Why are we still waiting for the male pill?

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Had there been a male contraceptive pill in 1976, I probably wouldn't be here to write this. That was the year when, after my mum – may she rest in peace – had been on the pill for 12 years, health worries made her doctor tell her to come off it. "She said to the doctor, 'I'll get pregnant'," my dad recalls. "And within a very short while, she was." He explains, much to my discomfort, that although my parents switched to condoms, I was conceived because "sometimes you feel reckless". But if a male pill had existed, my dad says, he'd definitely have used it.

So why didn't it exist? It certainly wasn't because of a lack of scientific interest. Gregory Pincus, who co-invented the female contraceptive pill, first tested the same hormonal approach on men in 1957, and various hormonal and non-hormonal methods have been explored since. And although attitudes among those who might use a male pill were once thought to be a daunting obstacle, it's now clear that many men want a new option.

Despite this, we're still waiting. Developing a method that men would accept has brought decades of frustration, yet researchers are as confident as they can be that they're close to overcoming the scientific barriers. But, crucially, drug makers' commitment to contraceptives has always been tentative, particularly when it comes to products for men – and today, the whole contraceptive industry is struggling. Now, the multimillion-dollar question seems to be: Who is actually going to make the male pill happen?

In the 1970s, when my dad might have used a contraceptive pill,

prospects seemed better in some ways. Male fertility control was an active research field, with governments backing various ideas to limit overcrowding on Earth. One product he might have been interested in – a non-hormonal drug called gossypol – was being tested on a scale that has never been matched since. At the UN's 1974 World Population Conference, Elsimar Coutinho, today a famous sex and fertility doctor in Brazil, was promoting the drug, which he was testing on men at the Federal University of Bahia. However, attitudes surrounding sex and reproduction can be unpredictable, and not everyone was convinced of its worth.

"The conference hall was full of women," Coutinho says on the phone, his gravelly voice matching his website's picture of a suave doctor with slicked-back grey hair. "I was going to tell them, 'Now you don't have to take pills if you don't want.'" Yet, having determined their own fertility through the contraceptive pill for little more than a decade, his female audience were determined not to relinquish control. "To my surprise, I was shouted down and booed out."

Despite such reactions, poorer countries with fast-growing populations found gossypol appealing because it could be extracted cheaply from cotton farming waste. Coutinho had first seen its potential while visiting Brazilian farmers who fed cotton plant debris to their bulls. "The bulls were having sex more often, the farmers thought it was good for sexual prowess," he recalls. But actually, the bulls were not making enough sperm and were therefore still surrounded by receptive, non-pregnant cows – and just doing what came naturally.

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From the 1960s onwards, Coutinho worked on contraception with the Chinese government, which in 1972 ran trials with 8,806 men taking

gossypol pills. Daily doses successfully reduced the men's sperm count enough to satisfy the researchers, but side-effects were a cause for concern. One notable problem was that 66 of the men had low potassium in their blood. More importantly, sperm levels in many men didn't return to normal when they stopped taking the drug.

Researchers therefore conducted tests for years longer, showing in rats that gossypol doesn't just stop sperm moving, but also damages the lining of epididymis ducts, which store sperm made by the testicles. Eventually, an October 1986 symposium in Wuhan, China – whose sponsors included the Chinese government and the World Health Organization (WHO) – concluded that gossypol was "of little interest".

"You may call it a problem, but we saw it as a solution," Coutinho tells me. He felt that the fact it could be irreversible made gossypol a potential alternative to surgical vasectomy. He joined with an international team of scientists to conduct further trials, the last of whose results were published in 2000. They found no problems with potassium, putting the effects seen in China down to poor diet.

The researchers therefore applied to the Brazilian government for permission to sell the drug, needing to overcome the strong influence of the Roman Catholic Church, which forbids artificial contraception. On 14 June 2001, Josimar Henrique da Silva, founder of the Brazilian drug company Hebron, which was hoping to commercialise gossypol, wrote to Coutinho. "I'm working at the Ministry of Health in such a way as not to create more obstacles," Coutinho reads from the letter. "I can't fight against them. Give me two more weeks."

Coutinho never heard from da Silva again. The gossypol contraceptive saga ended in failure after more than three decades. Coutinho mischievously suggests Ministry machismo may have been a contributing factor. "We worked on this for many years and realised men are very

afraid of losing virility," he says. "Maybe those judging our application were amongst them."

By contrast, my dad apparently wouldn't have seen a male pill as a threat to his virility, and I too would be interested in rather than threatened by a new male contraceptive – I believe it would benefit, rather than harm, the sex my partner and I have. Are we unusual in that?

Actually, plenty of men are interested in a male pill. In 2005, researchers in Germany published a study asking over 9,000 men from nine countries on four continents whether they'd use a contraceptive method "capable of preventing sperm production". Over half were willing, the proportion ranging from three-tenths to seven-tenths depending on the country.

Other surveys report similar attitudes. In 2011, Susan Walker at Anglia Ruskin University in Chelmsford, UK, published a small study including 54 men in an anonymous town in England. Twenty-six of them said yes, they would take it. "They were not concerned about losing fertility – as long as they could be sure of regaining it," Walker stresses.

They said, 'I've seen what the pill does to my girlfriend', 'What would the long-term effects on my fertility be?'

The remainder, who split between responding no and don't know, showed some gender-based reluctance. "It's a strange idea," one man said. "I'm so used to women taking the pill." Those who were unsure were more concerned about side-effects, Walker notes. "They said, 'I've seen what the pill does to my girlfriend', 'What would the long-term effects on my fertility be?', 'Could I be sure my fertility would return?', that kind of really quite sensible concern."

The survey also included 134 women, roughly half of whom would let

their partners use a male pill. However, more than half were worried that men would forget to take the pill regularly, whereas just one in six of the men had this worry. "Of course, women have the experience of having to remember to take the pill," Walker says. One study from 1996, in which 103 women were given electronic pill dispensers that monitored what they'd taken, found that they missed 2.6 pills per month on average.

"The general concept is that there are men out there that would use it," says Richard Anderson, a professor of reproductive science at the University of Edinburgh. And some women would trust them – although often media coverage might suggest otherwise. "Whenever there's a study published, a radio journalist will walk up and down the high street in their local town and ask women whether they'd trust a man to take a pill, and of course they all run for the hills. But if you ask a woman if they would trust their partner, who they share children, their bank account, and a bed every night with, then you're going to get a different answer."

In 1995 and 1996, researchers including Anderson interviewed 1,829 men across four cities: Edinburgh, Cape Town, Shanghai and Hong Kong. White men in Cape Town were most eager, with four-fifths saying they would at least probably use a male hormonal contraceptive pill. Hong Kong residents were least keen, with two-fifths saying that they would definitely or probably take a pill. Fewer were interested if the drug was injected – three-fifths of white men in Cape Town and a third of men in Hong Kong, for example. "It's not going to be right for everybody," Anderson says. "The whole concept is to provide a range of options so that individuals can find what suits them best."

A photo of Anderson's reveals the injection question's importance. In it, a woman is grinning as she depresses the plunger on the hormone-filled syringe she's injecting into her husband's naked bottom. This was the method used in the first WHO-backed clinical trial that Anderson was

involved in, back in 1991. "It was proof that you could use a hormonal method to produce real contraceptive efficacy," Anderson says. This trial also helped show that male contraceptives didn't need to cut sperm count to zero. With anything upwards of 15 million sperm per millilitre considered normal, the trial set its maximum threshold at 3 million per millilitre. The consensus today is that "anything below 1 million per millilitre is going to provide pretty good contraception," Anderson says.

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A single crumpled piece of A4 paper on an almost-bare wall in Anderson's office illustrates how hormonal male contraceptives work, reducing men to brain and balls. In the brain, it picks out the hypothalamus and pituitary gland. In the testicles it shows cells that make testosterone, and the tubules they neighbour, where sperm are made. Progestogen hormones like those used in female pills can stop the glands in a man's brain making luteinising hormone and follicle-stimulating hormone. The absence of these hormones stops the man's testicles producing sperm – but it also stops them producing testosterone. So testosterone replacement is given along with progestogens, to avoid undesirable effects like weaker muscles and lessened sex drive.

The Edinburgh scientists' various trials have long attracted media attention. "'100% success' for male pill trial," trumpeted the BBC in 2000, reporting on the suppression of sperm production in 30 men – reportedly without side-effects – from a combined progestogen pill and testosterone-releasing implant. Both hormones came from the Dutch drug company Organon, which, after what Anderson calls "a lot of persuading", began to pay attention.

Eventually Organon teamed up with Germany's Schering on a larger clinical trial in 2003–04. Researchers gave 297 men progestogen implants Organon was developing for women and injections of a

Schering testosterone product. They gave around 52 more men placebos – all the participants were also using other contraception – and monitored their sperm count. For almost nine-tenths of the men on the hormonal contraceptive, sperm counts fell below the million mark, and once the trial was over they all recovered normal fertility after around four months. But not everything was ideal. More men taking hormones suffered 'adverse events' like acne, sweating, and effects on weight, mood and sex drive than the placebo group. Some of these were more serious and even life-threatening, including one attempted suicide.

This would be the pinnacle of Big Pharma's interest. Between running the trial and publishing results in 2008, Schering was bought by German rival Bayer, which ended work on the subject. Organon likewise ended its interest, which Herjan Coelingh Bennink, global executive vice-president in the company's reproductive medicine programme until 2000, believes is partly because this work lacked support in the company. Encouraged by the survey done by Anderson and his colleagues, Coelingh Bennink had pushed the approach, and helped design the joint trial. But – echoing Coutinho's account of his experience with gossypol – among Organon's most senior leaders attitudes were not as open as elsewhere.

"At board level it was only middle-aged white males," Coelingh Bennink recalls. "I tried to explain how important it could be, but they never got further than saying to each other, 'Would you do it?' 'No, I wouldn't do it.' It was not considered male behaviour to take responsibility for contraception."

On leaving Organon, Coelingh Bennink founded Pantarhei Bio. There, he has overseen development of an improved female contraceptive pill that offers lessons for the male version. When women start using hormonal contraceptives, there's a possibility that blood clots can form. While the risk is very low, it does happen and can lead to serious

complications – for the women and for the drug companies. For example, Bayer is estimated to have paid around $2 billion to women who have sued it over such blood clots. Likewise Merck and Johnson & Johnson have paid millions of dollars to settle similar cases brought against them. The new drug "most likely" doesn't cause clots, Coelingh Bennink says.

In 2016, the new female pill will enter large-scale phase III human trials – the ultimate test of whether drugs work – to determine whether government regulators will approve its sale. But Coelingh Bennink estimates these will cost €50–100 million, and Pantarhei doesn't have the money. Instead, it has sold rights to the drug to a Belgian company, Mithra Pharmaceuticals, who are running the necessary clinical trials.

Getting to this point has taken Pantarhei 14 years, and finding a partner prepared to risk large-scale testing has been one of the hardest parts. Contraceptive drug companies have all drastically cut funding for new products, Coelingh Bennink says. "It's a disastrous world to develop drugs in. It's much more profitable to develop another cancer drug. Contraceptives are a retail business – it's a matter of selling a lot, and profit is low."

US-based Transparency Market Research estimates that people across the world spent almost $16 billion on contraceptives in 2013. Roughly two-thirds of that was on contraceptive devices, including condoms, implants and intrauterine devices (IUDs, or 'coils'). Meanwhile, the IMS Institute for Healthcare Informatics estimates that in 2014 the world spent $100 billion on cancer drugs, and that figure has been growing at 6.5 per cent per year. Contraceptive drug expenditure is set to grow at just 1.3 per cent a year. Add to this the risk of getting sued, and the continued belief that men won't take a contraceptive pill, and Coelingh Bennink believes no drug company will get involved. "This is a task for public organisations," he says.

The WHO continues to fulfil this role – but it too has hit problems. In 2011, another progestogen–testosterone trial on over 200 couples, run by the WHO and the non-profit research organisation CONRAD, was stopped early. CONRAD announced two serious adverse events as the reason, although full details are still to be published.

Yet Anderson, who helped run the WHO–CONRAD trial, points out that some researchers are already offering the method to men outside of trials, and even using it on themselves. For him, the biggest obstacles are not scientific. "Getting male fertility down to acceptable levels is difficult but not impossible, and there have been many years of experience of how to do that," he says. "What the field has really lacked is a champion with lots of money and enthusiasm. Thereafter you get industrial involvement."

That champion may not yet have emerged, but in the USA, two women are at least providing the enthusiasm.

"We're talking about drugs men are going to take for a really long time, so the pathway for approval is long too," says contraception researcher Diana Blithe. "So when scientists say, 'I have a product in mice that looks promising, we'll have a drug in five years,' it's very unrealistic." Nevertheless, she admits to being "really excited" about the approaches she's supporting.

Blithe is director of the male contraceptive development programme at the US National Institute of Child Health and Human Development (NICHD) in Bethesda, Maryland. She's responsible for one of the largest pots of male pill research money available today and believes a hormonal method is most likely to do the job.

She points out that American men can already buy testosterone gels that could form part of a male contraceptive, and which show how to get a

male hormone product approved. Adverts everywhere in the USA talk about "low-T" – low testosterone levels – and the gels men can rub into their skin to treat them. Similarly, NICHD funds researchers at the University of California, Los Angeles and the University of Washington to do clinical trials using testosterone and progestogen in gels.

NICHD is also closing in on an elusive pill-form male hormonal contraceptive. Forms of testosterone that we can absorb from our stomach and gut rapidly break down in the body, meaning men would have to take pills three times a day. "Would men take a pill?" Blithe asks. "We think they will – but not every eight hours." Therefore NICHD has developed a hormone that does the job of both progestogen and testosterone and only needs to be taken once a day. This too is moving into clinical trials.

Although she's enthusiastic about these ideas, Blithe stresses that NICHD can't do what Coelingh Bennink wants them to, and take male products through to approval independently. Instead, she and her colleagues are continuing to seek involvement from drug makers. "Our hope is to show that it works well and men like it, and then a pharmaceutical company will recognise that it's safe," she says. "We are doing phase II now on the gels and if it works really well and we still don't have a partner, I don't know what the Institute's decision will be, whether they will want to continue."

While scientists can work on how hormonal drugs are taken and their side-effects, one downside seems unavoidable. It takes one to four months to clear out already-made sperm and achieve the contraceptive effect, and a similar period for fertility to return. NICHD is therefore also backing research on non-hormonal methods that might be effective more quickly, but Blithe admits these are "way further back" in animal testing.

If NICHD worked in the UK, they might therefore be interested in Nnaemeka Amobi from King's College London's non-hormonal 'instant male pill'. Also known as the 'dry orgasm pill', Amobi's contraceptive stops men releasing semen and the sperm it contains. He stresses that otherwise the normal physical processes involved in a man's orgasm are unaffected.

"The movement of semen from the testes to where it stays until you have the projectile phase of emission, called ejaculation, happens long before climax," Amobi says. "As soon as you're aroused, spermatic fluid is moved towards the seminal vesicles and prostate. Our pill stops that initial movement by inactivating the tubes that propel fluid from the testes to the prostate."

Amobi and his fellow researchers started from two existing drugs that had caused dry orgasms as an undesirable side-effect. They redesigned the drugs to remove the original intended actions and focus on this. Animal tests suggest that they have succeeded. "We used rams because rats and rabbits don't have seminal fluid like humans," Amobi says. "We tried boars, and boars produce 250 millilitres of semen. Can you imagine that? Rams have 1 millilitre, closer to humans' 2–5 millilitres."

These tests show the method could become effective within 3–4 hours, and wear off after a day. "A woman can say, 'Here's the pill – let me see you take it'," Amobi says. And as well as avoiding pregnancy, preventing semen emission should help reduce sexual transmission of semen-borne diseases, such as HIV.

One potential backer interested in the drug was the Parsemus Foundation, a small private organisation based in Berkeley, California. Ultimately, though, its founder Elaine Lissner faced a tough choice between funding Amobi's research and another promising new male contraceptive technology. She chose to spend the foundation's little cash

on the latter. Amobi isn't bitter because, in his opinion, Lissner is the main reason people still talk about male contraception. But she still has regrets. "It's shocking that they can't get backing for the first new idea about HIV transmission prevention in ages."

Having started the Parsemus Foundation in 2005 with a little of her own money, Lissner has a personal relationship with how it's spent. In contrast to Blithe, she dislikes hormonal approaches because of their side-effects, and she also dislikes risk. Parsemus has therefore adopted an approach similar to one already tested in men, in India. But it's not a pill – it's a 'hydrogel' injected into the vas deferens, the tube linking the epididymis to the penis.

Called Vasalgel, it lets through semen but not sperm, and is intended to be washed out by another injection when men want the use of their sperm back. The blocked sperm are cleared from the epididymis and eaten up by immune cells, as happens normally if a man hasn't had an orgasm for a while. Lissner publicises Vasalgel energetically, and one glance at its thriving Facebook page should dispel any doubts that men would be interested. "People are crazy for Vasalgel, desperate for it," she says. "We have over 32,000 people on the mailing list waiting to hear about clinical trials."

One man who's keen to try it is Justin Terry, a married 30-year-old machinist who makes vehicle parts in Alabama. He and his wife don't have children, and his wife is taking the contraceptive pill. "We've been married ten years," Justin says. "She doesn't want kids and neither do I, really. She wants to get off the pill." The pill gives his wife tender breasts, and she is concerned about adverse effects of continuing to take it. As with hormonal approaches, his sperm would still flow for weeks after Vasalgel is injected, but this doesn't bother Justin. He has considered vasectomy, as have I, but has hesitated in part because it's not completely reversible. "Vasalgel sounds like it will be reversible and

would involve much less invasive surgery," he says.

Parsemus's efforts have been helped by the David and Lucile Packard Foundation, also based in California, which provided $50,000 to help them test the approach in baboons. "We expected to be out of money last year and we're not," Lissner says. "But the clinical trial is half a million dollars, so that's a different scale, and beyond that it's multimillions." The trial will involve about 30 men and will test Vasalgel as a vasectomy alternative, without looking at reversibility.

Knowing the field's status, Lissner is not relying on government or the pharmaceutical industry. Instead, she's looking for backing from wealthy 'social investors' – and of course potential end users – and is publicising what might be possible in the field to bring interested parties together. "The difference is that we have built an infrastructure where the public is able to channel its support," she says.

On Blithe's suggestion, I'm watching a documentary called The Great Sperm Race, made by the UK's Channel 4, showing the journey sperm make through a woman's uterus to her fallopian tube. It has cast people dressed in white clothing as sperm, dying in vast numbers. From millions of sperm ejaculated, just 20–100 get close enough to the egg to try to fertilise it.

As I watch, I imagine the white-clad actors instead represent the many possible male pills. There have been and still are masses of ideas, far more than I've been able to mention. Yet, like the unsuccessful sperm, so many have fallen by the wayside. I think of the contraceptive drug industry's current status and I can't help think we have missed its fertile period. If the perfect idea were to fight its way through development today, there's only a tiny chance that there would be a partner to meet it and eventually produce a fully formed male pill from it.

It seems obvious that if a new male contraceptive does make it to maturity, it will come thanks to the efforts of people like Blithe and Lissner. They, as much as anyone, are trying to create environments where the right technology can take seed. Without keen interest from the industry that we have traditionally relied on to supply our contraceptives, that requires enormous effort. Lissner's energetic exertions to concentrate support from men like Justin Terry, my dad and me could prove critical.

And Lissner is adamant that the ideas that seem to have faltered are not dead, they're just resting. "We keep collecting new methods and never finish the ones we have," she fumes. "Pick one and make something! Finish the job!"