

# On The Pill



Illustrations by JT Morrow

This month marks the fiftieth anniversary of the approval of oral contraception in the US, and the Pill's age is starting to show. Problems abound with its delivery, dosage and side effects. **Ellen Friedrichs** investigates how researchers have conceived of new ways to deliver birth control.

Had she been a little older, Susan Magill would have faced a quandary familiar to many prior generations of women: how to effectively control her fertility while staying sexually active. Fortunately, by the time she needed birth control the most—at 26 years of age, after the birth of her second child—Magill was in luck.

It was 1964, and four years earlier the US Food and Drug Administration (FDA) had approved Enovid, a combination hormonal pill, for contraceptive use. “I didn’t know too many people taking it, but I trusted that it was safe,” recalls Magill, a retired drug and alcohol policy planner now living in Hamilton, New Jersey. “It made my periods regular, and it was very convenient because you didn’t have to use any other contraceptives.”

The social stigma surrounding premarital sex meant that birth control was often unavailable to women who were not married. But as a married woman with kids, Magill’s gynecologist promptly prescribed

‘the Pill’ upon request. And for the next 13 years, Magill relied on this oral method of hormone-based contraception to keep herself pregnancy free.

Today, the number of women on the Pill has skyrocketed; the UN estimates that more than 100 million women worldwide now take some form of hormonal contraception. Nevertheless, compliance issues and side effects remain problematic. Researchers have tinkered for decades with delivery systems and dosages to address these issues, yet the promise of nonsteroidal methods, male options and contraceptive microbicides continues to dangle just out of reach.

Now, fifty years after the Pill first appeared on the scene, the trusty oral daily dose remains the mainstay of women’s handbags and bathroom cabinets. Even so, many unanswered questions remain about a drug that, more than any other, changed the reproductive landscape. Here are some of the most intriguing.

## How does the Pill really work?

The primary goal of hormonal contraception is to prevent pregnancy by controlling a woman’s ovulation. As early as 1945, Harvard endocrinologist Fuller Albright suggested that oral regimens of synthetic estrogen could do the trick. Although the Pill ultimately came to depend on synthetic progestones (called progestins) often combined with estrogens, Albright’s basic premise was accurate, and today most birth control methods upset a woman’s natural cycle by flooding her body with hormones.

The hormone surge causes a negative feedback loop that decreases the brain’s production of gonadotropin-releasing hormone, which, in turn, prevents the anterior pituitary gland from releasing other reproductive hormones, namely luteinizing and follicle-stimulating hormones. The primary effect is suppression of ovulation. Secondary outcomes, such as thicker cervical mucus and thinning of the uterine lining, also help prevent any eggs that are released from implanting.

This much we know. What we don't know, for example, is whether certain side effects are pharmacological or psychological, or why an immature egg's surrounding follicle doesn't develop properly after estrogens and progestins bind the surface receptors. These questions deserve further exploration, but researchers are much more interested in finding a product that works better.

"Fifty years after the Pill, all we have are incremental improvements," says Michael Harper, director of the Consortium for Industrial Collaboration in Contraceptive Research at CONRAD, a reproductive health research organization based near Washington, DC. Vanessa Cullins, vice president for medical affairs at Planned Parenthood Federation of America, adds, "We always welcome methods that work differently and may be associated with different forms of convenience."

#### How can drug delivery be improved?

Although they remain the most popular form of birth control, oral contraceptive pills face increasing competition. Over the past 20 years, shots, implants, patches and vaginal rings have all entered the market. Commercial motivation has driven this development, of course. But so, too, has the fact that no single method offers a perfect delivery system. Pills are forgotten, patches cause irritation and implants or injections must be administered by a medical professional.

To move away from pill popping and address many of the compliance issues of the other approaches, Régine Sitruk-Ware, a reproductive endocrinologist and executive director of research and development at the Population Council's Center for Biomedical Research in New York, is working on an easy-to-apply transdermal gel that, like hormone-based lotions developed to treat menopause, can be absorbed through the skin.

Last October, Sitruk-Ware and her colleagues completed a phase 2 trial testing three hormone doses of such a contraceptive cream. Their unpublished data show that a midlevel dose of the ointment sufficiently blocked ovulation with few serious side effects. Most importantly, perhaps, "women who participated in the studies liked the gel," Sitruk-Ware says. "This was not a visible method and not detectable, even by their partners."

A gel isn't the only new delivery method on the horizon. The US National Institute of Child Health and Human Development,



in collaboration with the World Health Organization and CONRAD, is developing a new shot involving levonorgestrel, a progestin that is thought to have less of an effect on bone mass density than does the existing injectable, Depo-Provera. However, this product won't be available anytime soon. Toxicology and pharmacokinetic studies in animals have been completed, but similar studies in humans have not yet begun.

#### What about nonhormonal birth control?

Women in the US who are not candidates for hormonal contraceptives—either because of underlying health conditions, or because they experience severe side effects—have only two sets of reversible choices of birth control: barriers, such as condoms and diaphragms, and intrauterine devices (IUDs), small, T-shaped objects that are placed in the uterus to prevent pregnancy.

For women in India and Peru, however, there is a third option: a small molecule called ormeloxifene that prevents implantation by binding estrogen receptors to enhance the effects of the hormone in some parts of the body (such as bone) and block estrogen-induced gene expression in other parts (including the uterus). Marketed in India under the name Saheli, this weekly oral medication sells 25 million doses a year in that country and has been used as birth control for almost twenty years.

In all that time, however, ormeloxifene has never been available in the US because no company has risked taking the drug through the

FDA's regulatory gauntlet. That might soon change. Ormeloxifene became available in Peru in 2008, and its Indian manufacturer, HLL Lifecare Limited, is expanding into at least six other countries in South America, according to the company's manager of regional exports Vipin Raj. "We are also beginning the procedures to enter into the US market," Raj adds.

Another potential nonsteroidal option is the anti-inflammatory medication meloxicam, an inhibitor of the cyclooxygenase-2 enzyme, which prevents ovulation by stopping the release of the maturing egg from the surrounding follicle. A team led by Jill Schwartz, medical director for CONRAD, reported earlier this year that a 30-milligram dose administered for five straight days in the lead-up to ovulation was a safe and effective form of emergency contraception<sup>2</sup>.

Now, Schwartz and her colleagues are exploring whether meloxicam, a drug already on the market for arthritis, could be used more broadly as a daily method of pregnancy prevention. "The good thing about using something that is already out there and manufactured is that it will speed up the timeline" to regulatory approval, Schwartz says.

#### Don't we have a 'male Pill' yet?

The concept of manipulating male hormones to prevent contraception predates the approval of the female Pill by more than 20 years; in 1939, two independent research teams in the Midwest investigated testosterone's ability to block or severely reduce the production of sperm<sup>3,4</sup>. But, since female birth control pills took over the contraceptive market, nothing has been developed for men that is affordable, reversible, safe and more effective than a vasectomy—which has a failure rate of only 1 in 2,000.

Hopes were raised last year after a Chinese study showed that monthly injections of a long-acting form of testosterone could temporarily and reversibly prevent spermatogenesis<sup>5</sup>. That excitement faded, however, when it became clear that this formulation was less effective in non-Asian men, possibly because non-Asian men tend to have a higher body fat mass, which has been found to inhibit the response to androgens<sup>6</sup>.

Researchers are also considering options besides direct hormone injections, which can be inconvenient and produce mild, but unpleasant, side effects, such as changes in mood and blood cholesterol concentrations. Christina Wang, a reproductive endocrinologist who has been

heading up clinical trials of male hormonal contraceptives at Harbor-University of California–Los Angeles Medical Center, thinks that molecules that selectively modulate the hormones' receptors only in particular tissues could address some of these issues. Such selective androgen receptor modulators "will suppress sperm production and will have a good effect on muscles and bones and sexual function, and less of an effect on the prostate," says Wang.

Evidence that this idea could work came last year when a team led by James Dalton, a pharmacologist at Ohio State University in Columbus, showed that a small molecule called S-23 suppressed spermatogenesis in male rats; adding another steroid also kept the rats' sexual behavior intact<sup>7</sup>. According to Dalton, however, S-23 has not yet entered clinical trials.

### What new contraceptives prevent disease?

Condoms can reliably prevent sexually transmitted disease. But condoms aren't a universal solution, because they can be difficult to apply and may interfere with sex. Additionally, whereas many people accept male condom use, the female condom has yet to be embraced. In light of these issues, CONRAD's Schwartz knows exactly what she wants: "A contraceptive microbicide would really be best," she says. Such a form of birth control would prevent both pregnancy and certain sexually transmitted infections, thereby achieving the same benefit as a prophylactic without the physical barriers and psychological resistance that can arise with condoms.



Over the years, researchers have investigated a number of microbicidal agents to prevent HIV and other pathogens, but few of these candidate drugs have been designed to offer protection from pregnancy. One promising contender for a dual-acting, contraceptive microbicide is a naturally occurring antimicrobial peptide called nisin, a byproduct of culturing the bacterium *Lactococcus lactis*. K.V.R. Reddy of the National Institute for Research in Reproductive Health in Mumbai, India showed last year that nisin disrupts the membranes of both sperm and bacteria<sup>8</sup>. Since then, however, Reddy has also found that the compound kills many of the symbiotic microbes living in the vaginal tract. "Therefore, this may not be a good candidate microbicide," he says.

Microbiologist Adriano Brandelli and his colleagues at the Federal University of Rio Grande do Sul in Brazil discovered another antimicrobial peptide produced by a newly discovered *Bacillus* species that can also kill sperm without damaging surrounding tissue. "This peptide could be spermicidal if used in increased concentrations," says Brandelli, who reported the molecule's *in vitro* cytotoxicity in February<sup>9</sup>.

### Does the Pill offer other benefits?

Birth control is not without its risks. Some forms of the Pill have been linked to blood clots, and this medication can be particularly unsafe for smokers over 35. Advocates of the Pill, however, are far more likely to tout the benefits rather than the drawbacks of hormonal contraceptives. For example, last year's survey of 45 observational studies from 21 countries found evidence that the Pill offers some protection against colorectal cancer, benign breast disease and ovarian cysts, among other ailments<sup>10</sup>.

Last month, Scottish researchers also reported the results of a 39-year study that followed more than 46,000 women across the UK. They found that women on the Pill were less likely to die from any medical cause, including heart disease and all cancers, compared to those who had never taken oral contraception<sup>11</sup>. Although the study only considered early forms of the Pill, "it is not unreasonable to suppose that a similar overall lack of risk in the long term would also be found among today's oral contraceptive users," says lead author

Philip Hannaford, an epidemiologist at the University of Aberdeen, UK.

Some pharmaceutical companies have claimed that the Pill also decreases fatigue, anxiety, headaches, bloating and other symptoms of premenstrual syndrome. But many of these purported benefits are more speculative than proven. The pharmaceutical giant Bayer discovered the complexity of making such claims in 2008 after the FDA slapped the company with a warning letter for a series of television ads that overstated the approved use of its Yaz birth control pills. To date, more than 1,000 complaints have been filed against the company as part of a class-action suit alleging that these birth control pills also caused potentially fatal blood clots in otherwise healthy women.

### Where do we go from here?

On 10 May 1960, the day after the Pill gained FDA approval for contraceptive use, the *New York Times* ran a brief article about the event, quoting the agency's then associate commissioner, John Harvey. "Approval was based on the question of safety," Harvey explained. "We had no choice as to the morality that might be involved." It wasn't exactly an enthusiastic endorsement, but it wasn't a surprising statement either, given the climate of the times.

To be sure, questions of safety and morality still circulate today, as do those asking what it will take to deliver a better, more effective product. And although it's unlikely that the perfect contraceptive will ever be developed, it isn't such a stretch to assume that the next 50 years, like the 50 that came before, will continue to be a time of birth control innovation.

*Ellen Friedrichs is a writer and health educator living in Brooklyn, New York.*

"A contraceptive microbicide would really be best."

—Jill Schwartz

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