Reproductive health

outlook



Gynaecologists are working to give more people the chance of becoming parents.

How much is a baby worth?

Access to fertility treatments is limited by the cost in both high- and low-income countries. But new technologies and attitudes aim to fix that. **By Sarah DeWeerdt**

s someone who has struggled with infertility himself, Tinovimba Mhlanga knows first-hand the value of the fertility treatment known as *in vitro* fertilization (IVF). And as an obstetrician and gynaecologist at I.V.F. Zimbabwe in Harare, currently one of only two clinics in the country that perform IVF, he is well placed to help others facing similar problems.

Mhlanga trained in IVF techniques in South Africa when he and his wife were there to undergo the process. It is common to travel abroad to access IVF in sub-Saharan Africa because very few clinics offer the procedure.

In IVF, doctors use drugs to stimulate the ovaries to produce eggs, which are retrieved

using an ultrasound-guided needle before being mixed with sperm in a laboratory dish. Fertilized eggs are grown in the laboratory for several days, and then one or more embryos are introduced into the uterus where, if luck will have it, they attach to the uterine lining and eventually grow into a baby.

Since the first IVF baby was born in 1978, the process has led to the birth of 5 million more 'test-tube' babies. Unfortunately, the IVF procedures that Mhlanga and his wife underwent in South Africa did not result in one of those babies, but at least they were able to try. For many couples in Zimbabwe and other low- and middle-income countries (LMICs), however, the high cost means that IVF is out of reach altogether (see 'Uneven access'). In many of these countries, infertility receives little attention from governments and international aid organizations, which tend to focus instead on contraception.

Even in wealthy countries, the provision of fertility care can be patchy. Some countries make IVF widely available, whereas others limit access or leave couples to pay for the expensive procedures themselves. And the proliferation of 'add-on' treatments, many of dubious efficacy, further drives up the cost and increases the inequity of access to IVF.

But solutions are starting to emerge. Partnerships between fertility specialists in highand low-income countries, which helped Mhlanga set up his clinic in Zimbabwe, are bringing fertility treatments to new areas. Researchers are developing gentler versions of the treatment that also happen to be cheaper, and are introducing simpler approaches to IVF that minimize the need for expensive laboratory equipment.

Invisible burden

Even though LMICs tend to have high birth rates, infertility is at least as common there as in wealthier countries. The World Health Organization estimates that one in four couples in LMICs have fertility problems, and it has been estimated that 186 million couples in LMICs (excluding China) have spent at least 5 years trying to conceive without success.

Some medical conditions are common to fertility problems in countries across the wealth spectrum: polycystic ovary syndrome results in irregular ovulation; benign tumours in the uterus known as fibroids can interfere with fertilization or implantation; and low sperm count or motility make it harder to conceive. In many LMICs, blocked fallopian tubes are also common as the result of sexually transmitted infections or infections arising from childbirth, illegal abortions or female genital mutilation. Such infections mean that secondary infertility – difficulty getting pregnant or carrying a baby to term after having one child – is particularly common in Africa.

"Infertility is clearly a problem, and for an individual it can be disastrous," says Karin Hammarberg, who studies reproductive health at Monash University in Melbourne, Australia. On top of the grief of being unable to have a child, infertile women are often shunned by their families and excluded from social activities and cultural rituals. They are more likely to be victims of domestic violence or be divorced by their husbands. Infertility is just as likely to result from problems with the male reproductive system as the female one, but it's usually women who are blamed for the failure to produce a child.

Despite all this, there is little focus on fertility care in LMICs. Governments and international aid organizations focus on life-threatening problems such as malnutrition and infectious diseases. The emphasis is likely to be on family planning and reducing the number of children a couple has, rather than helping them have more.

The high cost is part of the problem. "You never can ask Bill Gates to pay US\$5,000 or \$10,000 for a baby in Africa," says Willem Ombelet, a fertility specialist at East-Limburg Hospital in Genk, Belgium.

Ombelet is a founder of the Walking Egg project, a non-profit organization that promotes family planning, maternal health care, and access to low-cost IVF in LMICs. He and others say that infertility care does not conflict with other public-health goals. Better maternal health care and prevention of sexually transmitted infections would reduce infertility caused by blocked fallopian tubes. And couples may be more open to family planning and spacing babies more widely if they know they can get help to have a baby if needed.

In 2001, the World Health Organization called for infertility to be recognized as a global health problem, and for assisted-reproduction technologies to be adapted for LMICs. The European Society of Human Reproduction and Embryology launched a task force on infertility in LMICs in 2006. But so far, such initiatives have led to little concrete action.

Cost of living

In many wealthy countries, infertility treatments such as IVF are partly or fully covered by national health-insurance schemes. In Belgium, the government covers the cost of up to six IVF cycles, and in Germany, public funds partly cover the cost of three cycles.

In the United Kingdom, by contrast, public funding for IVF is severely limited and varies from one area to the next, resulting in what some decry as an unjust 'postcode lottery'. In the United States, 15 states have laws requiring insurance companies to provide at least some infertility treatment. But most people who undergo IVF in the United States pay most, if not all, of the cost themselves.

"A lot of infertile couples pay much, much more than they should."

Where IVF is privately funded, there is often little regulation of what clinics can charge. "Each programme basically sets its fees based on what the market will bear," says Jonathan Van Blerkom, an embryologist at the University of Colorado in Boulder. The cost of an IVF cycle is therefore much higher in the United States than in comparable countries where the cost is subsidized by the government.

Moreover, clinics in the United States and some other countries are increasingly part of corporate chains. These clinics compete for customers by offering a range of procedures that they say will give couples the best possible chance of having a baby – but they also give clinics a chance to charge more. There is little evidence that many of these add-ons improve success, however. "The natural inclination is, well, it costs more, it must be better," Van Blerkom says. "And that is not necessarily true."

For example, a procedure known as intracytoplasmic sperm injection (ICSI), in which a single sperm cell is introduced directly into an egg, was developed to help couples with severe male infertility. But in some US clinics it has become a default procedure. Preimplantation genetic testing, in which a small number of cells are biopsied from a developing embryo to identify chromosomal abnormalities, is also becoming common. It is useful for people who have experienced recurrent miscarriages but it might not be necessary for everyone, says Van Blerkom.

"I think it's preying on the vulnerable," Hammarberg says. "A lot of infertile couples pay much, much more than they should."

There is even some evidence that past preimplantation genetic testing procedures might have decreased IVF success rates, leading to the possibility of paying more for a lower chance of having a healthy baby. And the high costs mean that many people, even in wealthy nations, cannot access IVF at all.

The high cost also creates more pressure to achieve a successful pregnancy with each cycle. This can lead to aggressive treatments that can have serious consequences. At high doses, the drugs used to make eggs grow can result in ovarian hyperstimulation syndrome, which can be life-threatening and might require expensive hospital care. And transferring several embryos at once can lead to multiple births, in which babies have a higher risk of premature birth, low birth weight and life-long disabilities such as cerebral palsy.

Rethinking reproduction

A small but increasing number of gynaecologists and fertility specialists around the world are beginning to focus on bringing down the costs of fertility treatment to make it more accessible.

One solution might be, paradoxically, to rely less on IVF. Up to 40% of couples who seek treatment for infertility end up conceiving naturally. Some researchers have suggested that carefully assessing the severity of a couple's infertility could free up money in healthcare budgets to provide IVF for the couples who are most unlikely to conceive without it.

Some clinics are also starting to compete on cost. Australia now has some no-frills clinics where the price of an IVF cycle closely matches the reimbursement rate from national health insurance. Such clinics will probably provide adequate care for relatively straightforward cases of infertility, Hammarberg says.

In the United Kingdom, a network of clinics called ABC IVF offers care for about half the typical cost. Some of the savings come from

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The ability to help couples conceive varies greatly around the world. Many African countries have no *in vitro* fertilization (IVF) clinics at all, whereas others have just a few to serve their entire populations — as well as travellers from neighbouring countries.



minimizing blood tests and other laboratory investigations, says the clinics' medical director, Geeta Nargund.

Nargund has also pioneered an approach to IVF known as mild or gentle stimulation. This procedure stimulates egg production with drugs at a lower dose and often lower cost, and for a shorter duration than with conventional IVF. "The objective of mild stimulation is quality, not quantity, of eggs and embryos, and keeping the lining of the uterus as healthy as possible for implantation," she says.

Evidence is emerging that this gentle protocol results in lower rates of prematurity and low birth weight than does conventional IVF. "The advantage of mild stimulation is not only the cost saving," she says, "but also better health outcomes for the mother and baby."

To make IVF more accessible in LMICs, some advocates suggest that doctors and clinics in wealthier nations could offer expertise and used equipment to clinics in low-income countries. This is the approach that helped Mhlanga and his colleagues open I.V.F. Zimbabwe. "Going back home after the failed cycles, with the knowledge I had acquired, I was determined to help with the little that I could manage," Mhlanga says.

Mhlanga worked with Hammarberg and other IVF specialists in Australia and Italy, who provided training and helped him to source equipment. His clinic has recently moved into its own building, so couples are no longer charged hospital costs for egg retrieval and embryo transfer.

An IVF cycle at Mhlanga's clinic costs \$3,500 – about the same as the cheapest centre in South Africa, he says. And it saves people the travel and accommodation costs of going abroad for treatment. Even so, he acknowledges that the cost still puts it "out of reach for the majority of the population". For this reason, for every eight paying clients, the clinic treats two patients *pro bono*.

Hammarberg says that compiling a database of people at clinics in wealthy countries who are willing to share expertise, or donate old but still functional equipment, could help more clinics like Mhlanga's to get off the ground.

But getting a clinic started is only the first problem. Many LMICs experience frequent power cuts or surges, which can destroy hightech equipment such as incubators and result in the loss of embryos. Mhlanga was lucky

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because his Australian collaborators helped him obtain an off-grid solar-power system for his clinic. Conventional IVF also depends on medical-grade gases because developing embryos require an environment high in carbon dioxide, but these are expensive and difficult to source in Africa.

Keep it simple

With these concerns in mind, some researchers are considering radical approaches to reducing costs, such as the simplified method of embryo culture developed by scientists associated with the Walking Egg project.

The system was inspired by a set-up that Van Blerkom once used to transport pig embryos from Arizona to Colorado when he was a graduate student. It consists of two test tubes, with stoppers, that are connected by tubing. One tube contains a precise mixture of citric acid and sodium bicarbonate. Adding water causes these chemicals to effervesce and produce an atmosphere with the appropriate carbon dioxide concentration for human embryos. The other tube contains the culture medium, into which the egg and sperm are introduced through a needle.

The system is not yet compatible with ICSI but it requires fewer sperm than does conventional IVF — potentially an advantage when treating couples with mild male infertility. Instead of requiring a high-tech tissue-culture incubator, this method leaves the embryos to develop for a few days in a more basic incubator, a water bath, or even a container of thermal beads or a high-efficiency thermos flask.

"We know what human embryos need to develop. They don't care whether they're in the uterus, or in a fallopian tube, or in a test tube in a thermos at 37 °C and it's dark," Van Blerkom says. The method can reduce the laboratory costs of IVF by up to 90%, and the overall cost of a cycle might be as low as one-fifth of that of conventional IVF.

In a clinical trial of the method in Belgium, Ombelet and his colleagues fertilized half of each woman's eggs with ICSI and incubated the resulting embryos using conventional techniques. The other half were fertilized and incubated using the Walking Egg method. The two approaches resulted in similar pregnancy and birth rates. Ombelet's group now has unpublished data on almost 200 babies born using the simplified culture system.

Van Blerkom has recently developed a powdered, shelf-stable culture medium that will help roll out the method in areas where refrigerated supply chains are unreliable. A few babies have already been born using the Walking Egg method in Accra, Ghana, and the team plans to test the system in clinics in other countries, including China and Paraguay.

Ombelet would like to set up a mobile clinic in South Africa that could travel to a different city every month. "We were almost ready to start with it," says Ombelet, "but then COVID-19 came." He is now trying to develop longdistance training, so personnel from clinics abroad can learn the Walking Egg method without having to travel to Belgium.

Meanwhile, back in Harare, Mhlanga's work continues. His team has so far treated 500 women, and more than 100 babies have been born from IVF and intra-uterine insemination. One of those babies is Mhlanga's own daughter, now two years old, and Mhlanga says it was worth the journey. "Being a parent is the best thing ever to happen to me," he says. "Every time I am working, I am motivated to help other subfertile patients so that they too can experience the beauty of parenthood."

Sarah DeWeerdt is a freelance science writer in Seattle, Washington.