

Chapter 25. Contraception

INTRODUCTION

The global population is at an all time high at over 6 billion people. A large percentage of this population growth is in less developed countries where access to reproductive health care is limited. However, even in industrialized countries, including the United States, it is estimated that approximately 10-15% of all sexually active women use no birth control, contributing to the almost 50% unintended pregnancy rate (1). About 850,000 of these unintended pregnancies in the U.S. occur in teenagers. While 2% of U.S. women have an induced abortion every year (2), about half of the unplanned pregnancies are carried to term (1). The rates of unwanted pregnancy in the United States are at least four times higher than some countries in Europe and Japan (3). These differences do not appear to be explained solely by exposure to the risk of pregnancy since other countries such as the Netherlands and Sweden have teenagers who engage in sexual activity earlier than most teenagers in the United States (4). The cost of contraception to the consumer and lack of insurance coverage for contraception contribute to the high unintended pregnancy rate in the U.S. (2) However, the varied reasons for problematic contraceptive use have yet to be fully elucidated and women in the United States are either not using their contraceptive method correctly and consistently or are choosing methods with high failure rates. Therefore, more reliable contraception and contraceptive management are necessary to reduce the unintended pregnancy rate in the United States.

Safe and reliable family planning directly improves public health. New methods are an area of ongoing research, such as the development of microbicides which will fulfill the unmet dual need of contraception and protection against sexually transmitted infections/human immunodeficiency virus in women. Women provided with effective contraception are protected against events that may threaten their personal and professional independence. Pregnancy and childbirth pose substantial health risks that should be actively avoided unless pregnancy is desired. The chance of death due to pregnancy and childbirth varies geographically, but is always higher than that associated with currently available methods of contraception (5).

There is an ever increasing variety of contraceptives available to couples. Each method has its own distinct advantages and disadvantages. The ideal contraceptive would be effective, reversible, easy to use, not coitally dependant, safe, free of side effects, and inexpensive. Because one objectively perfect method does not yet exist, the choice of a family planning method should be individualized to each couple and may change during a woman's reproductive life. The majority of contraceptives currently available can be divided into two groups: barrier methods and hormonal methods. Both work by preventing the sperm and egg from coming in contact with one another. Barrier methods prevent sperm from entering the upper female genital tract. Hormonal contraceptives have three main mechanisms of action, which include ovulation inhibition, thickening of cervical mucus, and an alteration of the endometrium. There have been, and there will continue to be, great strides to modify and optimize these methods. This chapter will serve as a review of contraceptive options with focus on the mechanism of action, efficacy, and non-contraceptive effects.

HORMONAL CONTRACEPTION

Steroidal contraception involves the use of a progestin alone or in combination with estrogen.

Pharmacology

Progestins The major portion of the contraceptive effect in hormonal methods

is due to the progestin compound. Progestins alone confer the contraceptive benefits, while estrogens, for the most part, serve to regulate bleeding. Progestins in oral contraceptives include are derived from 19 nor-testosterone and include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, norethynodrel, desogestrel, norgestimate, and gestodene. The last three are sometimes called the 'new progestins' or the 'third generation' progestins; however, this label is of no scientific or clinical value and was developed for marketing purposes. Progestins should be categorized according to their active structure and their parent compound. There are three molecularly distinct types of progestins: estranes, gonanes, and pregnanes. Estranes include norethindrone, norethindrone acetate, ethynodiol diacetate, and lynestrenol. Gonanes include desogestrel, norgestimate, and gestodene. Gonanes and estranes differ in their half-life and with respect to their estrogenic and anti-estrogenic effects. Drospirenone is a spironolactone analog with anti-mineralocorticoid and anti-androgenic activity. Pregnanes are used in injectable methods. Table 1 provides a summary of the progestins currently used as contraceptives. Table 2 provides a summary of the combined oral contraceptive preparations currently on the market in the USA.

Estrogens

In contrast to the long list of progestin formulations, only two estrogenic compounds are used in hormonal contraceptives: ethinyl estradiol (EE) and mestranol. EE is pharmacologically active whereas mestranol must be converted into EE before it becomes active. Contraceptives currently on the market contain 35 micrograms of estrogen or less. Ethinyl estradiol is absorbed rapidly and undergoes extensive hepatic first pass metabolism. Its plasma half-life has been reported to be in the range of 10-27 hours. Its half-life in tissue, such as endometrium, appears to be longer.

HORMONAL CONTRACEPTION

Table 1.

Class Compound	Name	Progestational Activity	Androgenic Activity
19 Nor-testosterone Progestins			
Estranes	Norethindrone	1	1
	Norethindrone acetate	1.2	1.6
	Ethinodiol diacetate	1.4	0.6
Gonanes	Levonorgestrel	5.3	8.3
	Norgestrel	2.6	4.2
	Norgestimate	1.3	1.9
	Desogestrel	9	3.4
	Gestodene	12.6	8.6
Pregnane Progestins			
	Megestrol acetate	0.4	0

Class Compound	Name	Progestational Activity	Androgenic Activity
	Medroxyprogesterone acetate	0.3	0

Table 2. Available Combination Oral Contraceptives:

	Name	Progestin (mg)	Type of Estrogen (mcg)
50mcg estrogen	Ogestrel/Ovral	Norgestrel (0.5)	EE (50)
	Necon/Nelova/ Norethin/Norinyl/ Ortho-Novum 1/50	Norethindrone (1.0)	Mestranol (50)
	Ovcon 50	Norethindrone (1.0)	EE (50)
	Norlestrin 1/50	Norethindrone acetate (1.0)	EE (50)
	Demulen 50/Zovia 1/50	Ethinodiol diacetate (1.0)	EE (50)
<50mcg estrogen plus monophasic	Lo-Ovral/ Low-Ogestrel	Norgestrel (0.3)	EE (30)
	Ovcon 35	Norethindrone (0.4)	EE (35)
	Desogen/ Ortho-cept	Desogestrel (0.15)	EE (30)
	Levlen/ Levora/ Nordette	Levonorgestrel (0.15)	EE (30)
	Ortho-Cyclen	Norgestimate (0.25)	EE (35)
	Necon/ Nelova/ Norinyl/ Norethin/ Ortho-Novum 1/35	Norethindrone (1.0)	EE (35)
	LO/OVRAL	Norgestrel(0.3)	EE (30)
	Brevicon/ Modicon/ Necon/ Nelova 0.5/35	Norethindrone (0.5)	EE (35)
	Loestrin 1.5/30	Norethindrone acetate (1.5)	EE (30)
	Alesse/Levlite 0.1/20	Levonorgestrel (0.1)	EE (20)
	Seasonale .15/30	Levonorgestrel (0.15)	EE (30)
	Loestrin 1/20	Norethindrone acetate (1.0)	EE (20)
	Demulen/ Zovia 1/35	Ethinodiol diacetate (1.0)	EE (35)

	Name	Progestin (mg)	Type of Estrogen (mcg)
<50mcg estrogen plus multiphasic	Ortho-Novum 7/7/7	Norethindrone (0.5, 0.75, 1.0)	EE (35, 35, 35)
	Tri-Levlen/ Triphasil/ Trivora	Levonorgestrel (0.05, 0.075, 0.125)	EE (30, 40, 30)
	Jenest	Norethindrone (0.5, 1.0)	EE (35, 35)
	Necon/ Nelova/ Ortho-Novum 10/11	Norethindrone (0.5, 1.0)	EE (35, 35)
	Ortho Tri-Cyclen	Norgestimate (0.18, 0.215, 0.250)	EE (35, 35, 35)
	Tri-Norinyl	Norethindrone (0.5, 1.0, 0.5)	EE (35,35)
	Eurostep	Norethindrone acetate (1.0, 1.0, 1.0)	EE (20, 30, 35)
	Mircette	Desogestrel (0.15)	EE (0.02, 0.01)
Other	Yasmin	Drospirenone (3)	EE (30)
EE: ethinyl estradiol			

Continuous Pill use (6): A new pill, 'Seasonale', requires women to take the pill for 84 consecutive days, and then stop for a week before inducing a withdrawal bleed. This method allows women to menstruate only once every three months. This regimen is especially useful for women who suffer from endometriosis, heavy periods or severe PMS or menstrual cramps. Clinical trials have highlighted breakthrough bleed as an adverse effect of this formulation.

Mechanism of action

While there is a great increase in the number of hormonal contraceptive options, most of these methods are a "variation on a theme" and have similar mechanisms of action. Most of the contraceptive efficacy is derived from the effects of the progestin. The mechanism of action of hormonal contraception is primarily through the suppression of ovulation. Progestational effects include (7):

- Inhibition of ovulation by suppressing luteinizing hormone (LH);
- Thickening of cervical mucus, thus hampering the transport of sperm;
- Possible inhibition of sperm capacitation;
- Hampered implantation by the production of decidualized endometrium with exhausted and atrophic glands.

Estrogenic effects include (8):

- Partial inhibition of ovulation in part by the suppression of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), depending on dose;
- Alteration of secretions and cellular structures of the endometrium within the uterus.

Efficacy

There are inherent risks in our methodology to define efficacy of a contraceptive method. If 100 women used a contraceptive method for a year and five became pregnant, we cannot say that the method was 95% effective. We do not know who would have become pregnant without using family planning. Thus, we rely on a failure rate to describe the effectiveness of a method. However, all failure rates are not calculated equally and have different implications.

Most estimates of a contraceptive's efficacy refer to the first year of its use. Overall, the longer a woman uses a contraceptive method the less likely it is to fail. Thus, the failure rate in the second year is lower than the first and the failure rate in the fifth year is lower than that of the second. There are two commonly used failure rates to compare contraceptive methods: typical use and perfect use. 'Perfect use' is a measure of efficacy if the method is used perfectly, consistently and according to specific guidelines. It compares to the efficacy of the method in the laboratory (method failure rate). 'Typical use' estimates the probability of pregnancy during the first year of typical use of the method. This measure of efficacy takes into account occasional non-use of the method, incorrect use of the method, as well as pure failure of the method. Generally speaking, methods that are coitally dependent such as condoms and diaphragms have a larger disparity between typical use and perfect use. The failure rate of perfect use for oral contraceptive pills is approximately 0.1-0.5% but the typical failure rate is about 5% (7). Methods that are long acting and require one visit to a clinician such as an injection or an implant have very little disparity between perfect use and typical use. The perfect use failure rate of Depo-Provera and Norplant are 0.03% and 0.05% respectively (7). The typical use is almost identical.

Non-contraceptive Benefits of Combined Oral Contraceptives

Today there is a range of non-oral, non-daily hormonal contraceptive available, and the face of contraceptive management has changed. However, oral contraceptives have been widely used for decades, and they represent the most extensively studied drug on the market. Research regarding oral contraceptives focused on possible health risks. Many of the concerns of these health risks have been allayed. There is now a large body of evidence demonstrating non-contraceptive health benefits of oral contraception. Table 3 is a list of potential non-contraceptive benefits. Specific clinical situations are described below.

Table 3. Advantages of oral contraceptives (8)

- Reversibility and quick return to fertility;
- Reduction of ovarian and endometrial cancer risk;
- Reduced risk of benign ovarian tumors and ovarian cysts
- Reduced risk of colorectal cancer
- Reduced dysfunctional uterine bleeding
- Decreased perimenopausal vasomotor symptoms
- Decreased benign breast disease
- Favorable bone mineral density profile
- Decrease in menstrual flow and menorrhagia
- Decrease in primary dysmenorrhea
- Decreased risk of iron deficiency anemia
- Improvement in hirsutism and acne
- Decreased risk of premenstrual syndrome (PMS)/premenstrual dysphoric disorder (PMDD)

Prevention of Ovarian Cancer: Reduction in ovarian cancer risk increases with greater oral contraceptive use although protection is provided after as little as 3 to 6 months (9). Compared to non-users, women who have used oral contraceptives for four years or less have a 30% decreased risk of ovarian cancer. If they used combined OC's for 5-11 years, they have a 50% reduction of risk; if they used combined OC's for more than 12 years, there is a 80% reduction in risk. This protective effect persists for at least 15 years after OC discontinuation (10, 11).

Prevention of Endometrial Cancer: There is a 50% reduction in endometrial cancer risk in OC users compared with never users (12). Reduced risk depends on duration of OC use. The risk is reduced by 20% with 1 year of use, 40% with 2 years of use, and 60% with 4 or more years of use (13). The actual duration of protection after discontinuation is unknown but is estimated to be at least 15 years (14).

Benign Breast Disease: OC use significantly reduces fibrocystic breast change and fibroadenoma development (15-17). The Oxford Family Planning Association Study found a decreased risk of benign breast disease with increasing duration of use; current users, however, were at lowest risk (18). Fibrocystic change is significantly decreased after 1 to 2 years of use (19), and lasts up to 1 year after OC discontinuation (18).

Bone Mineral Density: Studies of both premenopausal and postmenopausal women seem to favor bone-sparing effects of OC's. A past history of OC use provided protection against low bone mineral density in a cross-sectional, retrospective study (OR=0.4, 95%CI, 0.2-0.5) (20). The same study observed increasing protection with increasing duration of use. Few studies have shown a protective effect against fracture risk-a case-control study showed that use of any OC in women after the age of 40 years provided significant protection against hip fractures during their menopause (OR=0.7;95%CI, 0.5-0.9) (21). Many studies, however, have not found a favorable association between OC's and bone mass (22, 23). No study thus far has found a detrimental effect of OC's on bone mineral density (24).

Functional Ovarian Cysts: In general, studies of current monophasic or triphasic OC formulations demonstrate that OCs do not have a significant effect on the development of functional ovarian cysts (25, 26).

Colorectal Cancer: A meta-analysis of pooled relative risks of colorectal cancer for ever-use of OCs from case-control studies was 0.81 (95%CI, 0.69-0.94) and from four cohort studies was 0.84 (95%CI, 0.72-0.97) (27). Women using high-dose OCs (with 50mcg estrogen) for greater than 96 months had a relative risk of 0.6(95%CI, 0.4-0.9) (28). It is unclear if the results from this study apply to women using lower-dose oral contraceptives.

Relief from Menstrual Disorders: There are few studies that demonstrate the benefits of current low-dose OCs on dysmenorrhea and menstrual flow. A recent randomized clinical trial of patients with dysfunctional uterine bleeding showed an 81-87% improvement in bleeding within 3 months compared to a 36-45% improvement seen in placebo treated patients (29). The likelihood of iron-deficiency anemia appears to be decreased in both current and past combination OC users. Anecdotal reports of treating primary dysmenorrhea with OCs document their effectiveness (30).

Reduction of Acne: Recently, two randomized, placebo-controlled trials showed that nearly 50% of women treated with a triphasic OCs containing norgestimate had an improvement in acne compared to 30% of women on placebo (31, 32). Ortho Tri Cyclen and Estrostep are approved by the FDA for the treatment of acne. Another pill that contains ethinyl estradiol and drospirenone is also effective in treating this condition, and may lead to overall improvement in facial acne (33). Other OCs too are being evaluated for similar use (34, 35). All combination OCs likely reduce acne via an increase in sex hormone binding protein and a subsequent decrease in serum testosterone.

Reduced risk of adverse cardiovascular outcomes: In 2004, a study on the WHI database revealed that use of OCs is associated with better cardiovascular outcomes, including any cardiovascular disease, hypercholesterolemia, angina, myocardial infarction, transient ischemic attack, peripheral vascular disease, and need for cardiac catheterization. The data showed that increasing age, elevated body mass index and smoking greatly increased the risks, even in OC users (36, 37).

Risks

Many prescribing patterns of oral contraceptive and other hormonal contraceptive methods are based on perception rather than evidence-based medicine. Evidence-based medicine relies on the integration of clinical expertise with the best evidence from systematic review of research. As clinicians, we can use this methodology to refute misconceptions about oral contraceptives and promote many non-contraceptive benefits. In 2002, the finding of the Women's Health Initiative showed that there is an increased risk of breast cancer with use of menopausal combination hormone replacement therapy (38). The Women's CARE study, sponsored by the NIH and CDC indicate that regardless of period of use of OCs, age and family history, there is no relationship between breast cancer and OC use. Table 4 is a list of the disadvantages of combined oral contraceptives. Table 5 is a list of the contraindications of combined oral contraceptives.

Table 4. Disadvantages of oral contraceptives

- Lack of protection against sexually transmitted infections (STIs);
- Daily administration;
- Unwanted menstrual cycle changes (breakthrough bleeding);
- Nausea and vomiting;
- Headaches;
- Increased cervical ectopy and chlamydia infection;
- Potential risk of increased cardiovascular disease in women with increased age, body mass index and smoking;
- Gall bladder disease acceleration;
- Hepatocellular adenoma.

Table 5. Contraindications for the use of combined oral contraception

Oral contraception should not be used for women with the following conditions (39):

- Known presence or history of deep venous thrombosis or pulmonary embolism;
- History of cerebral vascular accident, coronary artery or ischemic heart disease;
- Diabetes with microvascular complications (neuropathy, retinopathy), duration greater than 20 years or older than 35 years;
- History of estrogen-dependent cancer including known or history of breast cancer;
- Current pregnancy;
- Migraines with aura, focal neurological symptoms, vascular risk factors, vascular disease, or age greater than 35 years;
- Smoking more than 20 cigarettes a day and age greater than age 35 years;
- Untreated hypertension (greater than 160/100) or with vascular disease;
- Liver disease (benign hepatic adenoma, liver cancer, active viral hepatitis, or severe cirrhosis);
- Major surgery with prolonged immobilization or any surgery of the legs;
- Presence or family history of hypercoagulable disorder;
- Less than 2 weeks post partum;
- Systemic lupus erythematosus with vascular disease, nephritis, or anti-phospholipid antibodies
- Hypertriglyceridemia.

Special considerations

Oral Contraceptive Use and The Risk of Thromboembolism

The link between estrogen use and venous thromboembolism was identified more than 20 years ago (40). Since then, there has been extensive literature that describes and attempts to elucidate this risk. A summary of this data shows relative risks of venous thromboembolism ranging from 2.1 - 4.4 (41). The strength of association is in the moderate to consistent range. It has been demonstrated that risk increases as estrogen dose increases. Despite these risks, it is still safer for a woman to use oral contraceptives than to become pregnant. The attributable risk, or number of new cases of venous thromboembolism attributable to estrogen, is on the order of about 6 per 100,000 women years (41). This is in contrast to the risk of venous thromboembolism in pregnancy - it is estimated that there are approximately 20 cases per 100,000 pregnant women years. Table 6 provides a summary of relative risk for VTE in different populations of women.

Table 6. Relative Risk of Venous Thromboembolism (VTE)

Population	Relative Risk(New cases per 100,000 women/year)
General Population	1 (4-5)
Pregnant Women	12 (48-60)
High-dose (>50 μ g EE) OCs	6-10 (24-50)
Low-dose (<50 μ g EE) OCs	3-4 (12-20)
Factor V Leiden carrier	6-8 (24-40)
Factor V Leiden Homozygote	80 (320-400)
Factor V Leiden carrier + OCs	30 (120-150)
Prothrombin G20210A carrier	3-4 (12-20)
Prothrombin G20210A mutation + OCs	7 (28-35)
Protein C or S deficiency	6-8 (24-40)
Protein C or S deficiency + OCs	6-8 (24-40)

Second Versus Third Generation Oral Contraceptives and Deep Vein Thrombosis There is no biological evidence that specific progestins have different effects on clotting factors. In the mid 1990's, however, epidemiological studies reported that women using "third generation" oral contraceptives (containing gestodene and desogestrel) had a higher risk of venous thromboembolism (VTE) compared to women using "second generation" OCs (containing norethindrone and levonorgestrel) (42-44). Studies performed after the initial observation demonstrate a weak association between oral contraceptive use and VTE (strength of association ranges from 0.7 to 2.3). Paradoxically, larger doses of estrogen are associated with lower risks for VTE. This finding has questioned the biological plausibility of the hypothesis of associating 'new progestins to an increased risk of deep venous thrombosis (DVT).

It was suggested that the original studies may have included newer users of oral contraceptives that may have been innately at higher risk for DVT, thus biasing the results (5, 45). After reanalysis of the data, the FDA issued a statement stating that the risk of DVT with the 'new progestins "is not great enough to justify switching to other products".

Recently, the association of second versus third generation progestin and the risk of VTE was further analyzed in 2 separate meta-analyses. Twelve observational studies were included in one meta-analysis of the relative risk of VTE for OCs containing either desogestrel and gestodene or levonorgestrel (46). The relative risk of VTE in users of OCs with desogestrel and gestodene to levonorgestrel was 1.7 (95% CI, 1.3-2.1), an increase of approximately 11 more cases of VTE per 100,000 women per year. When accounting for duration of use and new use (less than 1 year), this increased risk persisted.

These results were confirmed in another meta-analysis of seven cohort and case-control studies. The overall adjusted odds ratio for third versus second generation oral contraceptives was 1.7 (95% CI, 1.4-2.0). (47) Among first-time users (<1 year of use), the odds ratio for third versus second generation preparations was 3.1 (95% CI, 2.0-4.6), which decreased to 2.0 (95% CI, 1.4-2.7) in longer term users (1 year of use).

More recently, Lidegaard et al retrospectively assessed the influence of OCs on the risk of VTE in women aged 15-44 years. (48) After adjusting for age, BMI, length of OC use, and family history of coagulopathies, the odds of VTE among current second generation OC users compared to non-users was 2.9 (95% CI, 2.2-3.8) while the odds of current third generation OC users compared to nonusers was 4.0 (95% CI, 3.2-4.9). After correcting for duration of use and differences in estrogen dose, the

third/second generation risk ratio was 1.3 (95% CI, 1.0-1.8; $p < 0.05$), suggesting that third generation progestins are associated with a 33% increase in the incidence of VTE.

Factor V Leiden mutation may independently increase the risk of DVT. The Factor V mutation occurs in 3-5% of Caucasians and is responsible for the majority of cases of venous thrombosis in which a mechanism is identifiable. A recent study suggested that the combination of third generation oral contraceptives and the Factor V Leiden mutation may increase the risk of DVT 30-50-fold (49). This study has been criticized for its lack of validation and methodology.

Other inherited thrombophilias, such as the prothrombin G20210A defect, and Protein S or Protein C deficiency, have been associated with an increased risk of VTE. Multiple studies have shown that this risk increases in the setting of OC use.

A recent retrospective cohort study of patients with a documented VTE showed that compared to non-users, OC use increases the risk of thrombosis in carriers of antithrombin, protein C and protein S defects six fold (50). Interestingly, risk of VTE in carriers of Factor V Leiden was not significantly increased.

Another investigator retrospectively analyzed OC exposure and incidence of VTE in thirteen female patients with the prothrombin G20210A defect (12 of which were heterozygote for the defect). (51) All thirteen women took OCs for an average of 10 years without any thrombotic complication. Interestingly, the homozygote took OCs with a 'third generation' progestin for 6 years without a thrombotic event. Another investigator noted that those patients who develop VTE soon after initiating OCs (<6 months), most are thrombophilic. (52) Among women with protein C or protein S deficiency, antithrombin deficiency, Factor V Leiden or prothrombin 20210A mutations, the risk of developing a DVT during the first year of OC use was increased 11-fold (95% CI, 2.1-57.3). (53)

A pooled analysis of 8 case-control studies revealed that the odds ratio for VTE associated with OC use was 10.25 (95% CI, 5.59-18.45) in factor V Leiden carriers and 7.14 (95% CI, 3.39-15.04) in carriers of the prothrombin G20210A mutation(49). The crude odds ratios for VTE (not specifically analyzing the effect of OCs) were 4.9 (95%CI, 4.1-5.9) for factor V Leiden and 3.8 (95%CI, 3.0-4.9) for the prothrombin 20210A mutation.

Therefore, all healthy women who are diagnosed with a DVT while using oral contraceptives should be tested for possible Factor V Leiden mutation or Protein S or Protein C deficiency although screening beforehand is not warranted.

Oral Contraceptive Use and Risk of Myocardial Infarction Myocardial infarction is a very rare event in non-smoking women of reproductive age. For women younger than 35 who do not smoke, the incidence of myocardial infarction is less than 1.7 per 100,000 woman years (41). This rate is notably higher between the ages of 40 and 45 years and is about 21 per 100,000 woman years. Review of the evidence shows that the association between current combined oral contraceptive use (containing 35 micrograms of ethinyl estradiol or less) and myocardial infarction is weak, with a relative risk ranging from 0.9 to 2.5. There is no evidence to support an increased or decreased risk of myocardial infarction due to past oral contraceptive use compared to no use (54). Smoking has been identified as an independent risk factor for myocardial infarction; the combination of smoking and oral contraceptive use can be synergistic for increasing the risk of a MI.

The World Health Organization (WHO) has the following recommendations (54):

1. Combined oral contraceptives can be use safely by women of any age who are non-smoking, normotensive, and non-diabetic.
2. For women who smoke, and are 35 years or younger, oral contraceptives containing 35 micrograms or less are recommended.
3. For women who smoke and are 35 years or older, oral contraceptive use is contraindicated.

Oral Contraceptive Use and Risk of StrokeThe link between high dose oral contraceptive pills and ischemic stroke has historically been determined with a strength of association ranging from 2.9 to 5.3 (41). However, as dose of estrogen decreased, the odds ratio and relative risks in further studies all decreased as well. A summary of the data by the WHO (44, 45) concludes that there is no significant increased risk of ischemic stroke in women younger than 45 years old who use oral contraceptives. Overall, the strength of association between the use of lower dose oral contraceptives and stroke is weak, with odds ratios ranging from 1.1 to 1.8, with most 95% confidence intervals including 1.0 (41). There is no consistent strong evidence linking oral contraceptive use to hemorrhagic stroke. Women of any age who have migraines with aura should not take combination oral contraceptive pills (46). Since smoking, hypertension, and migraine headaches all are independent risk factors for stroke, it must be concluded that women with other independent risk factors may have a slightly increased risk of stroke while taking the oral contraceptive pill. There is ample evidence, however, to suggest that there is no significant increase in ischemic or hemorrhagic stroke in OC-using women with no other risk factors. Because the baseline risk of stroke is rare in reproductive aged women, the attributable risk of oral contraceptives is quite small. In summary, evidence shows that current low dose oral contraceptives are safe with regard to vascular disease for a great majority of healthy non-smoking women who seek an effective contraceptive method.

Neoplastic effects of hormonal contraception:The risk of neoplasm with the use of hormonal contraception has been extensively studied. As mentioned previously, use of combined oral contraception is associated with a reduced risk of cancer of the ovary and the endometrium and will not be addressed in this section.

Oral Contraceptive Use and Risk of Breast CancerThe relation between OC use and breast cancer remains controversial. Two recent studies provide evidence that OC use is not associated with an increase in breast cancer incidence. The first study was conducted by the Collaborative Group on Hormonal Factors in Breast Disease. This group reanalyzed approximately 90% of the epidemiologic data available worldwide concerning oral contraceptive use and breast cancer risk (47, 48). The findings included a slight increase in the relative risk of localized breast cancer associated with current oral contraceptive use (relative risk 1.24, 95% CI 1.15-1.33) or oral contraceptive use within 1-4 years (relative risk 1.16, 95% CI 1.08-1.23) compared to never use. The study also demonstrated that breast cancers diagnosed in OC users were significantly less advanced than those in never users (relative risk 0.88 for spread of disease beyond the breast). They also noted there was no change in the effect of OC use associated with breast cancer by family history. Importantly, they demonstrated no overall effect of OC use that was associated with breast cancer by duration of use, dose, formulation, age at use, or age at breast cancer diagnosis. Oral contraceptive users and non-users older than 50 years have the same cumulative risk of diagnosis of breast cancer. Oral contraceptive use may accelerate the diagnosis of breast cancer but does not affect the overall risk (48).

The second study involved over 8000 women, half of which had the diagnosis of breast cancer. (49) Overall, 77% of cases and 79% of controls had ever used OCs. Ever users and current users of OCs were found not to have an increased risk of breast cancer compared to women who had never used OCs (OR 0.9, 95%CI 0.8-1.0 and 1.0, 95% CI, 0.8-1.0, respectively). The relative risk did not increase with increasing duration of OC use or higher estrogen doses. In addition, family history of breast cancer did not significantly impact risk.

Oral Contraceptive Use and Liver CancerNon-case control studies of reproductive age women in western developed nations have reported an association between oral contraceptive and liver cancer. Recent population-based data, however, do not suggest any association between liver cancer and OC use among women in five developed nations. In addition, reassuring data from two studies in developing countries, including a large WHO study, do not support an increased risk of liver cancer with oral contraceptive use (60).

Oral Contraceptive Use and Gall Bladder DiseaseStudies suggested in the 1970's that

oral contraceptives were associated with an increased risk of gall bladder disease. Since then, numerous case-control and cohort studies have described an increased risk of benign gall bladder disease in oral contraceptive users. A meta-analysis of these studies published in 1990, however, found that few of these studies could stand up to internal validity measures. The relationship between benign gall bladder disease and oral contraceptives yields a relative risk of 1.1 with a 95% CI 1.1 - 1.2 (9).

New developments in combined oral contraceptive pills

The number of combined oral contraceptive pill preparations on the market has increased in recent years. There are new formulations of pills with a dosage of estrogen as low as 20 micrograms. Some preparations have changed the paradigm of 7 days of placebo (with 21 days of active pills) and now offer a 26 day active and two-day placebo period. Some physicians also use the 'Quick Start' approach to pill initiation, this allows for immediate ingestion of the first dose of the pill in the office after a negative pregnancy test. This approach disregards the status of the patient's menstrual cycle. A clinical trial has shown that this approach is safe, and results in higher ultimate rate of pill use than the conventional – after the onset of menses approach (61). In general, the efficacy, side effects and cycle control of these new preparations are similar to those with 35 micrograms of estrogen. The "lower" dose pills offer the theoretical advantage of less estrogen and therefore fewer estrogen side effects and medical complications. It remains to be determined if the new "lower" dose pills confer the same non-contraceptive benefits of the "higher" dose pills.

A new oral contraceptive containing 30mcg ethinyl estradiol and 3mg drospirenone, works in a manner similar to other oral contraceptives, effectively inhibiting ovulation and producing cervical mucus that is hostile to sperm motility. Unlike other progestins used in oral contraceptives, drospirenone is an analogue to spironolactone and has biochemical and pharmacologic profiles similar to endogenous progesterone (62). Drospirenone has both antimineralocorticoid and antiandrogenic activity. Its antiandrogenic activity may lead to suppression of undesired symptoms such as acne and hirsutism. Its antimineralocorticoid activity balances the aldosterone-stimulating effects of estrogen, thereby potentially reducing water-retention and weight gain.

Another preparation offers a hormone-free, placebo length of only 2 days. Twenty-one days of 20mcg ethinyl estradiol and 150mcg of desogestrel is followed by 2 days of placebo and 5 days of 10mcg ethinyl estradiol. Within 18 months of use, absence of withdrawal bleeding and intermenstrual bleeding have been reported to occur in 5.5% and 12% of total cycles, respectively. (63) Nearly three-quarters of participants in a large, open-label study reported one or more side effects, including headache, breast pain, dysmenorrhea, and menstrual irregularities.

Psychological/Behavioral effects of hormonal contraception: Few studies have investigated the effects of OCs on behavioral function. Some retrospective studies have shown that women discontinued the use of combined oral OCs due to negative mood changes (occurred in about 30% of women) (64). Women treated with lower doses of progestogen experience fewer symptoms than those treated with higher concentrations. The derivative compounds produced after metabolism of exogenous progestins contribute to the modulation of psycho physiological function. For example, oral micronized progesterone is metabolized to a product (3-alpha, 5-alpha-OH THP) that can cause sedation at high circulating concentrations (65). Furthermore, experimental studies have demonstrated anxiolytic effects of large doses of progesterone, which is mediated by 5-alpha reductase metabolites (66). This effect is observed in women affected by premenstrual dysphoric disorder; symptoms markedly improved during treatment with oral micronized progesterone. Interestingly, vaginal administration of progesterone is not associated with the above anxiolytic effects (67).

Combined non-parenteral administration Recent improvements in steroid hormone delivery have resulted in numerous new hormonal contraceptives methods. Effective, safe contraception is achieved with combination estrogen and progestin deliv-

ery via a monthly injection, contraceptive skin patch, and a vaginal ring. The general mechanism of action of these methods is similar to that of combined oral contraceptives. These methods offer the advantage of non-daily administration, relative ease of administration, potential greater compliance and thus potential greater efficacy.

Monthly injection

Features of a monthly injectable contraceptive resemble those of the combined oral contraceptive. Monthly combined injectables provide predictable monthly cycle control in a rapidly reversible method upon discontinuation. The combination hormone monthly injectable contraceptive contains 5 mg of estradiol cypionate and 25 mg of medroxyprogesterone acetate (E2C/MPA). After injection, the cypionate ester is cleaved so that the circulating estrogen is similar to the ethinyl estradiol found in oral contraceptives. The monthly injectable is administered during the first five days of a woman's cycle and re-injected every 28 days with a margin of error of five days (23-33 days) (68).

Lunelle was voluntarily recalled from the American market in 2002, however, three clinical trials in the United States have shown that the efficacy of the monthly injectable contraceptive is very comparable to that of combined oral contraceptives (68, 69). More than 7 thousand women participated in clinical trials prior to its FDA approval. Eighty-four percent of patients who received the monthly combination injectable characterized their experience as favorable or very favorable (70). Approximately 90% of responders reported that they would recommend this method of contraception to a friend (71).

Reported side effects associated with this method are similar to that of the combined oral contraceptive pill. Side effects include breast tenderness, gastro-intestinal complaints, emotional liability, acne, and weight change. The number of women experiencing side effects approached 9% although the majority of these side-effects were considered mild. Weight change among those taking the injectable medication follow no predictable pattern compared to those taking the combined OCs. Some women lost weight while others gained weight. Bleeding patterns were well controlled with the combination hormone monthly injectable; breakthrough-bleeding pattern was also similar to that of combined oral contraceptive pills. Over time, bleeding control improved by the fourth cycle. Amenorrhea was uncommon.

Metabolic Effects: Hepatic function, glucose metabolism, and renal function are minimally changed in women using this method of contraception. The monthly injectable produces a median 2.5 mg/dl rise in LDL and a median 7mg/dl reduction in triglycerides. This is in contrast to a 13 mg/dl gain in LDL and a 22.5 mg/dl median gain in triglycerides for women that used oral contraceptive pills (68). There are no observed differences after one year of treatment in terms of clotting factors.

Return to ovulation and fertility is achieved two to three months after discontinuation of this method (72). Return of fertility does not appear to be related to duration of treatment. The predictable pharmacokinetics explain its rapid reversibility and its predictable bleeding pattern. Serum estradiol levels reach peak concentration near mid cycle and decline after several days. Estradiol levels fall below the levels sufficient to maintain the endometrium, prompting a withdrawal bleeding, 2-3 weeks after administration (73).

The non-contraceptive benefits of this combined injectable contraceptive to date are unknown. Monthly injections of a combination of estrogen and progesterone regulate hormones in the same way as oral contraceptives. It is therefore likely that they have the same non-contraceptive benefits. Extended follow-up of women using this method will be necessary before long-term health benefits such as protection can be demonstrated.

Transdermal Patch

The once-weekly contraceptive patch delivers 150mcg of norelgestromin, the active metabolite of norgestimate, and 20mcg of ethinyl estradiol daily to the systemic circulation (74), and is currently used by 2% of American women. Typical use includes placement of the patch on the same day of each week for 3 consecutive weeks followed by a patch-free week. Serum levels of the estrogen and progestin components are maintained for 2 days beyond the recommended 7 days of wear. Therefore, patients do not have to change the patch at the exact same time each week.

The patch is composed of 3 layers: an outer protective layer of polyester, a medicated, adhesive middle layer, and a clear, polyester liner that is removed before patch application. Patients can maintain normal activity, including bathing, swimming and heavy exercise while using the patch. It is recommended that wearers avoid use of oils, creams or cosmetics that may interfere with adhesion of the patch.

Compared to OCs with 250mcg norgestimate and 35mcg ethinyl estradiol, the patch suppresses ovulation to a similar degree (74). It is as effective as oral levonorgestrel/ethinyl estradiol in altering cervical mucus and in providing cycle control. The overall and method-failure probabilities of the transdermal patch (through 13 cycles) are 0.7% and 0.4%, respectively (75). Perfect compliance (21 days of consecutive dosing followed by 7 days of no medication) was achieved in 90% of patients in the above study. However, efficacy trials of the patch have shown that participants less than 20 years age were less likely to use the patch correctly than the pill (76). The noncontraceptive effects of trans-dermal administration have not yet been studied, but are expected to be similar to the combined oral contraceptive pill. A recent clinical trial did not demonstrate the same improved continuation rates with the "quick start" method in patch users as was seen in oral contraceptive users (77).

Vaginal Ring

For numerous decades, the vagina has been identified as a potential organ for drug absorption (78, 79). The anatomy of the vagina allows for the easy placement of a ring to achieve this purpose.

A combination estrogen/progestin vagina ring was approved for use in 2001 and is used by 0.3% of US women of reproductive age group. It is a flexible transparent circular tube, 54 mm (2 inches) in diameter and 4 mm (1/4 inch) thick. The ring is made of ethylene vinyl acetate polymer and contains a hormone reservoir that releases 0.120 μg of etonogestrel and 0.015 μg of ethinyl estradiol each day over a three-week period (80). Hormone content in the ring is sufficient to provide a "grace period" of at least 14 additional days (81), so woman can leave it in place for a full month and then immediately replace it to avoid menstruation, if they so desire. Etonogestrel, also called 3-ketodesogestrel, is also a synthetic hormone. It is the active metabolite of desogestrel, the progestin component of commonly used oral contraceptives.

The mechanism of action of a vaginal ring is similar to other hormonal contraceptives. Initiating ring use during the first five days of a normal cycle ensures that ovulation in that cycle is suppressed. Similarly, allowing no more than seven ring-free days each month, and making sure that the ring is in place continuously, with no more than three hours out in one day are also important for efficacy (81). Overall pregnancy rates are reported to be 0.65 per 100 woman-years (all first-year users) (82). This level of effectiveness is similar to that found for women using combined oral contraceptives. Adherence to rules for ring use was very high, with consistent and correct use reported in 90.8% of all cycles. Women using the ring also reported good cycle control, with expected withdrawal bleeding in 98% of cycles, and bleeding at other times in only 6.4% of cycles (82).

The ring can be placed in any position in the vagina that is comfortable. A total of 8% of women note the sensation of the ring in the vagina. If the ring is removed for intercourse it can be cleaned with water and must be replaced within three hours. Risks

and adverse reactions possible with use of combined hormonal oral contraceptives also are likely to apply to the vaginal contraceptive ring. The ring does not prevent against sexually transmitted disease. Some women using the ring experienced side effects related to the device itself including vaginal discomfort or problems during intercourse, vaginal discharge, or vaginitis. These device-related problems were reported by 2-5% of women (82). Overall acceptability and tolerability of the ring were very high in the clinical trials performed to date.

PROGESTIN ONLY HORMONAL CONTRACEPTIVES

Current progestin-only methods include Depo-Provera, progestin-only pills and intrauterine devices impregnated with progestin. A new etonorgestrel implant system awaits final approval from the FDA.

Mechanism of action: Progestin-only methods have many documented mechanisms of action, including inhibition of ovulation, thickened and decreased cervical mucus, suppression of mid-cycle peaks of LH and FSH, inhibition of progesterone receptor synthesis, reduction in the number and size of endometrial glands, reduction in ciliary activity within the fallopian tube, and premature luteolysis (decreased functioning of the corpus luteum) (83-86). Progestins at high concentrations likely suppress the initiation of folliculogenesis at the level of the hypothalamus. At slightly lower concentrations folliculogenesis can be initiated but the progestin prevents the LH surge at the level of the pituitary and therefore prevents ovulation. At even lower concentrations, progestins alter cervical mucus, tubal motility and/or the endometrium (87).

Advantages: Progestin-only methods do not have an estrogen component, thereby decreasing the complications attributable to estrogen (such as thrombophlebitis, cardiovascular disease and pulmonary embolism). Specific non-contraceptive benefits of these methods include scanty or no menses, decreased menstrual cramps and pain, suppression of pain associated with ovulation, decrease in endometrial cancer, ovarian cancer, and pelvic inflammatory disease, and potential improvement of the pain associated with endometriosis. All progestin-only contraceptive methods are reversible. Non-parental administration of progestin provides long term, effective contraception, decreases the risk of ectopic pregnancy, and is not coitally dependent. Specific indications for these methods may include women who are breastfeeding, women who are at greater risk for thromboembolic events, and women who cannot take estrogen.

Disadvantages: These methods do not protect against sexually transmitted disease and HIV and can alter the menstrual cycle (including breakthrough bleeding with an increased number of days of light bleeding, and potential amenorrhea).

The contraindications to progestin-only contraceptives are listed in Table 7. The only absolute contraindications methods include pregnancy, unexplained abnormal vaginal bleeding suspicious for a serious underlying condition, or breast cancer. Active liver disease has been deleted from the list of contraindications to DMPA. In general, one should exercise care when using this method in women with acute, severe liver disease or liver tumors.

Table 7. Contraindications to Progestin-only Hormonal Contraceptives

Oral contraception should not be used for women with the following conditions:

- Known or suspected pregnancy
- Unexplained vaginal bleeding
- Breast cancer

Additional contraindications that apply to Norplant only include:

- Medication that cause progestins to be metabolized more rapidly:
 - anti-seizure medications: phenytoin, phenobarbital, carbamazepine, primidone, phenbutazone, and
 - antibiotics: rifampin/rifampicine)
- Active thrombophlebitis or pulmonary emboli*

*There is no evidence that progestin-only methods increase the risk of cardiovascular events in a fashion similar to the combined oral contraceptive pill. Even though there is no evidence that progestin-only contraceptives do cause cardiovascular events, the product labeling might still list active cardiovascular disease (or history of disease) as a contraindication.

PROGESTIN-ONLY ORAL CONTRACEPTIVES

Progestin-only pills, also called the 'minipill', are used in a manner similar to combined OCs. The progestin-only minipill has a dose of progestin that is very close to the threshold of contraceptive efficacy. Therefore these pills must be taken at approximately the same time each day and are taken continuously for 28 days of the month without a pill-free interval. Less than one percent of oral contraceptive prescriptions in the United States are for the progestin-only oral contraceptive (88). This form of contraception is traditionally most often used in women who are breastfeeding or in women who have contraindications to estrogen, however, most women are candidates for this method. Since the 1970's, two progestin-only formulations are available in the United States, one that contains 75mcg of norgestrel and the other, 350mcg of norethindrone. It is important to note that ovulation is not always inhibited with the use of progestin-only pills. Approximately half of cycles have suppressed ovulation and thus contraceptive efficacy is dependant on the other progestin related mechanisms listed previously. (88)

Efficacy: The typical failure rate of progestin-only pills is similar to that with combined oral contraceptives (89), despite the fact that efficacy is only for 27 hours and requires consistent administration. Serum levels of progestin peak 2 hours after administration and return to near baseline levels within 24 hours (88). Variation of only a few hours in administration can be the difference in the progestin-only pill providing its contraceptive protection. Women should be prepared to use a back-up method if they are three hours late in taking the pill, if one pill is missed or if there is a delay in its administration.

Side Effects: The main side effect associated with progestin-only pills is menstrual cycle irregularity. Spotting or breakthrough bleeding, amenorrhea, and shortened length of menstrual cycles are the most common irregularities experienced. A randomized, double-blind study by the WHO showed that an average of 53% of users had frequent bleeding, 22% had prolonged bleeding, 13% had irregular bleeding, and 6% had amenorrhea within 3 months of initiation (90). Menstrual irregularity is a common reason for method discontinuation. Other less common side effects include

nausea, dizziness, headache, and breast tenderness.

Risks: In general, any contraceptive method protects against ectopic pregnancy. However, if progestin-only pill users get pregnant, on average 6-10% of the pregnancies will be ectopic, higher than the rate seen in women not using any method of contraception (2%) (88). The overall risk, however, remains lower than the general population because so few women actually become pregnant (7%) while using this method of contraception.

A recent WHO case-control study of cardiovascular disease and progestin-only pill use found no significant increase in the risk of acute myocardial infarction (RR=1.0, 95%CI, 0.2-6.0), stroke (RR=1.1, 95%CI, 0.6-1.9), or venous thromboembolism (RR=1.8, 95%CI, 0.8-4.2) (91). Thus far, progestin-only pills appear to have little or no effect on lipid metabolism, carbohydrate metabolism, hypertension, and coagulation factors (88).

PROGESTIN-ONLY INJECTABLES

Depo- medroxy progesterone acetate (DMPA; Depo-Provera®) is a deep intramuscular injection of 150 mg of medroxyprogesterone acetate (MPA) every 12 weeks. Pharmacologically active levels (>0.5mg/ml) of MPA are achieved within 24 hours of injection. Serum levels remain >1.0ng/ml for approximately three months after administration. By the fifth month, levels drop to 0.2mg/ml (92). DMPA's main mechanism of action is inhibition of ovulation.

Non contraceptive benefits of DMPA (93).

Decreased risk of:

- Endometrial cancer
- Iron deficiency anemia
- Pelvic Inflammatory diseases
- Ectopic pregnancy
- Uterine Leiomyomata

Improvements of the following conditions:

- Menorrhagia/Dysmenorrhea
- Premenstrual syndrome symptoms
- Pain in women with endometriosis
- Seizures refractory to conventional anti-convulsants
- Hemoglobinopathy
- Endometrial hyperplasia
- Vasomotor symptoms in menopausal women
- Pelvic pain/dyspareunia in ovarian origin post hysterectomy
- Metastatic breast cancer
- Metastatic endometrial cancer

Efficacy: With typical use, the failure rate is 0.3 per 100 woman-years which is similar to rates found with surgical sterilization (94). Variations in body weight and concurrent medications have not been shown to alter efficacy (95).

Side Effects: The most commonly cited side effects of DMPA are changes in menstrual patterns, weight, and mood. After 3 months of use, almost one-half of DMPA users report amenorrhea with the majority of the remaining women complaining of irregular bleeding (96). By the end of one year, nearly 75% of users will experience amenorrhea

(97). Short courses of high dose estrogen do little to reduce bleeding among DMPA users (98). In addition, early readministration of DMPA (at 8-10 weeks instead of 12 weeks) does not reduce bleeding (99). Although many users of DMPA report weight gain, recent controlled studies show that its long-term use does not cause a significant increase in body weight (100). Product labeling for DMPA includes depression as a possible side effect. Two well-designed studies addressed the issue of depression and DMPA use. Patients followed up to one year after DMPA initiation showed no worsening of depressive symptoms compared to those who did not use Depo-Provera (101,102). Clinical trial setting, DMPA does not cause statistically significant weight gain (103-105). However, African American women and Navahos and women with high baseline body mass index may be predisposed to weight gain with the use of this method (104). New studies have shown that neither DMPA nor progestin only injectable is associated with increased risk of breast cancer.

Risks: A recent review showed that levels of triglyceride and total cholesterol do not change with DMPA use (106). Seven of the ten studies that measured serum lipid levels revealed a decrease in high density lipoprotein (HDL) while three out of five studies showed an increase in mean low density lipoprotein (LDL) levels. The clinical significance of these findings remains to be determined. In contrast to combination OCs, Depo-Provera is not associated with increases in coagulation-related factors or in blood pressure (107). A small but nonsignificant increase in the risk of VTE is noted in users of progestin-only injectable contraception (91). Recent studies provide reassuring evidence that decreases in bone mineral density in current and recent Depo-Provera users are reversible and appear to be similar to changes seen in lactation (108).

Bone loss: On November 17, 2004, the FDA placed a black box in DMPA package labeling regarding the long-term use of DMPA and bone loss. Anecdotally, this warning had an immediate impact on decreased prescription of DMPA. Depot medroxyprogesterone acetate use has not been linked to menopausal osteoporosis or fractures. A Cross-sectional study from the WHO demonstrated that in that years after use, BMD in former adult DMPA users is similar to that of never users (109) The 2002 cohort study of BMD in adult women performed by Scholes et al. (110), a National Institutes of Health-funded investigator in Seattle, demonstrated that at 3 years of follow-up, BMD of former DMPA users was comparable to that of never users of injectable contraception. While the FDA warning also specifically heightened concerns about teens and bone loss in the setting of DMPA, a 2005 report from Scholes et al. (111) showed that use of DMPA in this population does not put patients at risk for osteoporosis later in life. This cohort study followed 170 adolescents (including 80 who used DMPA at baseline) and found that recovery of BMD was complete within 12 months following DMPA discontinuation. BMD was ultimately observed to be higher in the former than in the never users of DMPA. Duration of DMPA use was not observed to impact speed of BMD recovery following DMPA discontinuation.

PROGESTIN-ONLY VAGINAL RINGS

Progestin-only rings are now in development, contain 100mg medroxyprogesterone acetate (MPA), and suppress ovulation (112). These rings are placed on day 5 of the cycle and are removed after 21 days of use in order to provide a withdrawal bleed. Other progestin-only rings included those impregnated with norethindrone; these rings have been associated with irregular bleeding and ovulation (113,114).

INTRAUTERINE DEVICES

Although intrauterine devices (IUDs) are the most widely used form of irreversible contraception worldwide, they are an underutilized contraceptive method in the United States. (115).

Mechanism of action: There are two types of IUDs currently available in the U.S.: a copper IUD (Paraguard®) and a progestin-impregnated progestin intrauterine system (IUS), Mirena®. Both medicated and nonmedicated intrauterine devices (IUDs) have multiple mechanisms of action that provide for contraceptive protection. Both medicated and nonmedicated IUDs can alter the uterine lining so that it becomes unfavorable for implantation. Release of copper ions also alters fluid in the uterine cavity in a manner that impairs the viability of sperm, thereby inhibiting fertilization. This mechanism may be responsible for the high efficacy of copper IUDs as emergency contraception.

IUDs can also alter both sperm motility and integrity (116-119). Medicated, or hormonal IUDs, can interfere with sperm motility by thickening cervical mucus. Sperm head-tail disruption has been reported in the presence of a copper IUD (116). IUDs, whether hormonal or non-hormonal, do not provide protection against sexually transmitted diseases. However, it is important to recognize that IUDs do not cause PID (120, 121), and that the historical associations that both physicians and the lay public maintain between IUDs and PID/tubal infertility are false.

Timing of IUD insertion: The IUD can be inserted at any point in the cycle as long as the patient is not pregnant. An IUD can be inserted immediately postpartum, post abortion, or as an 'interval' insertion. However, the progestin IUS, Mirena®, is generally inserted in the first five days after menses because this is how the clinical trials were performed, and it is not known if Mirena® has the same post-coital contraceptive effects as the copper IUD (Mirena® should not be used as an emergency contraceptive).

Interval Insertion: An 'interval' insertion is defined as insertion in women who are neither postpartum nor post abortion, or an insertion in women 6 weeks after delivery (122). Traditionally, physicians were taught that the best time for IUD insertion was either during menses or immediately after menstruation. Limiting insertion to these time points, however, created a barrier to their use. Data now suggest that IUD insertion between cycle days 12 to 17 results in greater IUD continuation rates. The Centers for Disease Control and Prevention reviewed data from more than 9,000 copper T-200 IUD insertions and found that IUDs placed after cycle day 11 resulted in fewer IUD removals during the first 2 months of IUD use. Insertions after day 17 resulted in more frequent IUD removal due to pain, bleeding, or accidental pregnancy (123).

Progestin-only IUD: The levonorgestrel intrauterine system (Mirena LNG IUS) releases 15mcg of levonorgestrel per day from a polymer cylinder mounted on a T-shaped frame containing 52mg levonorgestrel; it is covered by a rate-releasing controlling membrane. It is approved for 5 years of use. The failure rate is low: 0.16 per 100 woman years of use. Its mechanisms of action include production of an atrophic and inactive endometrium, disturbed ovulation, and thickening of the cervical mucus. Ovulation may be inhibited in some women, but this is not the main mechanism of action. Both the volume of menstrual flow and the number of days of bleeding are reduced (124). The mean number of bleeding and spotting days is initially increased but in 3-6 months' time, the number of bleeding and spotting days is similar to users of the copper-IUD. During the first year of use, about 20% of women will become amenorrheic (124). A recent meta-analysis of randomized controlled trials reveal that LNG IUS users were significantly more likely than all other IUD users to discontinue its use because of hormonal side effects and amenorrhea (125), so appropriate counseling is an important component of success. Initial irregular spotting or bleeding, and hormonal side effects like acne and ovarian cysts may occur in some users. In part because there is no user-dependence, the LNG IUS offers improved effectiveness over other hormonal methods (125).

Non Contraceptive uses of LNG IUS: Multiple descriptive studies and clinical trials have been performed on the non contraceptive benefits of the Levonorgestrel IUS (LNG-IUS) (126-132).

- Treatment of menorrhagia in women with uterine fibroids and adenomyosis

- Treatment of pain in women with endometriosis
- Alternative to hysterectomy for women with menorrhagia
- Prevention of endometrial hyperplasia in menopausal women using estrogen therapy
- Prevention of endometrial proliferation and polyps in breast cancer survivors taking tamoxifen

One such study evaluated the efficacy and performance of the LNG-IUS in 44 women with menorrhagia after medical therapy had failed. (132) At 12 months, 79.5% of participants continued use of the LNG-IUS. After LNG-IUS insertion, the most common bleeding pattern at 3 months was spotting followed predominantly by amenorrhea or oligomenorrhea at 6, 9, and 12 months. Hemoglobin levels significantly increased from 102 g/L before insertion to 128 g/L at 12 months ($p < 0.01$).

The LNG-IUS is an effective treatment for menorrhagia. It remains unclear if the LNG-IUS is effective in reducing menstrual blood loss in women with menorrhagia due to the presence of intramural or subserosal fibroids.

Another prospective study observed that the 20mcg LNG-IUS provides effective protection against endometrial hyperplasia in post-menopausal women on estrogen replacement therapy (in the daily dose of 2mg of estradiol valerate).

EMERGENCY CONTRACEPTION

Emergency contraception prevents pregnancy after unprotected sexual intercourse. Emergency contraception (EC) does not protect against sexually transmitted infections. The emergency contraceptive formulations available in the United States include combined oral contraceptive tablets, two levonorgestrel 750mcg tablets (Plan B), and the Copper "T" IUD (133-135). The combination EC formulation (Preven) is no longer available in the US. The current treatment schedule for emergency contraceptive pills (ECPs) is one dose within 72 hours of unprotected intercourse and the second dose can be given at the same time as the first (136), or 12 hours after the first dose. Combined and progestin-only ECPs reduce the risk of pregnancy by about 75-88% (137, 138). Effectiveness declines with increasing delay between unprotected intercourse and initiation of treatment (139).

Mechanism of action: Emergency contraception likely inhibits or delays ovulation (140). Some investigators have shown histological alterations in the endometrium suggesting impairment of endometrial receptivity to implantation (141) while others have found no such effects (142, 143). Other possible mechanisms include interference with corpus luteum function, thickening of cervical mucus, and alterations in tubal transport of sperm, egg, or embryo (144). Emergency contraceptives do not interrupt an already established pregnancy.

Progestin-only emergency contraceptives are more effective and associated with significantly less nausea and vomiting than combined emergency contraceptive pills (145). The only absolute contraindication to the use of emergency contraceptive pills is a confirmed pregnancy. The absence of contraindications is likely due to the very short duration of exposure and low total hormone content. There are no conclusive studies of women who were already pregnant when they took emergency contraceptive pills or of women pregnant after failed emergency contraception. However, there is no epidemiologic evidence that progestins are teratogenic and observational studies provide reassurance regarding birth defects (146).

The FDA has not granted approval for the over the counter use of EC for prevention of pregnancy (147). Evidence has been reported that making ECPs widely available does not increase risk taking behavior or increase the incidence of unintended pregnancy (148). Additionally, it has been demonstrated that women most likely to seek emergency contraception are those already concerned about or using contraception (149).

Copper IUD's can be inserted up to five to seven days after ovulation to prevent pregnancy. Insertion of a Copper IUD is significantly more effective than the use of hormonal emergency contraception. The use of a Copper IUD can reduce the risk of unintended pregnancy by more than 99% (150).

BARRIER METHODS

Multiple forms of barrier methods are currently used: male and female condoms, the diaphragm, the contraceptive sponge, and cervical cap. Vaginal barriers are easy to use and are non-invasive. They can be used with little advance planning. Consistent and correct uses are absolutely essential for barrier effectiveness; most failures occur due to improper or inconsistent use. The 'typical use' pregnancy rate for these methods can be as high as 20-30%. The male condom has a 'typical use' failure rate of 14%. Recent studies have shown that teens were most likely to use condoms for birth control and 66% used a condom when they became sexually active (151).

Mechanism of action: Both the male and female condoms provide a physical barrier that prevents sperm and egg interaction. They are intended for one time use only. Condoms also provide some protection against HIV and STI.

Diaphragms and cervical caps use two different mechanisms, a physical barrier as well as a spermicidal chemical. They are available by prescription only, and must be sized by a health professional for a proper fit. They are always used with spermicidal agents. Diaphragm provides protection for 6 hours and cervical cap for 48 hours after insertion.

The contraceptive sponge is a disc shaped poly urethane device and contains a 1,000 mg of nonoxynol-9. It does not require prescription, and provides protection for up to 24 hours after insertion. The typical use pregnancy rate for this method is 10-40%.

Vaginal barriers have many advantages: protection against sexually transmitted infections provides immediate protection without much prior planning, easy access, and no systemic side effects. Disadvantages include: discomfort with placement and use, possible latex allergy (for condoms), increased incidence of urinary tract infections and bacterial vaginosis; and associations have been reported with toxic shock syndrome. In addition, a health care provider may be required to do the initial fitting for diaphragms, necessitating an extra visit to the physician's office. A comparison of the ability of contraceptive methods to reduce sexually transmitted disease is found in table 8.

Table 8. Effectiveness of Contraceptive Methods: Pregnancy Prevention and STD Protection

Contraceptive Method	Effect on Reproductive Tract	Effect on Bacterial STDs	Effect on Viral STDs
Diaphragm/Cervical cap/Sponge	Reduces risk of PID; associated with vaginal and urinary infections	Some protection against cervicitis; increases organisms associated with bacterial vaginosis, candidiasis and urinary tract infections	No protection against vaginal infection or external genitalia transmission; prevention of HPV controversial. No protection against HIV

Contraceptive Method	Effect on Reproductive Tract	Effect on Bacterial STDs	Effect on Viral STDs
Female condom	Occasional local irritation	In vivo protection against recurrent trichomonal infections suggests possible protection against other STDs	In vitro impermeability to cytomegalovirus, HIV
IUD	Foreign body reaction within the uterus;	Copper IUD: No protection LNG-IUS: associated with decreased upper-tract infection	No protection
Latex male condom	Occasional latex allergy	Protection against most pathogens in genital fluids	Less protection against organisms transmitted from external genitalia (HSV and HPV)
Combination oral contraceptive	Increased cervical ectopy; decreased risk of symptomatic PID requiring hospitalization	No protection against bacterial STDs; possible increase in cervical chlamydia	Data on HIV transmission risks conflicting; role regarding risk of HPV infection and cervical dysplasia unclear
DMPA/ Implants	Atrophic endometrium; thickening of cervical mucus	Assume no protection	May promote HIV transmission
Spermicide with nonoxynol-9	Risk of chemical irritation of vaginal epithelium/alteration of the vaginal flora with high doses	equivocal	Data suggests increased HIV transmission risk
Tubal ligation	Changes associated with surgery	No protection	No protection
Contraceptive Vaginal rings	Increased Vaginal discharge in some users	No protection	No protection

BARRIERS

Spermicides

Spermicides can be purchased without a physician's prescription in supermarkets

and pharmacies. They can be used alone but are often used in conjunction with a vaginal barrier method (diaphragm, sponge, or cap). Nonoxynol-9 (N-9), the most commonly used spermicide, is an agent that destroys the sperm cell membrane, thereby immobilizing sperm. But, recent studies have shown that N-9 does not protect against STIs and HIV (152). Spermicidal formulations include gels, creams, suppositories, film and male condoms. Pregnancy rates among typical users range from 5% to 30% in the first year of use (7). Methodology in determining these rates has not been consistent leading to skepticism of much of the data. Like the barrier methods, the effectiveness of spermicides is dependent on their consistent and correct use. Its advantages are similar to barrier methods of contraception.

Microbicides

There is a consensus for the need to increase efforts to find innovative approaches to expand the focus of family planning methods beyond simple contraception to include the concern for reproductive health. Efforts to combine effective contraception and protection against HIV and STI transmission are of the utmost priority because the incidence of transmission of HIV and STIs is greatest in women of reproductive age (153).

Any substance that can substantially reduce the transmission of HIV and STI when applied to the vagina is considered a microbicide. Many other compounds are currently under development. These formulations will probably be used as an adjunct to condoms, but may be used as primary protection for those who are unable or unwilling to use condoms consistently. These microbicides will work by either killing or immobilizing pathogens possibly by forming a barrier between pathogen and vaginal tissues, preventing the infection from entering target cells, preventing a pathogen from replicating once it has entered cells, by boosting the vagina's or rectum's own defense system or by acting like invisible condoms. The most desirable qualities of a new formula microbicide would be that it is applicable hours before sexual intercourse, it is not messy or "leaky," and spreads rapidly and evenly over the vagina and cervix (79).

Currently it is estimated that more than 60 potential microbicides are in various phases of development. The class of new compounds can generally be stratified by their mechanism of action (154). The first generations of microbicides, which work on a charge basis as polyanionic molecules, are about entering Phase 3 clinical trials. However, many of these compounds are still in pre-clinical work. These drugs have previously been used in therapeutics, and are now crossing over. Anti-retroviral compounds, like tenofovir, have been formulated as a microbicide. Some of the newer NNRTIs are also being developed as microbicides. They are effective against herpes simplex, bacteria, yeast, fungi, viruses, and potentially effective against other STIs as well.

Surface Active Agents are compounds that penetrate cervical mucus readily, disrupt viral envelopes and cover the surface of viral STIs. Compounds such as nonoxynol 9, octoxynol 9, benzalkonium chloride, menfegol and N-docosanol are included in this category. Examples include C31G (Savvy Biosyn Inc), which is a mixture of two synthetic amphoteric surface-molecules (alkyl amine oxide and alkyl betaine). It has a broad spectrum of antimicrobial activity including activity against bacteria, yeast, fungi, and viruses (HIV, HSV, and HPV). Another example is Benzalkonium Chloride (BZK), (Axcan Ltd. Protecaid®). It is active against a broad spectrum of pathogens including HIV, chlamydia, and gonorrhea.

Sulfated Compounds are highly negatively charged. These compounds bind to virus or host cell receptors, thus blocking viral uptake; however they do not kill the virus. Examples include Dextrin Sulfate, Dextran 2 sulfate, Carageenan, Polystyrene Sulfonate, Heparin Sulfate: Cholic Acid, Cellulose Sulfate, PC-515, and Naphthalene Sulfonate (PRO 2000).

Anti-HIV Compounds are antiretroviral agents and prevent virus replication. Products such as X-2371 (Low-molecular-weight, non-peptide oligospecific integrin modulator, PMPA (Adenine Anti-retroviral Drug), Serine Proteinase Inhibitor, Novel Aryl Phosphate Derivatives of AZT, nevirapine gel/cream, and cyanovirin N (selectively inhibits binding of HIV molecule to receptor) are all also under development as topical microbicides.

Some compounds may increase the host natural defenses against certain sexually transmitted pathogens by maintaining the normal acidic pH of the vagina in the presence of semen. They contain lactobacillus which naturally resides in the human vagina and produces hydrogen peroxide to kill HIV and STDs. Examples are: Lactobacillus suppositories, Buffer gel, and Acid gel (ACIDFORM).

Invisible Condoms: Thermoreversible Gel - Prevents infection by forming a protective barrier after being inserted into the vagina or rectum. It is a liquid at room temperature and quickly turns into an impermeable gel inside the rectal/vaginal canal.

Natural Family Planning Methods:

Abstinence: Couples who avoid sexual intercourse are practicing abstinence. Effectiveness for preventing pregnancy is 100%, but HIV and STIs may spread through the oral or rectal mucus membrane.

Coitus Interruptus: Also known as the withdrawal method, coitus interruptus entails withdrawal of the penis from the vagina (and external genitalia) immediately prior to ejaculation. Effectiveness depends largely on the man's ability to withdraw prior to ejaculation. Its actual efficacy is difficult to measure but the probability of pregnancy among perfect users is estimated to be approximately 4% in the initial year of use. (155)

Fertility Awareness: Symptothermic method -Natural family planning methods use the signs, symptoms, and timing of a normal menstrual cycle to avoid intercourse during fertile intervals. These methods are effective because of periodic abstinence during the fertile period of a woman's menstrual cycle. The fertile period of a woman's menstrual cycle can be determined by using cycle beads, a calendar, measuring basal body temperature and monitoring cervical secretions. (156)

Calendar Method: Estimating the fertile period during each menstrual cycle is based on 3 assumptions: (1) ovulation occurs on day 14 (± 2 days) before the onset of the next menstrual flow, (2) the ovum survives for approximately 24 hours, and (3) sperm remain viable up to 5 days. Past cycle lengths give an estimate of fertile days within a given cycle. Avoidance of pregnancy is achieved by abstinence beginning about 5 days before and ending nearly 5 days after ovulation.

Basal Body Temperature: Most ovulatory cycles demonstrate a biphasic temperature pattern with lower temperatures in the first half of the cycle and higher temperatures beginning at the time of ovulation and continuing for the remainder of the cycle. Because this method does not adequately predict ovulation in advance, couples are instructed to abstain from intercourse or use a barrier method of contraception for the first half of the menstrual cycle until at least 2 days after a rise in temperature signifying ovulation.

Cervical Secretions: Changes in the character of cervical mucus can signify the fertile period of a woman's menstrual cycle. Cervical mucus that is abundant, clear or white, stretchy, and slippery represents the fertile period. Ovulation most likely occurs within 1 day of the appearance of cervical mucus that is abundant, stretchy and slippery. After ovulation, cervical secretions appear thick, cloudy and sticky. Couples are counseled to avoid intercourse when cervical secretions are first noted until 4 days after the peak of clear and slippery cervical mucus.

Couples can also use a combination of natural family planning methods (i.e., basal body temperature measurements and cervical secretion monitoring) to further avoid an undesired pregnancy. In addition, recent advances in home hormonal detection

kits allow for detection of ovulation and better timing of abstinence for avoidance of pregnancy.

Lactation Amenorrhea Method (LAM) - Breastfeeding: Breastfeeding provides more than 98% protection from pregnancy in the first 6 months after birth (157) This method of contraception requires complete or nearly complete infant dependence on breast milk so that frequent suckling (at least 6-10 times per day) prevents ovulation. High frequency of feeds, long duration of each feed, night feeds, and short intervals between breastfeeds delay the return of ovulation. (158, 159) Infant suckling disrupts the pulsatile release of gonadotropin releasing hormone (GnRH) by the hypothalamus resulting in abnormal pulsatility of LH and subsequent anovulation (160). Ovulation however can occur even in the absence of menstruation. The probability of ovulation occurring before menstruation increases with time after delivery; the probability that women will ovulate before the resumption of menses increases from 33-45% during the first 3 months after delivery to 87-100% more than 12 months from delivery (161). To maintain effective contraception, another method should be used as soon as menstruation resumes, the frequency or duration of breastfeeding is reduced, food (or bottle) supplements are introduced, or the duration since delivery is 6 months. This method provides no protection against sexually transmitted diseases, but may help reduce post partum bleeding.

FUTURE DEVELOPMENTS

The next generation of contraceptives will likely be focused on new mechanisms of action. Targets include all aspects of the female and male reproductive system from gamete development to gamete delivery, fertilization and implantation. The goal of these new methods will be the interruption of key components of the system allowing safe, effective contraception with a minimum of side effects. The challenge facing the development of these new methods is the refinement of methods that allow modification or interruption, of only the reproductive system with a minimum of effect on other body systems. Specifically, an optimal method would provide reversible interruption of reproductive capacity of the male and/or female without affecting the endocrine system. This is particularly important in the male as secondary sexually characteristics, and even behavior, are closely linked to any change in the hormonal milieu. Other challenges include the development of simple and cost effective methods. The next breakthrough in contraceptives will be the identification of a key molecular aspect of reproduction. If a key specific receptor can be identified, an antagonist can be developed. If a critical enzyme is identified, an inhibitor can be synthesized.

Areas of interest will be in disruption of ovulation with anti-progestins or blocking the action of matrix metalloproteases needed for the physical breakdown of the follicle. Folliculogenesis may be blocked by specific FSH antagonists, or interruption of folliculogenesis at the local level growth differentiation factor-9. Other possible targets are to block resumption of meiosis in the oocyte, or to block egg activation (which is necessary before an egg is capable of fertilization and to prevent polyspermic fertilization). Finally the specific steps necessary for implantation may be identified and selectively disrupted – and research on molecules involved in implantation and angiogenesis is currently being done in mouse models.

Male Pill: Future Male Related Contraception may be aided by the dramatic increase in our understanding of the molecular genetic control of male reproduction. In particular, the identification of genes in various aspects of testicular steroidogenesis, spermatogenesis and sperm maturation may provide novel targets for fertility regulation. Progestins act on the hypothalamic pituitary axis and suppress spermatogenesis and production of the hormone testosterone. It has been hypothesized that progestin implants along with long acting add back testosterone injections, oral progestagens with testosterone injections, or oral desogestrol with testosterone implants may produce azoospermia without affecting the other physiological and biological effects of testos-

terone (162). Future work will determine if these targets can be useful in developing novel strategies for male contraception.

CONCLUSION

Despite availability of highly effective reversible contraceptive steroids, nearly half of all pregnancies in the United States are unplanned and about one-fourth are electively terminated. By age 45, 43% of women have had an elective abortion. It is, therefore, imperative that new rapidly reversible contraceptives be developed and introduced. Microbicides, by their dual action of preventing pregnancy and the spread of HIV/AIDS show much promise. The trend towards recent contraceptives includes improvements in efficacy and safety. New trends include a levonorgestrel-releasing intrauterine system, an upcoming single progesterone releasing implant, a weekly transdermal estradiol and progestin patch, and a combination vaginal ring. The overall acceptance of these new methods has been high and hopefully their availability will decrease the incidence of unintended pregnancy and offer greater options to couples choosing family planning.

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