Contemporary Oral Hormonal Contraception

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*"There's no such thing as **the Car** or **the Shoe** or **the Laundry Soap**. But everyone knows the Pill whose FDA approval 50 years ago rearranged the furniture of human relations in ways that we've argued about ever since."* - Time International

Since 1960s birth control pills have revolutionized women's lives, sexual behavior and society. The pill has empowered women to make the choice and exert control over when, or if they wanted, to have children. Of course over these decades the pill has evolved over four generations into a safer, more versatile, convenient, lower dose, multi formulation avatar.

The **early formulations** had high doses and long half lives ensuring continued suppression of LH and FSH during hormone free interval. The scientific rationale that justified 7 days of break or placebo pills, allowed virtually every woman enough time to start withdrawal bleeding before next pack was introduced at introduction. The adverse effects included headaches, breakthrough bleeding, bloating and swelling, nausea, breast tenderness and fluid retention, chloasma and mood changes and these continue to be the prime concerns of women advised COCs even today.

The **newer formulations** have lowered the dose of ethinyl estradiol to less than 50 μg per day then going down to 30 ug and finally 20 μg and simulltaneously introduced a range of options for the progestogen. Besides these conventional combined preparations the desogestrel progestogen only pill for estrogen free contraception and the levonorgestrel pill for emergency contraception have added facets and extended oral hormonal contraception into new indications. The pharmacological options and dosage combinations these newer formulations now offer the possibility of tailor made choices for contraception as also treatment of a variety of conditions.

An overview of the newer formulations widely available in clinical practice is presented in Table 1.

Combined oral hormonal contraception

Estrogen component

It is worthwhile to note that the estrogen component is universally ethinyl estradiol albeit in different doses while the variable component of the pill is the progestin compound. Combined hormonal pills are safe and suitable for nearly all women and that includes women who are nulliparous or multiparous, sexually active or not and at ages ranging from adolescence to perimenopause with a long list of non contraceptive applications, just after an spontaneous or induced abortion and even those with anemia, moderate smokers or having varicose veins.

The primary effect, as also the main contraindications for the pill are related to the estrogen component. Contraindications for the use of combined oral contraception are primarily due to the

Table 1

Newer oral hormonal contraception

	Estrogen	Progestin	Dosage schedule
Monophasic preparations			
Second generation			
Low dose	EE 30 ug	LNG 0.15 mg	21 active with 7 pill free
Ultra low dose	EE 20 ug	LNG 0.10 mg	21 active with 7 pill free
Third generation			
Low dose	EE 30 ug	DSG 0.15 mg	21 active with 7 pill free
Ultra low dose	EE 20 ug	DSG 0.15 mg	21 active with 7 pill free
Fourth generation			
Low dos	EE 30 ug	DRSP 3 mg	21 active with 7 pill free
Ultra low dose	EE 20 ug	DRSP 3 mg	24 active with 4 pill free
Antiandrogenic preparation			
Low dose	EE 35 ug	CYP 2 mg	21 active with 7 pill free
Extended cycle preparation			
Low dose	EE 30 ug	LNG 0.15 mg	84 active with 7 pill free
Triphasic preparation			
Low dose	EE 30/40/30 ug	LNG 0.05/0.075/0.125 mg	21 active with 7 pill free
Progestogen only oral hormonal contraception			
Minipill	–	LNG 0.30 ug	Continuous
Estrogen free pill	–	DSG 0.75 ug	Continuous
Emergency hormonal contraception			
Yuzpe regime	EE 100 ug	LNG 0.5 mg	Repeated after 12 hrs
Levonorgestrel	--	LNG 1.5 mg	Single or divided dose
Mifepristone	--	MFP 10 - 200 mg	

EE Ethinyl estradiol; LNG Levonorgestrel; DSG Desogestrel; DRSP Drospirenone; CYP Cyproterone acetate; NE Norethindrone; MFP Mifepristone

Table 2

Comparative actions of various progestins

Progestin content	Antiestrogenic	Androgenic	Antiandrogenic	Other Activity
Second generation				
Levonorgestrel	++	+	-	--
Third generation				
Desogestrel	++	+	–	--
Fourth generation				
Drospirenone	+	–	+	Antimineralocorticoid
Antiandrogenic preparation				
Cyproterone acetate	+	–	++	Glucocorticoid

+ distinct effect; – no effect; ++ stronger effect.

estrogen content and are limited - lactation for up to 6 months postpartum, elderly smoker, uncontrolled hypertension, diabetes for more than 20 years with end organ damage, gall bladder disease, ischemic heart disease, thromboembolism or ischemic heart disease, breast cancer, migraine with aura and major surgery with immobilization. and Every effort should be made to use the lowest required quantity of ethinyl estradiol.

Progestin component

The rationale for choosing the progestin component is based on the pharmacologic actions and potency of the different agents as shown in Table 2.

Side effects due to progestin component are mainly the androgenic effects, mood changes and water retention related bloating, weight gain and PMS symptoms.

Selection of formulations

Levonorgestrel is more potent than first generation progestins, chemically derived from testosterone with a low degree of androgenic activity. Highly effective for contraceptive purposes and for cycle regulation and are given as 21 active pills with either 7 inert pills or 7 pill free days.

Second generation progestins continue to be used for cycle control and dysfunctional uterine bleeding with a higher safety margin in women at risk of venous thrombeembolism.

Desogestrel is more selective than levonorgestrel and demonstrates high progestational activity and low androgenic activity. This gives better cycle regulation with fewer side effects. Dosing schedule is 21 active pills with 7 pill free days.

Third generation progestins are favored for cycle control and dysfunctional uterine bleeding with a more favorable metabolic profile and with a higher safety margin in women at risk of arterial disease.

Drospirenone introduced in 2001 is structurally related to spironolactone and exhibits progestogenic, antimineralocorticoid and antiandrogenic effects. It has some diuretic action and thus helps weight loss and relieves progestin side effects due to water retention. Dosing schedule is 21 active pills containing 30ug EE with 3 mg drospirenone, with 7 pill free days.

With a further reduction for the estrogen content, a new dosing schedule with 24 days active pills with 20 ug EE and 3 mg drospirenone with 4 pill free days has been approved. This improves bleeding profile and decreases the incidence of ovulation and pregnancy that may occur if there is delay in starting the active pills in next cycle. These pills are particularly beneficial in patients with PCOS without androgenic manifestations like acne, hirsutism with no reported adverse effect on the weight of patients. Also currently they are the only OC pills approved by FDA for Premenstrual syndrome. However contraceptive pills containing drospirenone have a higher risk of thromboembolism compared to women who do not take any contraceptive pill and a marginally higher risk than the contraceptive pill containing levonorgestrel.

The game changer 24/4 regimen is the first major change in dosage schedules since the introduction of COCs. A pill use of 24 days with 4 pill free days has shorter pill free days with decreased withdrawal adverse effects (7%) and constant ovarian suppression with better inhibition. A recruitment of follicles during shortened interval is suppressed increasing contraceptive safety.

Fourth generation progestins are favored for the least disruption they cause due to avoidance of fluid retention and PMS like symptoms. Besides specific approval they have been granted for the treatment of the premenstrual syndrome, they also have a favorable antiandrogenic profile making them an option to the antiandrogen containing preparations.

Cyproterone acetate is a progesterone derivative that acts as an androgen receptor antagonist with weak progestational and glucocorticoid action. Being antiandrogenic it is the drug of choice for patients of PCOS with androgenic side effects like acne and hirsutism. Higher doses can cause liver

toxicity and monitoring is needed. Contraceptive pills containing cyproterone acetate have a higher risk of developing thromboembolism compared to women who do not take any contraceptive pill and a marginally higher risk than the contraceptive pill containing levonorgestrel.

This antiandrogenic substitute for progestin gives the best cosmetic effect in the treatment of hyperandrogenism while also maintaining the contraceptive effect.

An extended regimen OC (Seasonale) was approved in 2003 by FDA as a product containing 30 ug of ethinylestradiol and 0.15 mg of levonorgestrel to be taken for 84 continuous days followed by 7 day pill free week. It thus reduces scheduled withdrawal bleeding episodes from 13 to 4 per year.

Progestogen oral hormonal contraception

Progestin only pills – labeled minipills or estrogen free pills exclusively contain a progestin dose and are to be taken continuously without a pill free interval.

The first POP used chlomadinone acetate 0.5 mg. Second generation POPs used 19-norsteroid derivatives norgestrel 0.075 mg, norethindrone 0.35 mg, lynesternol 0.5 mg, quingestanol 0.3 mg and levonorgestrel 30 ug. These traditional POPs had the drawback of significant irregular bleeding, increased risk of ectopic pregnancy and lower contraceptive efficacy.

The third generation of POPs has desogestrel (Cerazette, Organon; Zerogen, GSK), a selective progestogen with lower androgenic activity than traditional POPs. While doses as low as 30 ug were shown to inhibit ovulation, the 75 ug dose is preferred since it had the least follicular development with the most acceptable bleeding patterns.

In a comparison of desogestrel 75 ug and LNG 30 ug for 13 consecutive treatment cycles, DSG users had higher incidence of amenorrhoea and infrequent bleeding with tendency to bleed less with a Pearl Index 0.14 with DSG and 1.17 with LNG.

Suitable candidates for progestogen only pills are women for whom estrogen is contraindicated, those with multiple cardiovascular risk factors or migraine, lactating women and anticonvulsant therapy like valproate and benzodiazepines. The main disadvantage is the strict compliance needed for optimum effectiveness with a missed pill to be taken within 3 hours for levonorgestrel pills and within 12 hours for desogestrel containing pills. Besides this many women are disturbed by the abnormal and unpredictable bleeding pattern.

The introduction of desogestrel into progestogens only contraception and by its effectiveness in causing anovulation besides the cervical and endometrial effect has made this estrogen free preparation a true alternative to combined hormonal contraception.

Emergency hormonal contraception

Yuzpe's regime comprises of 4 tablets of a COC with ethinyl estradiol 30 ug or 2 tablets of a COC with ethinyl estradiol530 ug both with levonorgestrel 0.15 mg taken within 72 hours and repeated again after 12 hours. Preventing 74% of expected pregnancies it is most effective within 24 hrs. The regime was associated with significant gastrointestinal side effects limiting use.

Levonorgestrel use comprised 75 ug within 72 hours and repeated again after 12 hours. Preventing 85% of expected pregnancies a single dose of 1.5 mg has similar effectiveness.

Mifepristone a progesterone receptor antagonist has been used effectively for emergency contraception in doses ranging from just 10 mg to 200 mg. This has great promise for the future emergency contraception.

Ulipristil acetate is a selective progesterone receptor modulator (SPRM) is used for emergency contraception in a dose of 30 mg within 120 hours after an unprotected intercourse or contraceptive failure. Contraindications are severe liver disease. It is found to be embryotoxic in animals and

lactation has to be suspended for 36 hours after administration.

Most emergency contraception today uses a single dose of levonorgestrel. This and every other preparation for emergency contraception works better if taken at the earliest. Emergency contraception is safe and an excellent opportunity to introducing a more effective, regular and contemporary method.

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