

Consensus Statement

Consensus Statement on the Use of Oral Contraceptive Pills in Polycystic Ovarian Syndrome Women in India

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ABSTRACT

Objective: To provide consensus recommendations for health-care providers on the use of oral contraceptive pills (OCPs) in polycystic ovarian syndrome (PCOS) women in India.

Participants: Extensive deliberations, discussions, and brainstorming were done with different fraternities (specialists) being involved. These included endocrinologists, gynecologists, reproductive endocrinologists, dermatologists, public health experts, researchers, and a project manager with a team to develop the guideline.

Evidence: Published literature was retrieved through searches of Medline and The Cochrane Database from January 2003 to December 2017 using appropriate-controlled vocabulary (e.g., oral contraceptive pills, polycystic ovarian syndrome, long term outcomes, infertility). Clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies' publications and data were also reviewed to suggest the recommendations.

Quality of evidence

Quality of evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect. Several high-quality studies with consistent results In special cases: one large, high-quality multicentric trial
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. One high-quality study Several studies with some limitations
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One or more studies with severe limitations
Very Low	Any estimate of effect is very uncertain. Expert opinion No direct research evidence One or more studies with very severe limitations

Process: The working group for guideline committee included members from the PCOS Society (India), Indian Society for Assisted Reproduction, The Mumbai Obstetric and Gynecological Society, The Endocrine Society of India, Indian Association of Dermatologists, Venereologists and Leprologists, Cosmetic Dermatology Society (India), Academicians from Medical Colleges, National Institute for Research in Reproductive Health, and a Research Associate. The core team included five reproductive endocrinologists, five gynecologists, five dermatologists, three endocrinologists, two public health experts and one research associate.

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Grades of recommendation

Note: The grade of recommendation relates to the strength of evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	Evidence from meta-analysis of randomized controlled trials Evidence from at least one randomized controlled trial
B	Systematic review of (homogenous) cohort studies of 'exposed' and 'unexposed' subjects Individual cohort study/low-quality randomized controlled trials Systematic review of (homogenous) case-control studies Individual case-control studies
C	Case series, low-quality cohort, or case-control studies
D	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Good Practice Points (GPP)

✓	Recommended best practice based on the clinical experience of the guideline development group
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Conclusions: This consensus statement provides the guidance/recommendations for Indian practitioners regarding the use of OCP in women with PCOS. PCOS is one of the common endocrinopathies encountered in gynecological/endocrine practice. The spectrum of this disorder may range from prepubertal girls with premature pubarche, young girls with hirsutism, acne and anovulatory cycles, married women with infertility, and elderly women. Although obesity is a common feature for most PCOS patients, 'lean PCOS' also exists. For several years, OCPs have played an important role in the symptom management of PCOS women. This is due to the fact that OCPs decrease the luteinizing hormone, reduce androgen production, and increase sex hormone-binding globulin, which binds androgens. Several new formulations of OCPs have been developed to decrease the side effects. This includes use of less androgenic progestins and lower doses of ethinyl estradiol. These consensus recommendations help the health provider to choose the right type of OCPs, which will alleviate the symptoms with least side effects. It also gives insight into the indications, contraindications, and concerns regarding its short, intermediate and long-term use.

KEYWORDS: *Acne, anovulatory cycles, endometrial carcinoma, hirsutism, oral contraceptive pill, polycystic ovarian syndrome*

BACKGROUND

Oral contraceptive pills (OCPs) have been the first-line therapy for concurrent treatment of menstrual irregularity, acne, and hirsutism in women with polycystic ovarian syndrome (PCOS), thus playing an important role in the symptom management of the PCOS women. The Combined OCP (COCP) also improve dysmenorrhea and menorrhagia, treat premenstrual syndrome, prevent menstrual migraines, treat pelvic pain related to endometriosis, and decrease the risk of endometrial and ovarian cancer.

The association of PCOS with metabolic syndrome brings up the debate regarding the risks versus benefits of OCP use in PCOS women. Moreover, the presence of confounding factors such as obesity, smoking, diabetes, and other cardiometabolic comorbidities is a significant limitation in comparing the different OCPs as well as the risks and benefits associated with their use. With this in mind, the PCOS Society (India) had a consensus meeting with a multidisciplinary faculty on providing recommendations for the use of OCPs in PCOS women in India. These recommendations were provided keeping in mind the phenotype of Indian women, who tend to have a higher risk of metabolic syndrome and insulin resistance.

PCOS is associated with several comorbidities such as obesity, diabetes, metabolic syndrome, and mood

and anxiety disorders. Side effects of COCP such as weight gain, mood changes, and adverse effects on cardiometabolic risk factors may at times exacerbate the problems in PCOS women. Thus, before initiating treatment with OCPs, thorough counseling is essential and this should be backed up by stringent monitoring at every follow-up visit.

Prescribing information of OCPs in PCOS women should include the choice of cyclic versus continuous use and COCP with different types of progestins and pills with progestin only options.

Though weight reduction, exercise, and lifestyle modification are the first line of management with beneficial effects, especially in the obese PCOS women, COCP have been recommended to improve the clinical manifestations.

PHARMACOLOGY

There are two types of OCPs: combined pills (combined oral contraceptive [COCP]), containing an estrogen and a progestogen, and progestogen only pills. The COCP is a combination of two types of steroids; ethinyl estradiol (EE) as the main estrogenic component, with the dose varying from 20 to 50 µg per tablet (usually 30–35 micrograms), and progestins essentially derivatives of 19-nortestosterone (norethisterone,

levonorgestrel, and more recently desogestrel, gestodene, norgestimate, and drospirenone). Reduction in the dose of estradiol was possible due to the availability of progestins with high antigonadotropic activity. The metabolism of EE is similar to that of endogenous estradiol, i.e., it undergoes oxidation at various carbon atoms.^[1,2]

Contraceptive efficacy of COCP with 15 and 20 µg EE, measured by the Pearl index, is in the range of 0.07–0.88 and is therefore similar to that of COCP containing 30 µg EE (0.06–0.88).^[3]

Estradiol undergoes an intensive first-pass effect in the cytochrome P450 (CYP) 3A system of the liver, leading to the formation of its metabolites: estrone, estrone sulfate, and estrone glucuronide.^[4] Approximately 95% of the oral dose is metabolized before going into systemic circulation. The half-life of estradiol in plasma is ~2.5 h, whereas the terminal half-life is ~13–20 h and depends on enterohepatic circulation and on circulating levels of sulfate and glucuronide metabolites. On stopping treatment, estrogen concentrations return to basal levels within 2–3 days. Estradiol is mainly eliminated in the urine; ~10% is eliminated in feces.

MECHANISM OF ACTION OF ORAL CONTRACEPTIVE PILL

Mechanism for the action of OCPs is shown in Figure 1.

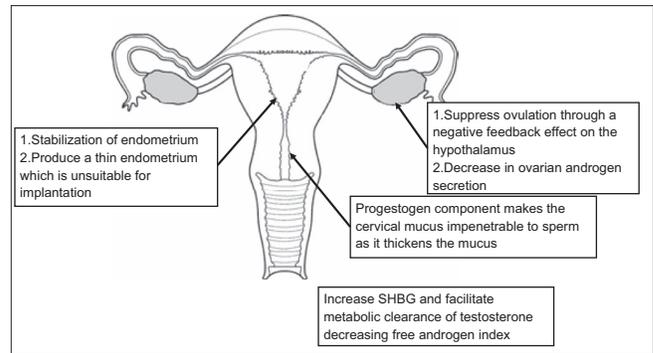


Figure 1: Mechanism of action of oral contraceptive pill

TYPES OF ORAL CONTRACEPTIVE PILL

OCPs contain potent, synthetic estrogen, EE, in combination with a progestin which may be derived from testosterone or those that are structurally unrelated to testosterone and function as androgen receptor antagonists (cyproterone acetate [CPA] and drospirenone). Low-dose OCPs contain EE (20–35 µg) along with low androgenic progestin, such as desogestrel or gestodene, or an antiandrogen, such as cyproterone acetate, chlormadinone acetate, or the spironolactone derivative drospirenone.

Originally, the manufactured combination OCP formulations were monophasic, with each active tablet containing a fixed dose of estrogen and progestin throughout the cycle. Multiphasic preparations (biphasic and triphasic) were developed in the 1980s to reduce the total dosage of progestin throughout the cycle without increasing the risk of breakthrough bleeding.

Different generations of OCPs^[5] are highlighted in Table 1.

Table 1: Different generation of oral contraceptive pills

Year	Progression	Estrogen component	Dose (mcg)	Progesterone component	Dose (mg)	Activity of progestins		
						Estrogen	Progesterone	Androgenic
1960-1963	First-generation oral contraceptives	Mestranol (ethinyl estradiol - 3 methyl ether)	75	Norethynodrel	5	++	++	++
			50	Norethisterone acetate/norethindrone	4			
1970s	Second-generation progestin	Emergency contraceptive pill	100	Norethindrone	2	-	++++	++++
			-	Norgestrel, Levonorgestrel				
1980s	Low estrogen doses	First Bi-phased and tri-phased pills	100	Norgestrel	1			
			-	Norethindrone	0.35			
			35	Norethindrone	1			
2000-2010	Regimens with reduced hormone-free interval, new progestins	Ethinyl estradiol	20-35	Norgestimate, gestodene, desogestrel	0.15	-	+++	++
			20	Levonorgestrel	0.1			
1989	Lower estrogen	Ethinyl estradiol	20	Levonorgestrel	0.1			
1997	Fourth-generation progestin	Ethinyl estradiol	30	Drospirenone	3	-	+/-	Antiandrogenic

Indications and contraindications for the use of oral contraceptive pills

Indications for the use of OCPs are enumerated in Table 2.

Table 2: Indications for the use of oral contraceptive pills in polycystic ovary syndrome and nonpolycystic ovary syndrome women

Non-PCOS women	PCOS women
Contraceptive	Contraceptive
Menstrual disturbances	Menstrual disturbances
Dysmenorrhea	Hirsutism
Premenstrual syndrome	Acne
Assisted reproductive technology	Assisted reproductive technology
Prevention of colorectal cancer	Prevention of endometrial cancer
Improved bone mineral density	-
Pain due to endometriosis	-

PCOS=Polycystic ovary syndrome

Contraindications for the use of OCPs are enumerated in Table 3.

Table 3: Contraindications for the use of oral contraceptive pills

Absolute contraindications	Relative contraindications
Thrombophlebitis or thromboembolic disorder	Age >45 years
Cerebrovascular or coronary artery disease	Diabetes
Carcinoma of the breast or other estrogen-dependent neoplasia	Hypertension
Undiagnosed abnormal genital bleeding	Smoking
Known or suspected pregnancy	Gallbladder disease
Benign or malignant liver tumors	History of gestational cholestasis
Cholestatic jaundice of pregnancy (or jaundice with previous OCP use)	History of renal disease
Hepatic neoplasia, abnormal liver function	Impaired liver function
Hypersensitivity to OCPs	Hyperlipidemia
Pregnancy	Varicose veins and superficial venous thrombosis
	History of migraine with focal aura
	Major surgery with prolonged immobilization

OCPs=Oral contraceptive pills

Summary of evidence

In women more than 40 years with PCOS, the use of OCPs outweighs the theoretical or proven risks. The use of OCPs results in protection against endometrial and ovarian cancers. One randomized controlled trial (RCT) ($n = 83$), one nonrandomized trial ($n = 84$), and 11 cohort studies ($n = 3242$) were evaluated by World Health Organization (WHO) in the 5th (2015) guidelines on 'Medical Eligibility Criteria for Contraceptive Use.' Only one study showed duration response effect and nine studies showed oral COCP use associated with less bone mineral density (BMD) gain (or greater loss) than nonuse.^[6-8] One study suggested that among

women using OCPs with varicose veins, the rate of venous thromboembolism (VTE) and superficial venous thrombosis (SVT) was higher as compared with nonusers but was not statistically significant and the number of events was small.^[9] One study demonstrated that among women with SVT, the risk of VTE was higher in oral contraceptive (OC) users compared with nonusers.^[10] One case-control study suggested an increased risk for myocardial infarction (MI)^[11] and one retrospective cohort study suggested an increased risk for stroke and VTE^[12] among COCP users with hypercholesterolemia compared to nonusers. One prospective cohort study suggested no worsening of lipid abnormalities among COCP users with dyslipidemia compared to nonusers with dyslipidemia.^[13]

Recommendations

Number	Recommendation	Grade	Quality
1.1.1	Women aged 40 years and older can generally use COCP but should follow up on a regular basis for CV risk, dyslipidemia, and thromboembolism	B	Low
1.1.2	COCP use may decrease BMD in adolescents, especially in those choosing very low-dose formulations (<30 µg EE containing COCP). COCP use has little-to-no effect on BMD in premenopausal women and may preserve bone mass in those who are perimenopausal	B	Low
1.1.3	Women with varicose veins can use COCP without restriction	C	Very Low
	Women with SVT can generally use COCP but may be associated with an increased risk of VTE	D	Very Low
1.1.4	Women with known dyslipidemias without other known cardiovascular risk factors can generally use COCP. Routine screening for dyslipidemias is not required unless history of known severe genetic lipid disorders	B	Very Low

Drug interactions

Pharmacological interactions between OCPs and other compounds may be of two types: drugs may impair the effectiveness of the OCPs or OCPs may interfere with the metabolism of other compounds. Interactions of the first kind are due to interference with the absorption, metabolism, or excretion of estrogen, and interactions of the second kind are due to competition for metabolic pathway.

Summary of evidence

- Drugs may impair the efficacy of OCPs: Drugs such as anticonvulsants (phenobarbital, phenytoin, and carbamazepine) and rifampicin induce a cytochrome

P450, thereby increasing the clearance of the OCPs^[14-17]

Other antibiotics such as ampicillin, metronidazole, quinolones, and tetracycline, which reduce the bacterial flora of the gastrointestinal tract and increase enterohepatic recirculation, affect OC efficacy as a result of low bioavailability of EE^[18,19]

Ascorbic acid and paracetamol give rise to increased blood concentrations of EE due to competition for sulfation, which can increase the risk of its side effects^[20]

- b. OCPs may interfere with the metabolism of other drugs: OCPs reduce the clearance of benzodiazepines (chlordiazepoxide, alprazolam, diazepam) and nitrazepam.^[21] The concentration of theophylline, prednisolone, caffeine, and cyclosporine is also reduced in OCP users.^[22] Thus, lower doses of these drugs may be effective in OCPs users

The clearance of temazepam, salicylic acid, paracetamol, morphine, and clofibrac acid apparently is increased.^[23-25] OCPs users may require larger doses of these drugs. Serum concentration of some of the antiepileptic drug (AEDs) such as lamotrigine may vary during the cycle when OCPs are being used. Lamotrigine level decreases almost by 50% when on the pill resulting in poor seizure control. During 'pill-free' interval, the level may increase causing lamotrigine toxicities such as dizziness, double vision, and lack of coordination; therefore, the dose should be decreased during the pill-free period^[26]

- c. For women taking antiretroviral drugs that have significant pharmacokinetic interactions with hormonal contraceptives, an alternative or additional effective contraceptive method to prevent unintended pregnancy is recommended. Several ritonavir-boosted protease inhibitors (PIs/r), efavirenz (EFV), and elvitegravir/cobicistat (EVG/c) based regimens have drug interactions with COCP. These drugs decrease or increase the blood levels of EE, norethindrone, or norgestimate, which potentially decreases contraceptive efficacy or increases estrogen or progestin-related adverse effects (e.g., thromboembolism). EFV can decrease etonogestrel bioavailability and plasma progestin concentrations of COCP containing EE and norgestimate.^[27] Several PI/r and EVG/c decrease OC estradiol levels.^[28-31] Several pharmacokinetic studies have shown that etravirine, rilpivirine, and nevirapine use did not significantly affect estradiol or progestin levels in women with HIV using COCP.^[32-34]

Recommendations

Number	Recommendation	Grade	Quality
1.2.1	For woman on AEDs that may compromise the efficacy of OCPs, high-dose pills containing at least 50 mcg of EE should be prescribed	D	Low
1.2.2	Dose of lamotrigine may be doubled to maintain steady therapeutic levels, but its side effects can occur during pill-free interval, and the patient should remember to reduce the lamotrigine dosage during these days	B	Low
1.2.3	When on antibiotics, the OCPs user should use an additional method of contraception	D	Very Low
1.2.4	Lower doses of benzodiazepines (chlordiazepoxide, alprazolam, and diazepam) and nitrazepam theophylline, prednisolone, caffeine, and cyclosporine may be effective in OC users	D	Low
1.2.5	OCPs users may require larger doses of acetaminophen, aspirin temazepam, paracetamol, morphine, and clofibrac acid	D	Low
1.2.6	Those women on PIs/r should be advised to use the alternative methods of contraception	A	Low

Side effects

Summary of evidence

Side effects of oral contraceptives vary depending on the dose and type of hormone used in the OCPs. Side effects, in general, include breast tenderness, bloating, nausea, weight gain, migraine, insulin resistance, increased blood sugars, dyslipidemia, VTE, cardiovascular disease (CVD), vaginal spotting, and abnormal bleeding. Mild increase in blood pressure might occur with some newer OCPs formulations.^[35,36]

Specific types or dose of progestins, estrogens, or combinations of COCP cannot currently be recommended with inadequate evidence in adults and adolescents with PCOS, and the practice should follow general population guidelines.^[37] In smokers, the third-generation OCPs may have deleterious effects^[38] on and may increase the risk of VTE as compared to second-generation OCPs containing the androgenic progestin levonorgestrel.^[39,40] Women who are at risk of CVD, older age, presence of diabetes, hypertension, and dyslipidemias, who are obese, and who smoke should be counseled about the increased risk of CVD. We also know that PCOS itself is associated with increased incidence and risk of obesity, hyperlipidemia, and hypertension.^[37] As PCOS women are already at a higher risk of CVD, which can be exaggerated with the use of OCPs, close monitoring of

OCP users though recommended but, what constitutes close monitoring is not clear. Pharmacovigilance is the key in OCP users.

Figure 2 describes the side effects related to the dose and drug in the OCP.

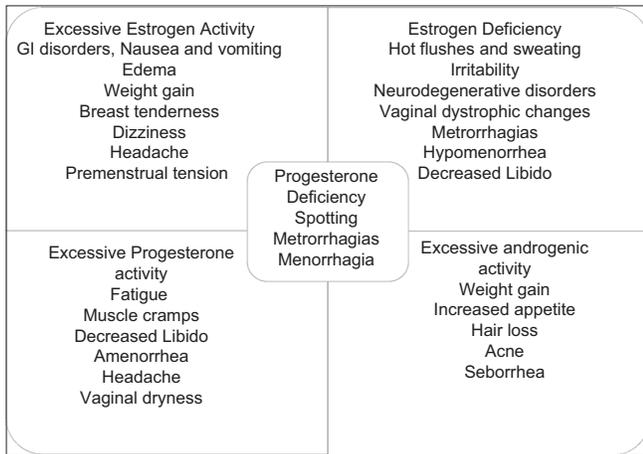


Figure 2: Side effects of oral contraceptive pills depending on dose and drug

Recommendations

Number	Recommendation	Grade	Quality
1.3.1	In PCOS women with insulin resistance, increased blood sugars, dyslipidemia, VTE, and CVD, OCPs should be used with caution and the right progestin chosen	B	Low
1.3.2	Specific types or dose of progestins, estrogens, or combinations of COCP cannot currently be recommended with inadequate evidence in adults and adolescents with PCOS, and the practice should follow general population guidelines	B	Low
1.3.3	Global CVD risk needs to be considered especially in women who are at risk of CVD, older age, presence of diabetes, hypertension, and dyslipidemias, those who are obese, and those who smoke before commencing the OCP	A	High
1.3.4	PCOS itself is associated with increased incidence and risk of obesity, dyslipidemia, and hypertension. Close monitoring of OCP users is recommended, but what constitutes close monitoring is not clear, and women should be made aware of the increased risk	C	Low
1.3.5	In smokers, the third-generation OCPs may have deleterious effects on coagulation and should be avoided	A	Moderate

COUNSELING

General counseling

Summary of evidence

To achieve maximum benefits and safety for each individual patient, for noncontraceptive use of COCP, detailed counseling regarding risks, benefits, and contraindications should be done. Counseling regarding the side effects such as weight gain, breakthrough bleeding, nausea, and breast tenderness is important. These women also need to be informed about the side effects such as decreased libido, melasma, and mood changes.^[41]

It is also important to discuss the interactions of OCPs with anticonvulsants, antibiotics, benzodiazepines, salicylic acid, paracetamol, morphine, and clofibrac acid. Women who want to start OCPs should also be counseled regarding the contraindications mentioned earlier.

Counseling is important when acne is treated with COCP as acne reduction may take a few months for the results to be evident, and therefore, combining COCP with other medications for early treatment of acne may be appropriate.

Recommendations

Number	Recommendation	Grade	Quality
2.1.1	Counseling regarding risks, benefits, and contraindications should be done in detail before starting OCPs	A	High
2.1.2	Important to discuss the interactions of OCPs with other drugs	A	High
2.1.3	Counseling regarding the period required for antiandrogenic action of OCPs to be evident is important	A	Low

Investigations before initiation

Summary of evidence

Clinical examination and laboratory tests after proper history taking are essential before the initiation of OCPs.

1. Medical history
 - Age
 - Past and present medical conditions
 - Any drug use
 - Migraine
 - CVD risk factors (smoking, obesity, hypertension, diabetes, dyslipidemia, and coronary artery disease)
 - Thrombophilia (any known disorder of thrombophilia, personal or family history of previous VTE)
 - History about usage of tobacco (oral, snuff, etc.)
 - History of smoking
2. Physical examination^[42]
 - Blood pressure measurement
 - Body mass index (BMI)

- Waist circumference
 - Pelvic examination
 - Breast examination
3. Laboratory tests in the presence of cardiometabolic risk^[37]
- A fasting glucose level or in the presence of overweight or other diabetes risk factors a 75-g 2-h standard oral glucose tolerance test (OGTT)
 - Lipid profile in overweight or obese PCOS.

Contrary to previous practice, pelvic examinations and Pap smears are not required before prescribing COCP medications according to recommendations by the WHO, the American Congress of Obstetricians and Gynecologists, and Planned Parenthood. This makes it more feasible for dermatologists also to prescribe COCP medications without gynecology consultation.^[43] Thrombophilia screen is not recommended routinely before prescribing an OCP unless there is a family history of VTE in a first-degree relative.

Recommendations

Number	Recommendation	Grade	Quality
2.2.1	Obtaining a thorough past medical/family history, calculating the BMI and measuring blood pressure, are important before prescribing a COCP	A	Moderate
2.2.2	Measuring blood sugar levels and OGTTs may not be recommended unless the women are overweight or have other diabetes risk factors Asian Indian race is high risk	A	Low
2.2.3	Evaluation of lipids should be done only in overweight women with PCOS, but it may not apply to Asian Indians	A	Low
2.2.4	Pelvic examinations and Pap smears are not required before prescribing COCP medications	B	Moderate
2.2.3	Thrombophilia screen is recommended only in the presence of family history of VTE in a first-degree relative	B	Low

Starting and stopping of therapy with oral contraceptive pills

Summary of evidence

OCPs are ideally started on any day between day 1 and 5 of the cycle, given for 21 days and stopped. This will be followed by withdrawal bleed. A new packet of pills is started counting the 1st day of withdrawal bleed as day 1. The patient should be called for follow-up after 3 months for the assessment of blood pressure and enquired for the presence of any other problems. Thereafter, annual visit is required for assessing side

effects, checking blood pressure, and evaluating glucose intolerance and lipids.

Since peak bone mass development occurs during adolescence and young adulthood, use of low-dose estrogen COCP early in the teen years may affect the bone mass,^[44] although some studies refute this observation.^[45,46] As definitive conclusions are not yet available, the use of COCP for acne should be avoided within 2 years of menarche or in patients who are <14 years of age unless it is clinically warranted. If the use of COCP is clinically warranted in the age group <14 years, it is preferable to use drospirenone and drospirenone/levomefolate, norgestimate, and norethindrone. During treatment, circulating androgen and sex hormone-binding globulin (SHBG) levels may be monitored to assess the adequacy of hormonal therapy, although clinical response will be the primary marker followed.

OCPs need to be stopped in the presence of any side effects or if abnormal glucose tolerance or dyslipidemia is detected.

Recommendations

Number	Recommendation	Grade	Quality
2.3.1	Proper patient selection is necessary to minimize risks associated with COCP use	A	High
2.3.2	In adolescent girls, it is best to wait for 2 years after menarche to prevent reduction in peak bone mass	C	Very Low
2.3.3	It is necessary to make women aware of increased risk of cardiometabolic disorders when on OCPs	B	Low
2.3.4	Regular follow-up for the assessment of side effects, abnormal GTT or lipids is necessary only in high-risk PCOS women. The data on Asian Indians may differ	C	Very Low
2.3.5	OCPs need to be stopped in the presence of any side effects or if abnormal glucose tolerance or dyslipidemia is detected	A	High

Long-term concerns

Summary of evidence

Three issues that need to be addressed include cardiovascular risks, thrombosis with risk of embolism, and cancer risks.

Cardiovascular thrombosis risk

Smoking, hypertension, and diabetes are the risk factors for CVS risks. Controlling these factors reduces the long-term risk of MI and stroke. Thus, counseling regarding these modifiable factors is very important. There is also an increased risk of deep vein thrombosis (DVT) in women using COCP. This risk is

3.4/10,000 to 9–10/10,000 woman-years at 1 year of COCP use as compared to 1/10,000 woman-years in those who do not use COCP.^[47] This risk increases in the presence of obesity, smoking, alcohol consumption, and positive family or personal history. Peragallo Urrutia *et al.* conducted a meta-analysis of 14 different studies, in which OCP users had three times increased odds for VTE compared with nonusers.

Initially, it was published that drospirenone-containing OCPs had an higher risk of DVT,^[48,49] but a recent large prospective trial has shown that the risk of thrombosis is not higher with drospirenone containing OCPs as compared with other OCP formulations.^[50] Obese women who use COCP are more likely to experience VTE than obese women who do not use COCP.^[51,52] Among women with very high BMI using COCP, evidence for weight gain when on COCP is inconsistent.^[53]

There is limited evidence and the results are inconsistent on the use of COCP among women with dyslipidemia and risk of cardiovascular outcomes. One study suggested an increased risk for MI among COCP users with hypercholesterolemia^[11] compared to nonusers without hypercholesterolemia, one study suggested an increased risk for VTE and for stroke among COCP users with dyslipidemia^[15] compared to COCP users without dyslipidemia, and another study suggested no worsening of lipid abnormalities among COCP users with dyslipidemia^[13] compared to nonusers with dyslipidemia. The presence of dyslipidemia may not be a contraindication for the use of OCPs. Women should be made aware of the fact that OCPs can change their lipid profile and therefore should be monitored based on metabolic risk profiles. No evidence of risk for pancreatitis was identified in OCP users.

Effect on bone mineral density

The evidence on fracture risk in COCP users is still inconsistent,^[54-65] although three recent studies show no effect.^[45,66,67] COCP use may decrease BMD in adolescents, especially in those choosing very low-dose formulations (COCP containing <30 µg EE containing COCP).^[67-80] It was also observed that COCP use has little-to-no effect on BMD in premenopausal women^[8,66,68-77,81-83] and may preserve bone mass in those who are perimenopausal.^[78-80,84-90] No impact of OCPs currently exists to caution their use with respect to bone health.

Visual disturbances

There is a cardiovascular background related to the expression of progesterone receptors in ocular tissues

for visual disturbances in women receiving COCP. The incidence of ocular complications is estimated to be 1 in 230,000, including dry eye symptoms, corneal edema, lens opacities, and retinal neuro-ophthalmologic or vascular complications.^[91]

Certain studies have reported an increased incidence of glaucoma in women over 40 years when OCPs were used for 3 years or more especially in those women who have additional risk factors for glaucoma.^[92] Both the physicians prescribing OCPs and the patients receiving them need to be made aware that there may be an concurrent risk of open-angle glaucoma. At present, there is no high-quality evidence for the occurrence of glaucoma in peri and post-menopausal women. These women should therefore be counseled and reassured that the studies do not show any causative effects, but women who have used oral contraceptives for 3 years or more and who have additional risk factors for glaucoma should be checked annually for the disease during their ophthalmic examinations. Thus, ocular pharmacovigilance may be needed only for long-term users or elderly or high eye risk cases.

Cancer risk

Slightly increased risk of breast cancer was reported in women who take COCP and is not related to PCOS women as such.^[93] The relative risk of breast cancer in the current COCP users was 1.24 (95% confidence interval [CI], 1.15–1.33), and this increased risk disappeared 10 years after discontinuation of COCP. There was also a higher risk of premature deaths due to breast cancer in the population who used COCP ($P < 0.0001$) for longer duration.^[94]

Earlier 24 observational studies showed a higher risk of cervical cancer in women who use COCP, especially with an increased duration of COCP use. This increased risk, once again, was not related just to PCOS women but in general to OCP use. This risk reduced after discontinuation of COCP and disappeared after 10 years of non use.^[95] Although a later published systematic review of nine pooled studies found no significant increase in the risk of cervical cancer among ever-users of COCP, it reported non significant increased risk of cervical cancer in women with >5 years of COCP use as compared to never users.^[96]

The use of COCP is associated with reduced risk of occurrence of endometrial and ovarian cancer.^[94,97] A 2008 meta-analysis of 45 different studies reported a significant correlation between duration of COCP use and reduction in risk of ovarian cancer ($P < 0.0001$).

Thus, healthcare professionals should be aware of impacts of the OCP on CVD, BMD (in adolescents),

venous thrombosis risk, hypertension, lipid profile, and breast (during or within 10 years of use) and liver cancer. Pharmacovigilance is the key and awareness should not impede therapy in genuinely indicated cases, especially for short duration. Often detailed history taking is needed.

Recommendations

Number	Recommendation	Grade	Quality
2.4.1	Smoking, hypertension, and diabetes are risk factors for CV risk. Controlling these factors reduces the long-term risk of MI and stroke	B	Low
2.4.2	Increased risk DVT in women using COCP warrants that DVT should be ruled out in all women on COCP who complain of edema feet or leg pain	B	Low
2.4.3	Obese women who use COCP are more likely to experience VTE than obese nonusers. COCP should be used with caution in obese PCOS	B	Low
2.4.4	Increased risk for MI among COCP users with hypercholesterolemia compared to nonusers. Use COCP with caution	C	Very Low
2.4.5	Mild dyslipidemia is not a contraindication to use OCP, but the women should be made aware of the fact that OCPs can change lipid profile and therefore should be monitored based on metabolic risk profiles	B	Low
2.4.6	Increased risk for VTE and stroke among COCP users with dyslipidemia compared to COCP users without dyslipidemia. Use COCP with caution	B	Low
2.4.7	Slightly increased risk of breast cancer was reported in women who take COCP. This requires stringent follow-up	B	Low
2.4.8	Higher risk of cervical cancer reported in women who use COCP, especially with an increased duration of COCP use. Therefore, it may be better to restrict the use of COCP to shorter duration	B	Low
2.4.9	Health-care professionals should be aware of impacts of the OCP on CVD, BMD (in adolescents), venous thrombosis risk, hypertension, lipid profile, and endometrial, breast (during or within 10 years of use), and liver cancer	A	Moderate

Follow-up on oral contraceptive pill therapy

Summary of evidence

No evidence exists whether a routine follow-up visit after initiating COCP improves correct or continued use and prevents side effects and/or long-term complications. After initiation of OCPs, it is best to

review after 3 months. Monitoring blood pressure and BMI is important for women using COCP.

A systematic review identified five studies that examined the incidence of hypertension among women who began using a COCP versus those who started a non hormonal method of contraception or a placebo.^[98] Few women developed hypertension after initiating COCP, and studies examining increase in blood pressure after COCP initiation found mixed results. At follow-up visit, it is important to ask for history of any side effects, breakthrough bleeding, and initiation of new medication.

Specific populations who might benefit from more frequent follow-up visits include adolescents and those with certain medical conditions.

Recommendations

Number	Recommendation	Grade	Quality
2.5.1	No evidence exists whether a routine follow-up after initiating COCP is essential. It is best to schedule a visit for the assessment of blood pressure and any other problems after 3 months or earlier if required	GPP	Low
2.5.2	Specific populations who might benefit from more frequent follow-up visits include adolescents and those with certain medical conditions	A	Low
2.5.3	Monitoring blood pressure and BMI is important for women using COCP combined	A	Moderate

GPP: Good practice points

CHOICE OF ORAL CONTRACEPTIVE PILL FOR NONCONTRACEPTIVE INDICATIONS

For acne

Summary of evidence

PCOS is associated with elevated androgen levels of ovarian origin. Use of COCP is a safe and effective option for women who suffer from acne. The antiandrogen effect of COCP is through the actions of estrogen, by stimulating the hepatic synthesis of SHBG, which binds androgens and decreases levels of free testosterone, with dehydroepiandrosterone sulfate. Estrogen also inhibits 5-alpha reductase, which prevents the conversion of testosterone to the more potent dihydrotestosterone. Estrogen through its negative feedback action on pituitary reduces luteinizing hormone (LH), consequently reducing the synthesis of ovarian and adrenal androgen.^[99] Progestins may also contribute to the antiandrogenic properties of COCP by the reduction of gonadotropin-releasing hormone (GnRH) pulsatility and consequently LH production.^[100]

COCP with third-generation progestins (e.g., norgestimate or desogestrel) or later generations (e.g., fourth or fifth-generation progestin-containing

OCP formulations) are preferred because they have a lower androgenic activity as compared to first and second-generation COCP. Currently, four COCP are approved by the Food and Drug Administration (FDA) for the treatment of acne. They are EE/norgestimate, EE/norethindrone acetate/ferrous fumarate, EE/drospirenone, and EE/drospirenone/levomefolate.^[31]

Several RCTs have assessed the efficacy of COCP in the management of acne.^[101-110] A 2012 Cochrane meta-analysis assessed the effect of OCPs on acne in women and included 31 trials with a total of 12,579 women. Nine trials compared a COCP to placebo and the former reduced acne in almost all women. The progestins included in these nine trials were levonorgestrel, norethindrone acetate, norgestimate, drospirenone, dienogest, cyproterone acetate or chlormadinone acetate. Seventeen trials compared two different combinations of COCP but found no statistical difference between the two. Only one small study compared a COCP to an oral antibiotic, which found no significant difference.^[100] A nonsystematic narrative review based on a literature search of the PubMed database showed high efficacy of CPA 2 mg/EE 35 µg in the treatment of severe acne and hirsutism.^[111]

An Indian study by Bhattacharya *et al.* in the Indian population concluded that combination of EE and drospirenone (DRSP) is a good alternative to combination of EE and cyproterone acetate and has similar efficacy without affecting the insulin resistance.^[112]

Recommendations

Number	Recommendation	Grade	Quality
3.1.1	Estrogen-containing COCP are effective and recommended in the treatment of inflammatory acne in females	A	High
3.1.2	Both EE/DRSP and EE/cyproterone acetate combinations improve hyperandrogenic parameters significantly without affecting the insulin resistance adversely in Indian women with PCOS.	A	High

For hirsutism

Summary of evidence

Hirsutism is a clinical sign and is not a disease by itself. Its presence does not necessarily require treatment. However, as hirsutism can have great effect on the psychological well-being of women, treatment becomes necessary. Apart from plucking, shaving, waxing, electrolysis, and laser, OCPs are the first-line treatment for hirsutism, particularly in those women desiring contraception. Antiandrogens can be used for the treatment of hirsutism, but this can be associated with irregular uterine bleeding. When antiandrogens are combined with EE it not only regularizes the menstrual cycle but also provides

endometrial protection and improves hirsutism and/or acne by reducing the production of ovarian androgens.^[113,114]

Estrogen/progesterone combinations act by:

- Reducing gonadotropin secretion and thereby reducing ovarian androgen production^[115]
- Increasing levels of SHBG resulting in lower levels of free testosterone^[116]
- Inhibiting adrenal androgen production.^[116]

Cyproterone acetate (CPA) has strong progestogenic and antiandrogenic properties and decreases circulating testosterone and androstenedione levels through a reduction in circulating LH and has been used as an effective treatment for hirsutism.^[117] CPA is available in combination with EE (2 mg CPA and 35 µg EE/tablet).

Medical treatment for hirsutism is never curative and therefore should be administered for long term. The PCOS adolescent and women must be counseled that the effect of medical treatment is evident only after several months and therefore requires monitoring by an expert while on treatment.^[118,119] When OCPs and placebos were compared in two RCTs, OCPs showed a definite benefit with reduction in the hirsutism scores, although the evidence supporting this recommendation is of very low quality.^[120,121] When COCP containing low-dose antiandrogen (CPA 2 mg) were compared with finasteride an antiandrogen, both had similar effects on the hirsutism score at the end of 9 months.^[122]

Spirolactone 100 mg was more effective than COCP containing cyproterone acetate (2 mg/day) in combination with EE (35 µg/day). Moreover, cyproterone acetate may be associated with adrenal insufficiency and loss of libido.^[117]

The use of OCPs containing recent generation low androgenicity progestins such as desogestrel and gestodene and androgen receptor antagonists such as CPA and drospirenone (DSP) may confer a 50%–100% increased risk of VTE compared with OCs containing the second-generation progestin levonorgestrel. It is also the best to use the lowest effective dose of EE (20 µg/day) to reduce the complications. However, one must remember that PCOS itself may represent an additional independent risk factor for VTE.^[123,124]

Most general population guidelines do not recommend the use of OCPs with EE and cyproterone acetate (CPA) as the first-line treatment in adults and adolescents with PCOS. However, in the Indian context, OCPs containing an antiandrogen, such as cyproterone acetate,

or the spironolactone derivative drospirenone rather than COCP containing other progestins may be used for the treatment of hirsutism.^[125]

The use of OCPs results in a subjective improvement of symptoms in about 60%–100% of PCOS women.^[126] An Indian study by Bobde *et al.* compared COCP containing EE 20 µg + drospirenone 3 mg with a combination of COCP with metformin and metformin alone. They found maximum improvement in hirsutism in the combination group followed by OCPs and least in the metformin group. Since the sample size was very small, the quality of evidence is of very low quality.^[127] This was also demonstrated in two other publications.^[128,129]

Recommendations

Number	Recommendation	Grade	Quality
3.2.1	OCPs may be prescribed in adolescents with hirsutism accompanied by menstrual irregularities	B	Low
3.2.2	For most women, one OCP over another as initial therapy is not suggested. All OCPs appear to be equally effective for hirsutism, and the risk of side effects is low	B	Low
3.2.3	The progestins to be preferred in these patients are the antiandrogen progestins such as cyproterone acetate and drospirenone	B	Low
3.2.4	Preferable, to use an OC containing a progestin with low-androgenic activity (e.g., norethindrone acetate, ethynodiol diacetate, desogestrel, gestodene, norgestimate)	B	Low
3.2.5	If hirsutism does not respond to COCPs despite 6 months of monotherapy with an OCP, antiandrogens can then be added	B	Low
3.2.6	COCPs containing EE and antiandrogen when combined with metformin give better results than COCP alone	A	Low
3.2.7	Epilatory measures need to be used in conjunction with OCPs	B	Moderate

For menstrual irregularity and menorrhagia

Summary of evidence

PCOS is associated with menstrual irregularity and menorrhagia due to anovulation both in the adolescent girls and in women in their reproductive age. In the adolescent, a firm diagnosis of PCOS as a cause of menstrual irregularity and menorrhagia can be done only after 2 years of menarche.^[130-132] OCPs with antiandrogenic properties can control menstrual

irregularities and menorrhagia. OCPs with first and second generation progestins are preferred in acute menorrhagia for a few cycles. Once bleeding is relatively controlled, one can use the third and fourth generation OCPs.^[133,134]

Rathod *et al.* reported menstrual problems in 84.88% of adolescent population who had either menstrual irregularity, menorrhagia, or dysmenorrhea.^[135] As menorrhagia may be an important clinical manifestation in inherited bleeding disorders, it needs to be evaluated before embarking on the use of COCP.^[136]

ESHRE/ASRM-sponsored PCOS consensus group recommendations^[137] and The Endocrine Society's clinical practice guidelines^[138] suggest OCPs as the first-line management for amelioration of clinical and biochemical androgen excess and menstrual irregularity. There is no difference in the efficacy with the use of various combination pills.^[137,138]

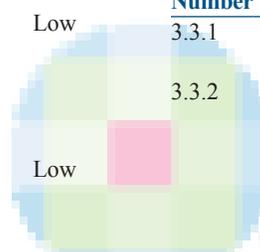
Recommendations

Number	Recommendation	Grade	Quality
3.3.1	COCP is effective in treating irregular cycles and menorrhagia	A	High
3.3.2	OCPs with the first and second-generation progestins are preferred in acute menorrhagia and a few subsequent cycles. Once bleeding is relatively controlled, one can use the third and fourth generation OCP	A	High
3.3.3	In adolescent population and women with menorrhagia, it is important to rule out hemoglobinopathies and coagulopathies	B	Moderate
3.3.4	Levonorgestrel intrauterine device can be offered in those with menorrhagia	A	High

Oral contraceptive pills for long-term therapy in polycystic ovarian syndrome

Summary of evidence

The two main concerns when COCPs were used in PCOS women are decrease in bone density and fear of VTE. A positive linear relationship was also found between duration of OC use and risk of hypertension. The risk of hypertension increased by 13% for every 5-year increment in OC use.^[139] The estrogen content also has a dose dependent effect on lipid profiles.^[140] Moreover, OCPs use is also linked to cervical, breast, and liver cancers.^[141] Long-term use of OCPs has also been associated with increased risk of glaucoma, especially when used for 3 years or more.^[142,143]



Recommendations

No	Recommendation	Grade	Quality
3.4.1	Careful monitoring of PCOS women who take OCPs for BMD, venous thrombosis, hypertension, lipid profile, and breast, cervical, and liver cancer is essential	B	Low
3.4.2	Routine ophthalmic examination (at least yearly) should be advised to monitor for glaucoma	C	Very Low

During infertility management

Summary of evidence

Actions of COCP on reproductive function in PCOS women^[144] are shown in Table 4.

Table 4: Actions of combined oral contraceptives in PCOS

<p>Estrogen Components (ethinyl-estradiol)</p> <ul style="list-style-type: none"> • Suppression of FSH • Stabilization of endometrium • Potentiation of progestin action • Suppression of dominant follicle formation • Increase in sex hormones binding globulin • Decrease in free androgen 	<p>Progestin Component</p> <ul style="list-style-type: none"> • Decreases the frequency of GnRH pulses • Suppression of LH • Inhibition of LH surge • Unreceptive endometrium • Hostile Cervical mucus • Decrease in ovarian androgen and estrogen secretion • Possibly androgen-blocking effects • Increases SHBG concentration
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LH=Luteinizing hormone, FSH=Follicle Stimulating Hormone

During treatment with hormonal contraceptives, serum concentrations of follicle-stimulating hormone (FSH), LH, and estradiol decrease.^[145,146] Thus, COCP is associated with suppression of ovarian and endometrial function.^[147-150] Markers of ovarian reserve are lower in women using sex steroids for contraception. When compared with non-users: anti-Müllerian hormone (AMH) 19% lower (95% CI 9.1%–29.3%); antral follicle count (AFC) 18% lower (95% CI 11.2%–24.8%); ovarian volume 50% lower (95% CI 45.1%–53.7%).^[151-153] Thus, there is a risk of falsely identifying a low ovarian reserve in OCP users. Ovarian reserve, therefore, should be assessed with caution immediately after stopping the OCP. The AMH and AFC should ideally be tested only 3–6 months after stopping the pill.^[153,154]

There is also a reduction of the endometrial thickness, and the pinopod expression is delayed in women using OCP as compared to normally cycling women or those using clomiphene citrate (CC).^[155-157] When given for a minimum number of days, and if controlled ovarian stimulation (COS) is started after a washout period, OCP pretreatment might not have a negative effect on endometrial receptivity.^[158]

The effect of OCP pretreatment on assisted reproductive technique (ART) outcome depends on the type and protocol of OCP used and washout period before initiation of ovarian stimulation.^[159,160] No differences were found in ongoing pregnancy rate in GnRH agonist long protocol when pretreated with OCP.^[161] Although initial publications did not show any negative impact on the ART outcome in GnRH antagonist cycles, recent publications and meta analyses suggest the contrary.^[162] There were two studies which showed a beneficial effect of OCPs on the ART outcome in the GnRH antagonist cycle,^[163,164] but later studies did not show any beneficial effect of pretreatment with OCPs in the ART cycles using GnRH antagonist.^[165-167]

Outcome of ART after OCP pretreatment depends on pill-free interval and duration of pill administration. It is the pill-free interval that strongly influences gonadotropin recovery. After stopping OCPs, both pituitary and ovarian activity will recover. The LH levels remain low for a longer time (21–28 days),^[168] as compared to FSH, which recovers in 5–7 days after stopping the OCP.^[169-171] If the estrogen content of the OCP is <30 µg, there could be an earlier rise in FSH levels, which can have an effect on the COS. The progestin concentrations also become low 5–7 days after discontinuation of OCPs. Thus, a 5-day washout period after OCP is optimal before the initiation of COS.^[170] Duration of pill administration may also have an impact on the reproductive hormones and endometrium.^[169] More than 16 days of pill administration results in greater suppression of pituitary–ovarian axis, which is then associated with a longer duration and higher consumption of gonadotropins.^[162,165] There was no difference in the ART outcome noted if the pills were administered only for 12–16 days and there was a washout period of 5 days.

OCP pretreatment before COS could also be successfully applied to schedule patients and for synchronization of follicular cohort, although the dose of gonadotropins required is higher and also associated with extra 1–2 days of stimulation.^[172]

It was also reported that OCP pretreatment for 2 months followed by CC, at dosage of 100 mg/day on days 5–9 of the cycle, is associated with excellent ovulation rates and pregnancy rates.^[173,176]

In PCOS women with OC induced menses in an antagonist protocol cycle resulted in a significantly lower clinical pregnancy rate and live birth rates as compared to spontaneous menses or progestin-induced menses. In an antagonist cycle where freeze-all policy was adopted and FET (Frozen Embryo Transfer) done where OCP was used to induce menstrual bleeding resulted in significantly

higher rates of conception, clinical pregnancy, and live birth compared with fresh embryo transfer.^[156]

The choice of COCP for the treatment of endometriosis as compared to other medical treatments such as progestogens (Level A), antiprogestogens (Level A), or GnRH agonists (Level A) depends on patient preferences, side effects, efficacy, costs, and availability. All these points should be taken into consideration when choosing hormonal treatment for endometriosis-associated pain.^[174-177]

Despite limited evidence of effectiveness, COCP are widely used in women with endometriosis for the treatment of pain. COCP offer some practical advantages such as contraceptive protection, long-term safety, and control of menstrual cycle.^[178]

Recommendations

No	Recommendation	Grade	Quality
3.5.1	Ovarian reserve markers are lower in women using sex steroids for contraception	A	Moderate
3.5.2	OCPs pretreatment for 2 months followed by CC at dosage of 100 mg/day on days 5-9 of the cycle is associated with excellent ovulation rates and pregnancy rates	A	Low
3.5.3	OCPs cyclical pretreatment before ART could improve pregnancy outcome due to reduction of LH, hyperandrogenism, and antral follicle excess	B	Low
3.5.4	Pretreatment with OCPs before starting the GnRH agonist cycle Permits normalization of the LH/FSH ratio Reduces ovarian androgen concentrations Attenuates the initial flare response to the GnRH agonist No increase in live birth rate in long agonist protocol and in short agonist protocol	B	Low
3.5.5	COCP pretreatment in antagonist protocols was associated with a lower rate of LBR or ongoing pregnancy than no pretreatment and this is related to the pill-free interval	A	Low
3.5.6	COCP pretreatment in antagonist protocols is also associated with higher gonadotropin usage and duration of stimulation	A	Low
3.5.7	Benefits of synchronization of follicular cohort and cycle scheduling must be weighed against the drawbacks with pretreatment OCP in GnRH antagonist	B	Low
3.5.8	COCP in FET cycles may reduce the risk of pregnancy loss	B	Low
3.5.9	COCP reduce endometriosis-associated pain, dyspareunia, and dysmenorrhea	B	Low

Use of oral contraceptive pills in lean and obese women

Summary of evidence

The prevalence of obesity is higher in PCOS women with increased visceral adiposity.^[179,180] There is insufficient evidence to support a causal relationship between use of OCPs and weight gain.^[181] In lean adolescents and adults, OCPs treatment is associated with an increase in total and abdominal fat mass,^[182-184] despite significant decreases in serum androgens, suggesting other underlying mechanisms for potential increase in fat mass. On the contrary, no change in body fat distribution was observed in obese PCOS women after 12 months OCP use.^[185]

In the OWL-PCOS study, treatment of overweight/obese PCOS women with OCPs for 4 months resulted in a significant decrease in visceral fat distribution.^[186]

It is also reported that PCOS women showed 96% higher circulating C-reactive protein (CRP) levels as compared to controls.^[187] In lean PCOS, slight increase or no change in CRP levels was seen after 6 months of OCP treatment.^[188-190] No change was noted in obese PCOS.

The effects of OCPs on adiponectin levels (which has insulin-sensitizing, antiatherogenic, and anti-inflammatory properties) in women with PCOS is still unclear. Some studies report no change in adiponectin levels using a third-generation OCP for 6–12 months,^[185,191] while others report an increase in serum adiponectin levels after 6 months of treatment in obese women.^[187] Increase in inflammatory gene expression in subcutaneous adipose tissue biopsies was seen in adolescents, after treatment with OCPs.^[188]

It is also important to consider the impact of OCPs on adipose tissue distribution and function in lean and obese PCOS women. The evidence is very low as all studies included small numbers of PCOS women. OCPs, when used in obese PCOS women, have increased negative metabolic effects on triglyceride and total cholesterol levels and also aggravate insulin resistance.^[141] The use of OCPs in obese women especially with BMI of >30 kg/m² will considerably increase the risk of CVD. Therefore, all obese women on OCPs should be carefully monitored. OCPs should not be used in obese women with BMI >30 kg/m² associated with other risk factors for VTE.^[192]

Recommendations

Number	Recommendation	Grade	Quality
3.6.1	OCPs when used in lean and obese PCOS desire increased awareness of the patients to the side effects and complications	B	Low
3.6.2	OCPs use in lean PCOS is associated with an increase in total and abdominal fat mass	B	Very Low
3.6.3	OCPs use in obese PCOS is associated with no change in body fat distribution or decrease in visceral fat	A	Low
3.6.4	OCPs use in obese PCOS has additional metabolic risk and should be carefully monitored by appropriate surveillance including blood pressure and weight	B	Moderate

Oral contraceptive pills for added benefit of contraception

Summary of evidence

OCPs, apart from the other benefits also, offer contraception to those PCOS women who do not want to conceive. The data available on use of hormonal contraceptives other than OCPs in PCOS women are sparse; progestin only contraceptives pill or levonorgestrel containing intrauterine system can be used in PCOS women where use of estrogen is contraindicated or when androgen excess does not exist.

Depot medroxyprogesterone and etonogestrel containing implant should not be used in women with PCOS as they are associated with weight gain, insulin resistance, and worsening metabolic profile. The former is also associated with decreased BMD.^[193]

Recommendations

Number	Recommendation	Grade	Quality
3.7.1	COCP offer contraception to those PCOS women who do not want to conceive	A	High
3.7.2	Progestin-only contraceptive pill or levonorgestrel-containing intrauterine system can be used in PCOS women where the use of estrogen is contraindicated or when androgen excess does not exist	B	Low
3.7.3	Depot medroxyprogesterone and etonogestrel-containing implant should not be used in women with PCOS	B	Low

For prevention of Cancer in Polycystic Ovarian Syndrome

Summary of evidence

Most PCOS women have anovulatory cycles with disruption of normal reproductive physiology, which increases the risk of the development of cancer of the endometrium, ovary, and/or breast, either directly or mediated by its associated reproductive metabolic alterations.^[194-197] Women with PCOS have a 2.7-fold (95% CI, 1.0–7.3) increased risk

for endometrial cancer, which is well differentiated and has a good prognosis. There are limited data on increased risk of ovarian and breast cancer in PCOS women. Cancer risk with PCOS is difficult to separate from other recognized risk factors such as nulliparity, infertility and its treatment, anovulation, and obesity.^[134]

Use of OCPs in PCOS women showed a protective trend against endometrial cancer. In endometrial cancer, the estimated relative risk decrease is ~50% with 4 years of use, ~70% with 12 years of use, and decreasing with further use. After ceasing oral contraception, the risk begins to rise from its reduced levels, but it is still ~50% even after >20 years after its last use.

Relative risk of ovarian cancer decreases by ~20% for each 5 years of OCPs use. Risk is ~50% for 15 years of use and decreasing with further use. The protective effect gained declines as time passes from its last use, but a significant effect remains for a long time after cessation of OCP use. OCPs do not protect from mucinous types of ovarian tumors.^[198,199]

Linear coefficient exists for increased protective effects of OCPs, and duration of its use and is independent of type of formulation.

Recommendations

No	Recommendation	Grade	Quality
3.8.1	OCPs have protective beneficial effect against endometrial cancer	B	Moderate
3.8.2	Protective effect of OCPs on ovarian cancer may be there	C	Very Low

Use of other drugs with oral contraceptive pills in Polycystic Ovarian Syndrome

Summary of evidence

Anti-androgens

In PCOS women with moderate or severe hirsutism and acne not responding to COCP, one can add antiandrogens (androgen receptor blockers and 5 alpha-reductase inhibitors).^[200]

Several RCTs have shown that flutamide 250 mg/day, finasteride 5 mg/day, or spironolactone 100 mg/day are effective in reducing the signs of hyperandrogenemia not responding to COCP of third and fourth generations.^[201-205]

In three double-blind studies, combination of an OC containing 2 mg of cyproterone acetate and either spironolactone 100 mg or finasteride 5 mg had better results in the treatment of hirsutism than OC alone.^[206,207,122]

At times, in PCOS women especially adolescent population, when antiandrogens such as cyproterone acetate and spironolactone alone are given, there

may be menstrual disturbances or even amenorrhea because of their strong progestin effects.^[207,122] This is the group which will benefit with combination of COCP and antiandrogens.^[207,122] Antiandrogens can also be combined with COCP when the women need contraception.^[208]

Insulin sensitizers

Insulin sensitizers improve insulin resistance and menstrual dysfunction and may also decrease serum androgen levels.^[209] The main insulin sensitizer is metformin and others include pioglitazone and saroglitazar. However, data on these agents are still emerging but may be valuable adjuncts in individualized situations.

When metformin is used alone, it is not effective in reducing the signs and symptoms of hyperandrogenemia compared to COCP and antiandrogens.^[36,210-216] While the literature on use of metformin plus OCP versus OCP alone is limited, metformin may lower risk and offset OCP exacerbated risk factors. Use of OCP plus flutamide and/or metformin reduced abnormal adipocytokine levels and adiposity, which are aggravated in women using OCPs alone increasing the risk of metabolic syndrome.^[185] Hoeger *et al.* compared OCP plus placebo versus OCP plus metformin and found beneficial effect on waist circumference and higher high-density lipoprotein cholesterol when OCPs were used with metformin.^[216] There was another study, which looked at the levels of adhesion molecules, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, cyproterone containing OCPs with or without metformin and found significant reduction when metformin was used.^[217] Metformin can be a valuable adjunct to OCPs in the treatment of Asian Indian PCOS women.

At present, there is either no evidence or it is sparse for the use of Myo-inositol or other inositols either alone or in combination with OCPs in women with PCOS. In the future, publications may become available on the use of Myo-inositol either alone or in combination with OCPs in PCOS women.

Glucocorticoids

There is no evidence for the use of glucocorticoids in women with adrenal^[218] or unselected hyperandrogenism^[219] and in women with idiopathic hirsutism^[220] as compared to OCPs or antiandrogens. Glucocorticoids with OCPs are beneficial in women with nonclassical congenital adrenal hyperplasia (NCAH) for prolonged remission.^[221]

Use of glucocorticoids can be associated with side effects, such as adrenal atrophy, increased blood

pressure, weight gain, Cushing's striae (particularly with dexamethasone), and decreased BMD. Therefore, the use of glucocorticoids along with OCPs should be restricted only to women who have NCAH.^[222]

Gonadotropin-releasing hormone analogs

Addition of a GnRH agonist to an OCP did not result in extra reduction in hirsutism scores when compared to OCP alone in two uncontrolled trials.^[223,224] One randomized, placebo controlled trial concluded that there was greater reduction in chin hair diameter, but not in Ferriman-Gallwey score with combined GnRH agonist therapy and OCP therapy, as compared to OCP treatment alone.^[225]

GnRH analogs can be used in selected patients with severe hyperandrogenism of ovarian origin who do not respond to other drugs as they reduce ovarian steroids including androgens. However, as GnRH analogs induce reversible menopause, it is usually used with OCPs to prevent menopausal symptoms.^[226]

Recommendations

Number	Recommendation	Grade	Quality
3.9.1	Antiandrogens are recommended along with COCP in women presenting with moderate or severe hirsutism, women presenting with a milder hirsutism, who do not reach a satisfactory control of hair growth using OCPs alone after 6-9 months of treatment	A	Low
3.9.2	Metformin or other insulin sensitizers should not be used as therapy for hyperandrogenemia as the evidence is unconvincing and possibly not superior to placebo	A	Low
3.9.3	Metformin can be used with COCP in PCOS women for management of cardiometabolic factor and prevention of weight gain and in those PCOS women who are obese and overweight. Use of metformin may be relevant in Asian Indians due to high risk	A	Low
3.9.4	Glucocorticoids and GnRH analogs should not be used regularly with OCPs for the treatment of hyperandrogenemia	A	Moderate
3.9.5	Glucocorticoids use should be restricted only to women who have NCAH	A	Moderate

CONCLUSIONS ON USE OF ORAL CONTRACEPTIVE PILLS IN POLYCYSTIC OVARIAN SYNDROME

In PCOS women who do not desire fertility, OCPs are the first-line treatment to improve clinical symptoms of androgen excess such as acne and hirsutism and also

help in regulating the menstrual cycles and protecting the endometrium against effects of unopposed estrogen action. Estrogen content in the OCP increases SHBG levels, thus decreasing the free circulating androgens. The progestin component of OCP suppresses the secretion of LH and decreases ovarian androgen production. It also competes for 5 alpha-reductase and the androgen receptor, with concomitant decrease in androgen action. OCPs may also reduce adrenal production of androgens. Menstrual irregularity gets corrected immediately, but acne and hirsutism may take a minimum of 6 months for its effects to be seen.

Low-dose COCP containing neutral or antiandrogenic progestins may be the OCPs of choice in the treatment of PCOS. Despite the potential adverse cardiovascular and metabolic effects of OCPs, the current evidence suggests that the benefits outweigh the risks for its use in most PCOS women. Use of OCPs in PCOS women should be individualized after risk stratification and not used if any contraindications exist.

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Conflicts of interest

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