Pipeline for contraceptive development

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The high rates of unplanned pregnancy reflect an unmet need for effective contraceptive methods for women, especially for individuals with health risks such as obesity, diabetes, hypertension, and other conditions that may contraindicate use of an estrogen-containing product. Improvements in safety, user convenience, acceptability, and availability of products remain important goals of the contraceptive development program. Another important goal is to minimize the impact of the products on the environment. Development of new methods for male contraception has the potential to address many of these issues of safety for women who have contraindications to effective contraceptive methods but want to protect against pregnancy. It would also address a huge unmet need for men who want to control their fertility. Products under development for men would not introduce ecotoxic hormones into the water system. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

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Investment in contraceptive research to identify new products for women has been limited in the pharmaceutical industry compared with investment in drug development for other indications. Pharmaceutical research and development for male contraception was active in the 1990s but was abandoned more than a decade ago. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has supported a contraceptive development program since 1969. Through a variety of programs, including research grants and contracts, NICHD has developed a pipeline of new targets/products for male and female contraception. A number of lead candidates are under evaluation in the NICHD Contraceptive Clinical Trials Network (CCTN) (1–3).

GREEN CONTRACEPTION

A goal of the NICHD's program is to develop safe, acceptable, highly effective contraceptive methods for women and men. Although use of any contraceptive method helps with reduction of unplanned pregnancies and therefore has a benefit in controlling overpopulation, there are a number of areas in which improvements can be made in limiting ecotoxic effects (4). The greatest impact, given existing methods, would be to encourage use and availability of long-acting methods. For development of new methods, we need to reduce ecotoxic hormone levels without compromising effectiveness. Although the processes are not entirely within our control, we can promote ecofriendly manufacturing techniques and reduce waste products where possible.

Steroidal estrogens in the environment come from a variety of sources, primarily excretion from pregnancy and from combined oral contraceptive (COC) pills (5). As the most popular form of birth control in the United States, used by 10.5 million women (6), estrogens from excretion of COCs are a significant risk to the environment. Nearly all COCs contain a synthetic estrogen, ethinyl estradiol (EE), and a progestin. The progestin inhibits ovulation. EE potentiates some of the progestin actions and helps regulate the endometrium to produce regular bleeding patterns when the product is used cyclically. The progestin-free interval induces endometrial shedding, resulting in artificial but regular cycles. EE is considerably more potent (150–600-fold) than natural 17β-E_2 or its metabolites, estrone or estriol, in a number of biologic assays (Table 1) (7). The extraordinary potency of EE is linked to a higher risk of venous thromboembolism (VTE) in the general population of women who use EE-containing hormonal contraceptives (2, 8). That risk is increased by age, smoking, obesity, and genetic predispositions. The potency of EE is also at

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TABLE 1

Potency of ethinyl estradiol (EE) and estrone (E_1) relative to estradiol (E_2).

		Potency	
Human assay (7)	**E_2**	**E_1**	**EE**
Serum FSH	1	0.8	150
Serum AGT	1	1.4	330
Serum SHBG	1	0.5	500
Serum CBG	1	1.0	614

Note: AGT = angiotensinogen; CBG = corticosteroid-binding globulin.

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least 30-fold higher than E_2 in several in vivo fish assays (9). The ecotoxicity potential is compounded by the failure of EE to be metabolized. High concentrations of EE found in waste water are from COC user excretion. The relative estrogenic contribution from pregnancy-related events represents 59% of initial load compared with 16% from EE; however, after 40 days, although only 1% of the estrogenic effects remain, 100% of those effects are from residual EE (5). Studies in controlled lake environments have shown that addition of 5–6 ng/L EE introduced into whole lakes caused near elimination (99% decrease) in fathead minnows in 2 years (10). The lake trout population declined by 25%. No effect was seen on bacteria or algae. The populations recovered 3–4 years after EE was removed (10). Thus, reducing or eliminating EE in contraceptive methods is beneficial to women who are at increased risk of VTE as well as to fish populations in rivers and lakes that would be exposed to waste water.

Female Hormonal Contraception

Most COC pills currently on the market contain 20–35 μg EE. A new product using a different synthetic estrogen, estradiol valerate, and the progestin dienogest has been approved by the U.S. Food and Drug Administration (FDA). Additional efforts have focused on use of natural E_2, 17β-E_2, which may have an improved safety profile over EE (2). A product containing E_2 and nomegestrol acetate as the progestin is approved for use in Europe but not in the U.S. It has been shown to achieve effective ovulation inhibition similarly to other pills on the market (11). Additionally, clinical trials of estetrol (E_4) combined with drospironone or levonorgestrel (LNG) have shown promise, although the amount of E_4 is quite high (15 mg) (12).

Another environmental concern is about waste products associated with contraceptive methods. Reassuring results were reported regarding the potential for EE leaching from discarded vaginal rings into landfills in The Netherlands (13). However, if use of the product increases markedly or waste disposal practices become less rigorous, leaching of EE from discarded monthly rings may become a problem. A vaginal ring delivering 15 μg EE with a potent progestin, Nestorone, has been developed by the Population Council and evaluated in the NICHD CCTN and by the International Committee for Contraceptive Research (14–17). A single ring can be used cyclically for 13 cycles, having the potential to improve acceptability, accessibility, and compliance by requiring fewer refills and only one ring per year to be discarded.

In an effort to eliminate EE in contraceptive products, new vaginal rings using a progestin and E_2 are in clinical development. One product, a monthly ring delivering 125 μg etonogestrel and 300 μg 17β-E_2, is in phase III clinical trials (18). Another ring undergoing dose-finding evaluation in the NICHD CCTN delivers Nestorone and E_2. This ring is designed to be used either cyclically or continuously for 3 months.

A nonoral combined hormonal transdermal patch containing EE and norelgestromin is currently on the U.S. market. New patches containing EE and gestodene or EE and LNG are in late-stage clinical development (19–21). A progestin-only patch using LNG is currently in phase II trials in the NICHD CCTN (2). Progestin-only formulations of Nestorone are under development for delivery as a transdermal gel and a Metered Dose Transdermal System spray (22).

Long-acting reversible contraceptive (LARC) methods are the most "green" forms of contraception from an environmental point of view. LARC methods are 10–80 times more effective than the typical failure rate for COC pills, vaginal rings, or patch methods (23). The most effective LARC methods are progestin implants (LNG or etonogestrel). With the lowest failure rate (<0.1%), high rate of continuation (82% at 1 year), and long duration of use (5–7 years), implants are extremely ecofriendly. The most common reason for discontinuation is irregular bleeding. LNG-releasing intrauterine systems have had a remarkable increase in popularity (24), and several newer versions (Skyla and Liletta) have entered the U.S. market in recent years. With a failure rate estimated at 0.2%, a 1-year continuation of 87%, and 3–5 years duration of use, these devices are highly ecofriendly. Many women reach amenorrhea, decreasing the use of sanitary products, and achieve potential health benefits in prevention of anemia or treatment of heavy bleeding. The nonhormonal LARC, a copper intrauterine device (IUD), also has a low failure rate (<1%), a 1-year continuation rate of 83%, and a duration of use of more than 10 years. The most common reason for discontinuation is heavy menstrual bleeding and cramping. There are almost no contraindications for using a copper IUD. Use in nulliparous women, including adolescents, is low, in part because of provider bias, but when women are given information about the relative effectiveness and safety of these methods compared with COCs and all other methods, LARCs have a very high uptake rate, especially if the device is available immediately (25). New copper IUDs are in clinical evaluation; it is possible that if bleeding and pain can be less of a problem for the newer devices, the popularity, especially in nulliparous women, may increase considerably. Increased numbers of women using these devices would likely have a marked reduction in the number of unplanned pregnancies in the U.S.

The two most effective progestin-only methods, implants and LNG-IUS, require a skilled provider for insertion or removal, which is a barrier for many women. Other progestin-only methods have much lower effectiveness in typical use but they may be easier to obtain.