A REVIEW OF COMBINATION HORMONAL CONTRACEPTION AND NEW CONTRACEPTIVE DELIVERY SYSTEMS

DADA, O. O*. AND OLUGBAKE, O. A.
Department of Clinical Pharmacy and Biopharmacy,
Faculty of Pharmacy, University of Lagos, Idiaraba Campus

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INTRODUCTION

The use of hormonal contraception has witnessed several developments since its debut in 1950's as birth control pills. Each development makes hormonal contraceptive safer and/or more tolerable. Until recently, women desiring effective contraception were limited to oral contraceptives containing 30-35 μg of ethinylestradiol (EE) in combination with one of a variety of progestins, progestin only pills or depot preparations and a copper or progesterone containing intrauterine device (IUD). The past decade has seen the introduction of contraceptives containing new progestins e.g. drospirenone and new doses of estrogens e.g. very low dose combination oral contraceptive. Also alternative delivery routes have been developed which improve adherence e.g. trans-dermal patches and vaginal rings.

The introduction of new drug entities, new delivery systems, combination injectables contraceptives and improvement and discontinuation of old delivery system makes a review of hormonal contraception imperative so that pharmacists and other health professionals can help clients make informed decisions about hormonal contraception.

Though contraceptive awareness was reported to be very high (91.3%) amongst Nigerians, the reported rate of use is however very low 23%[1,2]. The most commonly used contraceptive is the pill with a reported failure rate of 18.3% (perfect use failure rate in literature is supposed to be less than 1%)[1].

As these new products begin to make their entry into the Nigerian market, pharmacists will be inundated by clients desiring drug information. Pharmacists having adequate knowledge of these products and the basis for their existence will be better positioned to help their client.

HORMONAL CONTRACEPTION

Hormonal methods provide millions of users with safe and effective contraception. All hormonal methods are systemic in nature and involve the use of progestin alone or in combination with estrogen. The methods available include: Combined oral contraceptives (COCs); Progestagen-only pills; Progestagen-only injectables; Combined injectable contraceptives; and Subdermal implants.

ESTROGENS

PHARMACOLOGY OF ESTROGEN

The estrogen in most contraceptives is ethinyl estradiol (EE). Mestranol, present in a few older products, is metabolized to ethinyl estradiol. The estrogen dose of COCs has decreased from as high as 100μg/day in earlier formulations to as low as 20μg/day in some newer products[3]. Mestranol 50μg is equivalent to 35μg of EE[3]. EE is absorbed rapidly and undergoes extensive first pass metabolism. The plasma half life ranges from 10- 27 hours[4].

Mechanism of Action

The mechanisms of action of combination estrogen and progestin contraceptives are thought to be multiple. The primary mechanism involves estrogen-induced inhibition of the mid-cycle surge of gonadotropin resulting in the suppression of ovulation. Additionally, hormonal contraceptives suppress gonadotropin secretion during the follicular phase of the cycle, preventing follicular maturation[5]. Estrogen doses in these pills are not sufficient to produce consistent anti-ovulatory effect. The estrogenic component of oral contraceptive pills potentiates the action of the progestin and stabilizes the endometrium so that breakthrough bleeding is minimized.

Rationale for Estrogen Dose Reduction

The reduction in estrogen doses followed early research that related the likelihood of thromboembolic disorders to the size of the estrogen dose. The absolute risk of venous thromboembolism with COCs is low, with an estimate of one case per 10,000 women using the pill for a year. While pills containing 30μg of ethinyl estradiol (low dose COC) have lower risk than pills containing 50μg, the evidence does not support the idea that 20μg pills have lower risk than pills containing 30 - 35μg[3,6]. US clinical trials found that estrogen doses as low as 20μg, combined with a progestin, usually limit pregnancy rates to less than 1 per 100 women per year[7] and appears to have fewer side effects (Table 1) making them more tolerable[7].

Most women should be given a COC that contains no more than 35 μg of ethinyl estradiol though a 50 μg pill may be appropriate in special circumstances[6]. ▶

Table 1: Adverse Estrogen-Induced Effects

Too much estrogen > than 25μg	Inadequate estrogen in pills
Nausea, bloating, breast tenderness;	Early or mid-cycle breakthrough bleeding;
Increased blood pressure, melasma; Headache.	Increased spotting; Hypomenorrhea.

PROGESTERONE

PHARMACOLOGY OF PROGESTERONE

Progesterone is a naturally occurring steroid hormone. Progesterone serves as a precursor to the estrogen, androgens, and adrenocortical steroids. Progesterone is rapidly absorbed following parenteral administration but is poorly absorbed when given orally. Its half life in plasma is from 3-90 minutes; it's partially stored in body fat and is almost completely metabolized in one passage through the liver[8].

Due to the poor oral absorption of progesterone and its susceptibility to rapid first-pass metabolism in the liver a variety of oral, injectable and implantable synthetic analogs, called progestins, were developed. These synthetic compounds with biological activities similar to those of progesterone have been variously referred to in literature also as progestational agents, progestagens, progestogens, gestagens or gestogens[8,9]

Classification of Progestins

Progestins can be classified based on time since market introduction[9] as first-, second- or third-generation progestins. Another classification scheme (Table 2) based on structural derivation exists and divides progestins into estranes, gonanes and pregnanes[8,9,10].

The first progestins to be synthesized were the 17-acetoxy progesterone derivatives or pregnanes followed by the 2 types of 19-nor-testosterone derivatives, estranes and gonanes. The structural differences between progestins result in significant differences in their activity. All of the synthetic progestins are far more potent inhibitors of ovulation than progesterone, with gonanes being more potent than the estranes. The gonanes also have a longer half life, which makes possible, lower doses or less frequent dosing, which in turn may reduce side effects and facilitate greater compliance[11].

The anti-ovulatory potency of the different progestins varies. All progestins achieve the expected effect, but the less active compounds require higher doses to exert their anti-gonadotropic effect.

Table 2: Classification of Progestins[10]

Classification by structure	First Generation	Second generation	Third Generation
Estranes	Ethynodiol diacetate Norethindrone Norethindrone acetate		
Pregnanes	Medroxyprogesterone acetate		
Gonanes	Norgestrel	Levonorgestrel	Desogestrel Gestodene Norgestimate

Mechanism of Action of Progesterone

Progesterone causes infertility by antagonizing some estrogen actions. It maintains the endometrium in a hypoproliferative and hyposecretory state that is unfavorable to implantation of the fertilized ovum[12]. Progesterone suppresses gonadotropin-releasing hormone, thereby inhibiting the release of follicle-stimulating hormone and luteinizing hormone. This action prevents ovulation. The atrophic endometrium that results from prolonged exposure to progestins minimizes the likelihood of implantation. By promoting the development of thick cervical mucus, progestin-only contraceptives also make sperm penetration less likely. Progesterone can be used alone (mini-pills) or in combination with estrogen. Progestin-only contraceptive has less progestin than those used in combination products.

Rationale for New Progestin Entities

Progestins derived from 19-nortestosterone are considered to be strongly androgenic. Androgenic effects associated with older progestins include adverse lipoprotein and carbohydrate changes, weight gain, acne, hirsutism, mood changes and anxiety. Concerns associated with these adverse effects led to development of more selective, less androgenic progestins[10,13,14] giving rise to the third generation progestins - gonanes. These new progestins include desogestrel, gestodene and norgestimate. Oral contraceptive pills containing third-generation progestins reportedly have several benefits including minimal impact on blood glucose levels, plasma insulin concentrations and the lipid profile[14]. In addition, fewer incidences of contraceptive discontinuation have been reported with the newer progestins[15] because of lack of cycle control (i.e., breakthrough bleeding, spotting and amenorrhea). ▶

Table 3: Relative Progestin Potency and Androgenic Effects

	Progestin potency	Androgenic effect
Most potent	Desogestrel Levonorgestrel Norgestrel	Norgestrel Norethindrone Ethynodiol
Least potent	Norethindrone	Desogestrel Norgestimate

Intermenstrual bleeding occurs during continuous treatment with many progestins, thus it was found desirable to add estrogens. Estrogens not only helped normalize cycle bleeding but also contributed to contraceptive effect.

The progestins used in COCs vary according to progestin potency, as well as estrogenic, anti-estrogenic and androgenic activity (Table 3). In terms of progestin activity, desogestrel, levonorgestrel, and norgestrel are the most potent progestins in COCs. Norgestrel is the most androgenic progestin. Levonorgestrel is the active isomer of norgestrel, a racemic mixture. Desogestrel and norgestimate have reduced risk of myocardial infarction because of their low androgenic potency compared with other progestins[6,9].

Table 4: Adverse Effects of Progesterone

Too much progestin	Too little progestin	Too much androgen
Breast tenderness, headache, fatigue, changes in mood.	Late breakthrough bleeding,	Increased appetite, weight gain, acne, oily skin, hirsutism, decreased libido, increased breast size, breast tenderness, increased LDL cholesterol, decreased HDL cholesterol.

New progestin entities

Drospirenone (DRSP) is a spironolactone analog with anti-mineralocorticoid activity. DRSP is the most recent progestin thus clinical experience with this novel progestin is limited. DRSP has anti-androgenic and weak anti-mineralocorticoid effects, with a pharmacological profile similar to that of natural progesterone. DRSP exerts its effects by counteracting estrogen-induced stimulation of renin-angiotensin-aldosterone system. In studies conducted on more than 2300 subjects over a maximum of 26 months, Yasmin® (the OC containing EE/DRSP) has been shown to have contraceptive efficacy and cycle control similar to that of other Ocs[16].

DRSPs' potential to increase serum potassium levels has also led to unique contraindications, warnings and restrictive labeling by US FDA. The manufacturer recommends that a test for potassium levels be performed during the first treatment cycle for patients taking any other drug capable of increasing potassium levels with EE/ DRSP such as Nonsteriodal anti-inflammatory drugs, Potassium supplements, Potassium-sparing diuretics, Angiotensin-converting enzymes inhibitors, Angiotensin-II receptor antagonists and Heparin[13]. As with other oral contraceptives, this product is contraindicated in women with hepatic or renal insufficiency. It is also contraindicated in patients who have adrenal insufficiency[15].

Several new progestins synthesized in the last decade may be considered fourth-generation progestins. These include dienogest, drospirenone, nestorone®, nomegestrol acetate, and trimegestone. The fourth-generation progestins have been designed to have no androgenic or estrogenic actions and to be closer in activity to the physiological hormone progesterone[11].

Trimegestone and Nestorone are the most potent progestins synthesized to date, followed by two of the gonanes: keto-desogestrel and levonorgestrel. The new molecules drospirenone and dienogest have less potent antigonadotropic activity and higher doses are required to suppress ovulation. Levonorgestrel, etonogestrel and Nestorone have been incorporated into long-acting delivery systems for use as long-term progestin-only contraceptives[17].

COMBINATION HORMONAL CONTRACEPTION

Oral Contraceptives

The oral contraceptive is one of the most reliable birth control methods available. With perfect use for one year, 1 out of every 1000 women will become pregnant while 50 out of 1000 women will get pregnant with typical use for one year.[14]

Combination Oral Contraceptives

Combination oral contraceptives are formulations of combined progestin and estrogens. The most common estrogen used in combined pills is ethinyl estradiol (EE). Mestranol is used in some pills. At least seven different progestins are used in the different pill formulations. Most pills are packed in either 28 -day or 21-day pill packs. The 28-day pill pack has 21 active pills (containing hormones) and 7 placebos (sometimes containing iron). The pills in the 21-day packs are all active. One product exists in the market as 91-day pill packs.

1. **Monophasic pill formulation**- all the active pills contain the same amount of hormones. Monophasic formulations are preferable for the woman interested in controlling her cycle length or timing by eliminating all pill free intervals for medical indication or personal preferences.

2. **Multiphasic pills formulation**- contain active pills with varying amount of progestin and/or estrogen. There are two types; the biphasics and the triphasics.

   A. **Biphasic pills formulation**- the biphasic pills maintain constant estrogen dose ▶

throughout the cycle, with a change in progestin mid-cycle. It offers no particular advantage over the other two preparations and is not often prescribed[18]

B. Triphasic pills formulations provide three different hormonal dosage levels - one for each week of active cycle. Triphasic formulations contain less total progesterone (and therefore a lower overall dose of hormones) than the monophasic pill.

Rationale for triphasic pills formulations

Triphasics were originally designed to mimic a woman's natural hormonal pattern; the rationale being that mimicking natural cycle pattern will reduce discomfort like breakthrough bleeding (BTB) associated with pills. There is no definite research indicating the superiority of triphasic pills for women with BTB. It is sometimes preferable to use the triphasics to reduce some side effects (such as premenstrual breakthrough bleeding), when increasing hormone levels throughout the entire cycle is not required, when it is desirable to reduce the total cycle progestin level (e.g. in acne treatment) or to avoid weight gain when using monophasic pills.

3. **Extended cycle pill formulation**

The extended cycle OC was designed to reduce the number of menstrual periods from 13 to 4 per year. The 91-day regimen is taken as 84 active tablets followed by 7 placebo tablets. The product *Seasonale®* approved as extended cycle OC in the U.S contains levonorgestrel 0.15mg and 0.03mg EE. The users have their period once every season (i.e. once every 3 months). Use of this regimen may lead to an improvement in the following menstruation-related problems including menorrhagia, anemia, dysmenorrheal, endometriosis and menstrual headaches[3].

Rationale for Extended Cycle Pills [19]

A survey carried out in the U.S of women aged 18- 49 revealed that a good number indicated that their period caused them to miss important events and nearly 50% would prefer never to menstruate[19]. Until *Seasonale®* was approved, women's option for limiting the frequency of their menses included extended use of combination COCs. The pill- free intervals of a monophasic COC for two or three cycles are eliminated to achieve an extended cycle which is referred to as *bi- cycling* and *tri-cycling* respectively. Two progestin-only methods could also be used: depot medroxyprogesterone acetate (DMPA) and levonorgestrel releasing intra-uterine system (I.U.S.). Thus the extended cycle oral contraceptive *Seasonale®* was designed to meet the needs of women who require infrequent menstruation for medical, personal or social reasons.

COUNSELING CLIENTS ON COMBINATION ORAL CONTRACEPTIVES IN THE PHARMACY

The client should be shown the pack explaining where to start, day 1 through day 21 or 28. This is especially important when dispensing the multi-phasic pill packs.

COC client instructions

- Take 1 pill each day, preferably at the same time of day.
- Some pill packs have 28 pills. Others have 21 pills. When the 28-day pack is empty, start taking pills from a new pack immediately. When the 21-day pack is empty, wait 1 week (7 days) and then begin taking pills from a new pack.
- If vomiting occurs within 30 minutes of taking a pill, take another pill or use a backup method if you have sex during the next 7 days.

General Information

- Some nausea, dizziness, mild breast tenderness and headaches as well as spotting or light bleeding are common during the menstrual cycle (usually disappear within 2 or 3 cycles).
- Certain drugs (rifampin and most anti-epilepsy drugs) may reduce the effectiveness of COCs. Inform your doctor or pharmacist if new drugs are to be used alongside COCs.
- COCs do not provide protection against STDs, including the AIDS

Timing of Initiation

- **First day** of the menstrual cycle (first day of menstruation) is preferred as a start day or Day 1 because with this method a routine back up is not required.
- **Sunday start day** the pills could be started the first Sunday after menstrual bleeding begins, this could result in no period on weekends, but a routine back-up method must be used for seven days with this method.
- **Quick start** starting the pills on the day of counseling. This helps women, especially teens, to adapt immediately to COCs but routine back-up for seven days is required.

Managing Missed doses of Oral Contraceptives

Less than 24hours ago

If the missed dose is less than 24 hours since the last pill was taken, the patient should take a pill right away and then return to normal pill-taking routine.

24 hours

If about 24 hours has lapsed since the last pill was taken, the patient takes both the missed pill and the next scheduled pill at the same time.

Greater than 24 hours ago

If it has been more than 24 hours since the last pill was taken (i.e. two or more missed pills), the patient takes the last pill that was missed, throws out the other missed pills and takes the next pill on time. Additional contraception is used for the remainder of the cycle.

Safety of Contraceptives

Oral contraceptive pills unlike other drugs are taken by healthy women for long periods of time. Thus, it is►

important that pharmacists are conversant with the most recent information on the side effect profile of oral contraceptive pills and their risk-to-benefit ratios. Fortunately, the safety of oral contraceptive pills for most women is now well documented. A client leaving the pharmacy with a COC should know the danger signs that warrant contacting a health care provider and the troublesome signs that will subside with continuous use.

Early Pill Warning.

The client should be advised to contact their pharmacist or any other health care provider if any of these signs develop.

Abdominal pain (severe), yellow skin or eyes, Chest pain (severe), Headaches (severe), Eye problems, Severe leg pain or swelling in the calf or thigh. This is represented by the acronym ACHES[20]

W.H.O Precautions for Oral Contraception[21]

A careful personal and family medical history (with particular attention to cardiovascular risk factors) and an accurate blood pressure measurement are recommended before the initiation of oral contraceptives. The WHO and many leaders in the field of family planning now promote a graded scheme of precautions, rather than contraindications in considering which patients should not use oral contraception.

Category 1: women with these conditions have no restrictions on the use of oral contraceptives. Post partum >=21 days.
Post abortion with abortion performed in first or second trimester, history of gestational diabetes, varicose veins, vaginitis without purulent cervicitis, irregular vaginal bleeding without anemia, family history of breast, endometrial or ovarian cancer, mild headaches, history or/and risk of STIs or PID, past ectopic pregnancy, HIV positive, mild headaches, past, benign breast disease, cervical ectopy, viral hepatitis carrier, uterine fibroid, thyroid and obesity.

Category 2: Advantages of oral contraceptive pills generally outweigh theoretical or proven disadvantages. Oral contraceptive pills can generally be prescribed without restriction to patients with these conditions.

Severe headache after initiation of oral contraceptive pills, diabetes mellitus, major surgery without prolonged immobilization, sickle cell disease or sickle cell hemoglobin C disease, BP of 140/100 to 150/109 mmHg, undiagnosed breast mass, cervical cancer, age greater than 50 years, family history of lipid disorders and family history of premature myocardial infarction.

Category 3: Women with these conditions are those which the health provider should exercise caution in prescribing oral contraceptives and carefully monitors for adverse effects. Post partum <21 days

Lactation (6 weeks to 6 months), undiagnosed vaginal or uterine bleeding, age greater than 35 years and smoke fewer than 20 cigarettes per day, history of breast cancer but no recurrence in past 5 years, interacting drugs and gall bladder disease effects.

Category 4: Women with these diagnoses should not be given oral contraceptive pills.

Venous thromboembolism, cerebrovascular or coronary artery disease, structural heart disease, diabetes with complications, breast cancer, pregnancy, lactation (<6 weeks post partum), liver disease, headaches with focal neurological symptoms, major surgery with prolonged immobilization, age greater than 35 years and smoke 20 cigarettes or more per day and hypertension (BP >160/100mmHg) or with concomitant vascular disease.

Emergency Contraception (EC)

Emergency contraception is used to prevent pregnancy after a coital act not adequately protected by a regular method of contraception. Emergency contraception is sometimes called the morning after pill or post coital contraception. The term emergency contraception is preferred because it avoids giving the impression that the treatment must be taken the morning after sex; moreover it emphasizes that the treatment is not intended to be used as an ongoing method of contraception[22].

Potential indication for use of EC

Lack of contraceptive use during coitus; Mechanical failure of male condom (breakage, slippage and leakage); Dislodgement, breakage or incorrect use of diaphragm, cervical cap or female condom; Error in practicing coitus interruptus; Missed COC (any two consecutive pills); Missed progestin only oral contraceptives (one or more); Exposure to potential teratogen while not using effective contraception; Late injection of injectable contraceptive (>2weeks for a progestin only or 3days for a combined formulation); and Rape[22]. EC can substantially reduce the burden of unintended pregnancy.

Types of Hormonal EC [22]

The two best-studied EC methods, and the most widely used throughout the world are Combined estrogen + progestin regimen and Progestin only regimen

Both regimens consist of two doses of contraceptive steroids taken 12 hours apart after intercourse. The combined regimen, also called Yuzpe regimen, contains 100µg of EE + 0.5mg of levonorgestrel (or 1 mg of norgestrel) in each dose. In the progestin only regimen, each dose is 0.75mg of levonogestrel. The progestin only regimen is preferred because it is more effective and causes less nausea and vomiting[22]. A randomized trial indicated that combined estrogen progestin regimens containing the progestin norethindrone instead of levonorgestrel may also be effective as emergency contraception, although they may not be as effective as the standard Yuzpe regimen[23].

Mechanism of Action

EC prevents a pregnancy from starting which differs fundamentally from interruption of an established pregnancy. Many health providers and clients confuse EC with medical abortion because both are used after intercourse. Six to seven days elapse between a coital act and establishment of a pregnancy, defined as implantation. EC acts within this interval to prevent pregnancy. Studies ▶

of high dose oral contraceptive pills suggest that the combined estrogen + progestin regimen and the progestin only regimen cannot interrupt an established pregnancy. By the time a pregnancy is diagnosed, EC will no longer be effective[22].

The mechanisms of action of the various forms of ECs have not been extensively studied and consequently are not well understood. Like all hormonal contraceptives, EC pills probably act through multiple mechanisms that may depend on the timing of their administration in the menstrual cycle. Various studies including a meta-analysis and a randomized trial indicate that emergency contraception used within 72 hours prevents at least 74% of expected pregnancies and may also retain sustainable effectiveness when used more than 72 hours after intercourse[24,25].

Medical contraindications
No contraindication to hormonal EC exists. It should not be used in suspected or confirmed cases of pregnancy though no harm will be done the foetus or woman if accidentally used[26].

Side Effects
The most common side effects are nausea and vomiting. An unknown proportion of women experience irregular vaginal bleeding after using EC. Other reported adverse effect events includes dizziness, fatigue, headache, breast tenderness, lower abdominal pain. These symptoms usually resolve spontaneously within a few days and may be treated symptomatically [22].

Repeat use of EC
Unlike regular contraceptive methods, EC pills are not intended for frequent use; they are less effective and have more side effects than other methods. However, studies of high dose levonorgestrel used for recurring post coital contraception indicates that the likelihood of harm due to repeated use is low. Though EC should not be denied solely because it's been used before women who have repeated contraceptive emergencies should be provided with extra contraceptive counseling and advice on how to avoid these incidents in the future[22].

NEW DELIVERY SYSTEMS FOR HORMONAL CONTRACEPTION

Recent research has concentrated on the development of new systems for delivering steroidal contraceptive agents as steroidal contraceptives are highly effective, relatively safe, and easy to use. Non-oral routes offer the advantage of avoiding the first pass through the liver, thereby allowing lower doses of hormone and reducing metabolic side effects. They also produce constant serum hormone concentrations and simplify compliance[27]. The new delivery systems are designed to enhance adherence therefore reducing failure rates.

VAGINAL RING (NUVA RING®):

It is a flexible, nearly transparent ring that is 54mm in outer diameter and 4mm in cross sectional diameter. The ring releases a constant rate of 15mcg of EE and 0.120mg of the progestin etonogestrel per day. Etonogestrel is the active metabolite of desogestrel. Each ring is used for 1 cycle and then removed. A cycle consists of 3 weeks of continuous ring use followed by a 1 week ring-free period[28]. Indication, Mechanism of Action and contraindication is similar to the COC.

Effectiveness
Combined rings release sufficient amounts of estrogen and progestin to prevent ovulation. The ring provides continuous daily release of etonogestrel 120mcg and EE 15mcg, and is associated with high contraceptive efficacy and good cycle control. The vaginal ring is appropriate for women who are comfortable with the insertion/removal process[13] and especially useful for women who require a means of contraception that does not require daily attention. In a pooled analysis of 2,322 women using Nuvaring in Canada, the U.S and Europe, there were 1.2 pregnancies per 100 women in the first year of use. Women used the ring correctly in 86% of cycle[21].

Side effects
Irregular bleeding which usually consist of spotting, hormonal side effects such as headache, nausea and breast tenderness, vaginal symptoms especially vaginitis are associated with nuvaring®. Although women or their partners may be aware of the device, only 1 to 2.5% of users discontinued the ring due to foreign body sensations, coital problems and expulsion. Vaginal discharge and irritation led to discontinuation in about 1-2% of women.

Initiation
The ring is used vaginally. The first ring cycle is started between days 1-5 of menstrual cycle. The ring is inserted and left in for 3 weeks and then removed for 1 week. Withdrawal bleeding usually occurs during the ring-free period. The ring-free interval should not be longer than 7 days. If the ring is expelled and has been out of the vagina for less than 3 hours, the user should rinse in lukewarm water and reinsert it. Back-up contraception is not required. If the ring is lost, a new ring should be reinserted. If it is out of the vagina for longer than 3 hours a back up method of contraception should be used for 7 days. The ring will not provide adequate protection if use exceeds 4 weeks[29].

To switch from the combined OC to the vaginal ring, the ring should be inserted no later than 7 days after the last OC tablet. To switch from a progestin only pill, the vaginal ring is inserted the day after the last pill is taken. When switching from an injectable contraceptive method, the ring is inserted on the day the next injection would be due.

Another ring, still in clinical trials releases a combination of 150mcg of a different progestin Nesterone and 15mcg of the estrogen ethinyl estradiol per day, this ring is being developed for use in developing countries. It will be effective for over 12 months, making it more cost effective than Nuvaring®[29].

TRANSDERMAL PATCH

The transdermal contraceptive patch is square, with each side being about 4.45cm long. It resembles a light brown bandage. The patch has three layers: an outer protective layer of polyester, a medicated adhesive middle layer, and a ▶

clear polyester release liner that is removed just before application. It contains progestin Norelgestromin (NGMN)-which is the primary active metabolite of norgestimate, and Ethinyl estradiol as the estrogen delivering 150mcg and 20mcg of each hormone per day.

Initiation

The first patch is applied on the first day of menses, if the patch is applied after the first day of menses, a backup method of contraception should be used for one week. A new patch is applied weekly for 3 weeks, week 4 is patch free. Withdrawal bleeding usually occurs during the patch free week.

The patch should be applied to clean, dry, healthy intact skin; the patch may be attached at the following sites: the buttocks, the abdomen, the upper outer arm, the upper torso but not directly on the breast. These four sites are therapeutically equivalent[11].

To switch, the contraceptive patch should be applied on the first day of withdrawal bleeding. If the patch is started after the first day of withdrawal bleeding a back up contraception should be used. Alternatively, the patch can be applied on the day after the hormonal pill is taken.

If the patch has either partially or completely detached for less than 24 hours, the patch should be reattached, if reattachment is not possible a new patch should be applied. The patch change date will remain the same. If detachment is greater than 24 hours a new patch should be attached and a backup method of contraception should be utilized[25].

COMBINED INJECTABLE CONTRACEPTION

A monthly injectable contraceptive composed of 5 mg estradiol cypionate and 25 mg of medrooxyprogesterone acetate (Lunelle®) was approved by the Food and Drug Authority (FDA) in the year 2000. It is administered by intramuscular injection, with no more than 33 days between injections. In a study of 782 American women followed over a year, there were no pregnancies. The mechanism of action is primarily by inhibition of ovulation. It has the indication and contraindication as combined oral contraceptives pills.

This method is appropriate for women who have difficulty remembering to take daily pills, who want monthly predictable bleeding, or have enteric absorption problems (e.g. inflammatory bowel disease).

When compared with DMPA, the combined monthly injectable has more frequent injections (every 28± 5days), and faster return to ovulation. The first normal ovulatory cycle occurs 63 to 112 days following the last injection of Lunelle®. The vaginal bleeding with this method is due to estrogen withdrawal, and usually occurs 3 weeks (days 22) after injection. When compared with combined COCs, the combined monthly injectable has less breakthrough bleeding, greater incidence of amenorrhea, better inhibition of ovarian follicular activity than a 20mcg ethinylestradiol pill, and a weight gain of about 7kg over 1 year[25].

HORMONE-IMPREGNATED INTRAUTERINE DEVICES

Hormone-releasing intrauterine devices have attracted interest for more than a decade. The initial problem of increased risk of ectopic pregnancy appears to have been overcome by increasing the dose of synthetic progestogen. A levonorgestrel-impregnated intrauterine device that releases 20 μg of levonorgestrel per day has been developed in Scandinavia. The hormone is placed in a Silastic capsule on a standard polyethylene frame. The cumulative rate of pregnancy after seven years of continuous use was reported to be 1.1 percent. When compared with inert or copper intrauterine devices, the device reduces menstrual blood loss, and many women become amenorrheic after the first few months of use. Amenorrhea is due to endometrial atrophy, and possibly to the destruction of endometrial estrogen receptors. Ovarian function is only infrequently affected, and 75 percent of women continue to ovulate. Thus, amenorrhea is not accompanied by hypoestrogenism. In addition to being a very effective contraceptive that may be attractive to older women with menstrual irregularities, the progestogen-impregnated intrauterine device opens new possibilities for the noninvasive management of menorrhagia regardless of the need for contraception[27].

MALE CONTRACEPTION

The development of reliable methods of hormonal contraception for men has proven difficult. The regulation of spermatogenesis is poorly understood, and the link between sexual activity and hormones is much more direct in men than in women. Any method that compromises the endocrine activity of the testes must also involve testosterone replacement if sexual function is to be maintained. The use of large amounts of testosterone to inhibit spermatogenesis is not new[30]. As early as 1950, azoospermia was achieved by the daily injection of 25 mg of testosterone proprionate. Testosterone is given by injection because orally active synthetic androgens such as methyltestosterone may cause liver damage. In a recent study, the use of testosterone enanthate given weekly in a dose of 200 mg intramuscularly showed complete azoospermia occurred in only 157 of 271 men, and it was more likely in Asian men than white men[31]. The combination of a potent antagonist of gonadotropin-releasing hormone and testosterone causes azoospermia more often, but the need for daily injections of antagonist makes this regimen impractical. Moreover, potential changes in clotting factors, enlargement of the prostate, and changes in serum lipoproteins raise concern about the long-term risks of such a treatment.[27]

NEW DEVELOPMENTS

The most promising development in the field of hormonal contraception has been the use of hormone agonists and antagonists. Agonists of gonadotropin-releasing hormone bind to gonadotropin-releasing hormone receptors on the anterior pituitary and, after initially stimulating the secretion of follicle-stimulating hormone and luteinizing hormone, produce a hypogonadotropic state by down-regulation of the receptors. Ovulation is inhibited during chronic intranasal administration of the gonadotropin-releasing hormone agonist buserelin. This agent could prove particularly useful as a contraceptive during breast-▶

feeding, since minimal quantities pass into the milk.

Antagonists of progesterone offer considerable potential for the regulation of fertility. Progesterone is essential for a range of reproductive functions, including the establishment and maintenance of pregnancy. Antagonists of progesterone, such as mifepristone, block the action of progesterone on the endometrium and hence produce an environment hostile to pregnancy. Mifepristone in combination with a prostaglandin is a highly effective and safe method for the termination of early pregnancy. When given in the early luteal phase of the cycle it prevents the development of a secretory endometrium, and preliminary trials indicate that it may be effective when given at that time as a once-a-month contraceptive. Continuous administration in daily doses as low as 1 mg inhibits ovulation, suggesting that it may be a useful alternative to contraception with progestogen alone[27].

CONCLUSION

The current methods of hormonal contraception have been in clinical use for more than 30 years and have proved to be highly reliable and acceptable to millions of women. Overall, the health benefits of these methods far outweigh their side effects and risks. The evidence suggests that once risk factors (e.g., smoking, hypertension, and obesity) have been identified, combined hormonal contraceptives, which may be used in various delivery formats, are safe for most women for most of their reproductive lives. The incidence of cancer of the ovary, uterus, cervix, and breast appeared to be related to the pattern of ovarian and sexual activity throughout the reproductive life rather than use of contraceptives[32,33].

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