The Anvisa rule that prolongs women's suffering

Rule complicates the supply of misoprostol, a safe legal abortion drug, to health facilities across the country

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Protest in Rio de Janeiro for the legalization of abortion. FERNANDO FRAZÃO (AG. BRASIL)

In January 2018, in the city of Macapá, in the north of Brazil, the psychologist Daniele Sampaio suffered a miscarriage at 13 weeks gestation. Advised by her doctor, she went to the *Mãe Luzia* Maternity Hospital to have the birth induced. What was supposed to be a simple procedure ended up lasting seven days of physical and psychological suffering.

During this time, Daniele was subjected to archaic procedures, such as the insertion of a probe into the vaginal canal to stimulate uterine contractions, and did not respond to treatment with oxytocin to dilate the uterus. All this while she waited, sharing the ward even with mothers and their newborn babies.

The reason for the delay in carrying out the standard procedure indicated by the World Health Organization (WHO) in these cases was the lack of misoprostol, a medicine listed as essential for Brazilian maternity hospitals. Daniele only had

access to the medicine after her father appealed in a Facebook post, which made the hospital administration aware of the need to provide the medicine on loan from another institution.

Four hours after using the misoprostol, the psychologist finally had the abortion. "It was a relief, but at the same time an indignation. The medicine went so quickly that I didn't even need another dose. All my suffering could have been alleviated if the maternity hospital had had the medicine on the day I was admitted," Daniele laments.

Misoprostol, popularly known in Brazil under the brand name Cytotec and currently sold under the name Prostokos by the company Hebron, is an essential medicine for women's health. It can be used in the induction of labor with a live or dead fetus, in the prevention and treatment of postpartum hemorrhage, in the treatment of incomplete abortion, whether induced or spontaneous, and in the termination of pregnancy. In Brazil, it is registered for hospital use in all these cases, except for postpartum hemorrhage.

Despite its widespread use worldwide and being the most studied and researched drug in the field of sexual and reproductive health in the world, according to a WHO report, in Brazil the drug is still surrounded by stigmas. "Misoprostol has to stop being seen only as an abortifacient, it has to be seen as a drug that saves women's lives," says Maria Esther Vilela, a doctor and general coordinator of Women's Health at the Ministry of Health from 2011 to 2017.

Necessary, but not available

Misoprostol is on the WHO list of essential medicines and the Brazilian National List of Essential Medicines (RENAME). The availability of the drug is part of the requirements of the Brazilian National Health Surveillance Agency (Anvisa) for the operation of obstetric and neonatal care services in Brazil. Even so, less than 25% of the more than 4,000 establishments with obstetric beds available to SUS (Brazilian unified public health system) received the drug in the last purchase disclosed in detail by the Ministry of Health, in 2016. In the 2018 purchase, the Ministry did not detail the number of hospitals in which misoprostol was distributed.

Although centralized purchasing does not oblige hospitals to obtain the drug directly from suppliers, only 1,180 health establishments purchased misoprostol directly from Hebron in 2018. The reasons for the shortage are diverse and come up against Anvisa's own restrictive regulations, the bureaucracy involved in acquiring the drug and the stigma of abortion.

"Brazil, unfortunately, I believe is the only country in the world that has such tight control over misoprostol. In pharmacies you can buy drugs that are highly dangerous to your health that are sold with a doctor's prescription and that, if taken incorrectly,

lead to death, but misoprostol is not sold," criticizes gynecologist and obstetrician Olimpio Barbosa de Moraes Filho, former president of the Abortion, Childbirth and Puerperium Commission of the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO).

Jefferson Drezett, a doctor and coordinator for 23 years of the country's main legal abortion service, the Pérola Byington Hospital in São Paulo, points out that "no other medication used nationally, such as chemotherapy, anesthetics or drugs that lead to chemical dependency or that can lead to death, has such rigorous and exhaustive control by Anvisa as misoprostol".

Anvisa's high level of control is due to Ordinance 344 of 1998, which placed misoprostol on the C1 list of controlled substances. In order to receive the drug purchased by the Ministry of Health, each public hospital must register with their state's health surveillance department. Private institutions also have to register, but purchases are made directly from one of Hebron's 12 distributors, under the supervision of Anvisa and the Federal Police.

State surveillance agencies have the autonomy to impose their own, more restrictive requirements on the purchase of the drug, with criteria and values set by different local managers. According to Maria Esther, it is the bureaucracy that restricts access to the drug. Data from the Hebron company shows that in 2010 a monthly average of 650 boxes of the drug were bought for the whole of Brazil.

Realizing the shortage of misoprostol, the Ministry of Health promoted the centralized purchase of the drug in 2011, after nine years of discussing this strategy. "The lack of access to the drug was causing women to die and suffer. The Ministry, in an effort to show the importance of misoprostol, made this supplementary purchase, which did not exempt the municipalities from also buying the drug so that there would be no shortage," explains Maria Esther.

The shortage of Prostokos in hospitals could have the immediate consequences of increasing the number of cesarean sections and the use of invasive procedures to treat abortion. "The lack of Prostokos in hospitals means more cesarean sections, because without the drug for inducing labor, around 70% of normal births will turn into cesarean sections," says Olímpio.

The solution is not for sale

Another current problem related to misoprostol is the delay in approving two new presentations of the drug, oral and sublingual, specifically for the treatment of postpartum hemorrhage, which has been pending at Anvisa since 2013. According to Olímpio, the drug would be essential especially for people in regions far from major health centers, such as the indigenous population. "This would certainly save

lives - postpartum hemorrhage is currently the second leading cause of maternal mortality in Brazil," Olímpio said.

The drug has been indicated by the World Health Organization for the prevention and treatment of this occurrence since 2011, with positive results in several countries in Africa, the Middle East and Asia, such as Bangladesh, Afghanistan, Mozambique and Nigeria. In Brazil, discussions for the new presentations began in 2013, at meetings between Hebron representatives and Anvisa and the Ministry of Health. "Anvisa is resistant to approving the registration of a product that hasn't had clinical trials in Brazil. It's a rework. There are countless clinical studies of misoprostol in other countries for postpartum hemorrhage. The US accepts the drug for this purpose, Europe does, but Anvisa doesn't," says Avaniel Marinho, director of Research, Development and Innovation at Hebron.

According to Anvisa, Ordinance 344/98 "is under review, in accordance with theme 1.12 of Anvisa's Regulatory Agenda, for the purpose of improving sanitary measures related to products subject to special control. According to good regulatory practices, social participation will be possible through the tools established by Anvisa, such as hearings and public consultations". The aforementioned item on the regulatory agenda deals with the national control and supervision of substances under special control and the plants that can produce them.

The only mention of bleeding in the Agency's responses to the report is that misoprostol, when used indiscriminately to terminate a pregnancy, not only causes abortion by directly stimulating the myometrium and inducing uterine contraction, but also causes bleeding and can lead to maternal death or serious complications."

The administration of misoprostol for postpartum hemorrhage, as a substitute for oxytocin, is indicated for home births and in places far from health centers, according to the WHO. The drug is more stable, easier to store and administer, and has a favorable cost-benefit ratio.

Brazilian women discovered the abortifacient use of Cytotec

The restrictive access to and control of the drug shows Brazil's different history of misoprostol use compared to other countries. Several studies show that women in the northeast of Brazil, together with pharmacists, discovered the abortifacient use of the drug.

Despite being marketed in 72 countries in the early 1990s, it was only in Brazil that the use of Cytotec as an abortion method gained visibility, given the magnitude and controversy of its use, points out the publication "A experiência brasileira com o Cytotec" (The Brazilian experience with Cytotec).

Today, misoprostol, combined with mifepristone, is one of the main methods used in countries where termination of pregnancy is legal. "I always say that if there were justice, Brazil would have won a Nobel Prize by now. Not our scientists, but the poor women of Brazil who revolutionized obstetrics. After them, everyone started researching and using misoprostol," says Olimpio.

In 1986, Cytotec began to be sold in the country's popular pharmacies for the treatment of gastric ulcers, by the company Searle. The drug soon became known for its side-effect of causing uterine contractions and started to be recommended in pharmacies for pregnant women who wanted to terminate their pregnancy.

In the 1990s, between 50.4% and 84.6% of women, mainly in the northeast and southeast, had abortions using misoprostol. A significant increase when compared to the figures from the previous decade, which ranged from 10% to 15%. The data is presented in the 2009 study "20 years of abortion research in Brazil", which retrieved more than 2,000 national publications on abortion.

"The advent of misoprostol, even from a clandestine point of view, changed the profile of abortion and first aid in obstetric and gynecological emergency rooms," says Rodolfo Pacagnella, President of Febrasgo's National Specialty Commission on Maternal Mortality. Needles and piercing objects, teas and herbs, poisons, caustic liquids and injections gave way to medical abortion, which represented fewer risks, lower costs and greater privacy. Several studies point to a reduction in maternal mortality from abortion in the 1990s, thanks to the entry of the drug into Brazil. According to a report by the Ministry of Health during a Public Hearing on abortion at the Supreme Court in 2018, there was a reduction in the number of hospitalizations and complications from abortion between 1992 and 2009 of around 41% and 69% for serious cases.

The misoprostol case

The increase in the use of Cytotec in the 1980s drew the attention not only of doctors and Brazilian women, but also of institutions linked to pharmacological surveillance, which advocated the withdrawal of the drug medicine on the market. During this period, the work of researcher Helena Lutéscia, from the Federal University of Ceará, stands out. The then professor became aware of the use of misoprostol as an abortifacient through reports from students taking her pharmacoepidemiology course. Believing they were facing a "drug epidemic", Helena and her students founded the Group for the Prevention of the Misuse of Medicines (GPUIM), whose first and main agenda was the rational use and greater control over misoprostol.

The increase in curettages, the hypothesis of abnormal development of the fetus subjected to the drug (teratogenesis), the vulgarization of its use and the lack of parameters for using Cytotec were the arguments defended by the GPUIM against the drug. "It wasn't really a question of joining the fight for restrictions, but of putting

society on notice of what was happening. There was a real epidemic of the use of a drug that had been marketed to treat ulcer problems and which was used as an abortifacient without any guidance, without any clarification and without anyone taking responsibility for it," Helena recalls.

Dedicated to showing the negative effects of misoprostol, the GPUIM's research gained international prominence with a report in The New York Times and the publication of the article "Misoprostol and congenital malformations" in the renowned scientific journal The Lancet.

Among the authors of this study is Walter Fonseca, the first Brazilian researcher to link misoprostol to a very rare fetal malformation, Moebius Syndrome. Babies born with the syndrome lack some facial and eye movements. For Anibal Faúndes, of the International Federation of Gynecology and Obstetrics (FIGO), these studies on teratogenesis were the main reason for withdrawing the drug from circulation.

The ban on the drug also involved another important sector. In 1990, the Brazilian Society for Drug Surveillance (Sobravime) was created and its first major issue was the withdrawal of misoprostol from the market. Together with the GPUIM, they were the main pillars of a historic movement of organizations linked to pharmacological surveillance for the withdrawal of misoprostol from pharmacies.

Among the founders of Sobravime were professor Helena Lutéscia and Elisaldo Carlini, coordinator of the National Health Surveillance Secretariat (SVS), the future Anvisa, between 1995 and 1997, when the ban on the drug was discussed. "As the dissemination of this information generated by GPUIM had a very big repercussion, the SVS had to take immediate action, because it was a scandal," says Helena. "I don't know if there needed to be a pro-life movement at that time forcing the withdrawal of misoprostol. Sobravime was enough for that," says Tânia Lago, a doctor who worked in the Women's Health technical area of the Ministry of Health at the time.

As a result, sales of misoprostol were suspended by court decision on July 9, 1991 in Ceará. Just a week later, the SVS ordered that medical prescriptions be presented in order to buy the drug throughout the country. Sales of misoprostol fell by 80% in 1992. The total ban on the sale of misoprostol in pharmacies came seven years later.

Tânia recalls that she found out about the ban from the doctor Anibal Faúndes, because nothing had been informed or consulted by Anvisa in the area of Women's Health. "Then I went to talk to Gonzalo Vecina [the first president of Anvisa], and he said that it was an ordinance that already existed, from the SVS, and that it had been produced by a committee of experts from each area. In the case of medicines for use in gynecology and obstetrics, there was a committee made up only of men, gynecologists and pharmacists. We didn't know if this committee had been set up or

not. And I remember talking to Faúndes about it, and he commented that the committee was totally against abortion," Tânia recalls. Studies from the time show that with Cytotec out of circulation there was an increase of almost 50% in infectious and hemorrhagic complications of abortion between the period of maximum commercialization and its prohibition.

Difficult access to medication causes extra costs for SUS

The history that led to the control of misoprostol, starting with Ordinance No. 344/1998, has consequences for the health of Brazilian women to this day, as well as having a direct impact on SUS spending. Its restricted use in hospitals, with the obligation to be hospitalized to ingest the drug, whether in the induction of labor with a living or dead fetus, in the voluntary interruption of pregnancy or in spontaneous abortion, generates unnecessary costs for the health system. For Maria Esther Vilela, legal abortion procedures of up to ten weeks and incomplete abortions could be carried out at home, but Anvisa's regulations make this unfeasible.

In some countries where termination of pregnancy is provided for by law, women are not hospitalized for the procedure, explains Anibal Faúndes. "This is the great advantage of treating legal abortion and incomplete abortion with misoprostol, because it's good for the woman who doesn't have to be separated from her family, it's good for the service because it avoids expenses and reduces the cost of care enormously, representing savings for the health system," says the doctor.

Joana* from Recife is part of the 2019 statistics of women who have accessed the legal abortion service. A month after being the victim of sexual abuse, the 19-year-old student noticed that her period was late. She sought support from Cisam's Comprehensive Care Service for Women and Adolescents in Situations of Violence, Pró-Marias, in order to have her pregnancy terminated under the law.

In the common ward, Joana received the first dose of misoprostol at 4pm on a Tuesday and was instructed to self-apply the drug every four hours. "I shared the ward with two other people and their companions, who didn't know I was going through the process of terminating my pregnancy. I always had to ask people to leave the room so I could apply the medicine, it was very uncomfortable."

After administering two doses, at midnight the student was told that the medicine had run out. "I went to ask the nurses about the medicine and the nurses, who were lying down, didn't even get up to say that there was no more medicine for me. My treatment didn't come back until 9am the next morning. That's when I found out that they were the ones who had refused to give me the medicine."

Due to the hours of delay in taking the misoprostol, Joana's treatment took longer, lasting a total of three days, at a cost of around R$1,200 per day of hospitalization for the institution. There were nine doses of the drug and an aspiration procedure.

The student believes that if the use of misoprostol could have been carried out at home or in another environment of her choice, it would have been better. "In any case, after receiving the medicine and the first instructions, I did the whole procedure alone".

SUS spending on spontaneous abortion, when women access the health service during or after the abortion procedure, is also significant. The Ministry of Health estimates that 25% of hospitalizations for abortion are due to miscarriages. In 2017, there were more than 200,000 hospitalizations due to abortion, whether normal or induced, according to the Ministry of Health.

In cases of induced abortion, the SUS figures are even more alarming. The Ministry of Health estimates that there were between 938,000 and 1.2 million abortions in 2017, with a total of 210,000 hospitalizations resulting from the procedure.

The treatment of complications from the voluntary termination of pregnancy includes hospital beds, medicines, blood bags, and even surgical centers, anesthesia and specialist care. According to estimates by the Ministry of Health in 2018, the cost of hospitalizations due to termination of pregnancy in the SUS in 2017 was 50 million reais.

But the main way to avoid spending money on the health system and save the lives of women who have clandestine abortions is to use misoprostol as a safe abortion option. "I think Brazil is a unique country in terms of misoprostol control and it's an international emergency because, of all the countries in the world, it has the least access to safe abortion drugs and the largest population. It's the only large country in the world that has this problem of millions of women suffering because of these state policies," says Beverly Winikoff, president of the sexual and reproductive health NGO Gynuity.

Countries such as China, India, Russia and the United States (depending on the legislation in each state) have legal abortion with misoprostol, either in the medical process or by aspiration. Other countries like Nigeria, which do not have the practice completely legalized and which have a large population, do not have as much control over the drug as Brazil.

There are countless countries that perform medical abortions safely, use misoprostol to prevent and treat postpartum hemorrhage and have easy access to it for inducing labor. In contrast, Brazilian women, the daughters and granddaughters of those who discovered the abortive use of one of the most important obstetric drugs in the world, continue to terminate their pregnancies in a clandestine and unsafe manner, and face barriers to accessing the drug in hospitals even in cases where its use is proven to be effective and can save their lives.

Medical abortion is common in countries where the practice is completely legalized

Abortion was legalized in 2012 in Uruguay after a years-long harm reduction strategy. To reach the status of legal and accessible in the public system, the country implemented a practice in which health professionals could advise women who were determined to have the procedure, indicating the safest and most effective methods, and the correct way to take the medication.

"This was a strategy that emerged in 2002, at a time of great economic crisis, when some professionals working in the country's main maternity hospital noticed that women were dying from abortions in an unusual way, with unsafe practices, such as the use of poison," recalls Lilián Abrascinkas, director of women and health (MYSU) in Uruguay. As a result, a health standard was created to reduce the damage and risks of pre- and post-abortion, which came into force in 2004, with the aim of preventing deaths due to misinformation or the unsafe use of abortion practices.

For Lilian, the most valuable thing about this strategy was that it highlighted the problem of clandestine abortion, because the harm reduction model was useful in reducing maternal mortality, but it still depended on women using misoprostol, which they could only access clandestinely and without health guarantees. The rule had its limits, but it was a first step towards the legalization of abortion there. Today, medical abortion is the most widely used form of abortion in Uruguay.

The procedure that brings greater autonomy and safety to women is also the most widely used in Portugal. Lisa Vicente, the doctor responsible for implementing the pregnancy termination service in the country, says that currently 71% of terminations in the country are carried out using a combination of mifepristone and misoprostol. In the national public health service alone, the rate is 97%.

"Before misoprostol, women in Portugal and in many countries around the world used other ways to terminate pregnancies. There were some horrendous methods, such as the use of drugs that would corrode the woman's vagina. Then women started using misoprostol, often without proper information, and that's why we still had some complications when terminating pregnancies. Since 2007, they have decreased dramatically, also because there have been fewer curettages and botched aspirations. The fact that there is legal and free abortion in hospitals, as well as contraceptive options, has meant that we no longer see complications from illegal abortion," says Lisa. Since the strategy was implemented, Portugal has had only one recorded abortion death.

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