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WOMEN'S HEALTH
Collateral Damage
Why can't we prevent more childbirth deaths? Blame abortion politics

- Janet Wells
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It was midnight in a village in the rugged jungle of eastern Burma, not far from the Thai border. The village headman's 14-year-old daughter had just given birth, on a mat in a bamboo-and-thatch hut she shared with her husband. It had been a difficult labor. The mother was petite and anemic, from malnutrition or a history of malaria or both, and the baby was breech. There was no hospital nearby, and no government-sponsored medical care in this part of the country, where dozens of villages like this one had sprung up in recent years to shelter thousands of families displaced by the country's long-simmering civil conflict. A traditional birth attendant, an older woman who relied on experience and local remedies, was the only person available to guide the young woman.

The baby finally emerged, a healthy squalling boy. But the placenta did not, and the situation quickly turned dire as the young woman began to bleed heavily. The attendant might have tried to staunch the flow with a longyi, a sarong-like cloth. She might have massaged the uterus from the outside. Most likely she simply waited, hoping it would stop. There was little else she could do. No electricity, no phones, no pharmacy. The attendant had none of the resources used to treat the nearly 100,000 American women each year who experience the same potentially devastating bleeding after childbirth. The husband finally got word to Nana, a trained medic and director of a tiny health clinic serving the region. By the time she arrived at the young woman's hut before sunrise, it was too late.

"I go and see her, and no life," said Nana, a 45-year-old mother of six. (Like many Karen, an ethnic minority in Burma, she uses only one name.) Nana's patient died nearly three years ago. But it could have happened yesterday. It did, somewhere.

There are 14 million obstetric hemorrhages a year, killing an estimated 128,000 women, almost all in the developing world, where most births happen at home without skilled medical care. Severe postpartum bleeding is the No. 1 cause of maternal mortality worldwide: One woman dies every four minutes.

Prevention is possible

Nana's story is the kind that makes Berkeley residents Martha Campbell and Dr. Malcolm Potts throw their hands up in frustration. Not because it's common. Because it's unnecessary. There's a cheap, easy-to-use, safe and effective drug to prevent and treat obstetric bleeding: misoprostol.

Without intervention, a woman with severe postpartum hemorrhage can bleed to death in three to four hours. The blood gushes out, "like cutting an artery" -- a terrifying situation for the woman, and for any health practitioner, said Potts, a Cambridge-trained obstetrician and the Bixby professor on Population and Family Planning at the University of California at Berkeley's School of Public Health.

Developed in the 1980s to prevent gastric ulcers, misoprostol is a hormone-like drug that stops the secretion of stomach acid. An Egyptian obstetrician working in London, Dr. Hazem El-Refaey, posited that the drug could work similarly on the uterus, making the muscle tissue contract, which stems bleeding.

"It is low cost, heat stable, could be given orally, rectally, vaginally. A dream product," said Potts. "If you give a dose rectally and put your hand on the uterus after delivery, you can feel it contract within a minute or two."

When asked if the drug might have saved the life of the village teenager, Nana nodded. "If had, not die."

So why isn't this drug in the satchel of every birth attendant in the world? Because misoprostol is also a cheap, easy-to-use, safe and effective drug that can induce abortion.

"Governments are reluctant to approve this drug because they are afraid people will use it to do abortions," said Campbell, a political scientist and health policy expert who lectures at Berkeley's School of Public Health. While misoprostol is registered worldwide as an ulcer drug, many countries -- including Thailand and Brazil -- have heavy restrictions on it because of its use in inducing abortions. In Burma and most of Africa, the drug is not available, except, perhaps, on the black market for prices out of most women's reach.

Potts and Campbell, who are part of a growing cadre in women's health who see misoprostol as a miracle drug for the developing world, are working country by country to take it out of the political realm. "Countries have made abortion illegal, and we've got to deal with that. But one of the things women use for an abortion is a rib of an umbrella or a bicycle spoke, and we don't make umbrellas or bicycles illegal," said Potts. "I think it's immoral not to save women's lives when they are dying from postpartum hemorrhage simply because they might use (a drug) for abortion."

The proselytizers

Potts and Campbell, husband and wife as well as colleagues, are too genteel to see themselves as drug pushers. But get them talking about misoprostol, about women's health, and it's hard to get them to stop. Campbell headed the Packard Foundation's

population program in the 1990s and co-founded UC Berkeley's Center for Entrepreneurship in Health and Development. An energetic 65-year-old, she is likely to invite anyone interested in misoprostol by the office for a chat. Potts, 71, teaches classes on contraception, AIDS prevention, international health and violence, and has amassed an impressive -- and often controversial -- array of accomplishments in women's health. In 1965, he opened one of England's first clinics offering contraception to unmarried women. He was the first medical director of the International Planned Parenthood Federation, from 1968-1980. He, along with inventor Harvey Karman, published the first papers on the manual vacuum aspirator, a tool still in use worldwide for abortions and incomplete miscarriages. Potts developed the first comprehensive study of maternal mortality in the developing world, which helped launch the worldwide Safe Motherhood Initiative in 1987.

Potts' feminist sensibility extended to his work as a historian, as well. "Albert and [Queen] Victoria had a very passionate sex life so she was always getting pregnant to her fury," said Potts, who wrote a book on the queen and the history of hemophilia. "She put all her own children out to wet nurses, and with a wet nurse, you ovulate very quickly. If she had breast fed, she would have had children much further apart."

At their north Berkeley house one Sunday afternoon, Potts pulled out scrapbooks from four decades of work in public health. Campbell served green tea, setting the tray on top of magazines and journals like "Population and Development Review." If asked, one or the other will root through an upstairs room to find a sample of misoprostol. Potts produced a framed black-and-white photo of a pretty, clear-eyed young woman taken in 1900. "My grandmother, who died in childbirth, most probably of postpartum hemorrhage," he said.

In 2000, with the goal of using technology and research to effect change on a large scale, Campbell founded the nonprofit Venture Strategies for Health and Development. Coincidentally, misoprostol, made by Pfizer Inc. and marketed under the name Cytotec, came off patent that year, which meant it could be made in generic form, and sold for far less. Said Campbell: "My husband pointed out that misoprostol was a huge opportunity for women's health."

Getting around the "A word"

Building a case for worldwide acceptance of a drug that has not been approved by the U.S. Food and Drug Administration (or by any European regulatory agency) for postpartum hemorrhage is no small challenge. Especially when that drug is an abortifacient.

The drug used most commonly in the West for postpartum bleeding is oxytocin. Research has shown it to be slightly more effective than misoprostol -- by 1 percent. But it has to be refrigerated and injected and costs more, making it impractical for the developing world.

There's a plethora of evidence supporting misoprostol in the OB-GYN arena, including more than 200 peer-reviewed articles on its use, safety and efficacy. As a result, and because the FDA gives physicians discretion to use an approved drug for off-label use, misoprostol has become part of every OB-GYN department's arsenal in the United States. It is used here to treat postpartum hemorrhage, to induce labor and to soften the cervix before some procedures and it is part of the medical abortion regimen.

Misoprostol is not risk-free. When used to treat postpartum hemorrhage, side effects can include nausea, vomiting, diarrhea, abdominal pain, chills and fever. Using the drug to induce labor presents an even more serious risk. Misoprostol tablets come in 200-microgram doses, but it takes only 25 micrograms to induce labor (as opposed to 1,000 micrograms to treat hemorrhage). One-eighth of the tablet is "just a speck," Potts said. While there are now 100-microgram tablets available, and some institutions (such as Kaiser Permanente) cut and repackage them for specific OB-GYN uses, many health practitioners -- especially in the developing world -- still must resort to cutting the higher-dose pills by hand.

"It's easy to overdose women," Potts said. "This drug is so powerful if you give it while the baby is still in the uterus, it can rupture the uterus." There have been cases of uterine rupture in connection with the use of Cytotec in the United States, and several infants have died in utero as a result, according to the FDA. In addition, there have been five deaths since 2003 in the United States linked to the FDA- approved medical abortion regimen, known as Mifeprex or RU-486 (mifepristone ends the pregnancy, and misoprostol causes the uterus to expel its contents). Four of the five women tested positive for a fatal bacterial infection, although neither drug in the regimen was contaminated, according to the FDA. The fifth death is still under investigation.

Overall, misoprostol's safety issues have been few, given the drug's widespread use. Its controversial status worldwide stems far more from its connection to abortion.

Just before the medical abortion regimen was approved in 2000, misoprostol's manufacturer -- at that time G.D. Searle & Co. -- fired off a letter to thousands of obstetricians and gynecologists warning them against its unapproved use in pregnant women. Searle has since merged with Pfizer Inc., which has also taken pains to steer clear of the drug's use in obstetrics. Pfizer, along with several other pharmaceutical companies, declined to manufacture the medical abortion regimen, according to a history of the abortion pill posted on the Legal Education Document Archive managed by the law schools at Cornell and Harvard universities. When the Danco Group was licensed to market the drug, the company shielded the name of the manufacturer willing to do the job.

But politics hasn't stopped Pfizer from selling Cytotec. A Pfizer spokesman said the company doesn't "report out sales, it's so small," and indicated that it was "somewhere south of about $180 million" annually. (The company's cholesterol drug Lipitor, by comparison, racked up sales of $12 billion last year.) Pfizer had no statistics available on how much of the drug is sold for off-label use. But more than one doctor made the

observation that while there are newer, perhaps better drugs to prevent gastric ulcers, misoprostol is still the top choice for several obstetric indications, and is the only FDA-approved choice to complete the medical abortion regimen.

Some in women's health circles think misoprostol should be promoted for abortion. While it is less effective than the dual medical abortion regimen, misoprostol alone has a pregnancy termination rate of 85-90 percent when used during the first nine weeks. New York-based Gynuity Health Projects and Reproductive Health Technologies Project of Washington, D.C., have posted instructions on-line for using the drug in obstetrics, including terminating a pregnancy.

"We're trying to develop (misoprostol's) possibilities for all aspects of women's health," said Dr. Beverly Winikoff, Gynuity's president. "Some people are trying to keep a firm line between abortion and other women's health issues. It's doesn't make sense."

Of the estimated 46 million induced abortions that take place annually worldwide, about 20 million are performed under illegal and unsafe conditions, with an estimated 68,000 women dying from complications. According to one study, access to misoprostol doesn't increase the number of abortions. It makes them safer. The study -- co-sponsored by Venture Strategies -- showed that in the Dominican Republic, since the introduction of misoprostol in 1986, the rate of abortion-related complications decreased from 12 to 2 percent.

Potts and Campbell agree that abortion is a critical women's health issue that needs to be addressed, but adding it to the misoprostol debate makes for a much tougher battle. Statistics aside, few government policymakers are going to step up and embrace a drug for abortion, Potts said.

"Giving people contraceptive advice or talking about abortion, there will be controversy," Potts said. "Stopping women dying in childbirth, that's a powerful thing. People can empathize with that."

Indeed, saving mother's lives is one of the foremost goals in health care worldwide. In its Millennium Declaration, the United Nations and its 189 members targeted a reduction in maternal mortality of 75 percent between 1990 and 2015. Sub-Saharan Africa, where the chance of dying in childbirth is as high as 1 in 16 over a woman's lifetime (compared with 1 in 3,800 in the developed world), has made no headway in increasing women's access to the skilled emergency obstetric care the United Nations says is necessary.

"That means a hospital, a gynecologist, a trained midwife," said Anke Hemmerling, a German obstetrician and Berkeley School of Public Health fellow working with Venture Strategies. "That's not going to happen in the next 10 years."

Campbell agreed: "There's no getting around the fact that without (miosoprostol) you cannot significantly reduce maternal deaths in the settings where most births occur."

It's all about gaining access

Venture Strategies was just getting off the ground six years ago when Potts and Campbell met three obstetricians from Kenya, Tanzania and Nigeria at a party in Washington, D.C. "They asked us, 'Please can you help us get this drug misoprostol in our countries?' " Campbell recalled. Campbell and Potts pulled together a multinational team of doctors and researchers for a collaborative effort that turned out to require patience and diplomacy. It meant meeting with ministers of health and government leaders who were skittish about potential political fallout. It meant sensitivity to cultural and religious strictures. It meant learning to design small studies to test the drug's efficacy and safety in the settings particular to each country. It meant finding drug manufacturers and distributors, and initiating the often costly and byzantine drug registration process.

It was slow going. Then, in 2004, a Venture Strategies' supported study in Tanzania demonstrated that illiterate traditional birth attendants can effectively administer misoprostol for postpartum hemorrhage. Meetings quickly followed in Kenya, Nigeria and Uganda. The group has facilitated additional studies in Bangladesh, Egypt and Nigeria, and is involved in forthcoming projects in Ethiopia, Afghanistan and Yemen. In January 2006, Nigeria approved the drug for treating and preventing postpartum hemorrhage -- becoming the first country in the world to do so. Ethiopia became the second in May. "The logjam," said Potts, "is beginning to break."

Venture Strategies has also helped smaller nonprofit groups working to increase access to misoprostol. In eastern Burma, where Nana's 14-year-old patient died, the maternal mortality rate is one of the highest in the world, with 1,000-1,200 deaths per 100,000 deliveries (compared with about 12 per 100,000 in the United States), according to data compiled by the Global Health Access Program, a Los Angeles nonprofit group. One-third of the women there who die succumb to postpartum hemorrhage.

"The fact that misoprostol isn't out there is just unbelievable," said Dr. Tom Lee, one of the program's co-founders and an emergency room physician from Southern California who volunteers his time on the Thai-Burma border twice a year.

For groups like the access program, doing international public health projects on a large scale via an official government route can be cumbersome, or in the case of Burma, virtually impossible. (The repressive military-controlled government has become increasingly isolated and uncooperative, even when it comes to humanitarian aid: The Global Fund to Fight AIDS, Tuberculosis and Malaria recently terminated nearly $100 million in aid to Burma because of government restrictions on travel, procurement of supplies and unencumbered access to affected populations.) Instead, with the help of Venture Strategies, the group procured misoprostol from a manufacturer in Egypt for 13.5 cents a pill -- four times less than it would have cost in the United States -- and designed a program to train 43 experienced health workers who could quickly implement use of the drug in Burma. Earlier this year, the health workers learned to use misoprostol in a clinic setting on the Thai-Burma border, and have now returned to their villages. In

the coming months, the health workers will teach other practitioners -- including traditional birth attendants -- about using the drug to treat postpartum hemorrhage.

Three of those health workers are in Nana's village, which means that next time there is a patient bleeding after childbirth, she has a much better chance of survival.

"The fact that there is a technology that can be used by illiterate traditional birth attendants that makes a huge difference over a very, very large scale is enormously exciting. To us it's one of the most exciting developments in public health," Campbell said.

"What we're really doing is making mothers stronger."

Janet Wells' last piece for The Magazine was on Lida Tan, the Environmental Protection Agency's China coordinator.

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