is used," he says.

One standard way of inducing labour uses synthetic hormones in an IV drip to start contractions and another drug to soften the cervix. Misoprostol does both jobs, and at a fraction of the price. The tablets are simply inserted in the vagina.

Before retirement, Dr. Marsden Wagner was responsible for maternal and child health at the World Health Organization. Now he is Misoprostol's most vocal critic.

Marsden Wagner"

We don't know about the safety of Misoprostol induction and that is the real bottom line here," he says. "Doctors are using a drug that is not known whether or not it really is safe."

The makers of Misoprostol, or Cytotec, know the pills are widely used off-label as a birth drug so they now spell out the dangers in a leaflet that comes with the bottle. Wanrings include hyperstimulation of the uterus, uterine rupture and maternal and

fetal death. And records from the American Food and Drug Administration link Misoprostol with 49 uterine ruptures and at least two deaths since 1998. Health Canada has one report of a fetal death.

"When the uterus ruptures, what this means is first of all that the woman is hemorrhaging to death," says Wagner. "Unless you dive in with heroic measures, that woman is going to bleed to death."

The big unknown is how often this happens with Misoprostol.

It would take a huge study to determine that and no one has done it. But many smaller studies have found the risks are rare and that's enough for the Americans. Their professional guidelines say it's okay to use Misoprostol in the delivery room. In the developed world, the Americans stand alone on this point.

Dr. David Young, who has done extensive Misoprostol research in Canada, is the incoming president of the Society of Obstetricians and Gynecologists. Their guidelines say that because there's not enough safety information, Misoprostol should be confined to clinical trials.

"There is still a concern about, have we found the right dose yet that would be the safest possible but yet effective dose?" says Young. "And all the studies that have been done to this point still show some increase in what's called hyper-stimulation, which is too frequent or too strong contractions that might produce deleterious effects on the fetus or new born."

"...it does not appear that Misoprostol carries any more risk than the other choices for inducing labour..."

At least two Canadian hospitals are not following the society's voluntary guidelines. They use Misoprostol routinely, outside clinical trials.

In Laval, Que., Dr. Pierre Choquette and his colleagues have delivered 5,000 babies this way.

Dr. Pierre Choquette: "You can have uterine rupture with any kind of medication that gives contraction. And we can have uterine rupture with normal labour. To deliver a baby has some risk."

CBC's Norma Lee MacLeod: "Does Misoprostol make it more dangerous?"

Dr. Pierre Choquette

Dr. Pierre Choquette: "I don't think so. To die? No, I don't think so."

CBC's Norma Lee MacLeod: "Do you think there is a woman out there who would choose to have a shorter labour if it means she would have to take a dangerous drug or a risky drug?"

Dr. Pierre Choquette: "Well, the matter is that you must prove that Misoprostol is a dangerous drug."

CBC's Norma Lee MacLeod: "Shouldn't you prove it's safe?"

Dr. Pierre Choquette: "I would say that in our experience, Misoprostol is a very safe medication. Very, very safe medication."


Dr. Gregory Davies

Dr. Gregory Davies in Kingston has had the same experience – 600 deliveries with Misoprostol, about half outside clinical trials, and no emergencies. He finds the research convincing.

"We don't feel there's a lack of safety information," he says. "In the context of term pregnancies, more than 6,000 women have been studied and their babies have been studied in labour. Based on that information, it does not appear that Misoprostol carries any more risk than the other choices for inducing labour, understanding that you can't pick (a) no-risk option. There's no such thing."

"...we don't know enough yet about these risks...
If we don't know enough about it, for heavens sakes don't use it."

"The only scientific answer is we don't know enough yet about these risks, we don't know enough yet about the safety," says Dr. Marsden Wagner. "And so the best scientists say, 'If we don't know enough about it, for heaven's sake don't use it,' which is why the FDA says don't use, why the drug company says don't use it, why the British Royal College of Obstetricians says no. Every single obstetric society in Scandanavia – no, no, no, no, no!"

No one argues Misoprostol's advantages. It's cheap, it's easy to store and it's fast. But when a drug has risks, doctors usually

ask how badly it's needed before deciding to use it. That's part of this debate because there are other options to Misoprostol.

Dr. David Young: "There's no compelling need right now. However, there is reason to look seriously at Misoprostol because in a per-dose basis, the cost of Misoprostol, that quarter of a tablet, is 10 cents or, you know, it's less than a dollar."

Dr. David Young

CBC's Norma Lee MacLeod: "Compared with?"

Dr. David Young: "$35 to $50 per dose for the commercially-available, approved medication."

CBC's Norma Lee MacLeod: "So this would be good for hospitals?"

Dr. David Young: "This would be good for hospitals and it would be good for health care in general if we can demonstrate to everybody's satisfaction that it is a safe medication and move towards it."

The experience has been emotionally and financially devastating for the Malone family. A $2-million settlement with the midwives helps pay the bills. And Ian has paid the highest price possible.

"People should be a lot more concerned about taking this drug," says Dylan Malone. "And remember, who is it convenient for? Is it convenient for your baby or is it convenient for a pharmaceutical company or an over-worked hospital staff?"

Molly Malone

Christine Malone has settled into the routine of caring for Ian. The brain damage he suffered at birth means he's more like an infant than a three year old.

Last year, the family added a new twist – Ian now has a younger sister. Molly is a healthy one year old. The other kids now see that having a baby usually means filling juice cups, not syringes.

Christine grilled her new obstetrician before Molly's birth. She wanted to know everything because with Ian's birth she feels she wasn't told enough about Misoprostol.

Christine and Dylan Malone

"I wish I was told that it wasn't approved for the purpose of labour induction, that it's possible for hyper-stimulation or at least incredibly long contractions to happen... things that seem to be known by the doctors who use this drug and yet none of that was shared with us," she says. "If those things were shared with us, I wouldn't have opted for the risk of doing it."

At Cite de la Sante hopsital in Laval, Que., no woman is induced with Misoprostol without first giving her informed consent. Almost 100 per cent of Dr. Pierre Choquette's patients choose

Misoprostol. They make their decision after a discussion on the benefits and risks.

Dr. Pierre Choquette: "We tell them that the medication can give sometimes contractions that are a little bit closer one to the other, and that nothing tells us that it could be dangerous for the baby."

CBC's Norma Lee MacLeod: "You don't tell them the uterus could rupture?"

Dr. Pierre Choquette: "We don't tell that it could happen because in the literature, that's very, very, very few cases of uterine rupture."

Since our interview, Dr. Choquette rewrote the consent form. It now tells women that some cases of uterine rupture have been reported in the U.S, but that it's uncertain whether Misoprostol is to blame.

At the Kingston General Hospital, Dr. Gregory Davies uses Misorpostol only in low-risk pregnancies, and only with the patient's consent.

"Misoprostol is prescribed to millions of people around the world to treat their stomach ulcers, or to prevent stomach ulcers so it's a medication we know a lot about. We know less about it when we use it in pregnancy," he says to one of his patients before spending 10 minutes to describe the research, the pros and cons of Misoprostol and the alternatives.

Two thirds of women offered Misoprostol choose it. Each must sign a consent form developed by the hospital. Under risks, it begins: "Misoprostol to induce your labour appears safe for you and your baby." It goes on, saying, "There is the possibility that the uterus might contract too often or for too long and rarely this could lead to abnormalities in your baby's heart rate."

CBC's Norma Lee MacLeod: "Where is the mention that it can cause death of the fetus or the mother? That's on the label.

That's part of the warning that comes with a package of Misoprostol."

Dr. Gregory Davies

Dr. Gregory Davies: "Well, what I talk about specifically is the experience in our clinical trials and I talk about specifically the experience of trials in general. What you're getting at is talking about, in providing informed consent, how far do you have to go so that the person truly has informed consent? What I don't do at every first prenatal visit, when somebody comes to see me and they're terribly excited and this is their first pregnancy and this is what they've been wanting for so many years, I don't say to them that, in fact, pregnancies significantly increases your risk of dying in the next year as compared to not being pregnant. I don't tell that to people. For the same reason, when we're talking about extremely rare outcomes with the use of Misoprostol or Dinoprostone or Oxytocin, death of babies and death of mothers has been associated with all of these."

Dr. Margaret Somerville, an expert in medicine, law and ethics in Montreal, says the Supreme Court is clear on informed consent.

"The test that the Supreme Court set down was, would the reasonable patient want to know this, not whether a reasonable physician thinks it should be disclosed, and that's a totally different test," she says. "In a very serious risk, such as a risk of death, the court actually mentioned that as the most serious risk you can have, that definitely has to be disclosed to the patient."

Dr. Davies says he doesn't tell women about the risk of death because he's found no evidence of death when the drug is used under his conditions.

Dr. Gregory Davies: "You would have to prove to me that there are deaths associated with the use of Misoprostal in the context in which we're using it that I don't know about," he says. "And if there are, I'd be quite happy to learn about them. I've read the 100 studies that have been reported using Misoprostol for the induction of labour in term and I don't know about the cases."

CBC's Norma Lee MacLeod: "Have you any plans to change the consent form?"

Dr. Gregory Davies: "Not based on what you've told me."

Still, Dr. Davies thinks it's time to settle the controversy. He hopes to get public money to pay for a large safety study, one that will tell doctors whether Misoprostol should be used routinely in the delivery room.

The Malone family

What began with hard labour is now a labour of love. The Malones focus on raising their family and making the most of Ian's limited life.

"It's terribly unfair what Ian has sacrificed," says Dylan. "Everyday I grieve for who Ian should have been and wish that it was us, or me anyway, instead of him."

The Malones have already made their decision about Misoprostol. But the medical jury is still out.

Misoprostol (Cytotec) for Labor Induction: A Cautionary Tale

by Marsden Wagner, MD, MSPH

[*Editor's note*: This article first appeared in Midwifery Today, No. 49 - Spring 1999

Check out the *Mother Jones*' article "Cytotec and Forced Labor"

In this issue of *Midwifery Today* Jennifer Enoch presents an excellent, thorough review of the use of misoprostol (Cytotec) for induction (1). A careful reading of this paper, however, raises a number of urgent questions: Misoprostol is on the market as a prescription drug because the Food and Drug Administration (FDA) has approved misoprostol for stomach problems, but not for induction of labor. Why not? What does the FDA say about this "off-label" use? What does the company manufacturing the drug say about this use? What do the scientific data show, and what do scientists say about this ongoing off-label use? A brief review of the evolution of the use of misoprostol for induction clearly illustrates several problems related to obstetric and midwifery practice in the United States.

Issue 49

Theme: Bridging the Gap

A thorough look at the use of misoprostol (Cytotec) gives readers some very compelling things to think about.

In South Dakota three months ago, an obstetrician bragged to me over lunch that he had introduced into his community the use of Cytotec for induction. When questioned, he admitted knowing the FDA does not approve such use of this drug but that nevertheless he does not inform women it is not approved for induction, nor does he ask for their informed consent. He scoffed at my suggestion that he is experimenting on women without their knowledge, much less consent. His excuse: "We will wait forever for the bureaucrats in Washington, D.C., at the FDA to approve drugs, so we must try them out ourselves if we want progress."

One month later, in Oregon, a local doctor told me (and repeated it on her local weekly *TV Health* program) that obstetricians in Medford told her they are thrilled with Cytotec for induction because they can bring women in first thing in the morning, give them Cytotec and have the babies out before 5 p.m.—a welcome return to daylight obstetrics. None of the hospitals in the Medford area required informed consent when using Cytotec for induction. The Oregon State Health Department told me that while collecting their statewide data on induction, they have observed that Cytotec has now become the most common method of induction.

While the United States has a system in place to ensure that all drugs must be evaluated by the FDA before being allowed on the market and that certain drugs are to be dispensed only through physician prescription, there is a hole in this system. Once a drug has been approved by the FDA for one use and put on the market, there is nothing to prevent a physician from using that drug for whatever use he wants and at any dosage. Trials for new uses of drugs are important as long as the trials are done as research and everyone understands that this use is experimental, with informed consent from the patient. Misoprostol induction shows potential

for certain benefits, but these benefits must be documented by careful research that at the same time looks carefully for the risks.

We can't just throw drugs at people in an uncontrolled way. If a practitioner hears about a new use and simply starts using the drug this new way, this is experimenting on patients without the usual safeguards in place for research subjects. And while practitioners should report to the FDA on such off-label trials and should always report to the FDA any side effects and risks found, in reality only a very small number of practitioners ever report anything to the FDA. As a result, a large information vacuum exists in the United States with regard to what prescription drugs are being used for which purposes and what side effects and serious risks have occurred.

So when practitioners simply begin to use a drug for a new purpose, there follows a phenomenon I have experienced for years as a practicing clinician but rarely see described in print—the informal spread of clinical experience. In hospital corridors, lunchrooms and staff lounges, doctors, midwives and nurses share their ideas and experience.

A recent technology makes it possible to listen in on such clinical chat—online Web pages and chat rooms. By accessing the World Wide Web and then using key words such as "misoprostol" and "pregnancy," many Web pages and chat lines appear. Clinicians, scientists, policy-makers and patients should read these Internet pages from time to time. While clinicians writing on the Web are not necessarily representative of all clinicians, it is possible to discover how at least some of today's clinicians think and act. It seems like eavesdropping because of their candor and their blunt way of expressing ideas and opinions and revealing their attitudes.

It is the informal communication of uncontrolled clinical experience that has driven the spread of misoprostol induction, as is apparent from the following actual statements taken from the Internet in 1998 (2):

"Cytotec is extremely effective at very low doses, is very cheap, and has been used on many, many women without their being aware that it really is still an experimental use."

"I must say that I have heard some great things about Cytotec myself. I know some people who have used it and say that they have pretty good luck with it. It sounds like your ladies are pretty happy with its effects—two-hour labors and such. Just be careful. I would have to say that the biggest danger is leaving the woman alone. The stuff turns the cervix to complete

MUSHIE (Web message emphasis, not mine) and opens it with a couple of contractions. So whatever you do, remember that you must not stay gone too long."

"At my suggestion our high risk OB referral hospital tried Cytotec—one-half tab per vagina—and after two cases of hyperstimulation stopped its use."

"We've seen no cases of hyperstimulation after Cytotec that did not respond to a two-gram bolus of MgSo4. You can almost count on a delivery 12 hours after inserting the Cytotec tablet."

"We are using it at Yale and although there is a format for how to give it, there is still controversy on to whom to give it. Pharmacy uses one of their nifty little pill cutters and sends us one-fourth of a 100 microgram tablet (remember this stuff was made for treatment of ulcers!)."

"I've personally used it twice and had excellent results in women wanting homebirths, but going postdates. I'm attaching my own protocol for anyone interested. Again I warn that I am no expert and I consider this protocol to be a "work in progress"—it will certainly change as I gather experience and information about this drug."

"We are using misoprostol regularly for induction—my department loves it. We use one of the protocols published on OBGYN.Net Web page."

"Our biggest fear is that the company will pull Cytotec from the market, since our internist/GI buddies tell us that it isn't worth a darn for its labeled indication."

What is apparent from this Internet medical practice is the lack of appreciation of any borderline between experimenting on patients and practicing medicine on patients and the absence of concern for patients' rights to informed consent.

Also apparent from reading the Internet is the inability of many clinicians to critically review published papers. The general assumption is that since there are, as stated in one Web message, "gobs of references" (2), the scientific work has been done, and it is OK to use this drug for this purpose. The tendency for clinicians to misinterpret scientific papers is in part because of a difference in approach, since scientists must believe they don't know, while clinicians, in order to do what they do, must believe they do know. A common attitude among clinicians, revealed by Internet

messages, is that pregnancy and birth are dangerous until proven safe, while technology and drugs are safe until proven dangerous.

Issue 51

Theme: Fathers in Pregnancy and Birth

Articles on ultrasound, Cytotec, natural family planning, the "call" to midwifery, placenta previa and much more round out the issue.

In the review of published randomized controlled trials (RCT) of misoprostol induction, Enoch mentions several weaknesses of these trials (1). A number of additional weaknesses of the trials Enoch reviewed must be added to produce the following, more complete, list:

1. All trials compare misoprostol with another inducing drug, but not with nonuse of a drug. Studies of the new use of a drug need to begin with comparing its use with nonuse, or no baseline data on effect exists.
2. None of the RCTs is blind.
3. No RCTs control for the risk status of the woman.
4. No RCTs control for whether the woman is in active labor and if so, what stage of labor.
5. No RCTs have adequate standard dosage regimes. Defining dose according to "adequate contraction pattern" is most inadequate.
6. Since both the dosages used and the drugs compared with vary from study to study, the studies cannot be compared with each other, nor can they be used for meta-analysis.
7. All RCTs have been done at university hospitals. While this may provide preliminary data on efficacy, it gives no information on effectiveness—that is, how effective is this use of this drug in the real world of community practice.
8. The total sample size (both arms of the trial) in all studies is far too small—between 126 and 220. This sample size is completely inadequate for measuring risks. Since the studies cannot be combined because they lack any standardization of methodology, adding up the samples to increase the sample size is not an option.

9. In no trials is woman or baby followed for any significant period of time to identify side effects or risks.
10. No trials report on certain, possibly rarer, risks, such as cervical laceration and severe perineal tears.
11. Of the six RCTs, five show significantly more fetal tachycardia in the misoprostol arm, and the sixth RCT shows more fetal tachycardia, which does not reach statistical significance. This sixth study also reports more abnormal fetal heart rate patterns and more meconium in the misoprostol arm. These results are preliminary given the small sample size, but they are most worrisome. When these results on risks in the RCTs are combined with the case reports Enoch reviews concerning uterine rupture after misoprostol induction, these very preliminary findings regarding risks of misoprostol induction cry out for further research.

In summary, the studies to date might be a bit helpful in fine tuning dose and dose interval and in suggesting possible efficacy, but they leave wide open serious concerns about risks. Turning again to the Internet and the gold standard of perinatal science, the Cochrane Library, a review of misoprostol induction in the second online issue in 1998 concludes:

"In dosages of 25 micrograms three hourly or more, misoprostol is more effective than conventional methods of cervical ripening and labour induction. The increase in uterine hyperstimulation with fetal heart rate changes found in this review is a matter of concern. Although no differences in perinatal outcome were shown, the studies were not sufficiently large to exclude the possibility of uncommon serious adverse effects. The increase in meconium-stained liquor in one study also requires further investigation.

"Thus, though misoprostol shows promise as a highly effective, inexpensive and convenient agent for labour induction, it cannot be recommended for routine use at this stage. It is also not registered for such use in many countries.

"Because of the enormous economic and possible clinical advantages of misoprostol, there is the need for trials to establish its safety." (3)

In other words, the opinion of the best perinatal scientists is that misoprostol induction is still experimental and should be done only in a controlled research setting with the usual protection of research subjects, including fully informed consent. This is because to date our scientific data are inadequate to tell us whether or not misoprostol induction is safe.

The alacrity with which a technology or drug is adopted and used is related to its advantages for the patient and, equally or more importantly, for the practitioner. We have struggled for years with little success to keep a lid on the medically unnecessary use of that most convenient obstetrical procedure—cesarean section. During this same time we have struggled with little success to promote the adoption of the evidence-based but inconvenient VBAC (vaginal birth after cesarean).

How do we hold back the rapid spread of misoprostol induction, which heralds the return of all the conveniences of daylight obstetrics? That the drug is not approved by the FDA for this purpose, not approved for this use by the drug manufacturer, not endorsed for this use by the American College of Obstetricians and Gynecologists or midwifery organizations, and not recommended for routine use by scientists (who tell us we do not know if it is safe) has had no apparent effect on the enthusiasm with which clinicians, both doctors and midwives, are starting to use it.

It is particularly disconcerting to learn from the Internet and from chatting with practitioners that some midwives are jumping on the misoprostol induction bandwagon. A homebirth midwife on the Internet talks of her "work in progress" protocol—an oxymoron, because protocols should never be based on brief experience but always on a thorough review of all the best current scientific data. Midwives need to make every effort to achieve evidence-based practice, particularly when using drugs and invasive technologies, and the clear lack of data on serious risks of misoprostol induction should be sufficient to deter all midwives from this procedure, whether in hospital or out of hospital.

The issue here is consumer protection and quality assurance in maternity care. We need a system of rational pharmaceutical management that guarantees adequate evaluation of every use of a drug prior to its use for that purpose as well as drug protocols developed by an officially recognized group of scientists, clinicians (including midwives), policy-makers, and consumers and based on the best scientific evidence. Present consumer protection systems in some countries, for example in Scandinavia, include mandatory prior evaluation and officially endorsed consensus protocols, and there is no evidence that progress in maternity care is held back.

However, in some countries such as the United States and the United Kingdom, the only way consumers of health care have found to protect themselves is through the courts, because this is the only place doctors

and hospitals cannot successfully stonewall information and opinion. Too many times clinicians are sued for the wrong reasons because there is not a system to guarantee prior adequate evaluation and evidence-based protocols with some weight to them.

The case reports on uterine rupture after misoprostol induction recommend not using this drug if the woman has a scarred uterus, and Enoch, in her review, wisely echoes this recommendation (1). But after more than a decade of cesarean section rates in the United States above 20 percent, a significant proportion of American women of childbearing age have a scarred uterus, and such a policy would sharply reduce the opportunities for daylight obstetrics. How many uteri will be ruptured before a court case finally applies a needed brake in this practice? I would welcome learning of cases where misoprostol induction was used without fully informed consent and there was subsequent uterine rupture, cervical laceration or other serious complications.

Marsden Wagner, MD, is a neonatologist and perinatal epidemiologist. He was responsible for maternal and child health in the European Regional Office of the World Health Organization for 14 years. Now living in Washington, D.C., he travels the world talking about appropriate uses of technology in birth and utilizing midwives for the best outcome.

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Midwives and Cytotec: A True Story
by Marsden Wagner MD, MSPH

[*Editor's note:* This article first appeared in *Midwifery Today* Issue 57, Spring 2001.]

Two direct entry, licensed midwives with their own freestanding birth center in the United States referred a woman at 39 weeks gestation to their consultant obstetrician for induction because of "unstable lie" and because the woman requested induction. Her two previous births had been vaginal and without complications although one was induced with prostaglandin gel. When the obstetrician said he would use Cytotec, the woman and her husband said they expected he would use prostaglandin gel but he said that he now uses Cytotec, as it is "more modern and reliable." They were not told Cytotec is not approved by the Food and Drug Administration (FDA) for this purpose nor were they told about any of the known risks such as hyperstimulation and uterine rupture. The obstetrician inserted 50 micrograms of Cytotec in the vagina, put several more tablets of Cytotec in an envelope, gave the envelope to the parents and sent them home, knowing the woman would be giving birth in the birth center.

I

ssue 51
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No labor ensued, however. But when the midwives learned of the use of Cytotec, they called the obstetrician because recently they had heard that Cytotec can result in "too fast labor." The obstetrician told the midwives Cytotec is "not risky" and "not to worry." So one week later the midwives again sent the woman to the same obstetrician for another try at induction, this time with no medical indication as the fetus now had a normal, stable lie. The obstetrician again inserted 50 micrograms of Cytotec into her vagina, gave the woman more tablets in an envelope and sent her home.

After a few contractions at home, the woman went to the birth center. The woman informed the midwives about the Cytotec insertion and the envelope of Cytotec pills. Six hours after the first Cytotec was inserted by the obstetrician, the woman and midwives agreed on another 50 microgram dose, this time orally, and six hours later on a third oral dose.

Active labor began which rapidly evolved into hyperstimulation. Because the labor was videotaped, later analysis has shown that, using the Williams Obstetrics definition of hyperstimulation—more than five contractions in a 10-minute period and/or contractions lasting longer than one minute—there was intermittent hyperstimulation throughout the 90-minute second stage. With hyperstimulation there is not enough time during and in between contractions for adequate oxygen flow to the fetus. During the last 17 minutes before birth there was difficulty in finding fetal heart tones and at the time of birth the baby was flaccid and blue with an Apgar of one. Emergency transport to the nearest hospital was expedited but, tragically, months later the baby clearly has severe neurological impairment, most likely as a result of hyperstimulation from Cytotec induction and the subsequent hypoxia.

In this case, the obstetrician must bear primary responsibility and liability for the severe uterine hyperstimulation during labor as he prescribed Cytotec, gave the first dose, gave the woman additional doses in an envelope and sent her home to labor knowing she planned to go to the birth center for the birth attended by midwives. The obstetrician did not give adequate informed consent and falsely reassured both the parents and midwives about the risks of Cytotec.

But the midwives must also bear responsibility. First, they seem too cavalier about pharmacological induction of labor, being willing to monitor a woman in their birth center who has been induced by a doctor in his office. They were obviously concerned about Cytotec induction but, unfortunately, were willing to be reassured by the obstetrician-"He said it's totally fine" and "I trusted him."

Because the obstetrician "prescribed" Cytotec and gave the first dose, the midwives did not feel they "administered" Cytotec even though they cut the tablets given to them by the woman and brought the tablets to her with a glass of water. It is extremely important for midwives to understand that a midwife (just like a nurse) who gives a drug to a woman or even watches a woman take a drug while under the midwife's care or in her care facility is personally responsible for and liable for being certain the drug is appropriate and in the correct dose, regardless of who prescribed or ordered the drug in the first place. This is why hospitals take away on hospital admission any drugs the patient may have brought with them, even aspirin.

Like the obstetrician, the midwives failed to give adequate informed choice on induction and on Cytotec. For example, they also never told the woman that Cytotec is not approved by the FDA for induction.

The midwives did not recognize the hyperstimulation when it occurred, not surprising since this would be a very rare phenomenon in a birth center or home birth practice where induction is not usually done.

Lessons? First, midwives must find the strength and courage not to be sucked into practicing a more interventionist type of care—resist the temptation to become a "medwife." One of the major advantages of midwifery care is avoiding unnecessary intervention. Pharmacological induction is just plain dangerous in any setting and doubly as dangerous in out-of-hospital settings. Midwives who begin trying more such "medical" type interventions will find themselves rapidly falling into a bottomless pit of risks for the woman and baby and liabilities for themselves—as this case shows. Midwives will also find themselves inheriting other problems associated with a more medicalized approach to birth, including difficulties in getting malpractice insurance and higher insurance premiums.

I

ssue 49
Theme: Bridging the Gap

A thorough look at the use of misoprostol (Cytotec) gives readers some very compelling things to think about.

And induction with Cytotec should never be attempted anywhere, most especially in out-of-hospital settings. Incredibly, the American College of Obstetricians and Gynecologists (ACOG) recently approved Cytotec induction: 1) in spite of lack of FDA approval; 2) in spite of a letter to doctors earlier this year from Searle (which manufactures Cytotec) imploring doctors not to use it for induction; 3) in spite of lack of approval from the Cochrane Library (the best scientific opinion); and 4) in spite of the fact that it is not approved nor used for induction in any country in Western Europe.

Recent articles in prestigious medical journals such as *The Lancet* have questioned the validity of standards of practice from professional organizations like ACOG, because their goal of protecting the health of women through using scientific evidence to guide members toward best practices too often conflicts with their other role as a trade union representing the interest of their members. As a result of this "trade union"

role, ACOG recommendations are too often compromised by the needs of the obstetricians. A classic example of putting the doctors' needs ahead of the families' needs is the ACOG recommendation not to permit videotaping by families of a hospital birth.

So ACOG quotes studies of Cytotec induction, none of which have a sufficient number of research subjects, and consequently, none of the studies quoted have sufficient statistical power to detect small but potentially important risks such as uterine hyperstimulation and uterine rupture. Furthermore, because published studies of Cytotec induction have such wide methodological variability, meta-analysis is impossible and the published attempts at such meta-analysis are seriously flawed. But Cytotec is a godsend for busy obstetricians, as its use allows them to schedule the woman's labor at a convenient time and speeds up the labor, resulting in a return to "daylight obstetrics"-pharmacological induction of labor has increased from 10 percent to 20 percent in the past decade in the United States. So with their members' needs in mind, ACOG plows ahead, ignoring the best scientific evidence as well as the recommendations of the best scientific bodies, of government agencies not only in the United States but in every country in Western Europe, and of the pharmaceutical company. Instead, ACOG uses weak, inadequate evidence to approve Cytotec induction. Midwives should stay as far away as possible from such vigilante obstetrics-obstetricians taking matters into their own hands while ignoring the recommendations of the real judges.

(Parenthetically it must be added that for these reasons ACOG recommendations should never be the only criterion used in developing standards of practice. Should the United Automobile Workers Union set the standards of safety for automobiles? The recent ACOG recommendation to allow vaginal birth after cesarean (VBAC) only in a hospital with a surgeon and anesthesiologist at the ready is yet another example of a recommendation based on weak, inadequate evidence but which is made nevertheless, as it benefits obstetricians even as it eliminates significant options for birthing women and further marginalizes midwives.)

Another lesson for midwives from this case: Midwives are personally responsible and legally liable for everything that happens to the women under their care. Midwives do not require "supervision" by obstetricians but need to collaborate with them as equals when necessary. This means that midwives should not try to blame or push off responsibility onto the doctor. In any case, whatever the doctor says, does or recommends, the midwife

remains responsible for whatever happens to her client as long as the client is in the care of the midwife.

Beware of reassurance, regardless of where it comes from. How can American midwives trust what American obstetricians say when there is such a gap between what these same obstetricians practice and what the evidence says they should be doing-obstetricians' episiotomy rates far above what the evidence says they should be is only one example among many. Research shows that doctors rely far more on the opinion of other doctors than on scientific evidence. Midwifery has an opportunity to lead the way in this country in providing maternity care in which any interventions, including the invasive ones also used by obstetricians, are based on the best evidence. Sure, a midwife should get the opinion of her peers and her consulting obstetrician, but she also should always get the best evidence from the literature (see notes at the end of this article) and then, together with the woman decide what is to be done. And then accept full responsibility for everything she does. And also lead the way in always providing full, unbiased informed choice, not because she is afraid of litigation (like doctors and hospitals), but because she respects her women too much to do it any other way. In the case of Cytotec induction, the information given to the woman must include that it is not approved for this purpose by either the FDA or the pharmaceutical company.

A sad postscript: In 2000, the family in this real case sued the midwives and their birth center and, in addition, sued the obstetrician—their child from this birth needs daily home nursing care for the rest of his life. The insurance company for the midwives made a pretrial settlement with the family for the upper limit of the midwives' insurance policy—two million dollars. The litigation with the obstetrician is still pending.

I know of legal cases of Cytotec induction and bad birth outcomes in Oregon, Washington, Idaho, Florida and other states and territories. Most of these cases are settled before going to court, so these tragic outcomes of Cytotec induction never see the light of day.

Marsden Wagner, MD, is a neonatologist and perinatal epidemiologist. He was responsible for maternal and child health in the European Regional Office of the World Health Organization for fourteen years. Now living in Washington, D.C., he travels the world talking about appropriate uses of technology in birth and utilizing midwives for the best outcome.

Good sources of evidence:

- Enkin, M. et al. (1995). *A Guide to Effective Care in Pregnancy and Childbirth*. Oxford: Oxford University Press.
- Goer, H. (1999). *The Thinking Woman's Guide to a Better Birth*. New York: Penguin Putnam.
- Wagner, M. (1994). *Pursuing the Birth Machine: The Search for Appropriate Birth Technology*. Sydney and London: ACE Graphics.
- MIDIRS (www.midirs.org).
- Cochrane Library (use nearest medical library).

Related information:

- Misoprostol: More on the dangers of Cytotec
- Misoprostol (Cytotec) for Labor Induction: A Cautionary Tale - by Marsden Wagner
- Technology in Birth: First Do No Harm - by Marsden Wagner
- Drugs in Labour - by Beverley Lawrence Beech
- Forced Labor - by David Goodman (*Mother Jones* magazine)
- Epidemics: Epidural, Ultrasound, Cytotec and More (Audiotape)Serving Women in Hospital Birth 5: Dealing with Consumer Demand (Audiotape)
- *Midwifery Today* Issue 49
- *Midwifery Today* Issue 51
- *Midwifery Today* Issue 57

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Cytotec

While the United States has a system in place to insure that all drugs must be evaluated by the FDA before they are allowed on the market and that certain drugs are to be dispensed only through physician prescription, there is a hole in this system. Once a drug has been approved by the FDA for one use and put on the market, there is nothing to prevent a physician from using that drug for whatever use at any dose. Trials of new uses of drugs are important as long as the trials are done as research and everyone understands that this use is experimental with informed consent from the patient. Misoprostol induction shows potential for certain benefits but these benefits must be documented by careful research which, at the same time, looks carefully for the risks.

We can't just throw drugs at people in an uncontrolled way. If a practitioner hears about a new use and simply starts using the drug this new way, this is experimenting on patients without the usual safeguards in place for research subjects. And while practitioners should report to the FDA on such off label trials and should always report to the FDA on side effects and risks found, in reality only a very small number of practitioners ever report anything to the FDA. As a result, a large information vacuum exists in the United States with regard to what prescription drugs are being used for which purposes and what side effects and serious risks have occurred. So when practitioners simply begin to use a drug for a new purpose, there follows a phenomenon I have experienced for years as a practicing clinician but rarely see described in print--the informal spread of clinical experience. In hospital corridors, lunchrooms and staff lounges, doctors, midwives and nurses share their ideas and experience.

A recent technology makes it possible to listen in on such clinical chat--online web pages and chat rooms. By accessing the World Wide Web and then using key words such as "misoprostol" and "pregnancy," many web pages and chat lines appear. Clinicians, scientists, policy makers and patients should read these Internet pages from time to time. While clinicians writing on the web are not necessarily representative of all clinicians, it is possible to discover how at least some of today's clinicians think and act. It seems like eavesdropping because of their candor and their blunt way of expressing ideas and opinions and revealing their attitudes. It is the informal communication of uncontrolled clinical experience which has driven the spread of misoprostol induction as is apparent from the following actual statements taken from the Internet in 1998: (2)

"Cytotec is extremely effective at very low doses, is very cheap, and has been used on many, many women without their being aware that it really is still an experimental use."

"I must say that I have heard some great things about Cytotec myself. I know some people who have used it and say that they have pretty good luck with it. It sounds like your ladies are pretty happy with its effects--two-hour labors and such. Just be careful. I would have to say that the biggest danger is leaving the

woman alone. The stuff turns the cervix to complete MUSHIE (web message emphasis, not mine) and opens it with a couple of contractions. So whatever you do, remember that you must not stay gone too long."

"At my suggestion our high risk OB referral hospital tried Cytotec--one-half tab per vagina--and after two cases of hyperstimulation stopped its use."

"We've seen no cases of hyperstimulation after Cytotec that did not respond to a two-gram bolus of MgSo4. You can almost count on a delivery twelve hours after inserting the Cytotec tablet."

"We are using it at Yale and although there is a format for how to give it, there is still controversy on to whom to give it. Pharmacy uses one of their nifty little pill cutters and sends us one-fourth of a 100 microgram tablet (remember this stuff was made for treatment of ulcers!)"

"We are using misoprostol regularly for induction--my department loves it. We use one of the protocols published on OBGYN.Net web page."

"Our biggest fear is that the company will pull Cytotec from the market, since our internist/GI buddies tell us that it isn't worth a darn for its labeled indication."

What is apparent from this Internet medical practice is the lack of appreciation of any borderline between experimenting on patients and practicing medicine on patients and the absence of concern for patient's rights to informed consent.

Also apparent from reading the Internet is the inability of many clinicians to critically review published papers. The general assumption is that since there are, as stated in one web message "gobs of references" (2), the scientific work has been done and it is okay to use this drug for this purpose. The tendency for clinicians to misinterpret scientific papers is in part because of a difference in approach since scientists must believe they don't know while clinicians, in order to do what they do, must believe they do know. A common attitude among clinicians, revealed by Internet messages, is that pregnancy and birth are dangerous until proven safe while technology and drugs are safe until proven dangerous. -Marsden Wagner, MD, Misoprostol (Cytotec) for Labor Induction: A Cautionary Tale. Read the entire article on the Midwifery Today website: www.midwiferytoday.com/articles/cytotecwagner.htm ====

The June 1999 issue of the American Journal of Obstetrics and Gynecology published the article "Uterine rupture associated with the use of misoprostol in the gravid patient with a previous cesarean section." The data in this article are truly frightening. "Uterine rupture occurred in 5 of 89 patients with previous cesarean delivery who had labor induced with misoprostol. The uterine rupture rate for patients attempting vaginal birth after cesarean was significantly higher in those who received misoprostol, 5.6 percent, than in those who did not, 0.2 percent or 1 in 423, p=0.0001)." Furthermore, a medical records review turned up

several more cases of uterine rupture associated with using Cytotec with VBAC not included in their calculations.

Be clear on what this says. Over five percent of women given Cytotec for VBAC had a ruptured uterus, a 28-fold increase over those who did not have Cytotec induction for VBAC. This is a truly shocking rate of uterine rupture. And one of the five women with uterine rupture ended up with a dead baby as a result of the rupture.

Just in case you think this paper reports an aberration, the same issue of this journal has a second paper in which three of eighty-one women receiving Cytotec for a VBAC had uterine rupture--a still shocking rate of 3.7 percent. And one of the three babies died in the NICU after the rupture. Both these papers were retrospective which means that none of the women given Cytotec were part of a research project. Thus, none had received the protection of research subjects, including information on the experimental nature of the drug given to them. So in these two papers, of 170 women given Cytotec for induction with VBAC, eight have lost their uterus and two lost a baby as well. It is my educated guess that to this day none of them has been told that they were given a drug for a purpose not approved by the FDA nor has been told their case is described in published papers saying this drug should not be used in this way.

These women and babies paid a very big price because their practitioners were willing to use a very powerful drug before it has been approved by the FDA for this purpose and before it was adequately evaluated by prospective, controlled research. Hopefully, no midwife will ever be involved in any birth where Cytotec is used for VBAC and all midwives will do everything possible to prevent the use of Cytotec for any type of induction until we have more complete evaluation.
-Marsden Wagner MD, MSPH
Go to: www.midwiferytoday.com/articles/Misoprostol.htm
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When uterine overactivity occurs [due to artificial means], an attempt must be made to remove the drug that is causing the problem. Turning off an oxytocin infusion is fast and easy, and usually results in a rapid return to more normal uterine activity. Some dinoprostone products are made with a string and are easy to remove quickly. When dinoprostone gel is used, attempts can be made to flush it from the vagina with sterile saline-clearly a slower and less effective procedure. With misoprostol, attempts can be made to remove the pill, if it has not yet been absorbed. More often than not, the pill has already been completely absorbed. In this case, there is no choice but to ride out the excessive contraction pattern with careful monitoring and measures to maximize the supply of oxygen to the fetus. -Jennifer Enoch, Midwifery today Issue 49
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Midwifery Today Issue 49 discusses at length the use of misoprostol (cytotec). To order the issue, go to:
www.midwiferytoday.com/Magazine/backissues.htm#49
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E-News readers talk about Cytotec:

A primagravida mom went a week postdates and her doctor wanted to induce labor. He admitted her at 9 pm, and started Cytotec at 9:45. At 1:45 she was checked, and no change was noted, so another dose was inserted. At 6 pm she was contracting mildly, about 7 mins apart. At her next vag check, she was found to be 2-3 cms and 80% effaced, which was great progress from 0 dilation and no effacement at all. I'm told by her there was no cervical discomfort with Cytotec, and no pain or cramping that she noticed. Other clients who have induced using Cervadil and Progestagel have complained of burning at the cervix and intense cramping from use. From this I would ascertain that Cytotec seems to be equally useful as an induction agent, but seems to be less uncomfortable for the moms. Has anyone else come to this conclusion? I would love to hear your stories.
-Gina Acosta,ICCE,CD,
Canyon Country, CA
DoulaGina@aol.com
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I can only provide insight from the patient's perspective as I have not used Cytotec in my clinical setting. Each of my pregnancies have been complicated by pregnancy-induced hypertension. With my fourth and most recent birth on August 4, I was induced at 38 weeks for PIH as my blood pressures on bedrest were 160s/100s (in labor they were as high as 200/100 and I got a dose of Apresoline). I had headaches for several days that wouldn't resolve with analgesia. I put off induction for a week, against the advice of two OBs and a perinatologist. Before the day I was induced, I was feeling well and had a Bishop's score of 5. I decided to go ahead with it as I just didn't have the same feeling of well-being that I had had in previous weeks. Something just wasn't right. I had a Bishop's score of 8 on the day I was induced and my baby's head was ballotable.

I had been induced with Pitocin twice before, once for PIH and once for severe preeclampsia. I opted to try Cytotec this time so that I could be more mobile and use hydrotherapy. After getting us settled in, my labor nurse inserted a 50 microgram tablet of Cytotec vaginally. In no time at all I was contracting every 1-2 minutes. Compared to Pitocin, my contractions didn't peak as fast with Cytotec and I felt I could cope with the discomfort better. I felt so tied down with Pitocin and felt more in control this time because I wasn't stuck in bed on my left side. I'm glad I had Cytotec as an induction option for this birth.
-Maurenne Griese, RNC, BSN, CCE, CBE
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When it was introduced at my hospital I did my own research and found many reasons not to use Cytotec at the dosage we use (100 mcg PO) but was told I either give it or quit. About two years later the research is still saying a lower dose is better as it doesn't carry the risk of hyperstimulation and is just as effective. Clinically, I must say I haven't seen the problems I had expected and it has proven to be much more effective than any other methods tried. One big advantage is the intermittent monitoring so women can be out of bed, walk,

enjoy the tub, etc. Because it is so cheap and easily obtainable I worry that it may be used out of the hospital. A friend of mine was given a few doses of Cytotec to be used for a clinic birth, suffered hyperstimulation, and the baby was born with a 0 Apgar, severely brain damaged and is unlikely to survive for long. Use EXTREME caution when using Cytotec!
-Valerie G., RNC, CD
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I am a CNM in an out-of-hospital (OOH) birth practice and I will admit to using Cytotec RARELY in the past few years. I am very well informed about the risk and benefits of Cytotec and that I can appropriately offer it to a RARE client for whom indications exist for getting labor going. I tend to resent the attitude of midwife purists who believe that, as an OOH birth midwife, I should only be catching babies that fall into my hands out of the lowest-risk moms--no interventions allowed. The idea, apparently, is that if a client is high enough risk to need Cytotec induction, she is too high risk for an OOH birth anyway.

This might be true in some cases and we OOH midwives need to remain sensible with our risk assessment, but there are certainly other cases in which the woman's risk is low, but clearly increasing with time. If we sit on our hands and wait indefinitely for labor, her risk continues to increase and she may well find herself in an interventive hospital birth situation, whereas if we push her into labor now, she will deliver OOH as a low-risk person.

Case in point: a 29-year-old motivated healthy G3P2 with a history of PIH in her first pregnancy (induced in the hospital at 42+ weeks), no PIH with second pregnancy (fast and easy homebirth at 42 weeks), developing PIH in the current pregnancy. She is extremely desirous of another homebirth, very adverse to hospital birth. Motivated and healthy, she eats a high-protein diet, rests on her left side at prescribed intervals, takes her cal/mag supplement, monitors her BP at home in-between visits. She does everything she can do to remain low-risk, but her BP is clearly climbing, from 112/72 in mid-pregnancy to 130/80 at 32 weeks to 140/84 at 36 weeks to 142/90 at 39 weeks to 150/92 at 40 weeks. She has no swelling or excessive weight gain, DTRs are WNL, her cervix is 3 cm, EFW is 8-1/2 pounds. Her history of two previous 42 week pregnancies would suggest that this kid probably planning to come out soon, but her BP is not one that you'd want to watch rising for another 2 weeks. She doesn't have fulminating preeclampsia, obviously, but her risk is clearly increasing with her BP.

She tries herbs, homeopathics, nipple stim, lovemaking, etc., and finally, after a long discussion of risks and benefits (and signing a consent form), we bring her into labor slowly with two small doses of Cytotec. Her healthy baby boy (8lbs 6 oz) is born easily at home that evening. Was it inappropriate to use the Cytotec in this case? I'm a nurse practitioner with prescriptive privileges, so it is within my professional authority to prescribe. It's legal, but is it good midwifery? Should I have allowed her to become more hypertensive, leading to increased risk for her and her baby and possibly an interventive hospital birth? Not in my mind.

If Cytotec is becoming the candy of the OOH birth midwife as people are reporting, we're in big trouble because women are going to get hurt (and midwifery will get hurt as well). But we don't need to throw the baby out with the bathwater. Clear indications for induction, extensive informed consent, extremely cautious dosing (max of two widely-spaced tiny doses in any day), and careful OOH monitoring need to be a part of any appropriate use of Cytotec OOH.
-Anon.

Cytotec, continued

Cytotec can be very useful in midwifery but it needs to be used with prudence. There doesn't seem to be common ground on what the dosage should be. Because it was never meant to be used on pregnant women, safe dosages have not been established. From my experience, you need very little--17-20 micrograms to start. It can be smeared on the cervix in situations where the woman has spontaneous PROM, she is postdates with a very large baby, or is exhibiting other signs of needing to have her baby.

Cytotec works differently on different women. Some need very little in their system, while others need several doses. Never administer more than 50 micrograms at a time, and that as a general rule is too much. Just because a

woman is obese does not justify a large dose; her cervix is still the same size. Contractions are very fast and close together without giving the baby or mom a chance to recover. Generally, I would say 89 percent of babies birthed with Cytotec induction suffer some degree of respiratory distress. Another side effect is that moms bleed, if not a major hemorrhage, the cervix will bleed because it has had to dilate so fast. I've seen Cytotec erase swollen anterior cervical lips.

Most midwives will not be comfortable using Cytotec because there is so much we do not know or understand about it and it was never designated for obstetrical use. However, I feel if it is used with prudence, it can be a very valuable tool in our birth bag. I believe that in the hospitals Cytotec is being used too frequently and at too high a dose. Its use with VBACS is totally contraindicated. We must remember that it cannot be turned off, up or down like Pitocin. Once it gets into the system, it takes several hours to clear out. As midwives we need to learn patience and watch and wait. Cytotec should never be used for our own convenience, or to induce a woman who is tired of being pregnant. It should be saved for rare situations, and treated with the utmost respect. -Cathy O'Bryant, CPM ====

With recent articles in several midwifery publications regarding the risks associated with the use of Cytotec for inducing labor, and reports that Cytotec is the induction agent of choice in many hospitals, readers may be interested in this memo. The manufacturer is finally taking a stand on the off-label use of this drug.
-Susan Hodges

IMPORTANT DRUG WARNING CONCERNING UNAPPROVED USE OF INTRAVAGINAL OR ORAL MISOPROSTOL IN PREGNANT WOMEN FOR INDUCTION OF LABOR OR ABORTION

Dear Health Care Provider:
The purpose of this letter is to remind you that Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion. Cytotec is not approved for the induction of labor or abortion. Cytotec is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer.

The uterotonic effect of Cytotec is an inherent property of prostaglandin E1(PGE1), of which Cytotec is stable, orally active, synthetic analog. Searle has become aware of some instances where Cytotec, outside of its approved indication, was used as a cervical ripening agent prior to termination of pregnancy, or for induction of labor, in spite of the specific contraindications to its use during pregnancy.

Serious adverse events reported following off-label use of Cytotec in pregnant women include maternal or fetal death; uterine hyperstimulation, rupture or

perforation requiring uterine surgical repair, hysterectomy orsalpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain.

Searle has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or for induction of labor, nor does Searle intend to study or support these uses. Therefore, Searle is unable to provide complete risk information for Cytotec when it is used for such purposes. In addition to the known and unknown acute risks to the mother and fetus, the effect of Cytotec on the later growth, development and functional maturation of the child when Cytotec is used for induction of labor or cervical ripening has not been established.

Searle promotes the use of Cytotec only for its approved indication. Please read the enclosed updated complete Prescribing Information for Cytotec. Further information may be obtained by calling 1-800-323-4204.
Michael Cullen, MD
Medical Director, U.S.
Searle