Good Clinical Practice Recommendations (GCPR) on Combined Hormonal Contraceptives: *Counselling and Use in Clinical Practice*

1. Background

According to the third National Family Health Survey (NFHS-3), which was conducted in 2005-2006 in India, 98% of women and 99% of men aged 15-49 years were aware of one or more methods of contraception[1]. In contrast,the Demographic Health Survey Data for India (2005-2006) revealed that 52% of illiterate women do not use any method ofcontraception[2]. Given that such women are mainly from low income households and have limited access to health care services, they comprise a particularly vulnerable section of the community.

Contraceptive use has been increasing in India over the last few decades. Oral contraceptives are being used by more than 100 million women worldwide, which vary generally by country, age, education, and marital status[3]. The most common methods of hormonal contraception include the combined hormonal contraceptive (CHC) pill and the mini-pill[4]. Currently, many newer brands of combined hormonal contraceptives use lower estrogen dosesthat have increased safety with equal efficacy[5].

1.1. Aim and Purpose

CHCs belong to a group of hormonal contraceptives, which are one of the most effective methods of preventing pregnancy. The current recommendationsfocus on the use of combined hormonal contraceptives in routine clinical scenario and the importance of structured counselling to patients. The objectives are as follows:

1. To enhance the awareness on contraception
2. To update physicians on CHC effectiveness and safety
3. To encourage acceptance of CHC in Indian women
4. To dispel the myths/ misconceptions around CHC
5. To update additional health benefits of CHC
6. To reassure safe use of CHC by providing comprehensive information to users

1.2. GCPR Methodology

The methodology for developing the guidelines is as follows:

- The clinical evidence for the guidelines were taken from global studies
- The guidelines were developed and reviewed by theexpert committee of FOGSI
- The guidelines were eventually finalized to be used by the health-care providers

1.3. Role of CHCs

Despite an overall decline inMaternal Mortality Rate from 212 (in 2007-09) to 178 in 2012, India still lags behind the target of 103 deaths per live births to be achieved by 2015 underthe United Nations- mandated Millenium Development Goals (MDG).

CHCs certainly have a great impact on reducing unwanted pregnancies and associated socio-medical morbidity[6]. They are considered as an extremely effective method of contraception and also have health benefits beyond pregnancy prevention. CHCs can provide relief from symptoms associated with menstruation including heavy menstrual bleeding (HMB), dysmenorrhoea and irregular bleeding, thus reducing the risk of iron deficiency anaemia by about 50%. CHCs also offer several important health benefits unrelated to birth control, which include reduced risk of benignovarian disease, ovarian and endometrial cancer, and benign breast disease[7].

2. Patient's expectations from modern day contraceptive

2.1. Contraceptive Efficacy

When used correctly, CHCs are an effective method of contraception as evident by their low Pearl Index. They also confer health benefits beyond pregnancy prevention.

2.2. Safety with few side effects

CHCs offer an effective, convenient, tolerable and well-accepted method of hormonal contraception.

2.3. Relief from menstrual symptoms

CHCs reduce the risk of iron deficiency anemia by 50% and provide almost immediate relief from troublesome symptoms associated with menstruation including heavy periods, dysmenorrhea, pre-menstrual dysphoric disorder (PMDD) and irregular bleeding.

2.4. Return to Fertility

Irrespective of duration of use of CHC, complete return to fertility usually occurs immediately after stopping CHC use[8].

3. CHC options available in India

3.1. Combined Oral Contraceptive (COC) pills

Combined Oral Contraceptives (COCs) consists of a combination of estrogen and progestin.

Estrogen: The past 2 decades has witnessed a trend towards lowering the Ethinyl Estradiol (EE) dosing. Formulations are available with EE dosingranging from 50 µg (high dose) to20 µg (ultra-low dose), but mostly are of 30 to 35 µg (low dose).

Progestins: Progestins are classifiedbased on their sequence of development as follows[9]

(Note: the definitions are not universally accepted)

1. **First generation**: (Estranes and Pregnanes)

   Estranesderived from 19-nortestosterone, e.g. Norethisterone acetate, Lynestrenol

   Estranesderived from 17-hydroxyprogesterone, e.g. Medroxyprogesterone acetate, Cyproterone acetate, Chlormadinone acetate
2. **Second generation**: *Gonanes*, e.g. Levonorgestrel or Norgestrel
3. **Third generation**: *Gonanes*, e.g. Gestodene, Desogestrel and Norgestimate
4. **Fourth generation**:

   19-norpregnanes, e.g. Nestorone, Nomegestrol acetate, Trimegestone

   Estranes (non-ethinylated), e.g. Dienogest

   Spironolactone derivative, e.g.Drospirenone (DRSP)

3.1.1. Pharmacology of COCs

Ethinyl estradiol is metabolized at several different sites. First, it is sulphated in the intestinal wall, then it is hydroxylated in the liver through the cytochrome P450 pathway, after which it is conjugated with glucuronides and passed into the enterohepatic circulation. Drug interactions may occur via alterations in absorption, serum protein bindingand receptorbinding or hepatic metabolism.

Major drug Interactions with COCs[10]:

Medications whose action may cause Contraception failure	Medications which may increase COC activity	Medications whose clearance can be decreased by COCs
Carbamazepine	Acetaminophen	Amitriptyline
Griseofulvin	Erythromycin	Caffeine
Oxcarbazepine	Fluoxetine	Cyclosporine
Phenobarbitol	Fluconazole	Diazepam
Phenytoin	Fluvoxamine	Imipramine
Primidone	Grapefruit juice	Phenytoin
Rifampin	Nefazadone	Selegiline
Ritonavir	Vitamin C	Theophylline
St. John's Wort		
Topiramate		

3.1.2. COC Preparations

3.1.2.1. Monophasic

Each pill contains fixed amount of estrogen and progestin. Theycome in various regimens and administrations like 21/7, 24/4 or 84/7 regimens.

3.1.2.2. Biphasic

In this preparation, the estrogen component remains fixed while the amount of progestin increases in the second half of the cycle.

3.1.2.3. Triphasic

The amount of estrogen dose here may be fixed or variable, while the amount of progestin increases in 3 equal phases.

Biphasic and triphasic preparations were developed to reduce the total steroid content of COCs[11].

3.1.2.4. Quadriphasic

These have been developed to reduce the side effects of oral contraceptives and are considered more physiological since they mimic the natural cycle[12, 13].Currently, there is one quadriphasic preparation available and it contains estradiol valerate 3 mg on days 1 and 2; dienogest 2 mg and estradiol valerate 2 mg on days 3 to 7; dienogest 3 mg and estradiol valerate 2 mg on days 8 to 24; estradiol valerate 1 mg on days 25 and 26; and placebo on days 27 and 28, howeverit is not currently available in India.

3.1.2.5. Continuous or Extended Cycle

This preparation involves the intake of active pills (generally 84/7 regimen) whereby the dose of estrogen increases at three distinct points over the first 84 days and the amount of progestin remains constant; this is followed by 7 days of inactive or low doseestrogen pills. This has shown to have advantages like decreased incidence of pelvic pain, headaches, bloating/swelling, breast tenderness, improvement in symptoms of endometriosis and polycystic ovary syndrome[14-16]

3.1.3. Regimens of Administration

3.1.3.1. 21/7 Regimen

The 21/7 regimen contains the same amount and combination of estrogen and progestin in each of the 21 active pills followed by 7 days of hormone free interval.

3.1.3.2. 24/4 Regimen

The 24/4 regimen consists of 24 active pills and 4 placebo or folate tablets, which are distinguished by a different color.

3.1.3.3. 26/2 Regimen

In the 26/2 regimen, hormones of varying doses are taken every day for 26 days, while the last two pills contain no active substances.

3.1.3.4. Extended day Regimen

The 84+7 day regimen contains 84 days of estrogen and progestin followed by 7 days of either placebo or very low-dose estrogen (10 µg/day). These products are designed for the occurrence of four withdrawal bleeds per year[17].

3.1.3.5. Continuous Hormone Regimen

Continuous hormone regimen contains EE 20 µg and levonorgestrel (LNG)90 µg. This product is packaged like a 28-day regimen, but each pill pack contains 28 days of active hormones, taken continuously with no hormone-free interval to induce scheduled withdrawal bleeding[18-20].

3.1.4. Initiation of COC

3.1.4.1. "Sunday start" method

Conventionally, the combined OC is started during the first 5 days of the menstrual cycle or on the first Sunday after menses begin. If the COC is started within the first 5 days of the menstrual cycle, a backup method of contraception is not necessary for prevention of pregnancy, provided that no pills have been missed[10].

3.1.4.2. "Quick start" method

Initiation on any day of the cycle is referred to as the "Quick Start" method. This eliminatesthe delay between receiving a prescriptionand starting the new contraceptive methodwhich may improve adherence."Quick Start" method significantly improves the continuation rate for COCs, reduces the likelihood of a potential unplanned pregnancy, and results in better adherence[21, 22].However one drawback with this method would be an inadvertent use of COC pillduring an undetected pregnancy[22].

3.1.4.3. Post-abortion use/ after miscarriage

After an abortion before 12 weeks gestation, oral contraceptives should be started immediately to inhibit the ovulation which may occur 2 weeks after the abortion. If the abortion is of more

than 12 weeks gestation, oral contraceptives should be started 1 week after the termination because of the uncertainty of the time of ovulation with regard to the 1st menstruation[23].

3.1.4.4. Post-partum use

If the woman has just delivered and is not breastfeeding, the COC pill can be started on Day 21 after the birth. If the pill is started later than 21 days after the birth, an additional contraception is required for the next seven days. If the female is breastfeeding and the baby is less than six months old, taking the COC pill can reduce the flow of milk. It is recommended to use an alternate method of contraception until breastfeeding is discontinued.

3.2. Vaginal rings

3.2.1. Pharmacology

The vaginal ring is a non-biodegradable, flexible, soft copolymerring that is placed inside the vagina. It is about 4 mm thick and 54mm in diameter.When inserted, vaginal rings release, on an average, 120 µg/day of Etonogestrel and 15 µg/day of EE over a three-week period of use[24]. This allows for lower doses, greater bioavailability and good cycle control.

Current prototypes in development include rings releasing progesterone receptor modulators, which would provide estrogen-free contraception, as well as combined rings releasing estradiol, having a better safety profile.

3.2.2. Regimen

The ring is inserted into the vagina and used continuously for 3 weeks. It is removed for a 1-week break period, during which a withdrawal bleed usually occurs. A new ring is inserted after 1 week.

3.2.3. Initiation and Use of Ring

The ring needs to be inserted on Day 1 of menstrual bleeding. However, if it is started on Days 2-5 then an additional method of contraception should be followed for 7 days.

3.2.3.1. Post-abortion use/ after miscarriage

The ring can be inserted within the first 5 days following complete first trimester abortion or miscarriage in which case no additional method of contraception is required.

3.2.3.2. Post-partum use

If the woman has just delivered and is not breastfeeding, the ring should be used no sooner than 4 weeks. However,women who are breastfeeding should be advised not to use the ring and to use other forms of contraception until the child is weaned or after six months from delivery.

3.2.3.3. Inadvertent removal/ expulsion

If the ring is accidentally expelled it has to be rinsed with lukewarm water and reinserted as soon as possible, but at the latest within three hours.

3.2.4. Insertion and removal of the ring

To insert the vaginal ring, it should be squeezed between the thumb and index finger and gently inserted towards the posterior fornix allowing it to take a comfortable position in the vagina. The vaginal ring is removed by hooking it with the index finger and gently pulling it out.

3.3. Injectables

3.3.1. Pharmacology

Though not available in India yet, a monthly injectable contraceptive comprising of 5 mg Estradiol cypionate and 25mg Medroxyprogesterone acetate was approved by the USFDA in October 2000[10]. Estradiol cypionate gave significantly lower peak levels of estradiol and estrone than Estradiol enanthate and valerate. Also, as it is administered by injection, the first-pass metabolism by the liver is avoided, thereby minimizing estradiol's effect on the liver.

3.3.2. Regimen

The contraceptive injection is usually given intramuscularlywith no more than a month's gap between injections. The vaginal bleeding with this method is due to estrogen withdrawal, and usually occurs 3 weeks (day 22) after the injection[25].

3.3.3. Initiation and Use of Injectables

The contraceptive Injection (0.5 mL) is administered intramuscularly into the deltoid, gluteus maximus, or anterior thigh.

First Injection

Within the first 5 days of the onset of a normal menstrual period, or

Within 5 days of a complete first trimester abortion, or

No earlier than 4 weeks postpartum if not breastfeeding, or

No earlier than 6 weeks postpartum if breastfeeding

Second and Subsequent Injections

Subsequent injections every month should be administered within 28 to 30 daysafter the previous injection, and should notexceed 33 days.

If the patient has not adhered to the prescribed schedule (greater than 33 days since last injection), pregnancy should be considered and she should not receive another injection until pregnancy is ruled out.

4. Non- contraceptive benefits of CHCs

The non-contraceptive benefits of CHCs are not only an added advantage to women who use this method but also have an important public health benefit. Currently, CHCs are increasingly prescribed for non-contraceptive indications.

4.1. Non-Contraceptive Indications

4.1.1. Acne

COCs provide considerable improvement in signs of hyperandrogenism which include acne and hirsutism[26]. COCs with newer progestins like Drospirenone having anti-androgenic activity are additionally indicated in mild to moderate acne.

4.1.2. Pre-menstrual dysphoric disorder(PMDD)

The 24/4 regimen containing a newer progestin Drospirenone is additionally indicated for relief from physical and emotional symptoms of pre-menstrual dysphoric disorder (PMDD) with improvements in health-related quality of life[26]. Using extended cycle or continuous CHC regimens to suppress menstruation and stabilize hormone levels, also seems to be effective.

4.2. Non-Contraceptive Benefits

4.2.1. Menstrual Irregularities&Dysmenorrhea

CHCs are often used as therapeutic drugs for women with heavy menstrual bleeding (HMB) and Dysmenorrhea. COCs are generally used to manage heavy and intermenstrual bleeding by restoring synchrony to the endometrium. COCs in conjunction with non-steroidal anti-inflammatory medications have also been postulated as first-line treatment for dysmenorrhea[27].

4.2.2. Anemia

COCs decrease menstrual blood loss and regulate menstrual bleeding, thus reducing the likelihood of iron-deficiency anemia by almost 50%. This benefits both current and past users of COCs[27].

4.2.3. Endometriosis

COCs can be considered as an alternative treatment for the painful symptoms of endometriosis. COCs have an advantage over Danazol or other GnRH agonists in having a better long term tolerability profile[27].

4.2.4. Bone Mineral Density (BMD)

COCs have been reported to have nil or even beneficial effects on bone mineral density (BMD). Its usein later reproductive years is associated with increased BMD, and longer duration of use with greater BMD[26].

4.2.5. Peri-menopausal hormonal replacement therapy (HRT)

For women with premature (age <40 years) or early (<45 years) menopause, HRT is recommended until the age of 51 years for the treatment of vasomotor symptoms and bone preservation[28]. A woman who is under 50 years and free of all risk factors for venous and arterial thrombosis can use a low dose COC to provide relief from menopausal symptoms, and for increasing BMD.

4.2.6. Endometrial/ Colorectal/Ovarian Cancer

COCs confer a 50% risk reduction from endometrial cancer with longer duration of use associated with greater risk reductions, and lasts up to 20 years.

COCs have also been shown to reduce the risk of colorectal cancer by 18% and ovarian cancer by approximately 20% for every 5 years of use. This protective effect also extends to low-dose pills[26].

5. Role of Counselling

Structured contraception counselling using standardized protocol and aids has shown to significantly increase the selection of modern contraceptive methods[29]. Adequate counselling prior to initiation of any CHCs helps in improving compliance (regular use) and adherence (continuation). Counselling is a key element in providing quality care and is also an important part of both initiation and follow-up visits. Women should be given adequate information with respect toeffectiveness of contraception, correct use, common side-effects, health risks and benefits along with dispelling any mythsin order to help make an informed and voluntary choice.

5.1. Counselling for COCs

5.1.1. Patient Assessment

- A thorough clinical history must be taken, which comprises of current andprevious medical conditions, menstrual and medication history.
- Specifically, enquire about risk factors like smoking, obesity, hypertension, thrombophilia, previous VTE and hyperlipidemia.
- The patients' preference and concerns about the COCs must be addressed.
- Blood pressure, body weight and preferably body mass index should be recorded.
- COCs should be used in caution with patients who are on liver enzyme inducerse.g. anti-epileptic and anti-tubercular drugs.

5.1.2. Initiating COC regimen

First time users should be prescribed a low dose COC containing no more than 35 µg EE[30]. Before starting a contraceptive pill, it is important to ensure that the woman fulfils the criteria of eligibility for use.

There are various regimens of COCsavailable and she should be informed about them. She should also be counselled regarding their proper use as well as management of missed pills.

5.1.3. "Missed pill"

Contraceptive pills can be started any time in the menstrual cycle if the woman is sure that she is not pregnant. It is very important to counsel and instruct woman in case of missed/delayed pills.

Recommended actions after late or missed COCs (monophasic)[17]

5.1.3.1.Missed 1 pill but less than 24 hours late (regardless of pill week)– take a tablet as soon as possible, continue regimen as prescribed (this measure means that in some cases two pills will be taken on one day)

5.1.3.2.Missed ≥ 1 pill in first week of the pill packet- take the last missed pill as soon as possible, continue regimen as prescribed (this measure means that in some cases two pills will be taken on one day); additional contraception for 7 days; consider emergency contraception (if unprotected sex has occurred in the last 5 days)

5.1.3.3.Missed < 3 pills (in the 2nd or 3rd week of pill packet)-take the last missed pill as soon as possible, continue regimen as prescribed (this measure means that in some cases two pills will be taken on one day); omit the pill free interval before beginning the next pill packet

5.1.3.4.Missed ≥ 3 pills (in the 2nd or 3rd week of pill packet)- take the last missed pill as soon as possible, continue regimen as prescribed (this measure means that in some cases two pills will be taken on one day); omit the pill free interval before beginning the next pill packet; additional contraception for 7 days; consider emergency contraception (where several pills have been missed or there has been a greater than 7 day period with no pills taken).

5.1.4. Non-contraceptive benefits

Patients should be counseled that apart from providing excellent contraception, COCs also help in the reduction of heavy menstrual bleeding and dysmenorrhea, reduction in the risk of ovarian, endometrial and colorectal cancer and improvement in acne vulgaris[31, 32].

Alsopills with newer progestins like Drospirenone having anti-mineralocorticoid activity lead to minimal or no “pill-related” weight gain.

5.1.5. Side effects

Side effects are generally experienced during the first 3 months with the most common being abnormal menstrual bleeding, followed by nausea, weight gain, mood changes, breast tenderness, and headache. Reassurance and adequate counselling about expected common side-effects can help to prevent discontinuation and enhance compliance.

5.1.6. COC and Risk of Cancer

COC reduces the risks of ovarian, endometrial and colorectal cancer. This reduced risk has also been noted in women who have a pathogenic mutation in the BRCA1 or BRCA2 gene.

Research is being carried out to assess the role of COCs and the risk of cervical cancer as virtually all cervical cancers are caused by persistent infection with high-risk, or oncogenic types of HPV, and the association of cervical cancer with oral contraceptive use is likely to be indirect[33]. As the risk of these events is very small, women should be carefully counselled regarding the same.

5.2. Counselling for Vaginal Rings

5.2.1. Patient Assessment

Similar to COCs mentioned earlier

5.2.2. Initiating Vaginal Rings

Though it is advisable to get the vaginal ring inserted by a health care professional, it is easy to insert and can be placedin the vaginaby the woman herself.After 3 weeks, the ring is removed and a new ring inserted with a gap of no more than 7 days.

If there is a problem with intercourse, the ring can be removed for up to 3 hours without loss of efficacy.

The ring can be inadvertently expelled from the vagina during removal of a tampon or bowel and bladder emptying, especially with straining and constipation.If the ring is out for more than

3 hours in the first or second week of usage, it can be rinsed with lukewarm water and re-inserted. Additional contraception should be used for the next 7 days.

5.2.3. Non-contraceptive benefits

Similar to COCs mentioned earlier

5.2.4. Side effects

Side effects commonly experienced with ring are irregular uterine bleeding, vaginitis, nausea, weight gain, mood changes, breast tenderness, and headache. Reassurance and adequate counselling about expected common side effects can help to prevent discontinuation and enhance compliance[10].

5.3. Counselling for Injectables

5.3.1. Patient Assessment

Similar to COCs mentioned earlier

5.3.2. Initiating Injectables

Though not yet available in India, they are administered by intramuscular injection, into the deltoid, gluteus maximus, or anterior thigh. Patient should be counselled to adhere with the administration routine.

5.3.3. Side effects

Side effects include unscheduled vaginal bleeding, weight gain, headaches, mood swings, breast tenderness and nausea.

6. Safety concerns with CHCs

6.1. Venous Thrombo Embolism (VTE)

Uses of CHCs are generally considered as a serious risk factor for venous thromboembolism (deep vein thrombosis and pulmonary embolism).

The incidence of venous thromboembolic disease (VTE) in healthy women of reproductive age is verylow, at around 4 to 5/10,000 women per year[34]. COCuse alters clotting factors and

fibrinolysis via its effect on liver metabolism, and can lead to a reversible activated protein C resistance (APCR). These effects contribute to an increased VTE risk with COC use of 9 to 10/10,000 woman years, a risk which is proportionate to the estradiol dose, and highest at the beginning of treatment. By comparison, this risk during pregnancy is around 29/10,000, and in the postpartum period, around 300–400/10,000 woman years[17].

Women should beadvised that although the risk of VTE with CHC is slightly higher than non-user, the risk is still considerably lower than the risk of VTE in pregnancy and postpartum.

6.2. Myocardial infarction (MI)

The increased risk of myocardial infarction in young women taking COCs is marginal. Additional risk factors such as age, hypertension, smoking, diabetes, hyperlipidemia, and high BMI must also be taken into account. In women taking COCs with EE dose of 50 µg or higher, MI risks increases 3-fold. However, the risk of MI seen with doses less than 50 µg of EE is insignificant, irrespective of age. Non-smokers at any age with no specific risk factors can be advised that they have no increased risk of MI with CHC use.

For women ≥35 years and who smoke ≥ 15 cigarettes per day, CHCs are not indicated and an alternative contraceptive method should be recommended[10]. Also hypertensive patients with systolic pressure of 160 mm Hg or over, and diastolic pressures of 100 mm Hg or over, COC should not be usedand an alternative contraceptive method should be recommended[17].

6.3. Stroke

Women should be counselled regarding a very small risk of ischemic stroke with CHC use. Patients with history of stroke should not be prescribed high doses of COCs. Other risk factors like smoking, hypertension, diabetes mellitus, and MI should also be considered as they have a compounding effect thus leading to higher chances of complications.

6.4. Breast Cancer

Numerous recent studies have concluded that the COC has either no influence or a very small influence onbreast cancer[17]. History of benign breast disease or a family history of breast cancer should not be regarded as contraindication to CHC use. Women aged over 40 years should be advised that any increase in risk of breast cancer associated with CHC use is likely to

be small and is in addition to their own background risk which increases with age. Also any increase in the risk of breast canceris reduced to no additional risk 10 years after stopping the CHC[35].

6.5. Cervical Cancer

Human papillomavirus (HPV) is the main etiology for cervical cancer. Women using oral contraceptives are more likely to be exposed to HPV than are those using barrier methods or not having sexual intercourse and should be counselled regarding the risks.Cervical screening is not 100% accurate but regular attendance reduces a woman's chance of developing cervical cancer by between 80 and 90%.Long-term use (≥5 years) of COCs is associated with a small increased risk of cervical cancer. However, the overall risk of cervical cancer is very low, whether hormonal contraception is used or not and the level of risk in COC users decreases to the risk seen in non-users within 10 years of stopping use[36].

7. Eligibility Criteria for Combined Hormonal Contraception in Special Situations[37]

Recommendations:

1 Method can be used without restriction;

2 Advantages of method generally outweigh risks;

3 Method not usually recommended unless other more appropriate methods are not available or not acceptable;

4 Method not to be used

Condition	*Qualifier for condition*	Combined Hormonal Contraceptive Methods		
		COC	Vaginal Rings	Combined Injectables
Lactation	< 6 weeks postpartum	4	4	4
	≥ 6 weeks to < 6 months postpartum (primarily breastfeeding)	3	3	3
	≥ 6 months postpartum	2	2	2
Hypertension	During prior pregnancy, now resolved	2	2	2
	Well controlled	3	3	3

	Systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg	**3**	**3**	**3**
	Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg	**4**	**4**	**4**
	With vascular disease	**4**	**4**	**4**
Valvular heart disease	Uncomplicated	**2**	**2**	**2**
	Complicated	**4**	**4**	**4**
Ischemic heart disease	Past or current	**4**	**4**	**4**
Smoking	Age < 35 years	**2**	**2**	**2**
	Age ≥35 years, < 15 cigarettes per day	**3**	**3**	**2**
	Age ≥ 35 years, ≥ 15 cigarettes per day	**4**	**4**	**3**
Migraine	Without aura, age <35 years	**2/3**	**2/3**	**2/3**
	Without aura, age ≥35 years	**3/4**	**3/4**	**3/4**
	With aura, at any age	**4**	**4**	**4**
Thyroid disease	Simple goiter, hyperthyroidism, hypothyroidism	**1**	**1**	**1**
Diabetes mellitus	History of gestational disease	**1**	**1**	**1**
	Without vascular disease	**2**	**2**	**2**
	With end-organ damage or > 20 years' duration	**3/4**	**3/4**	**3/4**
Liver disease	Cirrhosis, mild	**1**	**1**	**1**
	Cirrhosis, severe	**4**	**4**	**3**
	Tumors, benign	**2**	**2**	**2**
	Tumors, malignant	**4**	**4**	**4**
	Viral hepatitis, carrier	**1**	**1**	**1**
	Viral hepatitis, active	**2**	**2**	**2**
Gallbladder disease	Asymptomatic gallstones	**2**	**2**	**2**
	Symptomatic gallstones, without Cholecystectomy	**3**	**3**	**2**
	Gallstones treated with cholecystectomy	**2**	**2**	**2**
	Pregnancy-related cholestasis in past	**2**	**2**	**2**
	Hormone-related cholestasis in past	**3**	**3**	**2**
Anti-Microbial therapy	Broad-spectrum antibiotics	**1**	**1**	**1**
	Anti- fungals	**1**	**1**	**1**
	Anti-parasitics	**1**	**1**	**1**
	Rifampicin or rifabutin therapy	**3**	**3**	**3**
Anti-Retroviral therapy	Nucleoside reverse transcriptase inhibitors (NRTIs)	**1**	**1**	**1**
	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	**2**	**2**	**2**
	Ritonavir-boosted protease inhibitors	**3**	**3**	**3**

8. Conclusion

This GCPR regarding the CHC usage in Indian women is focused on the unmet need for the CHCs, their usage (contraceptive as well as non-contraceptive), side effects and the importance

of structured counselling to patients. We have also tried to stress the relevant safety concerns with CHCs including contraception in special situations and patient counselling tips for a better prescribing pattern along with customizing its usage as per the patient needs.

9. Glossary (Abbreviations)

APCR	Activated Protein C Resistance
BMD	Bone Mineral Density
CHC	Combined Hormonal contraceptive
COC	Combined Oral contraceptive
DRSP	Drospirenone
EE	Ethinyl Estradiol
GCPR	Good Clinical Practice Recommendations
GnRH	Gonadotropin Releasing Hormone
Hb	Hemoglobin
HMB	Heavy Menstrual Bleeding
HPV	Human papillomavirus
HRT	Hormone replacement therapy
LNG	Levonorgestrel
MDG	Millennium Development Goal
MI	Myocardial infarction
NFHS	National Family Health Survey
NRTIs	Nucleoside reverse transcriptase inhibitors
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
PMDD	Premenstrual dysphoric disorder
VTE	Venous thromboembolism

REFERENCES:

1 International Institute for Population Sciences (IIPS) and Macro International. 2007. National Family Health Survey (NFHS-3), 2005–06: India: Volume I. Mumbai: IIPS.

2 Dixit P. Linkages between Unintended Births and Contraceptive Discontinuations in India. Scientific Reports 2012;1:554

3 Shafiq M, Sheikh SA, Hassan SH. Combined oral contraceptive pills improve lung function variables. Pak J Physiol 2012;8(1):1-5

4 Spencer AL, Bonnema R, McNamara MC. Helping women choose appropriate hormonal contraception: update on risks, benefits, and indications. Am J Med. 2009;122:497-506

5 Sylvia L, Yeager BF. Update on Oral Contraceptive Pills. Am Fam Physician 1999;60:2073–84.

6 Baird AS, Porter CC. Teenage pregnancy: strategies for prevention. Obstetrics, Gynaecology and Reproductive Medicine 21:6;151-57

7 Mishell DR Jr. American Journal of Obstetrics and Gynecology 1982, 142(6 Pt 2):809-816

8 Selected practice recommendations for contraceptive Use - Department of Reproductive Health and Research Family and Community Health World Health Organization, Geneva, 2004 2nd edition, 2004

9 Nath A. and Sitruk-Ware R. Different cardiovascular effects of progestins according to structure and activity. Climacteric 2009;12(Suppl 1):96–101

10 SOGC Clinical Practice Guidelines-Canadian Contraception Consensus No. 143 – Part 2 of 3, March 2004

11 Upton GC. The phasic approach to oral contraception: the triphasic concept and its application. Int J Fertil 1983;28:121–40

12 The Merck Manual of Medical Information. Mark H. Beers et al., eds. 2nd Home Edition. Whitehouse Station, NJ: Merck; 2003.

13 Estradiol + dienogest. Oral contraception: estradiol does not provide a therapeutic advantage Prescrire Int. 2010 Apr;19 (106):65-7.

14 SulakP,KuehlT,Ortiz M, Shull B. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormonal withdraw symptoms. Am J ObstetGynecol 2002;186:114 (2–9).

15 Vercellini P, De Giorgi O, Mosconi P, StellatoG,Vicentini S, Crosignani PG. Cyproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. FertilSteril 2002;77(1):52–61

16 Falsetti L, Galbignani E. Long-term treatment with the combination ethinylestradiol and cyproterone acetate in polycystic ovary syndrome. Contraception 1990;42(6):611–9

17 Wiegratz I, Thaler CJ. Hormonal contraception--what kind, when, and for whom? DtschArztebl Int. 2011 Jul;108(28-29):495-505

18 Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. ObstetGynecol 2003;101:653-61.

19 Archer DF, Jensen JT, Johnson JV, Borisute H, Grub GS, Constantine GD. Evaluation of a continuous regimen of levonorgestrel/ethinyl estradiol: phase 3 study results. Contraception 2006;74:439-45.

20 Edelman AB, Gallo MF, Jensen JT, Nichols MD, Schulz KF, Grimes DA. Continuous or extended cycle versus cyclic use of combined oral contraceptives for contraception. Cochrane Database Syst Rev 2005;3:CD004695

21 Lara-Torre E, Schroeder B. Adolescent compliance and side effects with quick start initiation of oral contraceptive pills. Contraception. 2002;66:81-5

22 Lopez LM, Newmann SJ, Grimes DA, et al. Immediate start of hormonal contraceptives for contraception. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD006260.

23 When to start the pill after abortion. FamPlannInfServ. 1978 Feb;1(1):17.

24 TimmerCJ,Mulders TM. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. ClinPharmacokinet 2000;39(3):233–42.

25 GarceauRJ,Wajszczuk CJ, Kaunitz AM. Bleeding patterns of women using Lunelle monthly contraceptive injections (medroxyprogesterone acetate and estradiol cypionate injectable suspension) compared with those of women using Ortho-Novum 7/7/7 (norethindrone/ethinyl estradiol triphasic) or other oral contraceptives. Contraception 2002;62(6):289–95.

26 Armstrong C. ACOG Guidelines on Non-contraceptive Uses of Hormonal Contraceptives. Am Fam Physician. 2010 Aug 1;82(3):288-95

27 Non-contraceptive Benefits and Therapeutic Uses of the Oral Contraceptive Pill: Seminars in Reproductive Medicine /Volume 19, Number 4 2001

28 Hickey M, Elliott J, Davison SL. Hormone replacement therapy. BMJ. 2012 Feb 16;344:e763

29 Sheriar N, Joshi R, Mukherjee Pal B, Birla A, Ray SK. Impact of structured counseling on the selection of hormonal contraceptive methods: results of a multi-centric, observational study in India, J ObstetGynaecol India. 2014 Aug;64(4):241-50

30 Mills AM, Wilkinson CL, Bromham DR, Elias J, Fotherby K, Guillebaud J, Kubba A, Wade A. Guidelines for prescribing combined oral contraceptives. BMJ. 1996 Jan 13;312(7023):121-2

31 Burkman R, Schlesselman JJ, Zieman M. Safety concerns and health benefits associated with oral contraception. Am J Obstet Gynecol. 2004;190(Suppl):S5-S22.

32 Redmond GP, Olson WH, Lippman JS, et al. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. Obstet Gynecol. 1997;89:615-22.

33 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2007; 91:74–84

34 Heinemann LAJ, Dinger JC: Range of published estimates of venous thromboembolism incidence in young women. Contraception 2007; 75: 328–36.

35 Contraception for Women Aged Over 40 Years: Faculty of Sexual & Reproductive Healthcare Clinical Guidance RCOG 2010

36 International Collaboration of Epidemiological Studies of Cervical Cancer. Lancet 2007; 370: 1609–21

37 Medical Eligibility Criteria for Contraceptive Use: A WHO Family Planning Cornerstone. 4th edition. Geneva: World Health Organization; 2010. WHO Guidelines Approved by the Guidelines Review Committee.