Contraception: What's New? Literature Review

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Abstract

This article focuses on recent advances in hormonal contraception. Significant modifications of oral contraceptives such as lower doses, extended cycle regimens, and innovative delivery systems as well as new delivery systems and innovations such as vaginal rings, transdermal patches, a new implant, a new intrauterine device, and over-the-counter postcoital contraception are reviewed.

OVERVIEW

Unintended pregnancy is a serious public health issue. Contraceptive technology is rapidly advancing, and new developments may maximize compliance and efficacy. In the last 10 years, there have been significant modifications of oral contraceptives such as lower doses, extended cycle regimens, and innovative delivery systems. New delivery systems include vaginal rings, transdermal patches, a new implant, a new intrauterine device, and over-the-counter postcoital contraception.

Presently the view held about contraceptives is reviewed and presented under the following groups:

COMBINED ORAL CONTRACEPTIVES

Combined oral contraceptives (COCs) are currently used by approximately 100 million women worldwide. Two remarkable changes have occurred over the past four decades. First, there has been a significant reduction in the estrogen component, which is generally ethinyl estradiol. Second, there have been attempts to find new, safe progestins with various affinities to progesterone, estrogen, androgen and mineralocorticoid receptors. The main goal has been to increase the safety of COCs, particularly by decreasing the risk of venous thromboembolism. In the 1990s many of these progestins were classified as "third-generation progestins." It is based mainly on the historical development, and may be appropriate for 19-nortestosterone derivatives like desogestrel and gestodene. Also norgestimate has been included into that group, although it is metabolized to norgestrel. Instead, some old progestins like cyproterone acetate and newer progestins like dienogest and drospirenone are compounds with different molecular structures, and should not be called "third-generation COCs." After the new progestins were introduced, it surprising to see that the new COCs, in fact, run with a 1.4 to 4-fold risk for venous thromboembolism when compared with "second-generation" COCs containing levonorgestrel or norgestrel [$_1$]. In a small study, cyproterone acetate users were found to have more than three times the risk of idiopathic venous thromboembolism than users of levonorgestrel. Under in-vitro conditions, it has been shown that gestodene and desogestrel induce a resistance to active protein C which is of the same magnitude as the resistance induced by the mutation factor V Leiden. The second-generation pills showed only part of this effect .Still, the risk is low, being in the range of three to six per 10,000 women-years, while among nonusers it is one in 10,000 women-years.

DROSPIRENONE

Drospirenone is a unique progestin derived from anti-mineralocorticoid spironolactone. Drospirenone appears to have a pharmacological profile almost identical to natural progesterone and is therefore unique among synthetic progestogens in having anti-mineralocorticoid activity. COCs containing ethinyl estradiol 30mg and drospirenone 3mg (Yasmin, Bayer Schering Pharma) has emerged onto the market worldwide. Ethinyl estradiol tends to cause water retention, resulting in breast tenderness and feeling of bloating among some users of COCs. As drospirenone 3mg is equivalent to 25 mg of spironolactone, the water retention is counteracted by a natriuretic effect, and consequently, decreases in both the body weight and systolic and diastolic blood pressures are observed [$_2$]. The ethinyl

estradiol–drospirenone combination may be as effective for mild to moderate acne as cyproterone acetate-containing COCs [3], and seems to relieve the premenstrual syndrome [4]. The results of various studies suggest that the adverse cardiovascular and other serious events in users of a drospirenone-containing COC are similar to those associated with the use of other COCs. Recently, a low hormone version containing ethinyl estradiol 20 mg and drospirenone 3mg (Yasminelle, 21 tablets; Bayer Schering Pharma) has been marketed.

EXTENDED CYCLE

The first three-cycle regimen was attempted 30 years ago. When combined estrogen-progestin contraception was first devised over 50 years ago, debate raged over whether to design the dosing regimen to include monthly withdrawal bleeding. Cyclic withdrawal bleeding was certainly not necessary to obtain contraceptive efficacy. In fact, the estrogen component of the pill was introduced mainly for cycle control and not for contraception. In the early, revolutionary days of hormonal contraception, women's acceptance of the pill was partly predicated on the appearance of monthly menstrual flow to confirm that she was not pregnant, and also the reassurance that the process was "natural." To this day, some women feel that regular monthly cycles are somehow necessary to cleanse the uterus. However, most women today have a much better understanding of the birth control pill, and in fact are requesting formulations that reduce the number of menstrual cycles per year , a desire to maximize their ability to function in their active lifestyle and minimize disability and discomfort due to bleeding and dysmenorrhea. The most common formulations used in extended dosing are the low dose monophasic pills. Triphasic pills are not appropriate for extended use because of the increased incidence of breakthrough bleeding .The prepackaged formulation currently approved by the FDA for extended use is a 30-mcg EE/0.15-mg levonorgestrel (LNG) pill combination with 84 active pills and 7 days of placebo. Anderson and Hait [5] compared this regimen with a 30-mcg EE/150-mcg LNG conventional pill regimen and found that of the total number of possible days of unscheduled bleeding or spotting days that could be reported, patients reported a median of 3.6% days on the extended cycle regimen and 2.9% days on the conventional regimen. The most frequently reported side effects were increased weight, mood swings, and acne. Discontinuation for "unacceptable bleeding," whether cited as an adverse event or as an individual patient decision, accounted for 7.7% of extended cycle regimen patients and 1.8% of conventional regimen patients. For extended cycle regimen patients, the rate of discontinuation due to unacceptable bleeding decreased considerably after 2 extended cycles. The ultra-low extended regimen formulation consisting of 20 mcg EE and 0.1 mg LNG has also been introduced and has a similar bleeding profile [8].

TRANSDERMAL PATCH

There have been many attempts to try alternate routes of administration which would avoid food interactions as well as the first pass metabolism by the liver, and allow for greater convenience. In 2001, the FDA approved the first transdermal contraceptive patch, Ortho Evra (20-mcg EE and 150-mcg norlgestromin per 24 h). Norlgestromin is a metabolite of norgestimate, the third-generation progesterone. Three clinical trials have been conducted worldwide involving 4578 women, 3319 of whom used Ortho Evra [678]. Compared with daily OCs, the patch offered similar efficacy and menstrual cycle control, and had the added benefit of improved compliance. In theory, compliance should be greater with a patch that needs to be changed only once a week compared with a pill that must be taken at the same time every day. In the adolescent population, however, compliance is still less than ideal. In addition, some patients do not like the fact that the patch represents a visible evidence of contraceptive use, feeling that use of contraception is private. In clinical trials, most unintended pregnancies occurred in women weighing more than 198 lb (90 kg), suggesting that Ortho Evra may be less effective in women heavier than this weight. The most common adverse effects in clinical trials were, in decreasing order, breast tenderness, headache, skin irritation, and nausea. Ortho Evra patch should be started on the first day of the menstrual period or the first day of withdrawal bleeding in OC users. A new patch is applied weekly, on the same day each week, for 3 weeks. Week 4 is patch free, and withdrawal bleeding is expected during that time. As with the OCs, there should be no more than a 7-day hormone-free interval between dosing cycles. The patch should be attached to clean, dry skin on the buttocks, upper outer arm, lower abdomen, or upper torso (excluding breasts).

Ortho Evra should not be placed on skin that is red or irritated or where it would be rubbed by tight clothing. The patient should be encouraged to participate in her usual physical activities, including water-related activities.

INTRAUTERINE DEVICES

The use of intrauterine devices has a long past, falling in and

out of favor in the United States after the withdrawal of the Dalkon Shield over 30 years ago. The levonorgestrel steroid-releasing intrauterine system (LNG IUS) was developed in the late 1970s and is now approved for contraceptive use in the United States and in 100 countries throughout Europe, Latin America, and Asia. The device releases the potent 19-nortestosterone-derived progestin, LNG, directly into the uterine cavity at an initial rate of 20 mcg per day [18]. Maximum plasma levels are achieved within a few hours. Plasma levels of LNG stabilize at 100 to 200 pg/ ml within the first few weeks after insertion. This range is 4% to 13% of the levels observed with daily use of OCs containing 150-mcg LNG. The majority of women will have normal ovulatory cycles as the blood level of hormone is too low to suppress ovarian function. Direct delivery into the endometrial tissue provides local hormonal contraception with lower and more constant systemic levels of progestin . The high local concentrations of LNG trigger histologic changes that render the endometrium inactive and change the composition of cervical mucus, thus creating an environment unsuitable for sperm transport, implantation, or blastocyst development.

The LNG IUS is effective for at least 5 years due to the slow, sustained release of LNG from a rate-controlling polydimethylsiloxane membrane. The IUD's local effects also contribute to its non-contraceptive uses which include the treatment of menorrhagia, dysmenorrhea, and endometriosis. Unscheduled breakthrough bleeding occurs frequently in the first 4 to 6 months after LNG IUS insertions and usually presents as irregular spotting [9]. Thereafter, there is a decrease in the number of menstrual bleeding days and in the amount of objectively measured menstrual blood loss.

VAGINAL RING

There is so far only one vaginal contraceptive ring on the market (NuvaRing; Organon). It releases 15 mg of ethinyl estradiol and 120 mg of etonogestrel, an active metabolite of desogestrel, daily. Each ring is to be used for 3 weeks, followed by a 1-week ring-free interval. In a large multi-centre trial [10], the method failure rate was 0.77 per hundred women-years, and the user failure rate was 1.18 per hundred women years. The ring had good cycle control and was well tolerated. The controlled release design of the vaginal ring produces more uniform circulating concentrations of contraceptive hormones and avoids the daily fluctuations associated with the use of combined oral contraceptives (COCs). The once monthly dosing provides greater convenience and improved compliance in patients who cannot remember to take their pills at the same time every day.

INJECTABLE CONTRACEPTION

Depo-Provera (depot-medroxyprogesterone acetate) is the most commonly used and thoroughly studied injectable contraceptive. Evidence about the safety, efficacy, and acceptability of DMPA comes from countries including Sri Lanka, Indonesia, Thailand, and Mexico where DMPA has been used and studied for decades. It is given every third month, and can be given within 7 days after elective abortion, and within 3 weeks postpartum, if the mother is not lactating, and within 6 weeks, if lactating. It can be also given to rubella susceptible women who receive rubella vaccination to avoid the teratogenic effects of MMR vaccination. DMPA acts by inhibiting ovulation, and the contraceptive effect is very high. The only safety issue raised is due to the low estrogen level, with a possible negative effect on the bone mineral density [11].

Therefore, a new DMPA formulation has been developed (Pfizer). It is administered subcutaneously, contains 104 mg (30% less than the original Depo-Provera) and is still effective for 3 months. In a study with more than 16 000 cycles, no pregnancies occurred [12]. Due to subcutaneous administration, women can learn to take the injection by themselves.

For most teenagers requesting contraception, injectables could be a good option. They are independent of intercourse and of the user's memory (and thus of continuing motivation), other than remembering the 8- or 12 weekly appointments. Injectables offer the advantage of not requiring storage and not being obvious in use, enabling women, to maintain secrecy about their use of contraception. The probability of achieving amenorrhoea taking DMPA is higher than for other progestogen-only methods and is appreciated by teenagers. Like the combined pill, DMPA may offer protection against pelvic inflammatory disease because of the effect of progestogen on cervical mucus. This would make it a better choice than the intrauterine contraceptive device for young women who are forgetful pill-takers and may be at risk of sexually transmitted disease. There has been much discussion in the past 10 years about the possibility of a reduction in bone density with long-term Depo-Provera use, and whether the use of DMPA may interfere with the attainment of peak bone mass in adolescents. It appears, however, that women who choose, or

are advised, to use Depo-Provera, are more likely to have other risk factors for osteoporosis, such as smoking, low socio-economic status and a family history of the condition. If an individual is assessed clinically as being at potential risk, the only way to be certain is to measure bone density.

In November 2004, the Committee on the Safety of Medicines issued advice regarding the use of Depo-Provera [13] which states:

In adolescents, Depo-Provera may be used as first-line contraception but only after other methods have been discussed with the patient and considered to be unsuitable or unacceptable.

In women of all ages, careful re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than 2 years.

In women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered.

It is out of place to mention here that teenagers must meet Fraser criteria to allow health care workers to provide contraceptive advice and treatment to young people under the age of 16 years without parental consent.

The Fraser criteria outlines that the young person understands the advice.

The young person cannot be persuaded to inform her parents or to allow the clinician to inform them.

It is likely that the young person will continue to have sexual intercourse with or without the use of contraception.

The young person's physical or mental health may suffer as a result of withholding contraceptive advice or treatment.

It is in the best interest of the young person for the clinician to provide contraceptive advice, treatment or both without parental consent.

IMPLANTS

The initial purpose was to develop a long-acting, user failure-free method without estrogen-related side effects. Norplant (Schering) consists of six rods releasing levonorgestrel. The other implants on the market are Jadelle with two rods also releasing levonorgestrel (Bayer Schering Pharma), and a single rod etonogestrel releasing implant (Implanon, Organon). The nomegestrol acetate releasing implant (Uniplant, Theramex) is also a single rod implant [14]. Norplant was withdrawn from the US market due to product liability concerns. Jadelle consists of two 45 by 2.4 mm rods containing 75 mg of levonorgestrel each. The release rate is 100 mg/day in the beginning, stabilizing down to 30mg/day. In many countries, the duration of the treatment has been officially extended to 5 years. Plasma concentrations in the first month are over 400 pg/ml, decreasing to 280 pg/ml by the end of the fifth year. Serum concentrations are affected by the body weight of the user; in a person of 70 kg the serum levels are about half those in women weighing less than 50 kg. Norplant-6 and Jadelle have a Pearl Index of 0–0.3 in the first year. The cumulative pregnancy rate for 5 years has been around one [15].

Implanon is a 40_2mm rod containing 68 mg of etonogestrel. The initial serum concentration is about 800 pg/ml, decreasing to 150 pg/ml by the end of the third year of use. The required level to inhibit ovulation is approximately 90 pg/ml. Hence, this implant is meant for 3 years. With Implanon, the Pearl Index over 3 years has been zero [16].

TRANSCERVICAL STERILIZATION

The transcervical approach to permanent female sterilization has been studied for more than 150 years. Initial attempts at transcervical sterilization were not widely adopted due to an inability to occlude the tube reliably, resulting in pregnancy and/or high morbidity from the procedure. As a result, laparoscopic methods of tubal interruption became the predominant minimally invasive approach to permanent sterilization. However, laparoscopy requires general anesthesia in a hospital setting. Complications resulting from injury to internal organs from trocar injuries, bowel burns, and lacerations and trauma to major vessels, although relatively rare have resulted in significant morbidity and occasional mortality. Hysteroscopy is the current accepted method for accessing the tubes transcervically, although fluoroscopic methods have been described. New methods for hysteroscopic transcervical sterilization include the insertion of microinserts into the tubal ostia, causing proximal tubal occlusion. These methods rely on both mechanical occlusion and stimulation of tissue in-growth to effect tubal occlusion. The devices can be delivered to more than 90% of tubes, have very high success rates of pregnancy prevention (>99% in studies to date), are acceptable to patients [1718] and can be placed under local anesthesia in an ambulatory setting [19]. The Essure microinsert (Conceptus, Inc, San Carlos, CA) is the only device for hysteroscopic sterilization currently

approved by the FDA. It is a hybrid metallic and fiber coil that is placed into the tube under direct hysteroscopic visualization. The device, 4 cm in length, has an inner core of stainless steel and an outer coil made from a nickel titanium alloy. Running along the inner coil are polyethylene tetraphthalate (PET) fibers.

The device is placed in the proximal section of the Fallopian tube by a single handed control mechanism. Upon release of the guide wire, the outer coil rapidly unwinds and expands into the tubal lumen to anchor the device in place. Between 5 and 8 coils remain trailing in the uterine cavity to anchor the microinsert in place. The system can be delivered through a 5-French operating channel of a 3.5_5.5-mm outside diameter hysteroscope. The PET fibers then elicit a benign tissue in-growth, with fibrous tissue causing complete tubal occlusion in a 3-month period. The device can be placed under local anesthesia (paracervical or intrauterine) with or without intravenous sedation as tolerated by the patient.

Cooper [20] reported the outcomes from several phase 2 trials. Of 871 women involved in the studies, 745 (85%) had the procedure attempted with a placement rate of 627/745 (84%). Of the 603/627 women with correctly placed devices, bilateral tubal occlusion was demonstrated in 96% at 3 months by hysterosalpingogram, with 99.5% achieving bilateral tubal occlusion at 12 months.

EMERGENCY CONTRACEPTION

Currently, the best documented and most feasible method is to take 1.5 mg of levonorgestrel as soon as possible and, at the latest, 72 h after intercourse. In a WHO study [48], pregnancy rates of 0.4%, 1.2% and 2.7% were observed if two 0.75 mg tablets were taken 12 h apart, starting within 24, 48 or 72 h after the intercourse, respectively. It is preferable to take the tablets as a one-dose regimen with the same efficacy [21]. The most common side effects are nausea and vomiting, breast tenderness, low abdominal pain and dizziness. The safety of the method has allowed this product to be given in many European countries as an over-the-counter treatment without formal prescription. The possibility of an ectopic pregnancy must also be considered.

Mifepristone 10 mg has been compared with levonorgestrel for emergency contraception [22]. When taken within 120 h of unprotected coitus, the pregnancy rate was 1.5%, similar to that after 1.5 mg of levonorgestrel. In a sample of 635 women, after 25 or 50 mg of mifepristone, there were seven failures (1.1%), and it could be estimated that the pregnancy was prevented in 88% of cases [23].

CONCLUSION

Contraception has witnessed significant development in the recent past. Decreased dosage of estrogen content of OCs, introduction of the so-called third generation progesterones like gestodene, desogestrel and norgestimate, old progestins like cyproterone acetate and newer progestins like dienogest and drospirenone (compounds with different molecular structures) are used innovatively in newer OCs. Contraceptive user has a wide range of choice. Unfortunately, this wide range is still not available to the general population in developing countries.

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