CONTRACEPTION

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ABSTRACT

Contraception is important for the prevention of unintended pregnancies worldwide. Many contraceptives also have other medical benefits, such as decreasing endometrial and ovarian cancer risk or regulating the pain and bleeding of menstruation. It is essential for all physicians to have a basic knowledge of contraceptives, given that 99% of women in the United States will use contraception at some point in their reproductive lives. This chapter provides an overview of the various hormonal and non-hormonal methods. There is an emphasis placed on efficacy, pharmacology and the mechanism of action for each category of contraceptives. Progestin-only methods include the implant, intrauterine devices (IUDs), injectables and pills. Combined estrogen-progestin methods include pills, patch and vaginal ring. Non-hormonal methods include the copper IUD and barrier methods such as condoms or diaphragms. Non-contraceptive benefits and contraindications for each particular method are also described. Finally, some future developments are discussed. For complete coverage of this and all related areas of Endocrinology, please visit our FREE on-line web-textbook, www.endotext.org.

INTRODUCTION

The global population is at an all-time high at over 7 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, unintended pregnancies do occur. The rate of unintended pregnancies in the United States is higher than much of the industrialized world and approaches 50%.[1] About 12% of these unintended pregnancies in the U.S. occur in teenagers and 75% occur in women who are poor or low income.[2] While 2% of U.S. women have an induced abortion every year,[3] about half of the unplanned pregnancies are carried to term.[4] The rates of unwanted pregnancy in the United States are at least four times higher than in some countries in Europe and Japan.[5] These differences do not appear to be explained solely by exposure to the risk of pregnancy because other countries such as the Netherlands and Sweden have teenagers who engage in sexual activity earlier than most teenagers in the United States.[6] The cost of contraception to the consumer and lack of insurance coverage for contraception had been identified as contributors to the high unintended pregnancy rate in the U.S. prior to passage of the Affordable Care Act (ACA).[3] The ACA contraceptive mandate then required most insurers to cover contraception without cost-sharing beginning in August 2011.[7] However, not all women have insurance and the politics of contraceptive coverage are ever shifting. Even without cost sharing, women continue

to choose less effective methods and/or use methods incorrectly and inconsistently. While the varied reasons for inconsistent contraceptive use have yet to be fully elucidated, the rate of unintended pregnancies is declining as uptake of contraception, and long-acting reversible contraception (LARC), in particular, increases.[1]

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.[8]

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 dependent, 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. Currently, methods may be non-hormonal, progesterone-containing, or estrogen- and progesterone-containing. 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 efficacy, mechanism of action, and non-contraceptive effects.

EFFICACY AND EFFECTIVENESS

There are inherent risks in our methodology for defining the 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 in 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 represents the efficacy of the method in the laboratory setting (method failure rate). 'Typical use' estimates the probability of pregnancy during the first year of using the method in “the real world” setting. This measure of effectiveness 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 for perfect use for oral contraceptive pills is approximately 0.3%, but the typical failure rate is about 9%.[9] Given that it is impossible to predict if women will use a method perfectly, it is appropriate to quote typical-use failure rates in clinical counseling (Table 1). Methods that are long acting and require one visit to a clinician such as an IUD or an implant have very little disparity between perfect use and typical use, and thus are the most effective methods of contraception.

Method	Typical Use	Perfect Use

Implant	0.05	0.05
Male sterilization	0.15	0.1
LNG IUD (52mg)	0.2	0.2
LNG IUD (19.5mg)	0.2	0.2
LNG IUD (13.5mg)	0.4	0.4
Female sterilization	0.5	0.5
Copper IUD	0.8	0.6
Depo Provera	6	0.2
Pill	9	0.3
Patch	9	0.3
Ring	9	0.3
Diaphragm	12	6
Male condom	18	2
Female condom	21	5
Withdrawal	22	4
Fertility awareness	24	0.4-5
No method	85	85

Table 1: Typical use and perfect use one-year failure rates for contraceptive methods[9,10,11]

PHARMACOLOGY

Progestins

The major portion of the contraceptive effect in systemic hormonal methods is due to the progestin compound. Progestins confer most of the contraceptive benefit by suppressing LH and ovulation. Progestins in oral contraceptives are derived from 19 nor-testosterone and include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, norethynodrel, desogestrel, norgestimate, and gestodene.

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. Pregnanes are used in injectable methods. Drospirenone is a spironolactone analog with anti-mineralocorticoid and anti-androgenic activity.[12]

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).[13,14,15,16] 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.[17]

Estrogens

Estrogens primarily serve to regulate bleeding, but also inhibit FSH and prevent formation of the dominant follicle.[18] In contrast to the long list of progestin formulations, only a few estrogenic compounds are used in hormonal contraceptives: ethinyl estradiol (EE), mestranol, and estradiol valerate. Other estrogens, particularly estetrol, are being tested clinically in contraceptive preparations. EE is pharmacologically active whereas mestranol must be converted into EE before it becomes active. Most 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.

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." The mechanism of action of hormonal contraception is primarily through the suppression of ovulation, but progestational effects include:[19]

- 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:[20]

- 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.

PROGESTIN ONLY HORMONAL CONTRACEPTIVES

Current progestin-only methods include an etonogestrel (ENG) subdermal implant, intrauterine devices, depot medroxyprogesterone acetate, and progestin-only pills.

Advantages: Progestin-only methods do not have an estrogen component, thereby decreasing the complications attributable to estrogen (such as, cardiovascular disease, venous thromboembolism, and thrombophlebitis). 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-oral 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 all 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 2. The only absolute contraindications are pregnancy, unexplained abnormal vaginal bleeding suspicious for a serious underlying condition, and 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 2. Contraindications to Progestin-only Hormonal Contraceptives

Progestin-only contraception should not be used for women with the following conditions:

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

Progestin-only IUDs should not be initiated in the following conditions:

- Suspected uterine infection
- Cervical cancer

Caution should be used when prescribing progestin only pills in the following conditions:

- Concurrent medication that cause progestins to be metabolized more rapidly:
  - anti-seizure medications: phenytoin, carbamazepine, primidone, phenylbutazone, felbamate, ozcarbazine and lamotrigine (lamotrigine

levels decreased by progestins) • antibiotics: rifampin/rifampicin • ritonavir- boosted protease inhibitors • Women who have undergone bariatric surgery may have difficulty with absorption.
*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 cause cardiovascular events, the product labeling might still list active cardiovascular disease (or history of disease) as a contraindication.

PROGESTIN-ONLY IMPLANTS

There is one progestin-only implant available in the United States. It is a single rod that contains 68mg of etonogestrel (ENG). It is placed subdermally, usually in the upper extremity, in the office with local anesthesia. It is FDA approved for up to 3 years. Small studies indicate continued efficacy for 4 or even 5 years, but insufficient numbers of obese BMI women have been included to make definitive recommendations in that cohort.[21,22] Larger studies are needed to routinely recommend extended use.

Efficacy: The typical failure rate of the ENG implant is reported to be about 1 in 1000. However, there are compiled data that demonstrate a Pearl Index of 0.00 (1716 women with 4103 women years of implant use and no pregnancies.[23,24] There does appear to be a decrease in efficacy when combined with drugs that increase hepatic metabolism (Table 2).. Because of these possible interactions, the WHO classifies the implant in women taking these medications as category 2 (benefits likely outweigh the risks).

Side effects: The most common side effect and most reported reason for removal of the implant is an irregular or unpredictable bleeding pattern[24,25]. Approximately ¼ of women reported prolonged or frequent bleeding. Fortunately, most women state that menstrual flow overall decreases with each successive year of implant use and the most common patterns were infrequent bleeding and amenorrhea.[26] There appears to be a slightly increased incidence of clinically insignificant ovarian cysts in users of the implant. Unlike the concerns with depot medroxyprogesterone and bone mineral density (BMD), limited data suggest that the ENG implant does not have any effect on BMD.[27] Weight gain, however, has not been well studied. Some trials report an increase of BMI by less than 1%, and perhaps as many as 12% of women will report an increase in weight. When looking at reasons why women have the implant removed, only 3-7% state it was because of weight gain. Therefore, it appears that weight gain is clinically insignificant[25,28,29].

Risks: The risks and contraindications are the same as those for other progestin-only methods.

Non contraceptive benefits: The ENG implant likely improves dysmenorrhea. To date there is no randomized control trial comparing the implant to other acceptable treatments of dysmenorrhea. However, An observational study[26] of 315 women showed that of the 187 women who reported dysmenorrhea at baseline, 151 (81%) had improvement of their dysmenorrhea and 26 (14%) reported no change.

INTRAUTERINE DEVICES

Although intrauterine devices (IUDs) are the most widely used form of reversible contraception worldwide, they are an underutilized contraceptive method in the United States.[30] IUDs and implants are the most effective methods of reversible contraception (20 times as effective as the hormonal methods of the pill, patch and ring), and have high user acceptability, with few medical contraindications.[31]

Mechanism of action: There are five IUDs currently available in the U.S.: a copper IUD (Paragard®) and four progestin-impregnated intrauterine systems (IUS): Liletta®, Mirena®, Kyleena®, and Skyla®. Both medicated and non-medicated intrauterine devices (IUDs) have multiple mechanisms of action that provide for contraceptive protection. Both medicated and non-medicated 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.[30,32,33,34] 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.[30] IUDs, whether hormonal or non-hormonal, do not provide protection against sexually transmitted diseases. However, it is important to recognize that IUDs are not associated with PID,[35,36] 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 provider is reasonably certain the patient is not pregnant. An IUD can be inserted immediately postpartum, post abortion, or as an 'interval' insertion. 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.[37] 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.[38]

Progestin-only IUD: The 52mg LNG IUS (Mirena, Liletta) initially releases 20 mcg of levonorgestrel per day from a polymer cylinder mounted on a T-shaped frame (32mm x 32mm) containing 52 mg levonorgestrel; it is covered by a release rate-controlling membrane. Mirena is FDA approved for 5 years of use; Liletta is FDA approved for 4 years of use. However, large studies support continued efficacy for 7 years of use with either brand.[39] 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 about 20% of women, but this is not the main mechanism of action. The mean number of bleeding and spotting days is initially increased but

both the volume of menstrual flow and the number of days of bleeding are reduced over time.[40] During the first year of use, about 16% of women will be become amenorrheic and average menstrual bleeding days decrease to 2 per month by 12 months of use.[40] A recent meta-analysis of randomized controlled trials reveal that LNG-20 IUS users were significantly more likely than all other IUD users to discontinue its use because of hormonal side effects and amenorrhea,[41] 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-20 IUS offers much improved effectiveness over other hormonal methods.[41,31]

The 19.5mg LNG IUS (Kyleena) initially releases 17.5mcg of levonorgestrel per day during the first year from a 19.5mg reservoir mounted on a smaller T-shaped frame (28 x 30mm). Consequently, it has a more narrow insertion tube. 88% women in the first year and 100% of women in the third year of use will continue to ovulate.[42] Although decreased over time, average number of bleeding/spotting days is higher than with the 52mg IUS.[11] Kyleena is FDA approved for 5 years and there are no studies of extended use.

The 13.5mg LNG IUS (Skyla) has the same sized T frame and inserter as the 19.5mg IUS, but contains 13.5 mg of levonorgestrel, and initially releases 14mcg levonorgestrel per day, declining to 5mcg/day after 3 years. Less than 4% of women will have ovulation inhibition, and 6% of women have amenorrhea after 1 year. It is FDA approved for 3 years and there are no studies of extended use.[43]

Specific populations: One population of interest is nulliparous women. The failure rate of IUDs is low and similar for both parous and nulliparous women. Acceptability, using the surrogate marker of continuation rate, shows a 90% retention rate in nulliparous women at one year. As with efficacy, expulsion rates between parous and nulliparous appear to be the same, likely between 1-5% for all comers. The risk of infection does not seem to vary between the parous and nulliparous women.[44] The 19.5mg and 13.5mg IUSs are marketed toward nulliparous women, but it is unknown as to whether its structural differences confer any specific benefits over the 52mg IUS in this population.

Non-contraceptive uses of 52mg LNG IUS: Multiple descriptive studies and clinical trials have been performed on the non-contraceptive benefits:[45,46,47,48,49,50,51]

- 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.[51] 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 10.2 g/L before insertion to 12.8 g/L at 12 months ($p<0.01$).

The LNG-IUS is an effective treatment for menorrhagia. It is becoming increasingly evident that the LNG-IUS is also effective in the treatment of menorrhagia due to fibroids. All studies in a systematic review showed an increase in hemoglobin. Early observational data shows that the LNG-IUS does not appear

to decrease the size of the fibroids. Expulsion rates also varied in these studies from 0-20%, which probably reflects the great variety of cavity size and shape among women with fibroids.[52,53]

Another prospective study observed that the 20mcg LNG-IUS provided more effective treatment for endometrial hyperplasia than oral progestin.[54]

PROGESTIN-ONLY INJECTABLE

Depot medroxyprogesterone acetate (DMPA; Depo-Provera®) is delivered by a deep intramuscular injection of 150 mg of medroxyprogesterone acetate (MPA) every 12 weeks.[55] Pharmacologically active levels (>0.5mg/ml) of MPA are achieved within 24 hours of injection. Serum levels remain >1.0 ng/ml for approximately three months after administration. By the fifth month, levels drop to 0.2mg/ml.[56] There is also a subcutaneous preparation of Depo-Provera, which administers 104 mg of MPA. DMPA's main mechanism of action is inhibition of ovulation.

Non-contraceptive benefits of DMPA[57]

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 ideal use, the failure rate is 0.3 per 100 woman-years which is similar to rates found with surgical sterilization.[58] Variations in body weight and concurrent medications have not been shown to alter efficacy.[59] The typical-use failure rate is 6/100 women-years.

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.[60] By the end of one year, nearly 75% of users will experience amenorrhea.[61] Short courses of high-dose estrogen do little to reduce bleeding among DMPA users.[62] In addition, early re-administration of DMPA (at 8-10 weeks instead of 12 weeks) does not reduce bleeding.[63] 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.[64] 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.[65,66] In clinical trial settings, DMPA does not cause statistically significant weight gain.[67,68] However, African American women, Navajo Native Americans, and women with high baseline body mass index may be predisposed to weight gain with the use of this method.[69] Studies have shown that neither DMPA nor progestin-only injectable is associated with increased risk of breast cancer.[70]

Risks: A recent review showed that levels of triglyceride and total cholesterol do not change with DMPA use.[69] 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.[71] 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.[72]

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.[73] Depot medroxyprogesterone acetate use has not been linked to menopausal osteoporosis or fractures. A cross-sectional study from the WHO demonstrated that even after four years of use, BMD in former adult DMPA users is similar to that of never users.[72] The 2002 cohort study of BMD in adult women performed by Scholes et al.[74] 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.[75] 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. A Cochrane review indicated that there may be a small increased risk of fracture in women with increased duration of use.[76]

PROGESTIN-ONLY ORAL CONTRACEPTIVES

Progestin-only pills, also called the 'minipill' have a dose of progestin that is very close to the threshold of contraceptive efficacy; therefore, these pills must be taken continuously at the same time each day and without a pill-free interval. Less than one percent of oral contraceptive prescriptions in the United States are for the progestin-only oral contraceptive.[77] 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. Only one progestin-only formulation is available in the United States with 0.35mg of norethindrone per pill. 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 dependent on the other progestin related mechanisms listed previously.[77]

Efficacy: The typical failure rate of progestin-only pills is similar to that with combined oral contraceptives,[78] 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.[77] 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. Furthermore there are data to suggest that the efficacy of progestin-only pills in the setting of rifampin, certain anticonvulsants (excluding lamotrigine) and ritonavir-boosted protease inhibitors is decreased. The WHO subsequently categorizes progestin-only pills in these settings as risks may outweigh benefits.

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.[79] 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%).[77] 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) (34). Thus far, progestin-only pills appear to have little or no effect on lipid metabolism, carbohydrate metabolism, hypertension, and coagulation factors.[77]

COMBINED ESTROGEN AND PROGESTIN HORMONAL CONTRACEPTION

The bioavailability of progesterone is poor, so progestins derived from androgens are used instead. There are many active progestins in addition to norethindrone. They are classified into generations as shown in Table 3.[18,19]

Generation	**Progestins**	**Notes**
First	norethynodrel, norethindrone, norethindrone acetate, and ethynodiol diacetate	Low potency, well tolerated, more breakthrough bleeding with low doses of estrogen
Second	Levonorgestrel, norgestrel, norgestimate	Higher potency, less breakthrough bleeding, more androgenic side effects

Third	desogestrel, norgestimate, gestodene	Decreased androgenic side effects
Fourth	drospirinone	Anti-androgenic and anti-mineralocorticoid effects

EXTENDED AND CONTINUOUS REGIMENS:[80]

While manipulation of the timing of the pill-free-interval has been practiced by gynecologists for decades, there are now marketed ways to decrease the number of withdrawal bleeds experienced on the standard pill pack, which contains 21 active pills and 7 placebo pills ("21/7"). There are "24/4" regimens with only 4 days per month of placebo pills. Pills such as 'Seasonale' are packaged such that women take the pill for 84 consecutive days, and then stop for a week before inducing a withdrawal bleed. This method allows women to bleed 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 these extended formulations. However, many women favor the decreased number of bleeding days experienced with these newer regimens. Furthermore, there is evidence of greater ovarian suppression with potential for lower failure rates with these regimens.

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 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[20]

- Reduction of ovarian and endometrial cancer risk
- Decreased benign breast disease
- Reversibility and quick return to fertility
- Favorable bone mineral density profile
- Reduced risk of benign ovarian tumors and ovarian cysts
- Reduced risk of colorectal cancer
- Reduced dysfunctional uterine bleeding
- Decrease in menstrual flow and menorrhagia
- Decrease in primary dysmenorrhea
- Decreased risk of iron deficiency anemia
- Improvement in hirsutism and acne

- Decreased perimenopausal vasomotor symptoms
- Decreased risk of premenstrual syndrome (PMS)/premenstrual dysphoric disorder (PMDD)

Reduction in ovarian cancer risk: Reduction in ovarian cancer risk increases with greater oral contraceptive use although protection is provided after as little as 3 to 6 months.[81] Compared to non-users, women who have used oral contraceptives for four years or fewer 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 an 80% reduction in risk. This protective effect persists for at least 15 years after OC discontinuation.[82,83] These data hold true for women at genetically increased risk of breast cancer. The Society of Gynecologic Oncology (SGO) recommends OC use for women with BRCA1 and BRCA2 in the absence of contraindications. Given the devastating effects of this disease and our lack of success with screening and early diagnosis, the chemo-prophylactic effects of oral contraceptives should be emphasized.

Prevention of Endometrial Cancer: There is a 50% reduction in endometrial cancer risk in OC users compared with never users.[84] 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.[85] The actual duration of protection after discontinuation is unknown but is estimated to be at least 15 years.[86]

Benign Breast Disease: OC use significantly reduces fibrocystic breast change and fibroadenoma development.[87,88,89] 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.[90] Fibrocystic change is significantly decreased after 1 to 2 years of use,[91] and lasts up to 1 year after OC discontinuation.[90]

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).[92] 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).[93] Many studies, however, have not found a favorable association between OC's and bone mass.[94,95] No study thus far has found a detrimental effect of OC's on bone mineral density.[96]

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.[97,98]

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).[99] 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).[100] It is unclear if the results from this study apply to women using lower-dose oral contraceptives.

Relief from menstrual disorders: A 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.[101] 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.[102]

Reduction of acne: 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.[103,104] 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.[105] Other OCs too are being evaluated for similar use.[106,107] 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.[108,109]

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.[110] However, there are some important contraindications to the use of estrogen-containing hormonal contraceptives (Table 4).

Table 4. Contraindications for the use of combined oral contraception

Estrogen-containing contraception should not be used for women with the following conditions:[111]

- 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;
- Personal history of estrogen-dependent cancer including current or history of breast cancer;
- Current pregnancy;
- Migraines with aura, focal neurological symptoms, vascular risk factors, vascular disease, or age greater than 35 years;
- Smoker, age greater than 35 years;
- Hypertension
- Liver disease (benign hepatic adenoma, liver cancer, active viral

hepatitis, or severe cirrhosis);

• Major surgery with prolonged immobilization or any surgery of the legs;

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.[112] Since then, there has been extensive literature that describes and attempts to elucidate this risk. A summary of these data show relative risks of venous thromboembolism ranging from 2.1 - 4.4.[113] It has been a 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.[113] 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 5 provides a summary of relative risk for VTE in different populations of women.

Table 5. Relative Risk of Venous Thromboembolism (VTE)

Population	**Relative Risk (New cases per 100,000 women/year)**
General Population	1 (4-5)
Pregnant Women	20 (48-60)
High-dose (>50 μ g EE) OCs	6-10 (24-50)
Low-dose (<50 μ g EE) OCs	3-4 (12-20)

Population	Relative Risk (New cases per 100,000 women/year)
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)

Oral Contraceptive Use and Risk of Breast Cancer:

The relationship between OC use and breast cancer remains controversial. Two 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.[114,115] 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.[115]

The second study involved over 8000 women, half of which had the diagnosis of breast cancer.[116] 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.

In a third study,[117] the authors showed an increased annual risk of breast cancer diagnosis of one per 7,690 women per year using hormonal contraception. Important limitations exist in this recent paper. The research was conducted via multiple Danish registries, which are methods of data collection, but not a study design. Thus, these studies do not fall directly into standard epidemiologic classifications, and are subject to the biases of retrospective cohort studies. More specifically, the method of detection of the study outcome (breast cancer diagnosis) was not specified, nor was the stage of the diagnosis, nor whether or not the mortality due to breast cancer differed among women who had and had not used hormonal contraception. The clinical significance and health outcomes of higher breast cancer detection rates in the hormonal contraceptive users could not be determined. Finally and most importantly, the reference group, women who chose never to use hormonal contraception, may also make other behavioral, health and lifestyle decisions, including having additional clinical examinations, that affect their risk of cancer. This small absolute risk is unlikely to have clinical significance for women prioritizing pregnancy prevention, especially considering that previously published research[118] shows that users of oral contraceptives are protected from other cancers including colorectal, endometrial, and ovarian cancer.

Oral Contraceptive Use and Liver Cancer

Non-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.[119]

Oral Contraceptive Use and Gallbladder Disease

Studies 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 gallbladder 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 gallbladder disease and oral contraceptives yields a relative risk of 1.1 with a 95% CI 1.1 - 1.2.[81]

Second Versus Third Generation Oral Contraceptives and Deep Vein Thrombosis.

There is no strong biological evidence that specific progestins have differential effects on VTE risk. While clotting factors may be altered differentially by specific progestins such data are not clinically relevant because we do not have a proven surrogate marker for VTE risk.[120] In the mid 1990's pharmaco-epidemiological studies reported that women using "third generation" oral contraceptives had a higher risk of venous thromboembolism (VTE) compared to women using "second generation" OCs.[121,122,123] 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 in these studies. 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 included newer users of oral contraceptives that may have been innately at higher risk for DVT (new-user bias), thus biasing the results.[8,124] 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".

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.[125] The relative risk of VTE in users of OCs with desogestrel and gestodene v 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. However, differences in BMI and other comorbidities that may act as confounders were not accounted for in these studies.

The results in another meta-analysis of seven cohort and case-control studies similarly show the biases in these studies. The overall adjusted odds ratio for third versus second generation oral contraceptives was 1.7 (95% CI, 1.4-2.0).[126] 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). In this paper, the new-user effect is clearly demonstrated.

Lidegaard et al retrospectively assessed the influence of OCs on the risk of VTE in women aged 15-44 years.[127] 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; $p<0.05$).

If there is any increased risk of VTE with third generation OCPs, this is likely to be marginal, with small absolute risks. The majority of the risk is conferred by the estrogen, which should be factored into contraceptive decision-making. Despite the heated debate and the revealed flaws with such study designs, a similar argument is now in the literature with regard to drospirenone-containing OCPs. Several studies have investigated the risk of VTE associated with OCPs containing drosperinone vs other progestins. The EURAS study, initiated in 2001 and including more than 120,000 COC users in Europe, found comparable risk of DVT among the 3 categories of progestins.[128] This study was not only large, but also of prospective study design and the primary objective was to assess safety across COC user groups. Two other studies have shown an increased risk of VTE in drosperinone users.[129,130] These

studies are limited by flawed methodologies in a similar fashion to the studies that caused controversies around the 3rd generation progestins. In one study[131] only 1.2% of COC users used drosperinone-containing OCPs, which results in unstable estimates. In the other retrospective cohort study the relative risk for drosperinone-using women was elevated, but these one-year estimates are unreliable because of left censoring (women had varying risk-levels at entry to the study). The estimates of risk after the first year are in line with the EURAS study.

COC concerns for women with other risk factors*:*

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.[130] 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.[131] 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).[132] 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 of those patients who develop VTE soon after initiating OCs (<6 months), most are thrombophilic.[133] 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).[134]

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.[127] 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.[113] 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.[135] 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:[135,136]

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 stroke: The 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.[113] 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[123,124] 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.[113] 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.[137] 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.

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 physicians 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 regardless of menstrual cycle day. A clinical trial has shown that is approach is safe, and results in higher ultimate rate of pill use than the conventional approach that initiates pill use after the onset of menses.[138] 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 recent Cochrane review found that there is no difference in contraceptive effectiveness for lower dose pills. Compared to the higher-estrogen pills, several COCs containing 20 μg EE resulted in higher rates of early clinical trial discontinuation (overall and due to adverse events such as irregular bleeding) as well as increased risk of bleeding disturbances (both amenorrhea or infrequent bleeding and irregular, prolonged, frequent bleeding, or breakthrough bleeding or spotting). So, while COCs containing 20 μg EE may be theoretically safer, this has not been proven and low-dose estrogen COCs have in higher rates of bleeding pattern disruptions.[139]

An 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.[140] Drospirenone has both anti-mineralocorticoid and anti-androgenic activity. Its anti-androgenic activity may leads to suppression of undesired symptoms such as acne and hirsutism. Its anti-mineralocorticoid 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.[141] 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: Data from randomized controlled trials fail to support the assertion that combined oral contraceptives cause adverse psychological symptoms. One randomized double-blind study of 462 women looked at the percentage of traditionally “hormone-related” side effects in a 6-month comparison of COC versus placebo pill users. Symptoms of emotional lability and physical symptoms of headache, nausea, breast pain, abdominal bloating, back pain, weight gain, and decreased libido were studied, and there were no differences in the incidence of these symptoms between the COC and placebo groups.[142] In a 2002 review of prospective, controlled studies of the effect of COCs on mood, four studies found no significant group differences in negative affect across the entire menstrual cycle, one study found that COC users reported less negative affect across the cycle, one study found higher negative affect throughout the cycle of a monophasic but not a triphasic COC, and two studies found that COC users experienced higher positive affect.[143] Common to all the studies of the psychological effects of COCs was a beneficial outcome: there was less variability in negative affect, and less negative affect during menstruation in patients taking COCs.

Many studies have focused on the role of the progestin as a contributor to dysphoric mood. Two studies have shown worsening of mood with a higher progestin to estrogen ratio.[144,145] Thus, switching to a formulation with a lower progestin to estrogen ratio may improve mood in women who have negative mood symptoms with COCs. However, evidence regarding mood disturbances with COCs is sparse.

ALTERNATIVE METHODS

Effective, safe contraception is achieved with combination estrogen and progestin delivery via a contraceptive skin patch or 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.

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.[146] Ten percent of American women have used or currently used the patch.[147] 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[148]. 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.[146] 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 as compared with the pill.[149] The noncontraceptive effects of transdermal 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.[150]

Vaginal Ring

For numerous decades, the vagina has been identified as a potential organ for drug absorption.[151,152] The anatomy of the vagina allows for the easy placement of a ring to achieve this purpose.

A combination estrogen/progestin vaginal ring was approved for use in 2001 and was used by 6% of US women of reproductive age by 2006-2010.[147] 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.[153] Hormone content in the ring is sufficient to provide a "grace period" of at least 14 additional days,[154] 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 synthethormone. 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.[153] Overall pregnancy rates are reported to be 0.65 per 100 woman-years (all first-year users).[103] 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.[155]

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.[155] Overall acceptability and tolerability of the ring were very high in the clinical trials performed to date.

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 the CuT380A IUD,[156,157,158] ulipristal acetate (UPA) selective progesterone receptor modulator, and 150 mcg of levonorgestrel (Plan B and Plan B One-Step). Combined oral contraceptive tablets can also be used by following the "Yuzpe regimen," which can be found on the internet for various pill formulations.

The Copper "T" IUD can be inserted up to 7 days after unprotected intercourse and is ideal for women who desire long-term contraception going forward.[159] It is 99% effective for emergency contraception.

The current treatment schedule for emergency contraceptive pills (ECPs) is one dose within 120 hours of unprotected intercourse.[158] Ulipristal acetate is more effective than levonorgestrel for emergency contraception, especially in obese women. Estimates of effectiveness range from 62-85%.[160] Effectiveness is sustained throughout the 120 hours after unprotected intercourse. Combined and progestin-only ECPs reduce the risk of pregnancy by about 75-88%.[161] Effectiveness declines with increasing delay between unprotected intercourse and initiation of treatment.[162]

Mechanism of action: Oral emergency contraception likely inhibits or delays ovulation.[163] Some investigators have shown histological alterations in the endometrium suggesting impairment of endometrial receptivity to implantation[164] while others have found no such effects.[165,166] Other possible mechanisms include interference with corpus luteum function, thickening of cervical mucus, and alterations in tubal transport of sperm, egg, or embryo.[167] Emergency contraceptives do not interrupt an already established pregnancy. The Copper "T" IUD does not have an established mechanism of action as an emergency contraceptive but likely creates a hostile environment for sperm as well as for the egg and possibly an embryo.

Progestin-only emergency contraceptives are more effective and associated with significantly less nausea and vomiting than combined emergency contraceptive pills.[168] 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.[169]

The FDA has granted approval for the over the counter use of progestin-only EC for prevention of pregnancy. There are no longer any restrictions on age or gender for purchasing progestin-only EC. Evidence has been reported that making ECPs widely available does not increase risk-taking behavior or increase the incidence of unintended pregnancy.[170] Additionally, it has been demonstrated that women most likely to seek emergency contraception are those already concerned about or using contraception.[171,172]

Copper IUDs 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%.[173] Furthermore, 86% of parous and 80% of nulliparous women retain the IUD after insertion for emergency contraception.[162]

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.[173]

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 polyurethane 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, 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 and the orthoflex diaphragm), 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 6.

Table 6. Contraceptive Methods 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

Female condom	Occasional local irritation	In vivo protection against recurrent trichomonal infections suggests possible protection against other STDs	In vitro impermeability to HIV, cytomegalovirus
IUD	Foreign body reaction within the uterus;	Copper IUD: No protection LNG-IUS: associated with decreased upper-genital 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/altera tion of the vaginal flora with high doses	Equivocal	Data suggests increased HIV transmission risk that is dose and frequency dependent
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.[174] 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.[19] 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

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.[175]

Any substance that can reduce the transmission of HIV and STI when applied to the vagina is considered a microbicide. A randomized double-blind, placebo controlled trial studied tenofovir vaginal gel in 889 women in South Africa. The antiretroviral tenofovir gel is applied to the vagina sometime within 12 hours prior to sex and then again within 12 hours after sex. This study showed that it cut HIV transmission by approximately 39%. Even more encouraging were those women who were “high adherers” meaning they reported and demonstrated using the gel with >80% of each act of vaginal intercourse. This subcategory of women showed a 54% decrease in HIV infection compared to placebo. In summary HIV incidence in the tenofovir arm was 5.6 per 100 women years vs. 9.1 per 100 women-years in the placebo arm.[176] While this is promising, real world adherence is low, thus promoting the search for alternative delivery mechanisms, such as vaginal rings.[177] As many as 60 potential 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.[148]

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.[178]

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.[178]

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.[179] 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.[180,181] Infant suckling disrupts the pulsatile release of gonadotropin releasing hormone (GnRH) by the hypothalamus resulting in abnormal pulsatility of LH and subsequent anovulation.[182] 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.[183] 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 near future will bring improved modifications of current methods including barrier methods, hormonal methods and intrauterine devices. Combined oral contraceptive pills using estetrol for the estrogen component are being developed in Europe. Phase II studies using a combination of estetrol and drospirinone in a 24/4 pill show a favorable bleeding profile and have high user satisfaction.[184,185] 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 allowing modification or interruption of 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 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 metaloproteinases needed for the physical breakdown of the follicle. Folliculogenesis may be blocked by specific FSH antagonists, or interruption of folliculogenesis at the local level by growth differentiation factor-9. Other possible targets include blocking resumption of meiosis in the oocyte, or blocking 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 hormonal contraception: male hormonal contraception may come to light in the distant future. 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 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 testosterone.[186] Future work will determine if these targets can be useful in developing novel strategies for male contraception.

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