

## Review Article

# Newer Contraceptives

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### Introduction

The “reproductive revolution” has been one of the major demographic stories of the latter half of the 20<sup>th</sup> century. The 2004 World Population datasheet published by the Population Reference Bureau (PRB) [1] states that developing countries in Africa and Asia will account for about 90 % of the increase in world population projected by 2050, with Nigeria expected to be the fastest growing country between now and 2050. The population in India in mid 2004 was estimated to be 1086.6 million, with a birth rate of 25 per 1000 and a 1.7% rate of natural increase as compared to 0.1% for Japan. With 36% of the population in India below age 15, a 50% increase in population is envisaged by 2050.

The contraceptive prevalence rate for modern methods of contraception in India is 42.8% (48% for all methods), with female sterilization accounting for 34.2%, pill use for 2.1%, IUD use for 1.6% and condom use for 3.1% [2]. Male sterilization accounts for 1.9%. China has a modern contraceptive use rate of 83.3% with IUD use accounting for 36.4% and female sterilization for 33.5%. Despite the rise in use of family planning as evidenced in surveys, one-fourth of births worldwide are unplanned.

Over the past 30 years, there have been significant advances in the development of new contraceptive technologies, including transition from high dose to

low dose combined oral contraceptives and from inert to copper and levonorgestrel releasing intrauterine devices (IUDs). In addition, combined injectable contraceptives, a combined hormonal patch and ring and progestogen-only injectables and implants have been introduced in the last four years. This review will focus on the non-daily hormonal contraceptives introduced in the last few years, along with new evidence-based recommendations on other commonly used methods of contraception.

### Low Dose Combined Oral Contraceptives (COCs)

Low-dose COCs containing 20-35 micrograms of ethinylestradiol in combination with a progestogen have generally replaced older COCs containing 50 micrograms estrogen or more. Low-dose COCs are preferred because of a lower risk of venous thromboembolism (VTE). The progestogens used in COCs may be any of the following [3] (Table 1).

Drospirenone (a derivative of spironolactone) has been more recently developed. It has anti-androgenic properties and anti-mineralocorticoid activity (unlike most other progestogens). Yasmin® (ethinylestradiol 30 micrograms/drospirenone 3 mg) is the most recent COC to be licensed in the UK. Drospirenone combines anti-androgenic properties, and unlike other progestogens, it also has mild anti-mineralocorticoid activity - giving it a pharmacological profile similar to progesterone. Serum potassium levels should be monitored when women use this OC in conjunction with other drugs that increase serum potassium levels,

**Table 1.** Progestogens used in COCs

Pregnanes	Estranes	Gonanes 2 <sup>nd</sup> Generation	Gonanes 3 <sup>rd</sup> Gener:
Chlormadinone acetate	Norethindrone acetate	dl-Norgestrel	Desogestrel
Cyproterone acetate	Ethinodiol diacetate	Levonorgestrel	Gestodene
Nomegestrol.	Lynestrenol		Norgestimate *
Nestorone	Norethynodrel		

Norgestimate \* is sometimes considered 2<sup>nd</sup> generation as it is metabolized to levonorgestrel.

because hyperkalemia is a potential side-effect.

The U.S. Food and Drug administration (FDA) recently approved levonorgestrel – ethinylestradiol (Seasonale<sup>®</sup>) in an extended OC regimen of 84 days of active pills and 7 days of non-hormonal pills [4].

A recent Cochrane Review [5] that studied the different progestogens in low dose COCs found less discontinuation with second compared to first generation progestogen containing COCs. Cycle control was better with second compared to first generation progestogen containing COCs. Contraceptive efficacy, spotting, breakthrough bleeding and amenorrhea were similar for gestodene and levonorgestrel containing COCs, although there was less intermenstrual bleeding in the gestodene group (RR: 0.71; 95%CI: 0.55, 0.91). Drospirenone was similar compared to desogestrel regarding contraceptive efficacy, cycle control and minor side-effects.

A suitable first choice option is a monophasic COC containing 30-35 micrograms of ethinylestradiol with a low dose of either norethisterone or levonorgestrel [6]. Preparations containing desogestrel and gestodene may be less preferred as first-line options, as they are associated with a slightly increased risk of VTE compared with those containing levonorgestrel and norethisterone. Formulations containing 20 micrograms of estrogen offer limited advantages over preparations containing 30-35 micrograms of estrogen, and some women may experience breakthrough bleeding more frequently. At present there are insufficient data to assess the risk of VTE with Yasmin<sup>®</sup> use compared with second- and third-generation COCs. The incidence of VTE in women taking Dianette<sup>®</sup> (cyproterone acetate/ethinylestradiol) has been found to be at least twice as high as that in women using second-generation COCs.

### Non Daily Hormonal Contraception

Despite the efficacy of COCs, missed quite common and contribute to an unintended pregnancy. Many women in all population categories would benefit from the convenience and reliability of non-daily hormonal contraceptives. Patient and clinicians have many non-daily hormonal contraceptive options available from Depot quarterly injection to several new entries including Mirena 5-year intrauterine system, Lunelle<sup>®</sup> injection, NuvaRing monthly intravaginal ring and the Ortho Evra weekly transdermal patch.

### Combined Injectable Contraceptives (CICs)

Because the estrogen in CICs may be more physiologic and less potent compared to the synthetic estrogens of COCs, the type and magnitude of estrogen related side-effects associated with CICs may be different from those experienced by users [7]. In fact short-term studies of CICs have shown little effect on blood pressure, hemostasis and coagulation, lipid profile and liver function in comparison with COCs. In addition, the parenteral administration of CICs eliminates the first pass effect of the hormones on the liver. However, CICs are a relatively new contraceptive method and there is little epidemiological data on their long-term use. There is also the concern that while the hormonal exposure associated with OC pills can be reversed by discontinuing their use, this is not the case with CICs, whose effect persists for some time after the last injection. Therefore the World Health Organization (WHO) working group on medical eligibility criteria for contraception has stated that the evidence available for COCs applies to CICs most if not all categories [7].

Lunelle<sup>™</sup> monthly CIC, is available as a 0.025 mg aqueous suspension of medroxyprogesterone and 0.02 mg estradiol.

for Lunelle advises that repeat injections be given 28–30 days after the previous injection, without exceeding 33 days. The first injection should be given during the first 5 days of a normal period. Return to ovulation is faster as compared to DMPA.

### **Combined Contraceptive Patch (P)**

The combined contraceptive weekly patch uses a square 20 cm<sup>2</sup>, three-layer system applied to the buttocks, torso, abdomen or upper arm to release ethinylestradiol and a progestogen norelgestromin, (17 deacetyl norgestimate) transdermally. The contraceptive effect of the patch is achieved primarily through ovulation inhibition. The patch currently available for consideration is Ortho Evra. It contains 6.00 mg of norelgestromin and 0.75 mg of ethinylestradiol and releases 150 micrograms of norelgestromin and 20 micrograms of ethinylestradiol into the blood stream in 24 hours. The patch was approved for use by the U. S. FDA in 2002.

The patch is a new contraceptive method. Relatively limited information is available on its safety among healthy women and even less information is available for women with specific medical conditions. However, available evidence provides a comparable safety and pharmacological profile to COCs with similar hormonal formulations [6, 7]. A new patch is applied every week for 3 weeks. Ideally, the first patch is applied on the first day of the menstrual cycle (day 1); no additional contraception is needed if started on the first day of bleeding. Otherwise, a non-hormonal contraceptive method must be used concurrently for the first 7 days of the new cycle.

- After 7 days the patch is removed (at any time of the day), and immediately replaced with a new one. These change days will be days 8 and 15 of the cycle. The fourth week is patch-free, starting on day 22, during which a period should occur.
- A new cycle starts after 7 patch-free days, whether bleeding has stopped or not even started.
- Transient breast discomfort and skin site reactions have been reported in less than 25% of users [8]. The effectiveness of the patch may decline for women weighing 90kg or more.
- After abortion or miscarriage: If either occurs before 20 weeks' gestation, the patch may be started immediately. No back-up contraceptive is needed if the patch is started immediately. If

patch may be started either on day 21 post-abortion, or on the first day of the first spontaneous period, whichever comes first.

- After delivery: Users who choose not to breastfeed should start contraceptive therapy with the patch no sooner than 4 weeks after childbirth.
- When used correctly, it can be over 99% effective.

### **Combined Vaginal Ring (R)**

The combined contraceptive vaginal ring releases ethinylestradiol and a progestogen (etonogestrel) from a 54 mm ethinylvinyl acetate copolymer ring. Its contraceptive effect is achieved through ovulation inhibition. The vaginal ring formulation currently available for use is NuvaRing and it contains 2.7mg of ethinyl estradiol and 11.7 mg of etonogestrel, releasing on average 0.120 mg of etonogestrel and 0.015 mg of ethinyl estradiol per day over a 3-week period of use. Evidence among healthy women shows that it does not alter vaginal flora and limited evidence on women with low-grade squamous intraepithelial lesions of cervix found that use of the ring did not worsen the condition [9]. To date no studies have examined whether the avoidance of first pass effect of hormones on the liver lessens concerns about drug interactions or use of the ring among women with liver conditions. In the meantime, the prescribing recommendations are the same as for COCs [7].

### **Progestogen Only Contraceptives**

Progestogen only contraceptives include the progestogen-only pill (POP), depot medroxy progesterone acetate (DMPA, 150 mg) and norethisterone enanthate (NET-EN, 200 mg) injectables and the levonorgestrel (Norplant and Jadelle) and etonogestrel (Implanon) implants [6, 7].

**Progestogen-only pills (POPs)** are an alternative for women who want oral contraception, but who do not choose to use estrogen or where estrogen is contraindicated (e.g. women who are breastfeeding, smokers over the age of 35 years, and women with migraine with aura). First line POPs are those containing either ethynodiol diacetate 500 micrograms (Femulen) or levonorgestrel 30 micrograms (Microval, Norgeston) or norethisterone 350 micrograms (Noriday).

**Cerazette**<sup>®</sup> (desogestrel 75 micrograms) is included as a second-line POP option, as it is a black-

Committee on Safety of Medicines, UK) and there is no evidence to support its use as a first-line agent [6]. Bleeding patterns are unlikely to be any better with Cerazette® compared with other POPs, and it is notably more expensive. Cerazette® may have a role in carefully selected women. The user takes one tablet everyday without interruption.

**Implanon®** is a single-rod contraceptive implant that is inserted under the skin of the upper arm and it consists of a non-biodegradable rod measuring 40 mm in length and 2 mm in diameter. The rod slowly releases a progestogenic hormone, etonogestrel (68mg) at the rate of 40 micrograms per day for 3 years. This is the active metabolite of desogestrel, one of the components of many modern oral contraceptive pills. Like other progestogen-only contraceptives, the use of Implanon is associated with irregular menstrual bleeding and sometimes absence of bleeding, and counseling is required to ensure women make informed choices. Progestogen implants may be inserted within 5 days of the menstrual cycle or 21 days after delivery or second trimester abortion or immediately after a first trimester abortion [6]. The contraceptive effects reverse rapidly on removal of the implant, and there is a rapid return of the normal menstrual cycle.

#### Emergency Contraception

Currently, several interventions (IUD, the Yuzpe regimen, levonorgestrel, mifepristone, danazol and some combination regimens) are available for emergency contraception. A Cochrane Review [10]. Involving 48 trials with 33,110 women has stated that levonorgestrel is more effective than the Yuzpe regimen in preventing pregnancy. Single dose (1.5mg) administration seems to have similar effectiveness as the standard 12 hours apart dose, split-dose (0.75mg) of levonorgestrel. Levonorgestrel has similar effectiveness to low-dose ( $\leq 10$  mg) or mid-dose (25-50 mg) mifepristone. Delay in the onset of subsequent menses is the main unwanted effect of mifepristone and seems to be dose-related. The Yuzpe regimen can be used when levonorgestrel and mifepristone are not available. Half-dose Yuzpe with single administration is associated with fewer side-effects but it is not clear whether it is as effective as the standard Yuzpe regimen (RR 1.41; 95% CI: 0.76 to 2.61). The intrauterine device (IUD) is another effective emergency contraceptive when ongoing contraception is desired.

#### Intrauterine Devices And System

- Intra-uterine devices (IUDs) are particularly suitable for women who want effective long-term contraception, provided that they are at low risk of STI and do not have menorrhagia. Devices with a large surface area of copper (greater than 300 mm<sup>2</sup>) are more effective and are recommended [6]. The levonorgestrel-releasing intra-uterine system (LNG-IUS 20 mcg /24 h) is suitable for women who require effective long-term contraception, and particularly for those who have menorrhagia. It is also licensed to help prevent endometrial hyperplasia in women taking estrogen replacement therapy. It is effective for up to 5 years. Ideally the IUS should be fitted within the first 7 days of a period, and is then effective immediately. If fitted after this, any risk of pregnancy since the last period should be excluded, and an additional method of contraception should be used for 7 days.
- IUDs do not protect against (STIs) or Human Immunodeficiency Virus (HIV) infection. If a risk of STI or HIV is suspected the correct use of condoms (with or without other contraceptive method) is recommended.

#### Barrier Contraceptives And Spermicides

Newer barrier methods consist of the male latex (polyurethane) condoms and the female condoms.

#### Female Condom

- Currently Femidom is the only female condom available. Femidom is designed to line the vagina. It is made of soft, pliable polyurethane and is lubricated with dimethicone - an odourless, non-spermicidal lubricant. It is 7.8 cm in diameter and 17 cm long with two (labial and apical) flexible rings. It is available in only one size, and does not require fitting by a health professional. The device requires careful fitting in the vagina to be effective as it can be pushed into the vagina, or the penis can be inserted between the vaginal wall and Femidom. It has a shelf life of up to 5 years. Femidom has a failure rate of 5-21% [11].

#### Male Non-Latex Condoms

A recent Cochrane Review [12] has compared



(Avanti, Trojan Supra, eZ.on) with latex condoms in terms of efficacy, breakage, slippage, safety, and user preference.

- Latex condoms were found to be consistently highly effective at protecting against pregnancy, whereas non-latex condoms varied more from brand to brand, although efficacy was still within the expected range for barrier methods.
- Latex condoms had lower rates of clinical breakage and slippage.
- In almost all the comparisons, substantial proportions of participants preferred the non-latex condom for greater sensitivity as they transmit body heat better. Unlike latex condoms they are compatible with oil-based lubricants. They cost twice as much as latex condoms.
- Non-latex condoms still provide an acceptable alternative for those with allergies, sensitivities, or preferences that might prevent the consistent use of latex condoms.

Tactylon condoms, made from plastic material used in non-allergenic examination gloves were recently approved by the U.S. FDA [13]. Breakage rate is 3 to 5 times higher than for latex condoms. Only latex condoms are proven to protect against STIs/HIV. Nonoxynol -9 (N-9) the most commonly used spermicidal agent should not be

used to protect against HIV/STIs. Frequent use of N-9 products may cause epithelial damage and increase risk of infection.

### Contraceptive Counselling: How to Choose the Correct Contraceptive?

When counseling a patient for contraception, the physician should realize that the best contraceptive for the patient is the one she is willing to use reliably and correctly. The physician's role is to educate the patient about the advantages and disadvantages of each contraceptive method that is medically appropriate for that patient and then allow the patient to choose the method most desirable for her. The WHO has established medical eligibility criteria for contraceptive use [7]. Medical eligibility criteria address contraceptive use by people with specific medical needs. The guideline not only as a key intervention for improving the health of women, men and children, but also as also tabulates the choice of contraceptive by category of eligibility.

Reproductive and sexual health care including family planning services and information is recognized a human right. The development of international norms for medical eligibility criteria and practice recommendations has ensured quality of care in dispensing of contraceptives

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