

Freedom of choice

A range of contraceptives currently being developed will offer women an expanded array of options for controlling fertility. **By Elizabeth Svoboda**



Mithra Pharmaceuticals says its new oral contraceptive is 98% effective over one year.

By the time she was 30, Terra had tried a wide range of options to stop her getting pregnant, but she couldn't find one that suited her. "I never really felt like any of the available options were a great fit," says Terra, a clinical psychologist from San Diego, California. "I wanted something that would put me in control, that was hormone-free and effective."

So when she heard about clinical trials for Phexxi – an acid-based vaginal gel that is being developed at Evofem Biosciences in San Diego – she decided to sign up.

For years, millions of people like Terra have been searching for better forms of birth control. There are dozens of products already on the market, but many people develop unacceptable side effects or find them cumbersome to use.

"For a lot of people, they don't like the idea of something sitting in their body, or they like the control of taking something every day," says Nisha Verma, a gynaecologist at Emory

University in Atlanta, Georgia. People want a method that is easy to use, never fails and does not affect their quality of life – a combination that is proving elusive.

A fresh crop of birth-control options, some recently launched and others still in clinical trials, is aimed at addressing common concerns about existing methods. Some, such as the Ovaprene vaginal ring, developed by Daré Bioscience in San Diego, and a combined oral contraceptive pill called Estelle, from biotech company Mithra Pharmaceuticals in Liege, Belgium, provide an alternative to hormonal ingredients that can have disruptive side effects. Estelle has completed phase III clinical trials and is awaiting approval by the US Food and Drug Administration (FDA), whereas trials of Ovaprene are still under way.

Options such as Phexxi, which was launched in September after receiving FDA approval, complement the lifestyles of women who are not in long-term relationships and who need reliable, once-in-a-while contraception.

Clinicians say that these new approaches are welcome innovations in a contraceptive market that has stagnated. "These methods expand the options for people," Verma says. But each product has its own set of pros and cons, which would-be users need to understand before they secure a prescription.

A wider range

The first birth-control pill, Enovid, which the FDA approved for use as a contraceptive in 1960, contained 150 micrograms of an artificial oestrogen called mestranol. This is a huge dose that often led to serious side effects, such as breast pain, nausea and vomiting. Drug companies have since developed pill formulations that combine lower levels of oestrogen – typically about 20 or 30 micrograms – with progestin. Even so, some users still develop uncomfortable side effects, and people who take birth control that uses artificial oestrogen are more likely than non-users to develop dangerous blood clots.

Non-hormonal methods of contraception avoid these oestrogen-related side effects, but they often pose their own set of complications. Condoms are 98% effective when used perfectly, but that falls to 82% with typical use, which means that 82 of every 100 women who use them will remain pregnancy-free over the course of a year. To be effective, women must rely on their partners to use condoms properly, and many women want a product that gives them more control of pregnancy prevention. Diaphragms, when used as the only form of contraception, are considerably less reliable than the contraceptive pill. And copper intra-uterine devices (IUDs) are highly effective but cause heavy bleeding in some women.

Concerns about the risks of hormone-based birth control helped give rise to the Phexxi concept, says gynaecologist Kelly Culwell, Evofem's chief medical officer. Phexxi's active ingredients include three highly acidic compounds: lactic acid, citric acid and potassium bitartrate – a compound known as cream of tartar when used in cooking. Seminal fluid is alkaline, so after sex it temporarily raises the pH of the vagina, making it easier for sperm to thrive. Phexxi's viscous gel layer keeps vaginal

pH within a range of about 3.5 to 4.5, creating an acidic environment that kills sperm.

A similar effect has previously been achieved by gels, foams or films that contain the spermicide nonoxynol-9, which users can insert into the vagina. But in some women, nonoxynol-9 can cause pain and irritation. One of the concerns with traditional spermicide is that “it damages the cell walls of sperm, but can also damage the cell walls of the vagina”, Verma says. This damage can make spermicide users vulnerable to HIV and other sexually transmitted diseases. Verma thinks that Phexxi’s acid-based formulation should be gentler on the vagina. The gel might also be appealing for people who cannot tolerate hormones or who do not want a long-term prescription, Culwell says. “Some women don’t want to take a pill every single day.”

In clinical trials that monitored Phexxi’s performance in more than 30,000 sexual encounters, the gel was 86% effective at preventing pregnancy over the course of seven menstrual cycles (about six months). This puts Phexxi in the same efficacy range as condoms and diaphragms with typical use, although condoms and diaphragms perform better when they are used perfectly. When the Phexxi gel was used exactly as instructed, within an hour before each act of intercourse, its efficacy rose to above 90%.

But Phexxi’s efficacy still trails that of combined oral contraceptives, says Adeeti Gupta, a gynaecologist at Lenox Hill Hospital in New York City. The fact that the gel alters vaginal pH means that it is not ideal for those prone to yeast infections or urinary-tract infections because pH changes can disrupt the vagina’s natural microbial composition, increasing vulnerability to such infections.

Clinical trials of Ovaprene, which is another non-hormonal barrier method, have reported positive early findings. Its vaginal ring features a physical mesh barrier that releases ferrous gluconate, an iron-rich chemical that is known to interfere with sperm motility. It is designed to be replaced once a month and can be left in place through multiple acts of intercourse, so Ovaprene’s developer, Daré Bioscience, plans to market it as a hormone-free, set-and-forget option. Earlier this year, Daré signed a licensing agreement to let Bayer Pharmaceuticals, based in Leverkusen, Germany, commercialize Ovaprene if it receives FDA approval.

Daré reports that in post-coital tests on 38 women, those who used Ovaprene had more than 95% fewer sperm in their cervical mucus than did women not using the device. When the researchers examined the cervical mucus of Ovaprene users, they found fewer than five viable, moving sperm in each magnified

microscopic field of view – a number that is usually considered insufficient for pregnancy. On the basis of other birth-control studies, the company thinks this early finding predicts that the device will be more than 85% effective at preventing pregnancy over a six-month period. But full-scale clinical trials are not yet complete, so Ovaprene’s true efficacy remains unknown for now.

Sweeten the pill

Despite the profusion of birth-control pills on the market, scientists at Mithra Pharmaceuticals believed they could create a better version. The company is developing Estelle, a pill with two active ingredients: estetrol, which is a naturally occurring human oestrogen, and the progestin drospirenone. In a phase III clinical trial in 2019, Mithra reported that Estelle was 98% effective at preventing pregnancy over the course of one year. Mithra expects the FDA to issue an approval decision on Estelle in the first half of 2021.

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Estetrol’s efficacy is similar to that of some existing contraceptive pills. But unlike ethinyl oestradiol, the artificial oestrogen found in most birth-control pills, it selectively acts on the endometrial tissues that line the uterus. Jean-Manuel Fontaine, Mithra’s vice-president for external and scientific affairs, says this means that Estelle can achieve high birth-control efficacy with relatively few side effects compared with older birth-control pills. In earlier studies, researchers showed that estetrol does not affect cell receptors in breast tissue as strongly as ethinyl oestradiol does, resulting in less discomfort. “It’s important to have a contraceptive that doesn’t give you breast pain and tenderness,” Fontaine says. Estelle users have also reported quite low levels of mid-cycle spotting.

Estelle might also offer a lower risk of blood clotting than does ethinyl oestradiol, which increases the activity of coagulation factors in the blood. In a 2019 study at the Namur Research Institute for Life Sciences in Namur, Belgium, women who took estetrol did not exhibit notable increases in blood clotting factors such as fibrinogen or prothrombin.

People with a high risk of clotting, including those with high blood pressure or migraine with aura, are often advised not to take any oestrogen-containing form of birth control.

This advice might need to change once Estelle hits the market, Verma says. “That is one of the big advantages of this pill if it pans out – allowing us to use a combined birth-control pill in more patients,” although long-term data on how the pill affects clotting are still pending.

Like other contraceptive pills, Estelle must be taken at approximately the same time each day, so users must commit to the long haul and stick to a regular dosing schedule.

Costs and benefits

With a dizzying array of contraceptives already available, it is reasonable to ask whether people will be motivated to switch to new options. Verma thinks that some people will be willing to take a chance on something different, especially if their current contraception is not meeting their needs. “I see patients that are not doing anything for contraception,” says Evofem’s Culwell, who also works in private practice. “There are millions of women looking for alternatives.”

Phexxi and Ovaprene will not prevent pregnancy as reliably as combined pills such as Estelle and other hormonal choices. But Verma says they will still be valuable additions to the market if they prove ideal for people who have tried and discontinued other options. “If we’re only looking at effectiveness” compared to an IUD or a hormonal implant, “they’re not going to be as effective with typical use. But I think that’s just a small part of the whole equation,” she says.

As in the past, choosing a method of birth control will probably continue to require some trial and error for the user, to see whether it will work for them. Cost will also be part of the decision, says biomedical scientist Jerrica Breindel of Quinnipiac University in Hamden, Connecticut. Until generic versions appear, which is years away, the newest birth-control options will be pricier than older ones, which will limit people’s access to them.

For Terra, who took part in Evofem’s clinical trials, Phexxi turned out to be a pleasant surprise. “I was happy with my overall experience,” she says. “It was great for my husband and me, because it didn’t hinder our sexual relationship and I did not experience side effects.”

But not everyone in the Phexxi trial had such a smooth transition to the gel, and that kind of variation is exactly why contraceptive choice should continue to expand, Verma says. “It’s exciting to see more options come out – it’s such an individual decision. The more methods we have, the better people figure out what works for them.”

Elizabeth Svoboda is a science writer in San Jose, California.