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In Search of Breakthroughs: Renewing Support for Contraceptive Research and Development

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In the five decades since the birth control pill was first marketed in the United States, the number of contraceptive products available to women has expanded substantially. Still, these innovations overwhelmingly have been adaptations of existing technologies that offer variations on hormone dosages and routes of delivery, rather than true technological breakthroughs. At the same time, there is an ongoing and serious problem of high unintended pregnancy rates in the United States and around the globe. In addition, an expanding body of knowledge suggests that improving and expanding contraceptive use requires more than just access to existing methods, but also meeting women's needs and preferences for effective and satisfactory methods. For all of these reasons, new investments in contraceptive research and development are critical to achieving consistent and correct contraceptive use and lowering unintended pregnancy rates.

The Rationale for More Investment

In the United States, nearly half of all pregnancies—some 3.2 million annually—are unintended.[1] Accordingly, at current rates, more than half of all U.S. women will have faced an unintended pregnancy by age 45, and almost a third will have had an abortion by that age. Behind these startling statistics are real public health consequences from unintended pregnancies for maternal and child health, including foregone prenatal care, premature births, low birth weight, decreased likelihood of breastfeeding and increased likelihood of maternal depression and anxiety (see "The Case for Insurance Coverage of Contraceptive Services and Supplies Without Cost-Sharing," Winter 2011). Unintended pregnancies also extract a steep social and economic cost to women and their families, and ultimately society, through relationship instability and lost educational, job and other opportunities for life advancement (related article, page 8)

To be clear, the majority of American women consistently and correctly use contraceptives. In fact, two-thirds of women in the United States at risk of unintended pregnancy—those who are sexually active and able to become pregnant, but not seeking a pregnancy—use contraceptives consistently and correctly, and thereby only account for 5% of all unintended pregnancies.[1] Rather, it is the 16% of women at risk who do not practice contraception at all who experience the majority (52%) of all unintended pregnancies. And the remaining 19% of women at risk who use contraceptives inconsistently or incorrectly make up the remaining 43% of all unintended pregnancies.

The type of contraceptive method that a woman uses influences her chances of avoiding pregnancy. Over the last three decades, the pill has remained the most popular reversible method in the United States (see chart).[2] When used perfectly, it has an extremely low failure rate, as do most other modern methods (see table).[3] But in the real world, "typical" use of very effective technologies nonetheless results in significantly higher failure rates relative to "perfect" use. This gap illustrates the interaction between technology and human behavior, and reinforces the need for the development of contraceptives that meet human needs. The fact is that it is difficult for women to use most contraceptive methods correctly and consistently over the several decades of their reproductive lives that they wish to avoid unintended pregnancy. This is especially so for those

methods that are used at the time of intercourse (such as condoms), but it is also true, although somewhat less so, for those methods that must be used on a daily basis (for example, the pill).

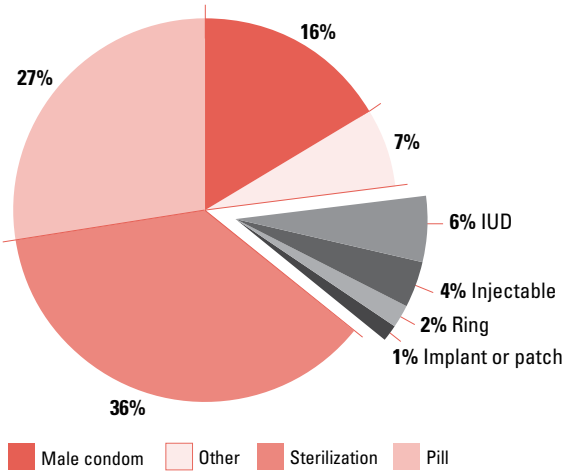
Guttmacher Institute research shows that U.S. women report a variety of reasons for nonuse or gaps in contraceptive use.[4] The most widely cited reasons involve problems using or accessing methods, such as concerns about side effects, dissatisfaction with methods, difficulty in paying for the method or lack of time for medical visits. Other common reasons for gaps in use include infrequent sexual activity, ambivalence about becoming pregnant and misperceptions about pregnancy risk. Moreover, women experiencing gaps are particularly likely to be facing important life changes, such as the start or demise of a relationship, a personal crisis, a job change or a new home.

According to a report released in February 2013 by the Centers for Disease Control and Prevention (CDC), among women of reproductive age who had had sexual intercourse, 47% of those who had ever used at least one contraceptive method had discontinued using a method due to dissatisfaction.[5] Particularly telling are the data on women who had used certain hormonal methods: Thirty percent of women who had ever used the pill, and almost half of injectable and patch users (46% and 49%, respectively), had stopped using those methods due to dissatisfaction. By far, the top reason why users of all three hormonal methods discontinued use from dissatisfaction was side effects, which was cited by 74% of injectable users, 63% of pill users and 45% of patch users. Some other common reasons for dissatisfaction among discontinuers included worry about side effects, menstrual cycle changes and difficulty of use. The CDC report also noted that method switching is common among contraceptive users: The median number of methods ever used by women was about three, and for 30% of women, it was five or more.

At the global level, the reasons for failing to use contraception are just as varied, and the health impacts of unintended pregnancies are even more dire. Among women of reproductive age in developing countries who are in need of contraception, 18% are not using any method at all—but they account for two-thirds (66%) of all unintended pregnancies.[6] Another 13% of unintended pregnancies occur to the 8% of women who are using traditional methods. The remaining 20% of unintended pregnancies are experienced by

ROOM FOR INNOVATION

Newer contraceptive methods, such as the IUD, the injectable and the ring, combined only account for 13% of contraceptive use in the United States today.



Notes: Sterilization includes female and male procedures. Other methods include withdrawal, periodic abstinence and over-the-counter products other than male condoms. *Source:* reference 2

METHOD EFFECTIVENESS

Long-acting and permanent methods of contraception are most effective in theory and in practice, but all contraceptive methods are far better than using no method at all.

	First-Year Failure Rates	
Method	Perfect use	Typical use
Implant	0.05	0.05
Vasectomy	0.1	0.15
Tubal sterilization	0.5	0.5
Copper IUD	0.6	0.8
Hormonal IUD	0.2	0.2
Injectable	0.2	6
Vaginal ring	0.3	9
Patch	0.3	9
Pill	0.3	9
Male condom	2	18
Female condom	5	21
Withdrawal	4	22
No method	85	85

Notes: Proportion of women who will become pregnant during their first year of use. "Perfect use" denotes effectiveness among couples who use the method both consistently and correctly; "typical use" refers to effectiveness experienced among all couples who use the method (including inconsistent and incorrect use). *Source:* reference 3.

women who use reversible modern methods of contraception. Of the 80 million unintended pregnancies that occurred in the developing world last year, half ended in abortions, the majority of which were unsafe. Satisfying the unmet need for contraception would prevent 79,000 maternal deaths and 1.1 million infant deaths each year.[7] And it would also lead to better health, social and economic outcomes for mothers, children and communities.

Addressing the unmet need for modern contraception of 222 million women in developing countries, however, will take more than just getting contraceptive methods into their hands. Guttmacher research on the reasons for women's nonuse of modern methods suggests a need for new methods that women find acceptable.[8] In particular, seven out of 10 women in Sub-Saharan Africa, South Central Asia and Southeast Asia—the three regions that account for the majority of women with an unmet need in developing countries—report that they do not use modern contraceptives because of concerns about health risks or side effects (23%); infrequent sex (21%); being postpartum or breastfeeding (17%); and opposition from their partners (10%). Addressing these concerns through a variety of methods more specifically suited to their particular preferences and needs could reduce unintended pregnancy in these regions by up to 59%. Indeed, in countries with increased contraceptive options, meaning easy access to several methods, not only is there better uptake of each individual method, but overall contraceptive use is greater than in countries with fewer choices.[9]

Current Priorities and Upcoming Products

Researchers and advocates have identified a number of contraceptive research and development priorities that would help address women's concerns. Certainly, one of the top priorities of a contraceptive research agenda is the development of methods with fewer side effects, such as irregular bleeding, weight gain, nausea or lower libido. Interrelated with this priority is a focus on nonhormonal methods, to both diminish the health concerns related to hormonal methods (such as headaches or increased risk of blood clots for some women) and to give another option to women who are against using hormones. Also near the top of the list are "pericoital" methods and additional long-acting methods. Pericoital methods—used right before or after sexual intercourse—may be attractive to those women who have infrequent or irregular sex. New long-acting methods, which do not pose the challenges of daily adherence, would be expected to have very low failure rates.

In addition to these characteristics, method development for women in the developing world requires other considerations. A preponderant concern is for methods suitable for low-resource settings, including products that are low-cost, not dependent on a skilled provider for initiation or removal, long-acting to avoid repeated clinical visits and capable of a long shelf life in low-infrastructure environments. Women who may face opposition to their use of contraceptives from partners, in-laws or others have indicated that they would also like methods that can be used without partner participation or notification. Other categories of women who have special needs include those who are breastfeeding; who face health risks from certain contraceptives because of obesity, diabetes and hypertension; who require easily reversible methods for birth spacing; and who use contraceptives for other health benefits.

Finally, two of the most important niches for the contraceptive development agenda include male methods and multipurpose prevention technologies (MPTs) that prevent both pregnancy and STIs, including HIV. The two existing male options stand in wide opposition to each other: condoms, used during every act of sex and with a relatively high failure rate, versus vasectomy, a one-time permanent procedure. Given this dichotomy, the introduction of any new male method—whether it be hormonal or nonhormal, self-administered or provider-dependent, daily use or long-acting—would be an improvement over the scant choices currently available. In a similar vein, the only options for dual protection against unwanted pregnancies and any STI are the male and female condoms. There is particular urgency for the development of a multipurpose prevention method in light of the AIDS crisis in many developing countries.

Coming Down the Pipeline

A 2011 analysis by the Bill and Melinda Gates Foundation documented 110 projects in the global contraceptive technology research and development pipeline.[10] Work on some of these projects has already been discontinued, and the majority of these leads will not make it through the rigorous, expensive and lengthy process to make it to the U.S. market, which requires preclinical laboratory testing, three phases of clinical trials to determine safety and efficacy, and review and approval by the federal Food and Drug Administration (FDA). Not surprisingly, most of the products that are expected to be introduced in the near future are variations of existing technologies, but they could provide substantial new benefits. For example, most recently, the FDA approved a new, lower-dose hormonal IUD, called Skyla, which is better suited for smaller-framed women, those who have not had children and those wanting children in less than five years.

The table below describes some of the methods being prepared for the U.S. market that are in the late-development or postdevelopment stage and are not new pill formulations.[11] Some of these methods are being adapted to developing countries through different delivery mechanisms. For example, a new formulation of the injectable will be piloted in several countries. Available in the Uniject injection device, the contraceptive comes in a single-dose, prefilled, nonreusable package; can be easily administered by community health workers; and carries the potential for self-injection.

Although the promising products expected to enter the market in the next few years address some of these priorities (see box), the prospects for other major breakthroughs are still uncertain or far off. For example, the elusive search for a new male method has been ongoing for decades, as there remains a high bar set for safety and effectiveness and few potential products have undergone the larger, longer-term studies needed for product approval. To be sure, there are some encouraging candidates for hormonal products: a gel combining testosterone and nestorone (a synthetic form of progesterone) to lower sperm count, which is undergoing Phase II clinical trials;[12] and a daily pill containing dimethandrolone undecanoate, which is in Phase I trials.[13] One of the most closely followed candidates is reversible inhibition of sperm under guidance (RISUG)—a potentially reversible, nonhormonal injection into the vas deferens that may provide 10 years' or longer protection. RISUG is undergoing Phase III clinical trials in India and could receive Indian government approval.[14–16] Nonetheless, overall, nonhormonal approaches to male contraception are further upstream than hormonal candidates and, thus, need more investment to develop a better safety and efficacy profile.

METHODS IN DEVELOPMENT

Upcoming product	Comparable or current product on U.S. market	New features	Status
Diaphragm	Provider-fitted diaphragm	One-size-fits-most cervical barrier device that does not require a fitting from a provider	Phase III trials completed and developers are working toward approval
Female condom	Female condom with rings on each end	Female condom that is designed with a dissolving capsule that is easier to insert and provides improved adherence to vaginal walls	Phase III trials being completed
Injectable	Progestin-only injectable administered every three months	Combined estrogen and progestin formulation with more regular bleeding patterns than progestin-only; administered monthly	Used in a number of developing countries; its developer will be seeking FDA approval
IUD	Hormonal (levonorgestrel) IUD	Significantly lower cost	Estimated completion date of ongoing Phase III trial is December 2018
Patch	Transdermal, weekly patch	Low-dose patch with fewer side effects and better adhesion than current patch	New drug application submitted to FDA and expecting decision in early 2013
Vaginal ring	Monthly ring	One-year ring (13 cycles) that does not require refrigeration or frequent refill visits as does current monthly ring	Phase III trials completed

Source: reference 11.

Similarly, MPTs have a ways to go before reaching the marketplace. Given the multidisciplinary research and regulatory path of MPTs, donors and experts have convened a working group to help assess and prioritize products for the MPT pipeline, including the development of products in categories covering sustained release devices (such as vaginal rings), long-acting injectables and on-demand or pericoital methods.[17] Some of the most promising technologies include a 60- or 90-day vaginal ring that combines a hormonal contraceptive with an antiretroviral drug (such as tenofovir or dapivirine) to suppress or control HIV; a single-size diaphragm used with a reformulated tenofovir gel that could offer protection for 24 hours; and a topical 24-hour gel that combines the hormonal contraceptive levonorgestrel with an antiretroviral.[18] None of these methods is past the early development stage of testing. A recently developed novel technology is a nanofabric that can be electrically spun to function in numerous ways, including by physically blocking sperm or by dissolving in the body and releasing drugs, such as contraceptives or antiretrovirals.[19] The availability of a new method that meets multiple sexual and reproductive health needs would represent a real game-changer in the field of contraceptive development.

Limited Funding, but Rising Interest

Generally speaking, new drug discovery and development is led by the private sector, but large pharmaceutical and biotechnology companies, for the most part, have abandoned the field of contraceptive research and development. Given the popularity and profitability of the birth control pill, new methods—especially those not dependent on daily consumption or designed to be marketed for low-income individuals—have not carried the allure of similar financial returns. Moreover, contraceptive drugs seem to have steeper hurdles to overcome for safety and efficacy testing than other drugs, which may dissuade companies from time-consuming and costly investments. Consequently, to the extent that the private sector has remained active, its resources have been focused largely on adapting existing contraceptive technologies, rather than developing new and innovative methods. Additionally, there may still be a chilling effect from high-profile lawsuits, such as those arising from the Dalkon Shield IUD, which led to thousands of injuries and even deaths in the 1970s, and from the Norplant implant in the 1990s, which caused serious side effects. Finally, a series of pharmaceutical company mergers over the last decade resulted in the deprioritization and shuttering of contraceptive research and development projects.

Against this backdrop, the public and philanthropic sector has an increasingly large void in funding to fill. Although exact figures are difficult to obtain, a 2010 review by the Gates Foundation estimated that donors from the developed world committed $85 million yearly toward the global contraceptive technology pipeline.[20] When adjusted for inflation, this amount represents a $39 million decline from 1980 levels.[21] At the same time, an estimated doubling of the current investment on a yearly basis is needed just to fully support products already in the research and development pipeline.[20]

Among donors, the U.S. government remains the largest source of contraceptive research and development efforts, carried out through the National Institute of Child Health and Human Development (NICHD) and the U.S. Agency for International Development (USAID). NICHD's Contraceptive Discovery and Development Branch supports basic, applied and clinical research on contraceptive methods, including mechanisms of action, the effects of contraceptive hormones and drugs, and optimal formulations of contraceptive agents. Unofficially, NICHD estimates that its FY 2012 funding for contraceptive research and development totaled almost $38 million. In its recent visioning statement to identify research priorities, NICHD marked the development of novel male and nonhormonal contraceptive agents as a goal for scientists to achieve within the next decade.[22] Even then, NICHD will have to depend on pharmaceutical companies to license, produce and distribute any new contraceptive product, as that is a task that the agency cannot assume.

Unlike NICHD's work—which has a large focus on domestic needs, albeit with significant spinoff

potential for developing country use—USAID research is concentrated on the development and introduction of methods that can be applied and used in low-income countries. That is not to say that USAID investments have not been beneficial for women in the developed world. Indeed, the hormonal Mirena IUD, copper ParaGard IUD, female condom and cervical barrier FemCap are just a few examples of products supported by USAID and used by American women. But USAID's three-fold objectives for contraceptive research and development remain firmly focused on developing countries: to refine existing methods to facilitate acceptability by focusing on products that have fewer side effects, are more affordable, can be delivered without skilled clinicians and promote ease of use; to develop and introduce new technologies to fill current gaps; and to develop and introduce MPTs. In FY 2012, USAID's budget for contraceptive research and development was approximately $12 million.

Other important donors in this area include the World Health Organization, as well as philanthropic organizations. The Gates Foundation, in particular, has helped to reinvigorate interest in contraceptive technologies, which was a prominent theme at the 2012 London Summit on Family Planning that it cohosted with the United Kingdom's Department for International Development. The summit garnered increased political and financial commitments to boost family planning globally and sought to address the unmet need for contraception in the world's poorest countries. Toward those ends, stakeholders pledged to increase support for contraceptive research and development to expand women's choices and meet their family planning needs. Notably, the United States, unable to make financial pledges during the summit, did offer its contribution to the global effort through increased emphasis on contraceptive research and development, particularly methods suitable for a low-resource context.

Although this emerging global and U.S. reengagement in contraceptive research and development is encouraging, the limited involvement of the private sector is worrisome. The role of private industry is essential, because public donors do not have the industry expertise and capacity to manufacture and distribute contraceptives on a large-scale or worldwide basis. And, at the end of the day, public sector funding is no match for the resources that could be brought to bear by the pharmaceutical industry. At the very least, increased public-private partnerships could be a major step in boosting research and development efforts. Indeed, industry partnership could fill key niches and provide a variety of forms of support, including shepherding a product through the regulatory process; direct funding; sharing of intellectual property, manufacturing capacity, market research and expertise; and other in-kind contributions. At the same time, the private sector could benefit from the resources of the nongovernmental sector, such as the ability of organizations to mobilize support for research trials in the community.

Advocates in the United States are watching and hoping that renewed interest in contraceptive research and development—in both the public and private sectors—translates into meaningful and sustained investment. Indeed, there is too much lost ground to cover, too many women's lives and health at stake, and too much potential for breakthrough to surrender to neglect any longer.

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