THE FUTURE OF CONTRACEPTION

North American women are having fewer children, and many of these women are conceiving at later ages than ever before. Fully one-fifth of North American women now have their first child after age 35. There is now a need for effective reversible contraception for larger numbers of women throughout the reproductive years. Contraceptives of the future will need to combine simplicity, efficacy, safety, tolerability, reversibility, coital independence and protection from sexually transmitted diseases. It is likely that a range of reversible and permanent contraceptive options will be required to deal with different medical and social situations, personal preferences, and differing contraceptive needs at different stages of reproductive life.

NATURAL FAMILY PLANNING

Natural family planning will be simplified in the future with the use of handheld electronic devices that determine and store information on basal body temperature and menstrual cycles in order to help women keep track of, and alert them to, their fertile period, allowing abstinence or use of barrier methods at that time. Already such devices have proven reasonably successful for highly motivated couples who are able to use and understand the technology.[1] New kits (Personae®) will soon allow women to use a home monitoring system that measures and records urinary estrone-3-glucuronide and luteinizing hormone in order to predict the fertile time of the cycle.

CONDOMS

Condoms made from strong, thin polyurethane and other newly developed polymers will soon be available.[2,3] These new contraceptive products will cause less interference with sensation, should provide excellent barriers to infection, be non-allergenic, and more resistant to breakage and degradation by heat, light and oily lubricants.

A range of female condoms have been tested. Satisfaction with most of these remains low, even in highly motivated couples.

NEW HORMONAL CONTRACEPTIVES

FEMALE

Standard oral contraceptives will be used more often by women in their later reproductive years, not only to provide contraception, but also to suppress perimenopausal symptoms and regulate abnormal bleeding.

In some developing countries, trials are underway with a long-acting, once-a-month oral means to avoid unintended pregnancy.[2] One approach, currently employed in China, involves taking a long-acting contraceptive steroid at the time of menstruation to prevent ovulation in the subsequent cycle. A second approach that seemed theoretically promising, but which has yet to prove effective in clinical trials, is the ingestion of a monthly pill designed to truncate the luteal phase and induce menstruation. For women having infrequent sexual intercourse, such approaches, or the use of postcoital methods (the Yuzpe method, or levonorgestrel-only regimen) might have appeal.[4,5]

A vaginal ring containing progesterone alone is under development for breastfeeding women, and combination estrogen-progestin rings will soon be available. These avoid the need to remember to take a medication every day and can simply be removed for one week of each month, or every second month, to allow menstruation to occur.

In the future, greater use of injectable steroids including depo-medroxyprogesterone acetate (recently

approved for contraceptive use in Canada) and subdermal implants, for example Norplant®, is likely.[6,7] The second generation of Norplant® will consist of two rods that are simpler than the original system to insert and remove. A four-cm ethylene vinylacetate rod releasing 3-keto-desogestrel, the biologically active metabolite of desogestrel (Implanon) provides effective contraception for up to two years.[8] Silastic implants releasing the progestin, Nesterone (ST-1435), provide two years of ovulation inhibition,[9] while those containing nomegestrol acetate work for one year.[10] All these systems offer high levels of contraceptive efficacy and simplicity, but share the problems of irregular bleeding and the need for insertion and removal.[5,11] Nesterone is orally inactive, hence, it may be safely used in lactating women, with no absorption from breast milk into the newborn.[12]

Researchers are now pursuing the possibility of biodegradable implants (poly E caprolactone [Capronor], which releases levonorgestrol, and a norethisterone-releasing implant) that will eventually dissolve in the body but will be removable and reversible in the initial period after insertion.[6]

Injectable microspheres containing 17β-estradiol and progesterone may also afford long-lasting contraception in the future.

Male

Attempts to find a hormonal means to induce reversible male sterility are lagging. Research studies which have used weekly testosterone injections to demonstrate the feasibility of this approach have been associated with a three-month delay until oligo- or azoospermia is achieved, and typically there is a three-month recovery period before the return of fertility after cessation of use.[5,13,14] Future trials will evaluate such long-acting testosterone esters as testosterone buciclate, injectable testosterone pellets or an implant releasing other synthetic androgens. Androgen therapy may result in side effects including increased irritability, lowered levels of high density lipoprotein and increased acne. Recent research suggests that the addition of progestin may afford contraceptive efficacy for men on lower androgen dosages, which would reduce side effects and improve safety.[2] Unfortunately, even this approach is not effective in all men, and this lack of predictability, together with the need for weekly injections, is likely to make it unacceptable for most couples.

A second approach has been to suppress testicular function completely with gonadotrophin-releasing hormone (GnRH) agonists or antagonists, and to give replacement androgens to retain muscle mass, male sexual characteristics and libido.[2] The expense and inconvenience of this method currently make its widescale acceptance doubtful.

Immunocontraception

Considerable effort has gone into the development of vaccines which may provide long-term reversible contraception.[2] Although promising results have been achieved in animal models and early human pilot studies, major hurdles remain before large-scale human clinical trials can commence.

Immunocontraceptives for Men

Attempts to develop vaccines for men have involved the production of antibodies to GnRH and to follicle stimulating hormone (FSH).[15] The former approach requires hormone replacement therapy because luteinizing hormone (LH)-stimulated testicular androgen production is suppressed by the lack of GnRH stimulation of the pituitary. In contrast, anti-FSH antibodies would not interfere with androgen production, but create the possible risk of systemic immune reactions. Antibodies to sperm surface proteins have been developed to immobilize sperm, but these carry a risk of inducing local testicular inflammation. To avoid this, antibodies are now being developed which attach to sperm only after they leave the testes and before ejaculation. These antibodies attack the sperm surface protein, fertilin, which undergoes subtle chemical changes that allow its recognition after the sperm exit the testes.

Immunocontraceptives for Women

Two approaches have been taken towards developing antibodies against the early embryo.[15] In India, an antibody has been developed to the native β-hCG subunit (as the α subunit of hCG is shared by other pituitary hormones). Because of concern about potential cross reactivity between antibodies to β-hCG and the pituitary cells, the World Health Organization has been working on another anti-β-hCG antibody that targets a 37-amino acid fragment of β-hCG. Unfortunately, these antibodies are effective for only a few months. Currently, researchers are testing the feasibility of incorporating

vaccines into biodegradable spheres which would allow their ongoing release. Because there is no change in menstrual cycle length, the developers of these technologies claim that they are working before pregnancy is established (i.e. completion of implantation) and, therefore, are not abortifacient. There has been strong political opposition in the USA to the development of anti β-hCG antibodies as a means for contraception.

Another approach has been to develop antibodies to glycoproteins from the zona pellucida. These would prevent fertilization.[15] Concern has been raised that antibodies to the entire zona pellucida could trigger autoimmune reactions which might lead to premature ovarian failure. Researchers are now working on vaccines for women which would be directed against sperm (which would be recognized as foreign within the female system). Circulating antibodies, however, are inadequate to immobilize the millions of sperm released into the genital tract and, therefore, mucosal immunity is required. Difficulties have been encountered in achieving such a level of immunity.

INTRA-UTERINE CONTRACEPTIVE DEVICES

An improved understanding about the mechanisms and effects of intra-uterine contraceptive devices (IUCDs) is now allowing longer-term placement, which minimizes the risks of perforation and infection associated with their insertion.[16-18] New types of IUCDs (e.g. GyneFix) employ smaller frameless and flexible devices fixed into the myometrium, resulting in fewer reports of cramps, bleeding and expulsion.[19] Hormone-containing intra-uterine systems (IUS), containing levonorgestrel, will soon become available in North America.[20] Levonorgestrel-containing IUCDs are effective for five years. They cause dramatic suppression of menstrual bleeding and may reduce the incidence of PID.

SPERMICIDES

Available spermicides work as detergents which degrade sperm. These detergents can also kill normal vaginal microorganisms, and result in vaginal irritation.[2] New chemicals which may impede sperm maturation, or prevent the acrosome reaction that precedes sperm-egg binding without these irritating effects, are being evaluated.[2,5]

To combat sexually transmitted diseases (STDs), newer chemicals are being tested which, when added to spermicides or vaginal lubricants, would coat the entire vaginal wall and cervix.[21] Delivery of spermicides may be achieved through their incorporation into vaginal sponges[22] or by their incorporation into hydrophilic lubricants that adhere to the cervical and vaginal surfaces, thus providing protection for extended intervals.[23]

STERILIZATION

Permanent sterilization will remain the preferred option for many couples. Vasectomy rates are increasing due to its safety and simplicity, as well as changing attitudes among North American men.[24]

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