The case for testing drugs on pregnant women

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When the heart stops beating, minutes matter. With every minute that passes before a rhythm is restored, a patient's odds of survival plummet. Which is why Anne Lyerly was surprised when, one night 20 years ago, she got a phone call from a doctor who had paused in the middle of treating a patient in cardiac arrest. Lyerly was a newly minted obstetrician; the caller was an internal medicine resident who was desperately trying to resuscitate a dying patient. A pregnant dying patient. He had called because his supervisor wanted to know whether a critical cardiac drug would be safe for the woman's fetus.

Lyerly was stunned. Most medications are never tested in pregnant women and, although she knew that there was a chance the compound might harm the fetus, her response was unequivocal. "You need to tell him he needs to save her life," she told the resident. "It doesn't matter what drug he's using. She's dying."

In the years since, Lyerly, now an ob-gyn and bioethicist at the University of North Carolina, has found herself fielding such questions again and again, from colleagues, patients and friends eager to know whether it is safe for a pregnant woman to stay on her antidepressants, take her migraine medication or use her asthma inhaler.

Sometimes the answer is obvious: a dying woman should get a drug that would save her life, regardless of the risk it might pose to the fetus. But often Lyerly didn't have such definitive answers. Because it has long been considered unethical to include expectant mothers in clinical trials,

scientists simply don't know whether many common medicines are safe for pregnant women. Of the more than 600 prescription drugs that the US Food and Drug Administration approved between 1980 and 2010, 91 per cent have been so meagrely researched that their safety during pregnancy remains uncertain.

Over the last few years, however, a small, tight-knit group of ethicists, including Lyerly, have become determined to reverse this longstanding scientific neglect of pregnant women. Science and society, they argue, have got it utterly wrong: our efforts to protect women and their fetuses have actually put them both in jeopardy. "Ethics doesn't preclude including pregnant women in research," says Lyerly. "Actually, ethics requires it."

On 16 December 1961, the *Lancet* published a short letter from an Australian obstetrician named William McBride. In the previous months, McBride wrote, he'd noticed a troubling pattern of birth defects: newborns with severely malformed arms and legs. Their mothers, he reported, had been taking a new drug called Distaval. Its active ingredient? Thalidomide.

Over the next few months, other doctors published similar observations. It soon became clear that thalidomide, a sedative that had been marketed as a safe treatment for morning sickness, was a major public health disaster, the cause of serious birth defects in as many as 12,000 children. A second crisis followed a decade later, when scientists realised that diethylstilbestrol, a drug widely prescribed to prevent miscarriages, increased the risk of cancer in girls who had been exposed to the drug while in the womb.

These tragedies left a lasting legacy. Expectant mothers became understandably nervous about taking medication. Scientists, drug companies and lawmakers grew reluctant to allow pregnant women – and

even women who were merely of childbearing age – to participate in drug trials. Subsequent regulations designated pregnant women a 'vulnerable population' that could participate in clinical research only under limited circumstances.

On the face of it, this caution seems sensible. Many medicines cross the placenta, and a high dose of the wrong drug at the wrong time can disrupt fetal development, leading to miscarriages, stillbirths or birth defects. But many mums-to-be have a legitimate need for medication. "Pregnant women get sick, and sick women get pregnant," says Brian Cleary, Chief Pharmacist at the Rotunda Hospital in Dublin, Ireland.

This year, some 130 million women will give birth around the world. Expectant mothers grapple with all kinds of health conditions, from depression to diabetes, migraines to malaria, epilepsy, Crohn's disease and more. Many are offered medications for their maladies: precise figures are hard to pin down, but according to several reviews of prescription databases, the share of pregnant women who receive at least one prescription during pregnancy is 56 per cent in Denmark and Canada, 57 per cent in Norway, 64 per cent in the USA, 85 per cent in Germany and 93 per cent in France.

But with so little data available about drug safety during pregnancy, many of these women will face a stark choice: use medications that have unknown effects on their developing children, or forgo treatments that are crucial to their own health.

In the autumn of 2013, Heidi Walker, a lab technician who lives in Nottingham, England, was hospitalised for severe depression. Over the course of her two-month stay, she slowly found her feet again, thanks, in part, to a drug regimen that included an antidepressant, an antipsychotic, an antianxiety medication and a sleeping pill. But just a few months after her release, Heidi unexpectedly found herself pregnant with her first

child: a girl. "She was a surprise baby," Heidi recalls. "Whether the medications I was on at the time were safe during pregnancy wasn't something I'd considered at all."

Heidi soon learned that none of the four drugs she was taking had been well-studied in humans, though animal studies had raised some concerns. Like many women with chronic illnesses, she found herself facing an agonising decision. On the one hand, Heidi feared what the pharmacopoeia might do to her developing daughter. "It was a lot of medication to be taking, and it's a risky thing to be doing," she says. "'Cause everyone's heard of thalidomide and things like that, haven't they?" At the same time, however, she worried about what might happen if she went off her meds and the depression returned. "Am I going to be able to take care of her?" she wondered. "Are social services going to get involved if I'm unwell?"

In consultation with her doctor, Heidi decided to give up all four drugs, ultimately replacing them with a low dose of sertraline, an antidepressant that has been relatively well-studied in pregnant women. But as she weaned herself from her old prescriptions, she experienced severe withdrawal. "It was physically quite rough," Heidi recalls. "I had brain zaps and shivers and was feeling very, very unwell." But she believes she made the right decision. "You just don't know," says Heidi, whose daughter was born last January. "Had something been wrong with her, and I'd carried on taking those medications, then you'd have a lot of guilt wouldn't you?"

Many other mothers-to-be come to the same conclusion. In the face of inadequate safety data, both women and doctors tend to err on the side of caution, discontinuing drugs with unknown risks.

After Rachel Tackitt conceived last autumn, her neurologist told her that there was little information available about the safety of a drug she was

taking to control her chronic migraines. "My neurologist said she could not with good conscience recommend it or allow me to take it because we don't know the risks," says Rachel, an engineer who lives in Tucson, Arizona. Rachel ultimately stopped taking the drug, as well as two other migraine medications, only to see her headaches come roaring back. Until she gave birth to her son in July, she suffered from two or three debilitating migraines every week; she spent a lot of time, particularly in her first trimester, lying in a dark room and waiting for the headaches to pass.

In some cases discontinuing a drug can have tragic consequences. The Confidential Enquiry into Maternal Deaths, a periodic report on maternal fatalities in the UK and Ireland, has identified cases in which pregnant women have died after giving up their asthma or epilepsy medications. Poorly controlled maternal illness is dangerous for a fetus, too. Untreated depression, for example, increases the odds of fetal growth restriction, premature birth and low birth weight. So does untreated asthma. "Oftentimes we end up harming fetuses even more by not attending to the health needs of pregnant women," says Maggie Little, a bioethicist at Georgetown University in Washington, DC, who specialises in reproductive and research ethics. "In general, what's good for a fetus is a healthy mom."

The guesswork involved in treating pregnant women has troubled Lyerly since her earliest days as a doctor. When she graduated from medical school in 1995, the field of medicine was just beginning to move toward an 'evidence-based' approach, in which doctors used rigorous clinical research, rather than intuition or anecdote, to determine the best way to care for a patient. But this new emphasis on evidence, Lyerly noticed, didn't seem to apply to the treatment of pregnant women. "It was well-known that we prescribed medications without a lot of good data about their safety or the right kind of dosing," she says.

This shortage of data frustrated Lyerly, who hated not being able to give her patients better guidance about their medications. And when, in the early 2000s, she began serving on institutional review boards – ethics committees that vet proposals for research involving human subjects – her frustration only grew. After spending hours with her pregnant patients, who peppered her with questions about their medications, Lyerly would then review proposals for studies that could potentially provide answers – and find that pregnant women were often excluded, as a reflex, even from research that posed minimal risk. "People were very quick to say, 'Well, it's unethical to include pregnant women in research,'" she recalls. "It struck me that people were hiding behind the veil of ethics."

Lyerly often found herself fighting back, arguing that the real danger to pregnant women was treating them without evidence, but for years, little changed. One day, in late 2007 or early 2008, a sympathetic-seeming scientist with a proposal before a committee she was serving on made a startling confession. As Lyerly recalls: "One of the researchers said, 'You know, I understand where you're coming from… but I gotta tell you, I just don't like including pregnant women in research. It's just my bias.'"

She had finally had enough. She reached out to two colleagues who had both done their own thinking on the issue: Maggie Little, the Georgetown bioethicist, and Ruth Faden, a bioethicist at Johns Hopkins University. The women talked and eventually met in Washington, DC, where they sat on Faden's porch, drinking coffee and lamenting how little scientists still knew about drug safety during pregnancy.

They were not alone in their concerns. "There's still many, many drugs, including many relatively frequently used drugs, that we don't know very much about," says Jan Friedman, a medical geneticist at the University of British Columbia in Canada. "There's not a lot of funding for this kind of research and not a lot of work that's being done." At the same

time, the scientists who are trying to gather this desperately needed data often struggle to get their studies approved.

Lyerly, Little and Faden decided that the cause needed more proactive advocates. So in the spring of 2009, the 'troika', as they call themselves, formally launched the Second Wave Initiative: a broad, multipronged campaign to promote ethically responsible research with pregnant women. Its name is a reference to the 'first wave' of clinical trial reform, in the 1990s, which spurred scientists to enrol more women in their studies. Since founding the Initiative, the troika have lobbied lawmakers, hosted and presented at conferences, and written a flurry of papers and editorials.

The Initiative flips the familiar script. For decades, ethics has been used to justify barring pregnant women from research. But now, Lyerly, Little and Faden are making the opposite argument: that conducting research with pregnant women is an ethical obligation. Side-lining this entire population, they say, is fundamentally unjust, depriving pregnant women of equal access to medical advances. "We support biomedical research with all of our tax dollars, with the understanding that all of us will benefit," Faden explains. "And not that only people who are not pregnant will benefit."

In addition to being unjust, the knowledge gap is also downright dangerous, they argue. Although many untested drugs are likely to be safe if used during pregnancy, the failure to study medications specifically in pregnant women means that some are on the market for years before scientists discover that they pose a risk. In 2006, for example, a paper in the *New England Journal of Medicine* reported that women who took angiotensin-converting enzyme (ACE) inhibitors – an exceedingly common class of drugs for high blood pressure – during the first trimester were nearly three times more likely to have babies with major birth defects. By then, ACE inhibitors had been on the market for

more than three decades, and they had traditionally been considered safe for use during the first trimester. If researchers had studied the drugs earlier, countless birth defects likely could have been prevented.

That's the irony of the thalidomide story. Traditionally, it is used to justify excluding pregnant women from research. But thalidomide wasn't actually tested in pregnant women before it went on sale. The drug is so catastrophically disruptive to fetal development that even a small trial would likely have revealed its dangers, sparing thousands of children. "If we did a better job of researching drugs in pregnancy before we approved them, we would have been able to avoid the thalidomide crisis," Little says. "The lessons we learn from the past aren't always the right lessons."

Denying pregnant women access to clinical trials also leaves doctors in the dark about how to treat expectant mothers who do fall ill. As Lyerly, Little and Faden have written, "Pregnancy, it turns out, is an 'off label' condition." In fact, in the months immediately after they founded the Second Wave Initiative, a wily new virus made this danger frighteningly clear. In April 2009, the US Centers for Disease Control and Prevention (CDC) announced that a previously unknown strain of H1N1, or swine flu, had sickened two American children. By June, the virus was in more than 70 countries, and the World Health Organization had declared a full-fledged pandemic. Pregnant women were at particular risk, being more likely to become seriously ill, require hospitalisation and die than those in the general population; during the first two months the virus was in the USA, at least six pregnant women died from it.

CDC recommended oseltamivir – an antiviral medicine commonly known by its brand name, Tamiflu – for pregnant women. Although a few small observational studies had suggested that the drug was unlikely to cause birth defects, the data was limited. What's more, many of the body changes that accompany pregnancy, including increases in blood

volume and changes in liver and kidney function, affect how the body processes drugs, often in unpredictable ways. Unless a compound has been tested in expectant mothers – and at the time, oseltamivir hadn't been – doctors can't be sure what dose to prescribe. "We were worried about the absence of good data about Tamiflu and the possibility that we might be dosing it wrong," Lyerly recalls.

They were right to be worried. Subsequent research, published in 2011, suggested that pregnant women clear the drug from their bodies more quickly than non-pregnant women, which means that expectant mothers who took the drug during the pandemic may have been significantly under-dosed. Indeed, some doctors speculated that one reason pregnant women appeared to be particularly vulnerable to the virus was because they were getting doses of antivirals that were too low. Pregnant women had been spared the risks of research, but they'd become guinea pigs all the same.

Over the past ten years, Shifneez Shakir, a former chemistry teacher who lives in the Maldives, has navigated three difficult – and very different – pregnancies. Shifneez has a severe form of sickle-cell disease, an inherited disorder that causes her red blood cells, which are normally plump and round, to transform into a crescent shape. These deformed blood cells can clog the circulation, starving the body's tissues of oxygen and causing periodic 'crises', or episodes of intense pain. Women with the disease are also at increased risk for having premature or abnormally small children, as well as miscarriages and stillbirths.

The only medication known to actually treat sickle-cell patients' underlying disease is an anticancer drug called hydroxyurea. Scientists have not systematically studied the drug's safety in pregnant women, but high doses can cause birth defects in lab animals, and women are typically advised to stop taking it before having children. And so during her first two pregnancies, in 2005 and 2008, Shifneez dutifully

discontinued the only medication that could keep her blood flowing smoothly and her crushing bone pain at bay. Her health deteriorated rapidly, and 11 weeks into her first pregnancy, she miscarried. "I was devastated," Shifneez recalls. Although her second pregnancy gave her a beautiful, healthy son, she had a major crisis in her second trimester and had to be hospitalised.

In 2013, when Shifneez got pregnant for the third time, she was determined to avoid another crisis. This time, she decided, she would not give up the hydroxyurea. Although she remained healthy throughout her pregnancy, few of her doctors supported her decision. When they discovered she was taking the drug, they flat-out advised her to get an abortion. And at first, Shifneez and her husband were reluctant to tell their friends and family that they were expecting another child, in case a termination became necessary. Shifneez believed that she had made the best decision she could, given the limited data, but she remained worried about the consequences. Even regular ultrasounds failed to allay all her fears. What if the baby had a defect or abnormality that the scans could not detect? "I kept mentally preparing myself for the worst," she says.

On 1 July 2014, her daughter Eiliyah was born. "And the first thing I asked was, 'Is she OK? Is everything OK with her?' I was very nervous. And then I saw her." She was 2.9 kgs, and she was perfect. "It was the most incredible moment," Shifneez says. And yet, with her daughter more than a year old, Shifneez finds that the anxiety lingers. She worries that the medication may have caused abnormalities that are not yet apparent and keeps a close eye on her daughter's development. "It feels like such an achievement when she crosses every milestone," she says.

For the millions of women around the world who may need medication while pregnant, there are no easy choices, or right answers. Each patient, experts say, should think carefully about her own health needs and priorities and carefully weigh the benefits and risks of her specific drug

regimen. Of course, that's difficult to do without data.

After the 2009 swine flu pandemic broke out, the US National Institutes of Health (NIH) launched a clinical trial of the new H1N1 vaccine specifically for pregnant women, who would be randomly assigned to receive one of two different dosages of the vaccine. The researchers filled their study quota quickly, and when Lyerly and Faden interviewed the volunteers, they learned that the women's motivations for participating were astute and varied. Some wanted early access to a potentially lifesaving vaccine, others wanted to help advance scientific knowledge, and others thought that it would be safest to get the vaccine within the context of a clinical trial, in which they'd be carefully monitored. "Women were beating down the doors to get into the flu vaccine study," Lyerly says. "The idea that pregnant women wouldn't participate in a study is not true."

But this willingness hardly matters if scientists don't launch such studies in the first place. Lyerly, Little and Faden hope that their latest endeavour will help remedy this problem by encouraging more scientists to perform research with pregnant women and making it easier for them to do so. Their new, NIH-funded project focuses on HIV. Although preventing women from transmitting HIV to their children has long been a scientific priority, pregnant women are still largely excluded from trials of HIV-related drugs that could benefit their own health. In 2013, the troika set out to help close this research gap, joining with Anna Mastroianni, a legal scholar at the University of Washington, to launch a project they called PHASES (Pregnancy and HIV/AIDS: Seeking Equitable Study).

The four women are working to understand the reasons pregnant women are routinely excluded from these trials and to devise potential solutions. By the time the project wraps up in 2019, they plan to have produced a set of "practical, user-friendly" guidelines for studying pregnant women.

Though their focus will be on HIV, the lessons they learn, and the guidelines they ultimately develop, should be relevant for scientists who want to study other illnesses. "Our goal is nothing less than coming up with an empirically grounded and consensus-based ethical and legal framework for how and when you can do research with pregnant women," Little says.

They will also highlight specific strategies for gathering data on pregnant women in an ethically defensible but scientifically rigorous manner. Although scientists can and should study expectant mothers who have already made the choice to take certain medications, tracking their pregnancy outcomes and drawing their blood to study how the drugs are being metabolised, these opportunistic studies have limitations. (Among them that it can take decades to find and enrol enough women to draw significant conclusions.)

Conducting a traditional clinical trial – the gold standard in medicine – is trickier, but not impossible, especially if scientists think creatively. The PHASES team has highlighted a series of trials of tenofovir gel, which can protect women from HIV when applied inside the vagina, as one particularly innovative model.

To learn about the drug's safety and dosing during pregnancy, a team of scientists based at the University of Pittsburgh gave a single dose of the gel to 16 pregnant women who had been previously scheduled to have Caesarean sections. The women received the drug just two hours before their deliveries, when the medication was unlikely to seriously harm a fetus. Once the researchers determined that pregnant women appeared to absorb the drug normally, and that very little of the compound reached the fetus, they pushed the exposure slightly earlier, giving the gel to women who were 37 to 39 weeks pregnant, and then to women who were 34 to 36 weeks along. Such studies will never be completely risk-free – nothing in clinical research or medicine is – but by being slow, deliberate

and patient, researchers can minimise the chance of harm.

New laws could also help nudge drug companies in the right direction. The USA has spurred paediatric research by offering pharmaceutical companies extensions of their drug patents if they conduct studies with children; a similar strategy might also stimulate research with pregnant women. (As it currently stands, pharmaceutical companies have powerful disincentives to conduct such studies. If a medication that's currently on the market turns out to cause birth defects, its manufacturer can argue that the compound was never approved for use in pregnant women. But if a company does conduct a small trial, labels a medication safe for use during pregnancy, and then the drug is later discovered to be dangerous? In that scenario, the pharmaceutical company has opened itself up to a barrage of lawsuits.)

There are small signs of progress. This autumn, the Council for International Organizations of Medical Sciences released a set of proposed revisions to its influential International Ethical Guidelines for Biomedical Research Involving Human Subjects. Among other changes, the new draft guidelines now emphasise the need for more research into the health needs of pregnant women and more clearly detail the level of risk that is acceptable in such studies. "The hope is that with more guidance, people will be less reluctant to conduct research," says Annette Rid, a bioethicist at King's College London and a member of the working group that revised the guidelines.

Meanwhile, pregnancy registries are continuing to track women who take certain medications, and several organisations and institutions have launched programmes to accelerate research. A handful of scientists are conducting full-fledged clinical trials with pregnant women, but the scale of the problem is huge, and experts say they need more funding for this work and more colleagues to join them in their efforts. In the meantime, pregnant women can seek advice on the risks and benefits of particular

drugs from free teratology information services, and those who want to help advance scientific knowledge can volunteer for pregnancy registries. But until scientists do more controlled, rigorous studies, millions of women will be forced to muddle through, making medical decisions without the scientific evidence that many other patients take for granted.

For each of the last several years, a professor at the University of North Carolina's Gillings School of Global Public Health has invited Anne Lyerly to give a guest lecture to her class. And every year, after Lyerly finishes her lecture, the professor announces that during her own pregnancy, several decades ago, she took a drug called Bendectin. The drug, which was used to treat morning sickness, was later pulled from the market after a barrage of lawsuits alleged that it caused birth defects. Reams of data now suggest that the medication is safe, and the Food and Drug Administration reapproved it, under a different name, in 2013. But this professor still couldn't quite shake the gut-wrenching fear that she had somehow hurt her child.

"This is no way to practice medicine," Lyerly says. "Women suffer. And they don't just suffer during pregnancy." Even when their stories have happy endings, the uncertainty can leave women with worries that ripple through their lives, an enduring unease that – simply by trying to alleviate their own nausea or headaches or depression – they might have harmed the people they love most.