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In This Issue

Preconception Care and Contraception

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Preconception Care and Contraception

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Educational Objectives:

The health care provider should be able to:

- describe the importance of preconception intake of folic acid
- counsel specific populations regarding the appropriate recommendations for folic acid supplementation
- describe management of anti-seizure medications
- list other teratogens

Healthy pregnancy outcomes often depend on a woman's history and health, and, in addition, may be influenced by one's lifestyle for the several months prior to conception. However, many women do not seek health care before becoming pregnant: in the 1995 National Survey of Family Growth (NSFG), an estimated 50% of pregnancies were unintended.^{1,2} Although highly effective methods of contraception are available, women using contraception may still be at risk for unintended pregnancy through incorrect or inconsistent use or actual method failure. Unintended pregnancy is more common with less effective contraceptive methods such as condoms or spermicides, but even oral contraceptives (OCs), the most common and effective method of contraception, have a first-year typical-use pregnancy rate of up to 8%.³ First-year typical-use pregnancy rates are expected to be similar (8%) for the transdermal contraceptive patch (Ortho-Evra®) and vaginal ring (NuvaRing®), although these newer methods have not been in use long enough to generate sufficient data on typical-use pregnancy rates.³

The first 4 to 10 weeks of pregnancy are the period of greatest fetal sensitivity to maternal health conditions and environmental exposures.⁴ Unfortunately, many women may not even be aware that they are pregnant during this time. Others, even if they are aware, may wait several months after conception before visiting a clinician. In the United States, nearly 20% of pregnant women have no prenatal care during the critical first trimester.⁵ Accordingly, prenatal care may begin too late to reduce the incidence of some adverse pregnancy outcomes.^{6,7} Often it is during the preconception period that improved health practices and risk factor modification can reduce preventable causes of adverse perinatal health outcomes. Recreational drugs, prescription medications, and alcohol are a few of the

lifestyle influences that may negatively affect fetal development during this critical time.

Adequate nutritional reserves are especially needed during this period, but women of reproductive age often have poor nutritional practices.⁸ The Third National Health Examination Survey of nonpregnant, nonlactating women aged 20 to 50 between 1988 and 1994 found that, irrespective of ethnic origin, 75% of women surveyed did not ingest adequate levels of calcium, and 90% of women had inadequate dietary intakes of folate and vitamin E.⁹ Despite much publicity regarding the benefit of supplemental folic acid for reducing the incidence of fetal neural tube defects, a March of Dimes study found that only 7% of women aged 18 to 45 in 2001 knew folic acid should be taken regularly before becoming pregnant,¹⁰ and a 2004 report from the Centers for Disease Control and Prevention found that only 40% of women aged 18 to 45 took such a supplement daily.¹¹

Importance of Early Preconception Care

Preconception care, including risk factor assessment and management of identified risks, should be targeted to all women of reproductive age at risk for pregnancy, including perimenopausal women, regardless of their intent to become pregnant. The large number of unintended pregnancies, women's overall nutritional status, and other factors that may affect early events in a developing fetus provide the basis for this recommendation.¹²

The goals of preconception care are: 1) to identify any medical or social condition that may put a prospective mother or fetus at risk of morbidity or mortality,¹³ and 2) to ensure that women and their partners are in an optimal state of physical and emotional health if a pregnancy were to occur.¹⁴

The US Department of Health and Human Services (DHHS) priorities for 2010 include an overall reduction of approximately 50% in unintended pregnancies; DHHS is also considering making preconception health promotion a priority.¹⁵ Women should be counseled about pregnancy and preconception care prior to discontinuing contraception. No reversible method of birth control has been associated with an increased risk of primary or secondary infertility, although there may be a delay in return to fertility following discontinuation of some steroidal methods, especially the long-acting

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progesterin injection (Depo-Provera®; depot medroxyprogesterone acetate [DMPA]).¹⁶⁻¹⁸

However, there is no reliable method to predict when an individual woman will become fertile after stopping any steroidal method of contraception, so women need to anticipate the possibility that pregnancy can occur shortly after stopping contraceptive use. Ideally, preconception counseling should occur at every clinician visit, prescription refill, or scheduled Pap test and mammogram to help make women cognizant of their well-being and enable them to maximize their health before a possible pregnancy. Family planning centers should include preconception counseling when discussing contraception.

Screening and Counseling

Preconception counseling should focus on factors that impact organogenesis during the critical period of 17 to 56 days after conception (Table 1).¹²

Medical History

Age

Fecundity declines with increasing age. However, with the advent of better fertility interventions, more older women are becoming pregnant. Chromosomal abnormalities also rise with increasing age.¹⁹ The American College of Obstetricians and Gynecologists recommends that maternal serum alpha-fetoprotein (AFP) evaluation should be offered to all pregnant women as an effective screening test for fetal neural tube defects.²⁰ Women with elevated AFP levels should have a specialized ultrasound examination to further assess risk of neural tube defects. In some cases referral for genetic counseling and consideration of invasive prenatal testing may be warranted. Newer, less invasive prenatal diagnostic testing may become feasible for pregnant women of all ages in the future.²¹

Chronic medical problems such as diabetes also are more frequent with increased maternal age. Women need to be counseled that age is a major factor adversely affecting fecundity. During well-woman or contraceptive visits, clinicians should discuss any plans for conception, including anticipatory guidance regarding the decline in fertility with advancing age.¹⁹

Chronic Medical Problems

Thorough review of each woman's medical history should delineate any chronic medical conditions. Health status should be managed and medications adjusted to optimize pregnancy outcomes. Women with chronic medical conditions require education about the importance of adherence to treatment prior to and during pregnancy. Conditions that may adversely affect pregnancy outcomes include asthma, hypertension, cardiac disease, thromboembolic disease, chronic renal disease, autoimmune disorders, diabetes, depression, and seizure disorders. Previous episodes of postpartum depression should also be identified.

Diabetes. Two thirds of women with diabetes have unplanned pregnancies.²² The risks of spontaneous abortion and congenital malformation are greatly increased in diabetic women who conceive while in poor glycemic control.^{22,23} Hyperglycemia during the period

Table 1. Preconception Health Care

Genetic

Folic acid supplementation:

- routine—0.4 mg daily
- diabetes—0.4–5 mg daily
- epilepsy—1–4 mg daily
- previous neural tube defect—4 mg daily

Carrier screening: Tay-Sachs disease

Carrier screening (family history):
cystic fibrosis

Screen for infectious diseases, treat,
immunize, counsel

HIV

Syphilis

Hepatitis B immunization

Preconception immunizations
(rubella, varicella)

Toxoplasmosis—avoid cat litter, garden soil,
raw meat

Cytomegalovirus, parvovirus B19 (fifth
disease)—frequent handwashing, universal
precautions for child care and health care

Environmental toxins

Occupational exposures—Material Safety
Data Sheets from employer

Household chemicals—avoid paint thinners
and strippers, other solvents, pesticides,
bleach, lye

Mercury from fish

Screen for alcoholism and use of illegal drugs

Medical assessment

Diabetes—optimize control

Hypertension—avoid ACE inhibitors,
angiotensin II receptor antagonists,
thiazide diuretics

Epilepsy—optimize control

DVT—switch from warfarin to heparin

Depression/anxiety—avoid benzodiazepines

Lifestyle

Recommend regular moderate exercise

Avoid hyperthermia (hot tubs, overheating)
Caution against obesity and being
underweight

Assess risk of nutritional deficiencies
(vegan, pica, milk intolerance, calcium or
iron deficiency)

Avoid overuse of:

- vitamin A (limit to 3,000 IU daily)
- vitamin D (limit to 400 IU daily)
- caffeine (inconclusive)

Screen for domestic violence

HIV=human immunodeficiency virus;
ACE=angiotensin-converting enzyme;
DVT=deep venous thrombosis.

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of organogenesis (4–8 weeks gestation) is the primary teratogen in women with diabetes.²³ Preconception care for women with diabetes should include education about the link between poor diabetic control and adverse perinatal outcomes. Glycemic control should aim for a hemoglobin A_{1c} level of 7% or lower prior to conception.

Epilepsy. Women with epilepsy have a two-to-three times higher risk of bearing children with congenital malformation than women without epilepsy.²⁴ Recent data have clarified that this increased risk of birth defects occurs because many commonly used antiepileptic drugs (AEDs) are teratogens.²⁵ Accordingly, women with epilepsy should be counseled before conception about the association between infant malformation and maternal medication use.²⁶ It has been determined that older AEDs—including phenytoin, phenobarbital, carbamazepine, and valproic acid—are teratogens.^{25,27-29} Whether or not newer AEDs—including gabapentin, lamotrigine, and topiramate—increase birth defect risk has not been determined.³⁰ Physiological changes during pregnancy may increase a woman's requirement for anti-convulsant therapy; coordination of care with the woman's neurologist includes consideration of alternative AEDs, frequent monitoring, and AED dose adjustment. Decisions regarding discontinuing or changing medications during pregnancy should be made in consultation with the woman's neurologist.²⁶

Infection History/Immunizations

Preconception counseling should include appropriate screening, prevention, and treatment of infectious diseases, as well as review of last time of administration of standard adult immunizations, including tetanus, rubella, hepatitis, varicella, and influenza.¹⁹ Women should delay pregnancy for 3 months following rubella or varicella vaccination.

Medications

A major objective of preconception care is to identify potentially teratogenic medications and, whenever feasible, avoid their use prior to conception and during early pregnancy.¹⁹ (Table 2^{12,19,25,31}) The FDA classifies drugs as A, B, C, D, or X according to their risk in pregnancy, with A including the medications known to be safe and X including those known to be unsafe and not to be used. Thalidomide (Thalomid[®]) is a good example of a medication that should be avoided during pregnancy. It is a potent teratogen that was responsible for numerous birth defects when first used to treat nausea of pregnancy. This drug, which has re-emerged as an effective antineoplastic agent, is absolutely contraindicated at any time during pregnancy,³² as is isotretinoin, a commonly used medication.³³

Diet and Vitamin Supplementation

Optimal preconception nutritional status can have substantial beneficial effects on fetal outcome.²⁶ Women should be reminded about the importance of diet, weight, and physical fitness both before and after conception. Most low-risk pregnant women benefit from having regular mild-to-moderate exercise regimens.³⁴ Women on restricted diets (eg, vegan, low-carbohydrate) should take a multivitamin supplement to ensure that sufficient folic acid, iron, calcium, and vitamin B12 needs are met. Because many US women are not ingesting their nutritional requirements through a typical diet, multivitamin supplements are a way to ensure that adequate intake levels are reached.

Folic Acid

In the United States, neural tube defects (anencephaly and spina bifida) occur at an incidence rate of 1.4 to 1.6 per 1000 total births, with a recurrence risk of 1.5% to 3.0%.³⁵ Folic acid deficiency has been associated with an increased incidence of neural tube defects and other congenital anomalies.³⁶⁻³⁸ A diet rich in food sources of folic acid—such as broccoli, spinach, lentils, and oranges—can help increase folate levels,³⁵ but these limited dietary sources of folate leave many women deficient in folic acid and without adequate stores. Supplementation by taking one conventional multivitamin with folic acid or prenatal vitamin tablet daily is the most effective way to ensure adequate folate intake.²⁰ In addition, many women of reproductive age do not have adequate stores of folate. Appropriate folic acid supplementation prior to conception and early in pregnancy is associated with a marked reduction in occurrence and recurrence of neural tube defects and other congenital anomalies.^{35,39} This evidence prompted the US Food and Drug Administration (FDA) in 1996 to require that some foods, such as grain products and rice, be enriched with folic acid.³⁶

Ongoing counseling about folic acid supplementation and prevention of fetal neural tube defects is important for all reproductive-age women, even if they are not currently considering pregnancy. Maximal benefit is achieved if folic acid supplementation is started at least 1 month prior to planning conception. Adequate folate must be present in the maternal circulation during the first 25 days after conception to prevent neural tube defects.⁴⁰ Preconception nutritional needs for folic acid differ depending on a woman's history and characteristics and are as follows:

Table 2. Drugs with Known Teratogenic Effects^{12,19,25,31,62}

Drug Class	Medications (FDA category D, X drugs)
Analgesics, antiarthritics	(D) All nonsteroidal anti-inflammatory drugs, third*; (X) Ergotamines (Ergostat [®]), diclofenac/misoprostol (Arthrotec [®])
Anti-androgen agents	(X) Finasteride (Propecia [®])
Anti-anxiety, sleep aids	(D) Most benzodiazepines (X) Flurazepam (Dalmane [®]), temazepam (Restoril [®])
Anticoagulants	(X) Warfarin (Coumadin [®])
Anticonvulsants	(D) Carbamazepine (Tegretol [®]), clonazepam (Klonopin [®]), phenobarbital, phenytoin (Dilantin [®]), primidone (Mysoline [®]), valproic acid (Depakene [®])
Antidepressants	(D) Amitriptyline (Elavil [®]), imipramine (Tofranil [®]), nortriptyline (Pamelor [®])
Antifungals	(D) Fluconazole (Diflucan [®]), first*; itraconazole (Sporanox [®]), first*; ketoconazole (Nizoral [®]), first*
Antihypertensives	(D) ACE inhibitors, angiotensin II receptor antagonists, beta blockers, second, third*; labetalol, second, third*; thiazide diuretics
Antineoplastics	(X) Thalidomide (Thalomid [®]), methotrexate, aminopterin
GI medications	(D) Bismuth subsalicylate (X) Misoprostol (Cytotec [®])
Lipophilic statins	(X) Simvastatin (Zocor [®]), lovastatin (Mevacor [®]), atorvastatin (Lipitor [®])
Miscellaneous	(D) Lithium, nicotine patches (NicoDerm [®]), nasal spray and inhaler (X) Nicotine gum, HMG-CoA reductase inhibitors, isotretinoin (Accutane [®]), megadose vitamin A
Herbals	Ginseng (not evaluated by the FDA)

* First, second, third designate trimester of pregnancy in which risk is present. When there is no trimester designation, the risk is present during all trimesters.

FDA pregnancy risk category D=positive evidence of human fetal risk, but benefits from use in pregnant women may be acceptable (eg, if drug is needed in a life-threatening situation or serious disease).

FDA pregnancy risk category X=positive evidence of human fetal risk outweighs any possible benefit; contraindicated.

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- Women of reproductive age (even those not trying to become pregnant), 0.4 mg folic acid daily.⁴¹
- Women who have had an infant with a neural tube defect, 4 mg folic acid daily beginning at least 1 month prior to conception and continuing through the first trimester.^{4,41} Excess folic acid in the presence of vitamin B12 deficiency can precipitate subacute combined degeneration of the umbilical cord. Therefore, when doses of greater than 1 mg of folic acid are taken, women with vitamin B12 deficiency may be at risk for this problem.³⁵
- Women with diabetes: Preconception folic acid supplementation recommendations for women with diabetes range from 0.4 mg²³ to 5 mg.^{20,35} If blood glucose is high during the first trimester, the risk of neural tube defects is increased.²³ Therefore, although outcome-based data regarding optimal dosage are limited, some clinicians recommend higher doses of folic acid, both preconceptionally and during the first trimester unless adequate control of blood glucose can be assured for the entire period.
- Women with epilepsy, 1 to 4 mg folic acid daily¹²; a higher dose is recommended for women taking AEDs, because these agents interfere with folate metabolism.

Rationale for OCs containing folic acid. The benefits of ingesting folic acid supplements for reproductive-age women to reduce the frequency of neural tube defects are well documented.^{35,39} However, informing women and persuading them to change dietary behaviors has been difficult. Mandatory food fortification with folate has reduced the occurrence of neural tube defects (23% decline between 1996 and 2001),⁴² but this method is dependent on the diet selected by the woman. Folic acid supplementation depends on a woman's knowledge, ability, and willingness to adhere to these recommendations.

Incorporation of 0.4 mg folic acid into OCs has been proposed as a measure to improve the dietary folate intake of women during their reproductive years.⁴³ Folic acid supplementation at recommended doses is safe. Body stores of folic acid will increase with chronic supplementation. Theoretically, women who discontinue OCs with folic acid should have adequate protection for several months, the period during which many women conceive, markedly reducing the likelihood of having an infant with a neural tube defect.^{37,44} The FDA has approved the concept of incorporating 0.4 mg folic acid into OCs,⁴⁴ and a combination product will undergo clinical trials.

Herbal Supplements

In a prospective, cross-sectional survey of 250 pregnant women, 9.1% of respondents reported the use of herbal supplements during the current pregnancy.⁴⁵ Many individuals believe that because plant-derived preparations are natural they are therefore safer than prescription drugs.^{46,47} However, compounds contained in plants can produce both beneficial and toxic pharmacological effects.⁴⁶ Women should be cautioned against using any over-the-counter herbal product during pregnancy.

Vitamin A

The recommended adult intake of vitamin A (retinol), commonly found in liver, eggs, oily fish, fortified margarine, and dairy products, is 3000 to 5000 IU daily.⁴⁸ Hepatotoxic effects, vision changes, hair and skin changes, and teratogenic effects can occur with intakes greater than 10,000 IU.⁴⁸ Acne is commonly treated with isotretinoin (Accutane®), a retinoid known to be a potent teratogen. Accordingly, isotretinoin should be used with extreme caution with periodic monitoring for pregnancy in reproductive-age women. Multivitamins containing vitamin A as beta-carotene are preferred over those offering vitamin A as retinol.³⁵ Women should not try to achieve recommended levels of folic acid, iron, or other vitamin/mineral needs by taking additional multivitamin tablets daily, because of the potential for overdoses of vitamin A.^{26,48}

Vitamin B12

Vitamin B12 (cobalamin) deficiency may occur in women on strict vegetarian or low-cholesterol diets or those undergoing bariatric surgery for weight loss; deficiency is rare among adults who consume animal products.⁴⁹ Observational data suggest that there is a moderately strong association between low maternal B12 status and the risk of fetal neural tube defects as well as other pregnancy complications, including spontaneous abortion, placental abruption, preeclampsia, and low birth weight.^{49,50} Vitamin B12 levels decrease throughout normal pregnancy.⁵¹ Women taking OCs may have clinically insignificant, falsely low B12 levels, which should be differentiated from true cobalamin deficiency.⁵²⁻⁵⁴ Regular multivitamin supplementation can prevent B12 deficiency.

Other Exposures

Approximately one third of pregnant women in the United States drink alcohol.¹⁹ Excessive alcohol use is associated with fetal alcohol syndrome and low birth weight.¹³ A safe level of alcohol intake has not been established. Therefore, all women should be instructed to avoid alcohol use during pregnancy.

Many nonpregnant women consume high amounts of caffeine and about 75% of pregnant women ingest caffeine during pregnancy.⁵⁵ Studies are divided regarding caffeine's impact on pregnancy. Several studies have suggested that high caffeine intake before and during pregnancy may be associated with an increased risk of spontaneous abortion.⁵⁶⁻⁵⁸ However, evidence for a causal link remains inconclusive.⁵⁹ One study has found that moderate caffeine consumption during pregnancy does not appear to be hazardous to fetal growth.⁵⁵

Many environmental toxins have teratogenic potential; exposures can be elicited through a detailed occupational history including employment, household, and hobby interests.¹⁹ Examples of environmental toxins include lead (from paint, plumbing pipes, crystal glassware), pesticides, organic

solvents (eg, alcohols, degreasers, paint thinners, varnish removers), and some household cleaning products (eg, bleaches, lye, oven cleaners¹⁹).⁶⁰ Further information about environmental toxins is available on the March of Dimes website at http://www.marchofdimes.com/printableArticles/681_9146.asp?printable=true.

Women should be made aware of the potential risks of recreational drug use (eg, marijuana, cocaine, intravenous drug use) to a fetus, including premature birth, spontaneous abortion, fetal growth retardation, and central nervous system dysfunction.²⁶ Women with a history of illicit drug use also have an increased risk for tobacco abuse, alcohol abuse, and nutritional deficiencies.²⁶

Approximately 15% to 20% of pregnant US women smoke.¹ Smoking cessation before or during gestation can help prevent low birth weight, placental abruption, prematurity, and lifelong disabilities.⁶¹ Clinicians can offer advice regarding various methods to assist with nicotine withdrawal symptoms and provide information regarding smoking cessation programs. Nicotine-containing "quit-smoking" aids may be useful before conception but are not advisable during pregnancy.¹² Other household members who smoke should also be encouraged to stop smoking, as passive smoke inhalation during pregnancy may increase the risk of having a low-birth-weight infant.²⁶

Summary

Proper preconception care can have a marked beneficial effect on pregnancy outcomes. Women of reproductive age, including those using steroidal contraception, should be counseled at every visit about preconception planning and care.¹⁵ Because clinicians regularly see women of reproductive age, they are well positioned to disseminate this valuable information prior to conception. An optimal time for preconception counseling is during well-woman visits for ongoing contraceptive care. Smoking cessation, glycemic control, folic acid supplementation, and preventing teratogenic exposures are examples of preconception health interventions that improve pregnancy outcomes.

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(continued on page 8)

Implantable Contraceptives

Philip D. Darney, MD, MSc, and Daniel R. Mishell, Jr, MD

Educational Objectives:

The health care provider should be able to:

- discuss the mechanisms of action of implantable contraceptives
- discuss the duration of action and reversibility of implantable contraceptives
- cite the safety and efficacy of these methods
- inform patients about the risks/benefits of the single-rod etonogestrel implant

Implantable contraceptives are long-acting, controlled systems that continuously release a progestin into the circulation.¹ These agents contain no estrogen. An implantable subdermal system using levonorgestrel (LNG; Norplant[®]) was initially developed.² In 1991 a six-capsule, Silastic, LNG-containing implant became the first approved contraceptive implant in the United States.^{3,4} The six-capsule LNG implant was highly effective, with pregnancies occurring in only about 1% of users during the 5-year duration of use.⁵ Nevertheless, the six-capsule LNG implant was withdrawn from US distribution in 2002 due to limitations in component supplies, and there are currently no implant systems available in the United States. Four progestins (LNG, etonogestrel [ENG]), nesterone, and nomegestrol acetate) are being utilized in various implantable contraceptives now being developed.⁴

A two-rod, LNG-containing implant (Jadelle[®]) releases the same amount of LNG at a rate similar to the six-capsule LNG implant.^{6,7} The two-rod LNG implant is as effective as the six-capsule system for 5 years after insertion.⁸ This device is approved by the US Food and Drug Administration (FDA) but is not marketed in the United States.

A single-rod, ethylene vinyl acetate (EVA) co-polymer implant containing ENG (Implanon[®]) is currently registered in Australia, Indonesia, and 11 European countries and is expected to become available in the United States in 2005.⁴ This ENG implant is effective for 3 years.

Contraceptive implants have been approved for use in more than 60 countries and have been used by approximately 11 million women worldwide, including 1 million US women who used the six-capsule LNG implant when it was available.^{4,9-14}

Progestins

The progestins LNG and ENG are both approved for contraceptive use in the United States. Both these agents are synthetic progestins derived from 19-nortestosterone.¹⁵ Because each of these progestins has high progestational activity, they prevent ovulation at very low doses.¹⁵ LNG is a gonane progestin that binds with high affinity to the progesterone, androgen, mineralocorticoid, and glucocorticoid receptors as well as to sex hormone binding globulin, but not to estrogen receptors.^{16,17} The active metabolite of desogestrel, ENG (also known as 3-keto-desogestrel)¹⁵, has no estrogenic, anti-inflammatory, or mineralocorticoid activity but has weak androgenic and anabolic activity, as well as strong antiestrogenic activity.¹⁸ ENG is bound mainly to albumin, the level of which is not altered by varying endogenous or exogenous estradiol concentrations.¹⁷

Mechanisms of Action

The LNG implants suppress follicular growth and inhibit luteinizing hormone (LH) release by exerting negative feedback on the hypothalamic-pituitary axis, causing a variety of changes ranging from anovulation to insufficient luteal function.⁷ Most women using LNG implants have follicular development and normal estradiol levels, so that no bone loss occurs.⁸ The ENG implant also suppresses ovulation by altering the hypothalamic-pituitary-ovarian axis,¹¹ which inhibits the midcycle LH surge but allows follicular development.¹

Even if ovulation occurs with these agents, the antiestrogenic actions of the progestins make the cervical mucus viscous, scanty, and impenetrable by sperm, so that fertilization does not occur.^{8,19} These mechanisms of action provide pre-fertilization contraceptive efficacy, and no signs of embryonic

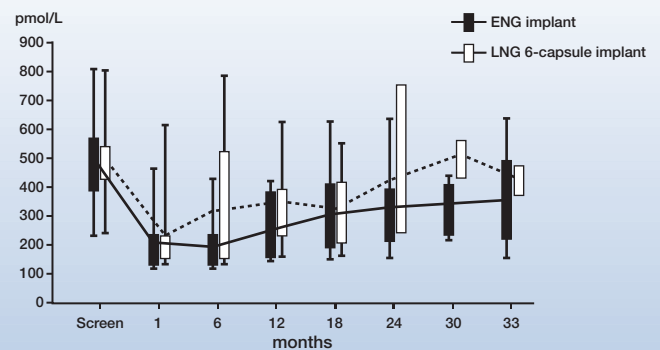
development have been found among implant users, indicating that progestin implants have no abortifacient properties.

The Single-rod ENG Implant

Pharmacology

The ENG implant consists of one EVA and ENG rod (40 mm X 2.0 mm) covered with a rate-controlling EVA membrane (0.06 mm).²⁰ The rod contains 68 mg ENG, which is initially released at a rate of 60 mcg per day and slowly declines to 30 mcg per day after 2 years of use.^{17,21} Sufficient serum concentrations (266 pg/mL) of ENG are reached within 1 day after insertion to inhibit ovulation (more than 90 pg/mL).^{11,22} Despite this effective suppression of ovulation, no clinically significant changes in endogenous serum estradiol levels occur, thus preventing bone loss (Figure 1).¹³ In an open, prospective, comparative study of the ENG implant and a nonmedicated intrauterine device (IUD), no adverse effects of long-term (2 years) use on bone mineral density (BMD) were observed in either group (Figure 2).²³

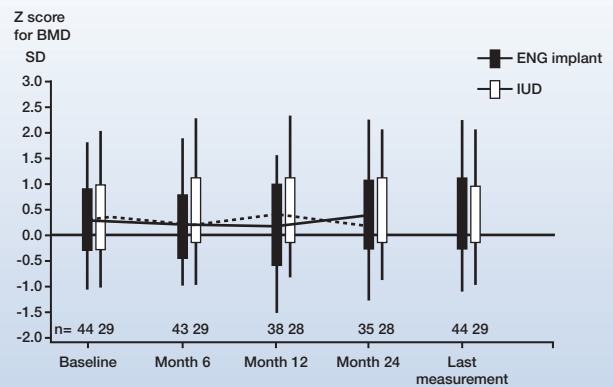
Figure 1. Mean serum estradiol concentrations with implants.¹³



ENG=etonogestrel; LNG=levonorgestrel; T bars=percentile range of P5-P95; boxes=percentile range of P25-P75.

Reprinted from *Contraception*, Vol 58, Croxatto HB, Makarainen L, The pharmacodynamics and efficacy of Implanon. An overview of the data, 915-975, 1998, with permission from Elsevier.¹³

Figure 2. Bone mineral density at lumbar spine (L₂-L₄): ENG implant vs nonhormonal IUD.²³



Medians are connected; z scores during treatment.

BMD=bone mineral density; ENG=etonogestrel; IUD=intrauterine device.

$z = \frac{\text{recorded BMD} - \text{mean BMD of (USA/Europe) reference population}}{\text{standard deviation of BMD of reference population}}$

Boxes=25 and 75 percentiles; whiskers=5 and 95 percentiles.

Adapted from Beerthuisen R, van Beek A, Massai R, Makarainen L, Hout J, Bennink HC. Bone mineral density during long-term use of the progestagen contraceptive implant Implanon compared to a non-hormonal method of contraception. *Human Reproduction*. 2000;15(1):118-122. © European Society of Human Reproduction and Embryology. Reproduced by permission of Oxford University Press/Human Reproduction.²³

Serum levels of ENG in women using this implant are reduced in women taking liver enzyme-inducing drugs such as rifampicin, griseofulvin, phenytoin, and carbamazepine, but are not affected by antibiotics.¹² Bioavailability of ENG remains nearly 100% throughout 2 years of use.²¹ After implant removal, serum ENG concentrations become undetectable (below 20 pg/mL) within 1 week.²¹ Return of ovulation occurs in 94% of women within 3 to 6 weeks after removal of the implant.^{13,22}

Efficacy

In clinical trials, the ENG implant achieved 100% contraceptive effectiveness with a Pearl Index of 0 per 100 woman-years (confidence interval [CI] 0.00–0.08).¹⁷ Up to 1998, the efficacy of the single-rod ENG implant had been studied in clinical trials in 2043 women for a total of 74,000 cycles of use.²⁴ Of these, 835 women had completed 2 to 3 years of use and an additional 526 had used the ENG implant for 3 years or longer. No pregnancies and no ectopic pregnancies occurred during these trials. In these trials there were 365 women whose body weight was 154 pounds (70 kg) or more.²⁴

Safety

Overall, progestin implants, including the ENG implant, are safe, with adverse event rates (including death, neoplastic disease, cardiovascular events, anemia, hypertension, bone density changes, diabetes, gall bladder disease, thrombocytopenia, and pelvic inflammatory disease) comparable to women not using implants.²⁵ Dysmenorrhea occurs in 40% of women having ovulatory cycles.¹² With the use of the ENG implant, uterine pain was reduced or eliminated in 88% of women previously experiencing dysmenorrhea, compared with baseline; pain increased in 2% of the ENG implant users.²⁶ In a study comparing 42 lactating mother-infant pairs using the ENG implant with 38 pairs using IUDs, there were no significant differences between groups in milk volume, milk constituents, timing and amount of supplementary food, or infant growth rates, indicating that this implant can be used by women who are nursing their babies.²⁷

Side effects associated with the ENG implant include menstrual irregularities (infrequent bleeding [26.9%], amenorrhea [18.6%], prolonged bleeding [15.1%], frequent bleeding [7.4%]), weight gain (20.7%), acne (15.3%), breast pain (9.1%), and headache (8.5%), but discontinuation rates because of these symptoms are small (see "Discontinuation Rates," below).^{11,26,28} A comparative study of bleeding patterns in ENG implant users and six-capsule LNG implant users found a statistically significantly lower mean number of bleeding/spotting days for the former than for the latter (15.9–19.3 vs. 19.4–21.6; $p=0.0169$).²⁶ Users of ENG implants had more variable bleeding patterns than users of the LNG implants. Unlike women who use the LNG implants and ovulate in the latter years of use, causing regular bleeding episodes, women using the ENG implant never ovulate and have persistent irregular bleeding during the 3-year duration of use.

Gradual increases in body weight have been observed in ENG implant users, but these gains are considered to be normal increases over time.²⁸ In a comparison of users of the ENG implant and users of a nonmedicated IUD, mean body weight increases were 2.6% and 2.4%, respectively, during 2 years.²⁸

Discontinuation Rates

Discontinuation rates for the ENG implant have varied by geographical region, from 30.2% in Europe and Canada to 0.9% in Southeast Asia.^{26,29} Bleeding irregularities are cited as the most common reason for discontinuation of the ENG implant.²⁶ Overall, after insertion 82% of women continued to use the ENG implant for up to 24 months.³⁰

Insertion and Removal

Only medical professionals trained in techniques of inserting the device should insert or remove the ENG implant.¹¹ Clinicians offering this method should attend a training course that includes theory, model arm training, and supervised live patient training.²⁴ The ENG implant comes preloaded in a disposable applicator (needle) for easy insertion. It is imperative that the implant be placed in the superficial subdermal tissue for easy removal. After insertion, the implant may not be visible but must be palpable. Average insertion time for the ENG implant ranges between 1.1 and 2.2 minutes.³¹ The ENG implant can be inserted in women who have been using any other contraceptive method or no method, as well as immediately post-delivery and post-abortion; the timing of insertion varies depending upon the woman's previous method and circumstances. The ENG implant can be removed at any time but should be removed after 3 years of use. Mean removal time is 2.6 to 5.4 minutes.³¹ Pain, swelling, redness, and hematoma have been reported following insertion and removal. Because return to ovulation is

rapid following removal, women still desiring contraception should begin another method immediately or have a new rod inserted through the incision made for removal.¹²

Clinical experience with the ENG implant has demonstrated that method effectiveness and satisfaction are closely associated with patient education and provider training. During the first 18 months of use after the ENG implant was introduced to Australia in May 2001, an unexpectedly high number of adverse incidents were reported and 100 unintended pregnancies occurred.³² Nearly all of these events were caused by failure of untrained clinicians to eject the capsule during the insertion process, and poor patient selection, timing, and counseling. Policies to adequately document the process, procedure, and patient consent were initiated by the Royal Australian College of General Practitioners and have corrected the problems.³²

Advantages and Disadvantages of Implants

Advantages

Implants, when they again become available in the United States, will offer a variety of benefits to women. They provide long-term, effective pregnancy prevention without the need for daily user action. Implant use is cost-effective compared to the cost of an unplanned pregnancy.³³ The sustained administration of a relatively low dose of progestin and maintenance of stable serum levels provide a long duration of action and a short time to recovery of fertility.¹⁷ The absence of an estrogen component allows the implant to be used in women over 35 who smoke and in women for whom exogenous estrogen is contraindicated. Implantable contraception is a good choice for lactating mothers³⁴ and can be inserted immediately following delivery.

Disadvantages

Insertion and removal of implants require minor surgical procedures performed by trained and experienced clinicians. Cost-effectiveness of the method depends upon long-term use; early discontinuation negates this benefit. Progestin implants may cause androgenic side effects (eg, acne) and unpredictable bleeding patterns.³⁵ Bleeding irregularities and disturbances are the main reason for early discontinuation of the ENG implant.²⁶ Lack of protection against sexually transmitted infections (STIs) is a disadvantage of all contraceptive methods except condoms and some other barrier methods.

Counseling

Preinsertion counseling and continued postinsertion follow-up increase continued use of implants. Satisfaction with the method increases with proper counseling and minimizes costly removals. Implant counseling should address the advantages and disadvantages of implants compared with other methods; possible side effects; absence of inherent protection against STIs and measures to overcome this deficiency; and the method's extremely high contraceptive effectiveness.^{20,36,37}

Counseling women to expect bleeding irregularities helps minimize concerns and reduces discontinuations. Women should be provided with anticipatory guidance regarding bleeding irregularities so they can make informed decisions regarding the side effects they are willing to accept in order to benefit from high contraceptive efficacy. Despite the presence of side effects and dependence on clinicians to acquire implants, most women using implantable contraception are satisfied with the method; users cite its long duration of use, convenience, and high efficacy as reasons for satisfaction.³⁸

Summary

Progestin-only contraceptive implants provide safe, convenient, and highly effective long-term contraception with high continuation rates. Currently, implants are not available for use in the United States. The ENG implant, expected to be available in the United States in 2005, will provide an additional contraceptive option to American women. This implant offers high effectiveness independent of user adherence to daily action, long duration of effectiveness, absence of estrogen, ease of use, reversibility, and overall safety. Clinicians will soon be able to offer a wider choice of contraceptive alternatives, so that each woman can select a method that best fits her circumstances, preferences, and lifestyle.

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Valuable Online Resources for Reproductive Health Professionals

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Reproductive health professionals who wish to remain current regarding family planning issues will benefit by regularly consulting such research-based vehicles as Web sites that offer practical, useful information.

World Health Organization

The World Health Organization (WHO) Web site (<http://www.who.int>) regularly issues documents on family planning that represent the latest evidence-based data and employ the highest standards for synthesizing practice guidelines. WHO posts important developments on its family planning Web site (http://www.who.int/reproductive-health/family_planning/updates.html), supported by the same quality of evidence as the published material; updates are posted after the publication of each traditional paper-format edition. Regularly reviewing the posted documents exposes the reader to a broad spectrum of relevant reproductive health literature worldwide.

One series of helpful documents is described as "evidence-based cornerstones of the WHO's new initiative to develop and implement evidence-based guidelines for family planning."¹ Two documents are available now and two are in planning stages. The two available WHO documents are described below.

Selected Practice Recommendations for Contraceptive Use

This WHO document¹ is useful for answering questions by providers and recipients regarding individual decision-making about contraceptive use.

This 2004 document summarizes the conclusions of an April 2004 expert Working Group meeting attended by 29 participants from 15 countries at the WHO in Geneva, Switzerland. The practice recommendations are based upon evidence obtained primarily from systematic reviews of the relevant literature published through February 2004.

The document is a collaborative effort between the WHO Department of Reproductive Health and Research and many international agencies and organizations active in the field of family planning policies and programs, including the Centers for Disease Control and Prevention, the National Institute of Child Health and Human Development, and the United Nations Population Fund.

The Working Group formed consensus responses (citing the level of evidence for most responses) to 33 questions about contraception.

Questions and relevant recommendations are grouped by subject area, including initiation/continuation, incorrect use, problems during use, menstrual abnormalities, pelvic inflammatory disease, pregnancy while using intrauterine devices, and programmatic issues (clinician procedures for providing contraceptives). A table lists examinations or tests recommended to be performed before a given method of contraception is prescribed.

The document may be downloaded in PDF format at http://www.who.int/reproductive-health/publications/rhr_02_7/index.htm.

Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use

The third edition of this document² provides detailed protocols for determining whether individual women are medically eligible to use a particular contraceptive method. Designed for quick reference at clinics in resource-poor settings where no physician is available, this document can also be used by reproductive health professionals to access evidence-based information for contraceptive recommendations to women.

The protocols in this volume delineate the latest evidence regarding the safety and use of contraceptives, including the relationship between contraception and human immunodeficiency virus (HIV) risk. In establishing these criteria, WHO intends to help national family planning programs update their policies and practices according to the latest scientific knowledge. Another objective is to ensure awareness of potential adverse effects of specific contraceptives without denying individuals the opportunity to choose among several safe and suitable methods.

In extensive tables of recommendations, the appropriateness of each known method of contraception is analyzed for women with all common medical conditions. The transdermal contraceptive patch (ORTHO-EVRA[®]) and the vaginal ring (NuvaRing[®]) have been added to the third edition. These agents have the same category rankings as combination OCs. Rankings for each method in the presence of each medical condition consist of four categories: no restriction on use of the method; advantages of use generally outweigh risks; risks of use usually outweigh advantages; and unacceptable health risk if used.

Some medical conditions are considered in great detail. For example, there are 16 main categories of reproductive tract infections and disorders. (See "Hormonal Contraception in Women With Common Medical Conditions" in *Dialogues in Contraception*, Vol. 8, No. 6.) Listings under cardiovascular disease discuss multiple risk factors, six subcategories of hypertension, and numerous other conditions, including known hyperlipidemias and valvular heart disease.

The document may be downloaded as a PDF from the WHO Web site at http://www.who.int/reproductive-health/publications/MEC_3/mec.pdf.

Other WHO Resources for Clinicians

Two additional documents, the third and fourth "cornerstones" of WHO's evidence-based family planning guidance series, are in preparation: the *Decision-Making Tool for Family Planning Clients and Providers*, and the *Handbook for Family Planning Providers*; they are scheduled to appear in 2005. Both volumes will include key points from the *Medical Eligibility Criteria* and *Selected Practice Recommendations* documents.

INFO Project

Clinicians and others seeking articles and news on family planning and reproductive health may find it helpful to access <http://www.inforhealth.org>, a Web site produced by the Information & Knowledge for Optimal Health (INFO) Project. Based at the Center for Communication Programs of the Johns Hopkins University Bloomberg School of Public Health, Baltimore, the project receives support from the United States Agency for International Development.

Visitors to the INFO site may obtain current and archived issues of *International Family Planning Perspectives* from the Alan Guttmacher Institute, *Population Reports*, and other publications free or at nominal cost. Subscribers to various free "e-lists" receive regular postings on topics of interest that they have identified. Members of the e-list "Continuous Investigation of Research Evidence (CIRE) Announcements" are notified whenever updates are made to CIRE, an online service focusing on new research findings that are potentially relevant to WHO's international family planning guidance project. CIRE can be accessed independently at http://www.inforhealth.org/cire/cire_pub.pl. Clinicians can search for articles and other information about a single method of contraception, a single condition, a combination of method and condition, or selected practice recommendations.

Association of Reproductive Health Professionals (ARHP)

This association's Web site (<http://www.arhp.org>) provides a variety of informational materials for clinicians, including *Quick Reference Guides* on various treatment issues; *Clinical Proceedings*, a periodic monograph series; *Health and Sexuality*, a quarterly magazine; and *ARHP Update*, a bimonthly newsletter.

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