Continued need for contraception

With a predicted scenario of median total fertility rate (TFR) at the replacement value of about 2.1, the world population will increase from 6.9 billion today to about 11 billion people by the middle of the next century before it gradually declines. According to United Nations Population Council estimates, even if a more rigorous low fertility rate of 1.6 or 1.4 is achieved (as it has been in some countries), the population is expected to grow steadily throughout this century.1

Regardless of the fertility scenario, family planning continues to be essential. In the United States, the TFR hovers right around replacement (2.12 in 2007),2 whereas in Canada the rate (1.6) is similar to that observed in Europe.3 The fact that approximately half of unintended pregnancies in the United States occurs among users of contraception4 indicates that the current contraceptive method choices are not meeting the needs of all couples. Therefore, to improve the utility of contraception, there is an urgent need to develop methods that are less difficult to use, have fewer side effects (real or perceived), and are more convenient and cost-effective than currently available methods.

Innovations in female contraception

Innovative contraception technology, research, and development programs are currently underway. In this review, they will be presented by categories. Many of the innovations have been studied in the United States through the Contraceptive Clinical Trial Network (CCTN). The CCTN, formed in 1996, consists of centers that conduct research in contraceptive technologies and methods and use resources of the Contraception and Reproductive Health Branch, of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH). The CCTN centers have conducted clinical trials of oral, injectable, implantable, and topical contraceptive drugs and devices.

Barrier methods

One of the benefits of barrier methods is the potential for protection against transmission of human immunodeficiency virus (HIV) infection and other sexually transmitted infections (STIs) in addition to providing contraception. A new woman’s condom that is soft, thin, and easy to use because it can be inserted like a tampon is being developed by the Program for Appropriate Technology in Health (PATH) and is currently being tested in phase 3 clinical trials in the CCTN. Another PATH product is a one-size-fits-all diaphragm. The effect of these methods on reducing the transmission of STIs is unknown and will require additional study.

Other methods undergoing study are vaginal gels that possess spermicidal and microbicidal properties. BufferGel (ReProtect Inc, Baltimore, MD) (an acid-buffering gel microbicidal/viricidal spermicide) and C31G have been investigated by the CCTN. In a study comparing diaphragm use with either BufferGel or nonoxynol-9 (N-9). The 6 month pregnancy rate per 100 women was 10.1% (95% confidence interval [CI], 7.1–13.1%) for BufferGel and 12.3 (95% CI, 7.7–16.9) for N-9.5 Overall, BufferGel was considered as safe and acceptable as N-9.5 However, BufferGel did not alter the risk of HIV infection in a recent randomized efficacy study in Africa.6

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subjects who experienced any treatment-related adverse events was significantly lower in the C31G-treated group (35% vs 41%, \( P = 0.02 \)). There was no significant difference in the proportion reporting genitourinary discomfort (C31G, 2.5%; N-9, 3.4%).

Notably, a large-scale, randomized study from Nigeria evaluating C31G vs placebo gel showed no reduction in the risk of HIV acquisition. In fact, the placebo gel showed no reduction in the study from Nigeria evaluating C31G vs

The principal vascular risks with COCs are associated with the estrogen component. This is due to estrogen-driven induction of prothrombotic globulins in the liver. Over the years, the safety modification has been dose reduction of ethinyl estradiol. More recently, the metabolic differences between ethinyl estradiol and natural estradiol have prompted interest in research with estradiol-containing pills.

Stradiol, once it is absorbed from the gastrointestinal tract, is largely isomerized to estradiol and estrone (and estrone sulfate) and circulates at lower serum levels. Although estradiol does exert a hepatic first-pass effect when taken orally, this isomerization reduces the impact during recirculation. Data from menopausal use have shown that transdermally and vaginally administered estradiol is not associated with an increased production of hepatic globulins and therefore has a lower risk for thrombosis. In contrast, ethinyl estradiol is a potent inducer of hepatic globulins if given orally or transdermally.

A new oral COC containing estradiol valerate and dienogest (Natazia; Bayer Healthcare, Wayne, NJ) has recently been approved by the US Food and Drug Administration. In a study comparing the estradiol valerate/dienogest COC with a monophasic COC containing ethinyl estradiol and levonorgestrel, the estradiol valerate/dienogest pill had a superior bleeding profile. Women who received the estradiol valerate/dienogest pill reported significantly fewer bleeding/spotting days than did those who received the COC containing ethinyl estradiol 20 mcg/levonorgestrel 100 mcg over the first (mean, 17.3 ± 10.4 vs 21.5 ± 8.6 days, respectively; \( P < .0001 \)) and second (13.4 ± 9 vs 15.9 ± 7.1, \( P < .0001 \)) 90 day reference periods. The favorable bleeding pattern associated with the estradiol valerate/dienogest COC has also been studied in women who experience well-defined heavy menstrual bleeding.

In a randomized, placebo-controlled study of 190 women without pelvic pathology evaluating the efficacy of estradiol valerate/dienogest for the treatment of idiopathic heavy or prolonged menstrual bleeding, the women who received the estradiol valerate/dienogest combination had a 67% reduction in bleeding that was evident with the first withdrawal bleed after starting active treatment.

These results are highly significant because prior studies of OCs that have used similar objective menstrual blood loss quantification methods to evaluate treatment response in women with heavy bleeding have shown a mean reduction of only 43% and 35% at 2 and 12 months’ use, respectively.

Another product containing estradiol and nomegestrol acetate is in clinical development. Unlike the majority of older progestins, which are 19-nortestosterone derivatives and were synthesized primarily for their antigonadotropic activity, nomegestrol acetate (NOMAC) is a 19-norprogesterone derivative that lacks affinity to steroid receptors other than the progesterone receptor. NOMAC exerts potent antiestrogenic effects at the level of the endometrium and has powerful antigonadotropic activity, without residual androgenic or glucocorticoid properties.

A review of the pharmacologic properties and safety profile of NOMAC showed that it has applications for the treatment of some gynecologic disorders (menstrual disturbances, dysmenorrhea, premenstrual syndrome, uterine diseases, and heavy menstrual bleeding), and in combination with estrogen, it is an effective contraceptive. At a dosage of 1.25 mg/d, NOMAC inhibits ovulation, and at dosages of 2.5 and 5 mg/d, ovulation and follicle development are suppressed.

A 6-cycle open-label, randomized study compared the effects of a contraceptive containing NOMAC/17beta-estradiol with one containing drospirenone/ethinyl estradiol. This study found that the NOMAC/17beta-estradiol combination achieved consistent ovulation inhibition, and its suppressive effects on the ovaries were similar to
those of the drospirenone/ethinyl estradiol combination.

Nonoral hormonal contraceptives
In addition to the current contraceptive patch, ring, and injectable contraceptives, a new injectable containing levonorgestrel butanoate is under investigation in the CCTN. This compound has been shown to suppress ovulation for up to 5-6 months after a single injection of 50 mg, and a 12.5 mg dose inhibited ovulation for an additional 2-3 months.24 It is hypothesized that the levonorgestrel butanoate injection may have fewer progestin-related adverse effects than the current medroxyprogesterone acetate injection.

A new combined contraceptive patch that delivers low-dose ethinyl estradiol and gestodene has been studied in an open-label study of ovulation inhibition. All of the treated women demonstrated suppression of follicle growth and rupture.25 The ethinyl estradiol dose (9 mcg/d) is much less than that of the currently available patch (20 mcg/d). Phase 3 clinical trials of this patch were recently completed in Europe and the United States.

A progestin-only patch is also in development. The levonorgestrel patch is estrogen free and therefore could be used in women with medical contraindications to estrogen (eg, thrombosis risk or migraine with aura) or in postpartum nursing women. This patch is in phase 2 testing through the CCTN, with endpoints of cervical mucus effects, follicle growth, and ovulation. Favorable results would set the stage for a phase 3 study.

Nestorone, a highly potent 19-norprogesterone derivative, is a novel progestin that has a neutral metabolic profile and is not active orally.26 Two large phase 3 efficacy studies were recently completed evaluating a contraceptive vaginal ring releasing 150 mcg/d of nestorone and 15 mcg/d of ethinyl estradiol (the same ethinyl estradiol dose as the current etonogestrel ring). Administered in a 21 day on, 7 day off regimen, the same ring is reinserted every month for a year. This may offer the advantage of fewer trips to the pharmacy, fewer copays, and greater convenience.

This product was developed by the Population Council and tested through the International Committee for Contraceptive Research and the CCTN. A new drug application is pending. Nestorone has also been tested in other products, including a combination-contraceptive vaginal ring with estradiol, and alone in gel, ring, and spray formulations.

A natural progesterone contraceptive ring releasing 10 mcg/d is available in open-label study of ovulation inhibition. The ring is effective for 3 months (although a study also showed efficacy for 4 months), has no effects on breastfeeding or infant growth, and was designed for contraception in lactating women.27,28

A new levonorgestrel intrauterine system (IUS) releasing 20 mcg/d is in clinical development. This is the same size and dose and similar in design (both use the Nova-T frame) to the currently marketed Mirena (Bayer Healthcare) system. Phase 3 trial is in progress, and the device may be approved within the next 3 years. Two low-dose levonorgestrel IUSs are also in clinical development. They are smaller than the current 20 mcg system and may offer advantages with ease of insertion and removal, particularly in nulliparous women.

NICHD has also funded projects investigating novel nonhormonal pathways in female fertility that could be exploited for contraceptive purposes. These include oocyte maturation, cumulus expansion, and follicle rupture. The phosphodiesterase-3 inhibitor ORG 9935, an inhibitor of meiosis, has been shown to prevent pregnancy in a small contraceptive study in breeding hares of cynomolgus macaques.29

Permanent contraception
Nonsurgical female sterilization is an area that has applicability in developing countries because it may be performed by nonphysician providers and could potentially be cost efficient. This same features could also make an appropriate technology highly popular in more developed nations.

Quinacrine is the best-characterized agent, with multiple human studies completed.30-33 Transcervical placement of quinacrine pellets at the uterine fundus produces documented tubal occlusion and significant reduction in pregnancy rate.35 A study of more than 30,000 Vietnamese women who underwent quinacrine sterilization demonstrated high acceptability of the method and a safety profile that contrasts favorably to the risks associated with surgical sterilization or unintended pregnancy.33 However, this study generated concerns regarding the lack of toxicology data for local application of quinacrine.

Currently the World Health Organization has a moratorium on funding further quinacrine studies, pending additional animal studies of long-term safety. Polidocanol is a nonionic surfactant, injected as a solution or foam that leads to endothelial disruption. It is commonly used as a sclerosant for vein occlusion.34 Preliminary experiments using a liquid form showed no effect in a monkey model,35 but the foam approach is currently being studied.

Emergency contraception
Ulipristal acetate is a novel antiprogestin that was developed at the NIH. It has been tested for a number of gynecologic applications, including contraception and treatment for fibroids.36 A continuous regimen of a vaginal ring formulation of ulipristal has been evaluated in phase 1 and 2 studies.

An oral form of ulipristal acetate was recently approved for emergency contraception. It is more effective than levonorgestrel emergency contraception when used within 24 hours or up to 5 days after unprotected sexual intercourse or suspected failure of a contraceptive method.37 Unlike levonorgestrel, ulipristal acetate inhibits follicle rupture after the luteinizing hormone surge.38 Combining data from 2 studies allowed analysis of a sample sufficiently large to demonstrate that ulipristal acetate almost halved the risk of pregnancy compared with levonorgestrel in women who received emergency contraception within 120 hours after sexual intercourse (odds ratio, 0.55; 95% CI, 0.32-0.93).37
When emergency contraception was used within 24 hours of unprotected sex, the risk of pregnancy was reduced by almost two-thirds in users of ulipristal acetate compared with levonorgestrel (odds ratio, 0.35; 95% CI, 0.11–0.93). 37

Single-dose levonorgestrel has also been studied, either orally to be taken up to 24 hours before sex or as a gel to be used during sex as a vaginal lubricant. 39 This application may cause irregular bleeding and is more appropriate for use in women who have infrequent sexual intercourse.

Other agents Methods that inhibit the prostaglandin endoperoxide-2 (COX-2) pathways may have an effect on follicular rupture. Several studies have evaluated meloxicam, a moderately selective COX-2 inhibitor. A dose effect leading to ovulatory dysfunction was noted when meloxicam was administered for 5 consecutive days in the late luteal phase in a strategy designed to test the potential as an emergency contraceptive. 40 A meloxicam dose of 15 mg added to the usual 1.5 mg dose of levonorgestrel used for emergency contraception increased the proportion of cycles with no evidence of follicle rupture. 41

Innovations in male contraception The research and development of male contraception has progressed. One of the major barriers to availability is the belief (not supported by studies) that agents would not be generally accepted or widely used. 42 Both hormonal and non-hormonal approaches have been investigated as well as novel approaches to nonsurgical sterilization.

Several promising approaches have been tested. A 500 mg monthly testosterone undecanoate injection has been evaluated in China. 43 The combined method failure rate was 6.1%, comprising 4.8% with inadequate suppression and 1.3% with postsuppression sperm rebound. No serious adverse events were reported and spermatogenesis returned to the normal fertile reference range in all but 2 participants. 43

Use of a progestin may increase the suppression of spermatogenesis with a lower dose of testosterone. Agents that have been tested include norethindrone or etonogestrel implants. 42 The Population Council has developed 7-alpha-methyl-19-nortestosterone (MENT) implants. Because MENT is so potent, the implants are small and have a long duration of action; 2 or 3 implants can deliver high MENT levels for up to a year. 44 MENT may be superior to testosterone because it is not metabolized peripherally nor does it undergo 5-alpha reduction. This reduces the impact on prostate growth and male-pattern baldness. MENT has additional benefits of favorable actions on muscle and bone, increasing lean body mass.

Summary Progress in reducing unintended pregnancies and providing adequate contraception with few side effects is a team effort that requires ongoing cooperation of clinicians, scientists, and clinical trial subjects as well as the cooperative support of industry, foundations, and the government. New contraceptive choices will improve opportunities for correct and consistent use of a highly effective method, thereby reducing nonuse and contraceptive failure.

REFERENCES