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Pipeline for Contraceptive Development

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Abstract

The high rates of unplanned pregnancy reflect 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 with regard to safety for women who have contraindications to effective contraceptive methods but want to protect against pregnancy. It also will address a huge unmet need for men who want to control their fertility. Products under development for men would not introduce eco-toxic hormones in the waste water.

Investment in contraceptive research to identify new products for women has been limited in the pharmaceutical industry relative to investment in drug development for other indications. Pharmaceutical R&D for male contraception was active in the 1990's but was abandoned over 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).

Keywords

contraception; female contraception; male contraception; non-hormonal contraceptive development; green contraception

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 benefit in controlling

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overpopulation, there are a number of areas in which improvements can be made in limiting eco-toxic 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 eco-toxic hormone levels without compromising effectiveness. Although the processes are not entirely within our control, we can promote eco-friendly 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 US, 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-estradiol or its metabolites, estrone or estriol, in a number of biological assays (Table 1) (7). The extraordinary potency of EE is linked to a higher risk of venous thromboembolism 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 least 30-fold higher than estradiol in several *in vivo* fish assays (9). The eco-toxicity 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 and also to fish populations in rivers or 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 FDA. Additional efforts have focused on use of natural estradiol, 17β-estradiol, which may have an improved safety profile over EE (2). A product containing estradiol and nomegestrol acetate as the progestin is approved for use in Europe but not the US. It has been shown to achieve effective ovulation inhibition, comparable to other pills on the market (11). Additionally, clinical trials of estetrol (E4) combined with drospironone or levonorgestrel have shown promise, although the amount of E4 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 the usage 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 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 estradiol are in clinical development. One product, a monthly ring delivering 125 μg etonogestrel and 300 μg 17β-estradiol, is in phase III clinical trials (18). Another ring undergoing dose-finding evaluation in the CCTN delivers Nestorone and estradiol. This ring is designed to be used either cyclically or continuously for three months.

A non-oral combined hormonal transdermal patch containing EE and norelgestromin is currently on the US market. New patches containing EE and gestodene or EE and levonorgestrel are in late-stage clinical development (19–21). A progestin-only patch using levonorgestrel 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 (levonorgestrel 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 eco-friendly. The most common reason for discontinuation is irregular bleeding. LNG-releasing IUSs have had a remarkable increase in popularity (24) and several newer versions (Skyla and Liletta) have been introduced to the US 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 eco-friendly. Many women reach amenorrhea, decreasing the use of sanitary products, as well as potential health benefits in prevention of anemia or treatment of heavy bleeding. The non-hormonal LARC, a copper IUD, also has a low failure rate (<1%), a 1 year continuation rate of 83% and a duration of use in excess of 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 due to provider bias; but, when women are given the information about the relative effectiveness and safety of these methods compared to 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 US.

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.

DMPA is the only injectable product in the US but a newer formulation that is injected subcutaneously (instead of intramuscularly) and may be self-administered, could potentially remove some barriers to continuation. NICHD and WHO have investigated levonorgestrel butanoate as an injectable method of contraception. The early studies done by WHO demonstrated inhibition of ovulation for up to 5–6 months with a single 50 mg dose (26), however, the original formulation was prone to aggregation. Recent formulations have solved the problem of aggregation but some women returned to ovulation by three months after injection (27). Additional studies to improve duration of effectiveness are underway.

Progesterone receptor modulators (PRM), which have tissue selective agonist-antagonist properties, may provide an estrogen-free contraceptive option (28). Ulipristal acetate (UPA), a 19-norprogesterone derivative, acts as an antagonist in the ovary to inhibit ovulation but may have protective effects on breast tissue (29). A daily low dose of UPA (available in Europe and Canada) has been shown to be highly effective against pain and heavy bleeding associated with uterine fibroids. Studies are ongoing to determine whether low dose UPA may work as an alternative to progestin-only pills with an improved bleeding profile or amenorrhea. UPA has also been studied in a contraceptive vaginal ring and may be explored in an IUS (30, 31).

FEMALE NON-HORMONAL CONTRACEPTION

Research into non-hormonal methods of female contraception has been limited. Barrier or on-demand methods remain a high priority focus. A new female condom, the Woman's Condom (32), was evaluated for contraceptive effectiveness by the CCTN. The product is available in some international locations but has not yet been submitted for FDA approval. The new SILCs diaphragm, (Caya® in the US), is a one-size fits most design that eliminates the need for fitting by a clinician (33). Amphora™ is a new spermicide in late stage clinical development (34). The typical failure rates and discontinuation rates of these methods are higher than hormonal methods and much higher than LARC methods. However, if these methods are more easily available, they may be the choice of individuals who do not have access to health care facilities or who have infrequent sex and do not wish to use a continuous hormonal method.

Identification of novel targets for potential fertility regulation in women remains an intriguing challenge. Novel targets such as Phosphodiesterase 3A (35), Wee2 (36), Erk1/2 (37), Juno (38), and Zar1 (39) have been identified as possibilities for fertility regulation. Efforts to identify specific inhibitors of these targets are ongoing; at present, no agents have progressed to early clinical development.

MULTIPURPOSE TECHNOLOGIES

Infection from HIV, HSV, and other pathogens is a problem worldwide. Some drugs (such as efavirenz) that have been used to prevent or treat HIV infection have been shown to

markedly reduce the contraceptive effectiveness of implants (the most effective method of contraception available to women) (40). This is alarming because the maternal mortality is high in some areas that also have a high prevalence of HIV infection. Studies of microbicides to prevent HIV acquisition have been disappointing, in part, because participants do not use the product consistently or at all. Thus, the concept of Multipurpose Prevention Technologies (MPT) is to develop products that would protect against infection as well as pregnancy (34). Combination products would use agents that would not interfere with one another. There might be better compliance with MPTs than with products for one indication alone. MPTs might address situations in which perception of risk for one outcome (either pregnancy or infection) is somewhat low but motivation for preventing the other outcome is high, or in circumstances in which the need for concealment prevents use of a product for one but not both of the indications (Trojan horse theory). Currently, condoms and abstinence are the only available methods for STI prevention, and, while these methods are also used for birth control, pregnancy failure rates with typical use are above 18% (23). Research has focused on three products; all are vaginal rings containing levonorgestrel and an agent for prevention of HIV infection. The agents are Tenofovir (TFV) (developed by CONRAD), Dapivirine (developed by International Partnership for Microbicides) or MIV-150 (developed by the Population Council) (41, 42). The amount of LNG planned for use in the rings differs. For the TFV/LNG ring, the goal is to permit ovulation in order to maintain regular bleeding cycles and to rely on local effects, such as thickening of cervical mucus, to prevent pregnancy. Low dose LNG rings had been used previously in studies conducted by WHO and were shown to be effective in women who weighed less than 80 kg but had higher failure rates in higher weight women (43). The current design of the Dapivirine/LNG ring is to find a dose of LNG that will inhibit ovulation (44). Early phase clinical studies of the rings are ongoing. Potential barrier methods include the SILCS diaphragm, combined with active antiviral agents such as Tenofovir gel (42), and the new Women's Condom (45); both developed by PATH.

MALE HORMONAL CONTRACEPTION

Male condoms are the only reversible contraceptive methods available to men. Typical failure rate is 18% (23). Studies indicate that > 50% of men say they would be interested in using a reversible method (46, 47). There is potential for improving overall protection against unplanned pregnancy if both partners are using a method or if men have more options to control their own fertility. Hormonal male contraception effectiveness has been established (48). The quest for a male equivalent of "the pill" has been hampered by the lack of oral androgens that are an essential component of the method.

Hormonal methods in men use a similar feedback mechanism to the hormonal methods in women. In healthy men, testicular testosterone is maintained at a level that is 40–100-fold higher than circulating serum testosterone levels. This high intra-testicular testosterone concentration is required to support spermatogenesis. Administration of exogenous steroids suppresses testicular testosterone production through feedback inhibition on the hypothalamic-pituitary axis. Exogenous androgens, alone or in combination with a progestin or gonadotropin-releasing hormone antagonist, suppress secretion of gonadotropins, resulting in marked reduction of testosterone production in the testes. Below a threshold

amount of testicular testosterone, sperm production does not take place. However, low testosterone levels in serum result in loss of other androgen-dependent functions such as libido, erection, ejaculation and maintenance of muscle mass; thus, it is necessary to add exogenous androgens to maintain sufficient serum levels to support those functions while maintaining testicular testosterone below the threshold levels needed to initiate sperm production. Studies using this approach have shown high rates of severe oligozoospermia (<1 million/mL) or azoospermia (no sperm) resulting in high contraceptive efficacy with minimal side effects. East-Asian populations are more sensitive to suppression than some Caucasians; however, addition of a sufficient dose of progestin pushes the effectiveness to nearly 100% in all populations (49).

The challenge for developing the “male pill” is that oral testosterone is cleared too rapidly to be effective as a single daily dose regimen even in combination with a progestin. Multiple doses of oral testosterone per day would be impractical for contraception. Although methyl-testosterone has better oral bioavailability, it caused hepatotoxicity when used long-term. NICHD has developed new androgens that also bind to progesterone receptors. These molecules have the potential to be single-agent male contraceptive drugs. The two lead candidates in clinical development are: Dimethandrolone Undecanoate (DMAU) and 11β-methyl-nortestosterone dodecylcarbonate (50, 51). The drugs are not susceptible so 5α-reduction which may be beneficial to prostate health or to prevention of male pattern baldness. When administered orally or intramuscularly, DMAU is hydrolyzed to the active drug, dimethandrolone, a novel derivative of 19-nortestosterone that binds to both the androgen and the progesterone receptors. The drug has been evaluated in early phase I clinical trials in the CCTN and it was well-tolerated. Oral absorption was improved if the drug was taken with food (52). A first-in-man clinical trial of 11β-methyl-nortestosterone dodecylcarbonate is underway in the CCTN. Longer term evaluation of progestagenic androgens is necessary to determine if the drug is safe and can effectively suppress sperm production. These clinical evaluations will demonstrate if either of these drugs can be used as a single agent hormonal contraceptive for men.

Another synthetic androgen, 7α-methyl-19-nortestosterone (MENT), is currently being evaluated as a possible male contraceptive (53). MENT is not a substrate for 5α-reduction and may provide selective sparing of the prostate while supporting other androgen-dependent functions. Initial evaluations of MENT implants for use as an anti-spermatogenic agent were comparable to initial studies with testosterone, with about two-thirds of men showing dose-dependent spermatogenesis suppression. Improvements of the MENT implant resulting in sustained levels of MENT release require further testing in clinical trials.

Although an effective oral testosterone product has not yet been developed, transdermal testosterone gel is widely used in the US to treat hypoandrogenism. Combining testosterone gel and injections of the progestin, DMPA (used for female contraception), resulted in effective sperm suppression in 90% of subjects (54). Notably, this method involved two FDA-approved products, albeit the use was for off-label indications.

Taking advantage of the transdermal effectiveness of testosterone, another regimen in development has evaluated daily applications of Nestorone (NES) gel and testosterone gel (T

gel) compared with T gel alone in a randomized controlled trial in the CCTN. The combined use of NES gel (8 mg) and T gel (100 mg) suppressed sperm concentration to <1 million/mL or to azoospermia in 89% of men compared to only 23% with testosterone gel and a placebo gel (55). Suppression of serum gonadotropins (LH and FSH) occurred rapidly. Gonadotropin hormone concentrations that were greater than 1 IU/L after 4 weeks of treatment predicted treatment failure (sperm concentration >1 million/mL) with 97% sensitivity (56). Most failure was due to inconsistent or non-use of the products rather than to non-response of the individual to the drug regimen. When asked about acceptability of the regimen, over half of participants reported being satisfied or extremely satisfied with this method of contraception (57). Studies are planned in the CCTN to evaluate the combined NES/T in a single preparation for use as a primary method of contraception in couples to determine if this user-controlled male method would be effective and acceptable for contraception.

Hormonal male contraceptive methods have proven effective. Long term safety needs to be demonstrated before any of the methods would be considered for approval by FDA. Any product used systemically must be extremely safe because men do not face the medical risks associated with pregnancy; thus, the risk/benefit ratio is altered. It's an interesting question to consider possible risk to one individual to prevent potential health consequences to another individual. The goal of identifying additional health benefits for male methods is especially attractive. Realistically, long-term trials in large numbers of couples means that it will be many years before a product could reach the market. Additionally, pharmaceutical investment will be needed to achieve that goal.

MALE NON-HORMONAL CONTRACEPTION

Non-hormonal options for male contraception are at an earlier stage of discovery or development. Research has focused on targets that would inhibit sperm production as well as targets that could inhibit sperm function. The most promising targets are those for which a small molecule inhibitor has been shown to regulate sperm production or function in an animal model or in studies in men.

One promising target is the pathway for retinoic acid (RA) synthesis. RA is essential for initiation of meiosis in spermatogenesis. Several approaches have validated this pathway as a promising target for non-hormonal male contraception. Bisdichloroacetyldiamines (BDADs) were long ago discovered to suppress spermatogenesis (58). One BDAD, WIN 18,446, was used to treat over 60 men for one year. It was well-tolerated and caused excellent inhibition of spermatogenesis. Unfortunately, use with alcohol caused a severe disulfiram reaction and the development of the drug was abandoned. The action of BDADS was discovered to block testicular RA biosynthesis through irreversible inhibition of alcohol dehydrogenase 1A2 (59). Inhibition of another target in the RA synthetic pathway, using a pan-retinoic acid receptor antagonist, BMS-189453, also demonstrated reversible inhibition of spermatogenesis in a mouse model (60). The pan-antagonist is not suitable for contraception due to potential for systemic toxicity at higher doses. The retinoic acid receptor α variant is essential for spermatogenesis and knock-out animals show no other defects. Molecular modeling and drug design are being used to develop highly specific potent drug candidates to regulate the RA synthetic pathway to inhibit sperm production without off-target effects.

Another promising target is BRDT, a testis-specific member of the bromodomain protein family that is critical for chromatin remodeling during spermatogenesis (61). Mice with homozygous *Brdt* mutations generated by targeted mutagenesis were viable but male animals were sterile (62). An inhibitor against bromodomain proteins suppressed spermatogenesis in mice, indicating potential for developing a more specific inhibitor of BRDT as a male contraceptive (63). Efforts are underway to design inhibitors with specificity for the testicular target.

Several drug candidates target Sertoli-germ cell adhesion to cause release of immature spermatids from the seminiferous epithelium. An indenopyridine, CDB-4022, has been shown to cause rapid inhibition of mature sperm production in primates and stallions with full reversibility and no apparent side effects (64, 65). Indazole carboxylic acid derivatives (H2-gamendazole and Adjudin) have been demonstrated to cause infertility in animal models. Oral doses of H2-gamendazole inhibited fertility in rats (66). The effects were reversible with low doses of drug but irreversible at higher doses. Targeting the drugs to the Sertoli cell is a challenge. The specificity of Adjudin for the testis germ cell-Sertoli cell junction was enhanced by conjugating the drug to a recombinant FSH-binding fragment (67); however, the peptide reduces the oral bioavailability and would not be practical for a commercial drug. Specificity, reversibility and safety need to be evaluated in higher mammals to determine if there is a safe therapeutic window for the drugs.

Targets that affect sperm motility have been identified. They include ion channels, ion pumps and kinases, which are considered easily druggable. CatSper, for calcium ions, and KSper, for potassium ions, are sperm-specific ion channels and both are required for male fertility (68). Gene mutations and deletions in animal models affect male fertility without apparent systemic effects. HC-056456, an inhibitor of the calcium ion channel, may represent a potential candidate, with initial promising *in vitro* studies showing that the drug prevents hyperactivation of sperm (69). Progesterone and prostaglandins activate CatSper through a non-classical binding domain, causing sperm tail hyperactivation. Physiologically, the likely source of progesterone is from the cumulus-oocyte-complex after it leaves the ovary, enters the fallopian tube and begins to migrate toward the ampulla region. Sperm enter from the other end through the utero-tubal junction and form a reservoir in the isthmus region (70). Although millions of sperm are ejaculated, only a few hundred bind to the wall of the oviduct and undergo capacitation (71). Sperm can remain viable for several days until progesterone and other signals cause them to detach, hyperactivate, and swim toward the ampulla of the oviduct where fertilization can occur. Disruption of the interaction of progesterone with sperm receptors may be another target for contraception either in men or women. This disruption of communication may be one of the mechanisms of action of drugs used for emergency contraception (72).

The sperm Na+/H+-exchanger (sNHE) and a soluble adenylyl cyclase (sAC) form a complex and both are important in sperm motility (73). Knock-out of the sNHE gene in mice caused infertility, making the exchanger another potential sperm-specific target for male contraception. The Na+/K+-ATPase (sodium pump) is also involved in sperm motility and capacitation (74). Na+/K+-ATPases are found in many tissues but the α4-subunit of the sperm Na+/K+-ATPase pump appears to be necessary for sperm function; α4-subunit

knock-out male mice are completely infertile (75). Cardenolide analogues are known to inhibit Na+/K+ pumps and have been used clinically to treat congestive heart failure. Ouabain, a cardenolide analog, has higher affinity for the α4-subunit than other sodium pump subunits in both mice and humans. Targeted drug design, using the ouabain scaffold may yield derivatives with specificity for the α4-subunit and with selective regulation of sperm function (76, 77).

Several testis specific serine/threonine kinases (TSSK) are important for spermatogenesis and are druggable targets. Male infertility in knock-out mice indicates a critical role for TSSK 1 and 2 in spermiogenesis (78, 79). Progress has been made on isolating a target protein, TSSK 2, and this will facilitate exploration for small molecular drug candidates that could regulate sperm production and function (80). Determining how to use such drugs, so that sperm remain irreversibly inhibited after ejaculation, remains to be demonstrated.

Additional targets arise in the epididymis. Eppin is an epididymal protease inhibitor added to the sperm surface. Inhibitors of eppin function can impair sperm motility (81). A number of ADAMs family proteins are expressed exclusively or predominately in the testis or epididymis (82). In ADAM-3 knock-out mice, sperm were unable to enter the oviduct (83); however, it is unclear if human sperm have the same requirement. Several ADAMs proteins form complexes that are required for sperm-zona pellucida or sperm-egg binding (82). Izumo1 is a sperm surface protein that binds to JUNO on the egg leading to sperm-egg fusion (84). Many other potential targets that effect sperm function have been identified. If these targets are to be utilized for male contraception, the challenge remains to show how they can be regulated in adult men to effectively inhibit sperm function after sperm enter the female reproductive tract.

The non-hormonal male contraceptive pipeline is robust but it is in an early stage of development. In addition to those described above, research is ongoing to further characterize targets and identify specific small molecule regulators. Effort and resources are directed toward discovery and validation of new targets, lead candidate identification, optimization, and eventual preclinical drug development to move compounds toward clinical evaluation.

CONCLUSION

A variety of new contraceptive methods are under development for both women and men. Existing and newly developed LARC methods remain the most effective and eco-friendly choice of contraceptive methods for women. Ideally, contraception should be highly effective with minimal side effects, easy to use, and widely accessible in order to have the greatest impact. For women who choose to use a non-LARC method, it is important that they have a method that is highly acceptable rather than merely tolerated since user compliance is the most likely determinant of effectiveness in short-acting or daily methods. Contraceptive products that bring additional health benefits may improve both uptake and compliance. Vaginal rings for contraception and for MPTs are in development. New male methods show promise but still remain a long way off from being approved by the FDA. The introduction of a male method to the mix has the potential to dramatically reduce unplanned

pregnancy rates. It likely represents a new market rather than a significant reduction in the use of female contraceptive methods. New directions of contraception research could incorporate the concept of ‘green contraceptives’. Contraception is already a primary tool for addressing population growth, which consequentially decreases the human burden on the environment. However, there are many opportunities in contraceptive design, manufacturing, materials, distribution, consumer use and disposal that could be improved if approached through an eco-friendly lens. By incorporating more environmentally sustainable practices now while increasing efficacy and availability of family planning globally, the contraceptive R&D community could play a significant role in the preservation of our environment.

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Table 1

Potency of Ethinyl Estradiol (EE) and Estrone (E1) relative to Estradiol (E2)

	Potency relative to E2		
Human assays [7]	**E2**	**E1**	**EE**
Serum FSH	1	0.8	150
Serum Angiotensinogen	1	1.4	330
Serum SHBG	1	0.5	500
Serum CBG	1	1.0	614