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## COMBINED INJECTABLE CONTRACEPTIVES (CICs)

Combined injectable contraceptives (CICs) provide for the release of a natural estrogen plus a progestogen and act through the inhibition of ovulation.<sup>1-5</sup> Two CIC formulations, both given at four-week intervals, are considered here:

- 1) **Cyclofem** = Medroxyprogesterone acetate 25mg plus estradiol cypionate 5mg
- 2) **Mesigyna** = Norethisterone enantate 50mg plus estradiol valerate 5mg

Because the estrogens in CICs may be more physiologic and may be less potent compared with the synthetic estrogens of combined oral contraceptives (COCs), the type and magnitude of estrogen-related side-effects associated with CICs may be different from those experienced by COC users. In fact, short-term studies of CICs have shown little effect on blood pressure, haemostasis and coagulation, lipid metabolism, and liver function in comparison with COCs.<sup>6-8</sup> In addition, the parenteral administration of CICs eliminates the first-pass effect of the hormones on the liver.

However, CICs are a relatively new contraceptive method, and there are few epidemiological data on their long-term effects. There is also the concern that, while the effect of the hormonal exposure associated with use of COCs and progestogen-only pills (POPs) can be reduced immediately by discontinuing their use, this is not the case with injectables, for which the effect continues for some time after the last injection.

Pending further evidence, the Working Group concluded that the evidence available for COCs applies to CICs in many but not all instances. Therefore, the Working Group assigned categories for CICs somewhere between the categories for COCs and POPs. However, for severe pathologies (e.g., ischaemic heart disease), the classification of conditions was the same as for COCs. The assigned categories should, therefore, be considered a preliminary, best judgement, which will be re-evaluated as new data become available.

## COMBINED CONTRACEPTIVE PATCH (P)

The combined contraceptive patch uses a square 20 cm<sup>2</sup>, three-layer system applied to the buttocks, torso, abdomen, or upper arm, to release ethinylestradiol and a progestogen (norelgestromin) transdermally. The contraceptive effect of the combined patch is achieved through inhibition of ovulation.<sup>9</sup> The combined contraceptive patch currently available for consideration was:

**Evra** = 17-deacetyl norgestimate (norelgestromin) 150µg plus ethinylestradiol 20µg (both dosages are approximate daily release rates).

The combined contraceptive patch is a new contraceptive method. Relatively limited information is available on the safety of the combined contraceptive patch among healthy women and even less information is available for women with specific medical conditions. Moreover, epidemiological data on the long-term effects of the combined contraceptive patch were not available for the Working Group to review and all available studies received support from the patch manufacturer.

According to available evidence, the combined contraceptive patch provides a comparable safety and pharmacokinetic profile to COCs with similar hormone formulations.<sup>9-18</sup> Reports of transient, short-term breast discomfort and skin site reactions occurred among less than 25% of combined contraceptive patch users.<sup>10-13</sup> Limited evidence suggests the effectiveness of the patch may decline for women weighing 90kg or more.<sup>10-11</sup> To date, no studies have examined whether the avoidance of the first-pass effect of hormones on the liver with patch use lessens concerns about drug interactions or use of the patch among women with liver conditions.

Pending further evidence, the Working Group concluded that the evidence available for COCs applies to the patch. Therefore, the patch should have the same categories as COCs. The assigned categories should, therefore, be considered a preliminary, best judgement, which will be re-evaluated as new data become available.

## COMBINED VAGINAL RING (R)

The combined contraceptive vaginal ring releases ethinylestradiol and a progestogen (etonogestrel) from a 54mm ethylene vinyl acetate copolymer ring. The contraceptive effect of the combined vaginal ring is achieved through inhibition of ovulation.<sup>19-20</sup> The vaginal ring formulation currently available for consideration was: **NuvaRing** = etonogestrel 120 µg plus ethinylestradiol 15 µg (both dosages are approximate daily release rates).

The combined contraceptive vaginal ring is a new contraceptive method. Relatively limited information is available on the safety of the combined contraceptive ring among healthy women and even less information is available for women with specific medical conditions. Moreover, epidemiological data on the long-term effects of the combined contraceptive ring were not available for the Working Group to review and all available studies received support from the ring manufacturer.

According to available evidence, the combined contraceptive vaginal ring provides a comparable safety and pharmacokinetic profile to COCs with similar hormone formulations.<sup>20-25</sup> Evidence among healthy women suggests the vaginal ring does not alter vaginal flora,<sup>23-24</sup> and limited evidence on women with low-grade squamous intraepithelial lesions found use of the vaginal ring did not worsen the condition.<sup>23</sup> To date, no studies have examined whether the avoidance of the first-pass effect of hormones on the liver with vaginal ring use lessens concerns about drug interactions or use of the ring among women with liver conditions.

Pending further evidence, the Working Group concluded that the evidence available for COCs applies to the ring. Therefore, the ring should have the same categories as COCs. The assigned categories should, therefore, be considered a preliminary, best judgement, which will be re-evaluated as new data become available.

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
<b>CONDITION</b>	<b>CATEGORY</b> I=Initiation C=Continuation			<b>CLARIFICATIONS/EVIDENCE</b>
	<b>CICs</b>	<b>P</b>	<b>R</b>	
<b>PERSONAL CHARACTERISTICS AND REPRODUCTIVE HISTORY</b>				
<b>PREGNANCY</b>	NA	NA	NA	<b>Clarification:</b> Use of CICs, P, or R is not required. There is no known harm to the woman, the course of her pregnancy, or the fetus if CICs, P, or R are accidentally used during pregnancy.
<b>AGE*</b>				
a) Menarche to < 40 years	1	1	1	
b) ≥ 40 years	2	2	2	
<b>PARITY</b>				
a) Nulliparous	1	1	1	
b) Parous	1	1	1	
<b>BREASTFEEDING*</b>				
a) < 6 weeks postpartum	4	4	4	
b) ≥ 6 weeks to < 6 months postpartum (primarily breastfeeding)	3	3	3	
c) ≥ 6 months postpartum	2	2	2	
<b>POSTPARTUM*</b> (in non-breastfeeding women)				
a) < 21 days	3	3	3	
b) ≥ 21 days	1	1	1	
<b>POST-ABORTION</b>				
a) First trimester	1	1	1	<b>Clarification:</b> CICs, P, or R may be started immediately post-abortion.
b) Second trimester	1	1	1	
c) Immediate post-septic abortion	1	1	1	

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
<b>CONDITION</b>	<b>CATEGORY</b> I=Initiation C=Continuation			<b>CLARIFICATIONS/EVIDENCE</b>
	<b>CICs</b>	<b>P</b>	<b>R</b>	
<b>PAST ECTOPIC PREGNANCY*</b>	1	1	1	
<b>HISTORY OF PELVIC SURGERY</b>	1	1	1	
<b>SMOKING</b>				
a) Age < 35 years	2	2	2	
b) Age ≥ 35 years				
(i) <15 cigarettes/day	2	3	3	
(ii) ≥15 cigarettes/day	3	4	4	
<b>OBESITY</b> ≥ 30 kg/m <sup>2</sup> body mass index (BMI)	2	2	2	<b>Evidence:</b> Limited evidence suggests the effectiveness of the patch may decline for women weighing 90kg or more. <sup>10-11</sup>
<b>BLOOD PRESSURE MEASUREMENT UNAVAILABLE</b>	NA	NA	NA	<b>Clarification:</b> It is desirable to have blood pressure measurements taken before initiation of CIC, P, or R use. However, in some settings blood pressure measurements are unavailable. In many of these settings, pregnancy morbidity and mortality risks are high, and CICs, P, or R may be one of the few methods available. In such settings, women should not be denied use of CICs, P, or R simply because their blood pressure cannot be measured.
<b>CARDIOVASCULAR DISEASE</b>				
<b>MULTIPLE RISK FACTORS FOR ARTERIAL CARDIOVASCULAR DISEASE</b> (such as older age, smoking, diabetes and hypertension)	3/4	3/4	3/4	<b>Clarification:</b> When a woman has multiple major risk factors, any of which alone would substantially increase the risk of cardiovascular disease, use of CICs, P, or R may increase her risk to an unacceptable level. However, a simple addition of categories for multiple risk factors is not intended; for example, a combination of two risk factors assigned a category 2 may not necessarily warrant a higher category.

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
CONDITION	CATEGORY I=Initiation C=Continuation			CLARIFICATIONS/EVIDENCE
	CICs	P	R	
<b>HYPERTENSION*</b>				
For all categories of hypertension, classifications are based on the assumption that no other risk factors for cardiovascular disease exist. When multiple risk factors do exist, risk of cardiovascular disease may increase substantially. A single reading of blood pressure level is not sufficient to classify a woman as hypertensive.				
a) History of hypertension, where blood pressure CANNOT be evaluated (including hypertension in pregnancy)	3	3	3	<b>Clarification:</b> Evaluation of cause and level of hypertension is recommended as soon as feasible.  <b>Clarification:</b> Women adequately treated for hypertension are at reduced risk of acute myocardial infarction and stroke as compared with untreated women. Although there are no data, CIC, P, or R users with adequately controlled and monitored hypertension should be at reduced risk of acute myocardial infarction and stroke compared with untreated hypertensive CIC, P, or R users.
b) Adequately controlled hypertension, where blood pressure CAN be evaluated	3	3	3	
c) Elevated blood pressure levels (properly taken measurements)				
(i) systolic 140-159 or diastolic 90-99	3	3	3	
(ii) systolic $\geq$ 160 or diastolic $\geq$ 100	4	4	4	
d) Vascular disease	4	4	4	
<b>HISTORY OF HIGH BLOOD PRESSURE DURING PREGNANCY</b> (where current blood pressure is measurable and normal)	2	2	2	

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
<b>CONDITION</b>	<b>CATEGORY</b> I=Initiation C=Continuation			<b>CLARIFICATIONS/EVIDENCE</b>
	<b>CICs</b>	<b>P</b>	<b>R</b>	
<b>DEEP VENOUS THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)*</b>  a) History of DVT/PE b) Current DVT/PE c) Family history of DVT/PE (first-degree relatives) d) Major surgery (i) with prolonged immobilization (ii) without prolonged immobilization e) Minor surgery without immobilization	          4 4 2  4 2 1	          4 4 2  4 2 1	          4 4 2  4 2 1	
<b>KNOWN THROMBOGENIC MUTATIONS</b> (e.g., Factor V Leiden; Prothrombin mutation; Protein S, Protein C, and Antithrombin deficiencies)	4	4	4	<b>Clarification:</b> Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening.
<b>SUPERFICIAL VENOUS THROMBOSIS*</b>  a) Varicose veins b) Superficial thrombophlebitis	  1 2	  1 2	  1 2	
<b>CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE*</b>	4	4	4	
<b>STROKE*</b> (history of cerebrovascular accident)	4	4	4	

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>					
<b>CONDITION</b>	<b>CATEGORY</b> I=Initiation C=Continuation			<b>CLARIFICATIONS/EVIDENCE</b>		
	<b>CICs</b>	<b>P</b>	<b>R</b>			
<b>KNOWN HYPERLIPIDAEMIAS</b>	2/3	2/3	2/3	<b>Clarification:</b> Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. While some types of hyperlipidaemias are risk factors for vascular disease, the category should be assessed according to the type, its severity, and the presence of other cardiovascular risk factors.		
<b>VALVULAR HEART DISEASE*</b>						
a) Uncomplicated	2	2	2			
b) Complicated (pulmonary hypertension, risk of atrial fibrillation, history of subacute bacterial endocarditis)	4	4	4			
<b>NEUROLOGIC CONDITIONS</b>						
<b>HEADACHES*</b>	I	C	I	C	I	C
a) Non-migrainous (mild or severe)	1	2	1	2	1	2
b) Migraine						
(i) without aura						
Age < 35	2	3	2	3	2	3
Age ≥ 35	3	4	3	4	3	4
(ii) with aura, at any age	4	4	4	4	4	4
	<b>Clarification:</b> Classification depends on accurate diagnosis of those severe headaches that are migrainous and those that are not. Any new headaches or marked changes in headaches should be evaluated. Classification is for women without any other risk factors for stroke. Risk of stroke increases with age, hypertension and smoking.					
<b>EPILEPSY</b>	1		1		1	
	<b>Clarification:</b> If a woman is taking anticonvulsants, refer to the section on drug interactions. Certain anticonvulsants lower COC effectiveness. The extent to which CIC, P or R use are similar to COC use in this regard remains unclear.					

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
CONDITION	CATEGORY I=Initiation C=Continuation			CLARIFICATIONS/EVIDENCE
	CICs	P	R	
<b>DEPRESSIVE DISORDERS</b>				
<b>DEPRESSIVE DISORDERS</b>	1	1	1	<b>Clarification:</b> The classification is based on data for women with selected depressive disorders. No data on bipolar disorder or postpartum depression were available. There is a potential for drug interactions between certain antidepressant medications and hormonal contraceptives.
<b>REPRODUCTIVE TRACT INFECTIONS AND DISORDERS</b>				
<b>VAGINAL BLEEDING PATTERNS*</b>				
a) Irregular pattern <i>without</i> heavy bleeding	1	1	1	
b) Heavy or prolonged bleeding (includes regular and irregular patterns)	1	1	1	<b>Clarification:</b> Unusually heavy bleeding should raise the suspicion of a serious underlying condition.
<b>UNEXPLAINED VAGINAL BLEEDING*</b> (suspicious for serious condition)				
Before evaluation	2	2	2	<b>Clarification:</b> If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated and the category adjusted after evaluation.
<b>ENDOMETRIOSIS*</b>	1	1	1	
<b>BENIGN OVARIAN TUMOURS</b> (including cysts)	1	1	1	
<b>SEVERE DYSMENORRHOEA</b>	1	1	1	
<b>TROPHOBLAST DISEASE</b>				
a) Benign gestational trophoblastic disease	1	1	1	
b) Malignant gestational trophoblastic disease	1	1	1	
<b>CERVICAL ECTROPION*</b>	1	1	1	

\* See also additional comments at end of table

COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)	CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.			
CONDITION	CATEGORY I=Initiation C=Continuation			CLARIFICATIONS/EVIDENCE
	CICs	P	R	
<b>CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)</b>	2	2	2	<b>Evidence:</b> Limited evidence on women with low-grade squamous intraepithelial lesions found use of the vaginal ring did not worsen the condition. <sup>23</sup>
<b>CERVICAL CANCER*</b> (awaiting treatment)	2	2	2	
<b>BREAST DISEASE*</b> a) Undiagnosed mass b) Benign breast disease c) Family history of cancer d) Breast cancer (i) current (ii) past and no evidence of current disease for 5 years	2	2	2	<b>Clarification:</b> Evaluation should be pursued as early as possible.
<b>ENDOMETRIAL CANCER*</b>	1	1	1	
<b>OVARIAN CANCER*</b>	1	1	1	
<b>UTERINE FIBROIDS*</b> a) Without distortion of the uterine cavity b) With distortion of the uterine cavity	1	1	1	
<b>PELVIC INFLAMMATORY DISEASE (PID)*</b> a) Past PID (assuming no current risk factors for STIs) i) with subsequent pregnancy ii) without subsequent pregnancy b) PID - current	1	1	1	

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
<b>CONDITION</b>	<b>CATEGORY</b> I=Initiation C=Continuation			<b>CLARIFICATIONS/EVIDENCE</b>
	<b>CICs</b>	<b>P</b>	<b>R</b>	
<b>STIs*</b>				
a) Current purulent cervicitis or chlamydial infection or gonorrhoea	1	1	1	
b) Other STIs (excluding HIV and hepatitis)	1	1	1	
c) Vaginitis (including trichomonas vaginalis and bacterial vaginosis)	1	1	1	
d) Increased risk of STIs	1	1	1	
<b>HIV/AIDS</b>				
<b>HIGH RISK OF HIV*</b>	1	1	1	
<b>HIV-INFECTED</b>	1	1	1	
<b>AIDS</b>	1	1	1	
On ARV therapy	2	2	2	<b>Clarification:</b> If a woman is taking antiretroviral (ARV) therapy, refer to the section on drug interactions. Because there may be drug interactions between hormonal contraceptives and ARVs, AIDS with ARV therapy is classified as Category 2.
<b>OTHER INFECTIONS</b>				
<b>SCHISTOSOMIASIS</b>				
a) Uncomplicated	1	1	1	
b) Fibrosis of liver (if severe, see cirrhosis)	1	1	1	
<b>TUBERCULOSIS</b>				
a) Non-pelvic	1	1	1	<b>Clarification:</b> If a woman is taking rifampicin, refer to the section on drug interactions. Rifampicin is likely to decrease COC effectiveness. The extent to which CIC, P, or R use is similar to COC use in this regard remains unclear.
b) Known pelvic	1	1	1	
<b>MALARIA</b>	1	1	1	

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
CONDITION	CATEGORY I=Initiation C=Continuation			CLARIFICATIONS/EVIDENCE
	CICs	P	R	
<b>ENDOCRINE CONDITIONS</b>				
<b>DIABETES*</b>				
a) History of gestational disease	1	1	1	
b) Non-vascular disease				
(i) non-insulin dependent	2	2	2	
(ii) insulin dependent	2	2	2	
c) Nephropathy/ retinopathy/ neuropathy	3/4	3/4	3/4	<b>Clarification:</b> The category should be assessed according to the severity of the condition.
d) Other vascular disease or diabetes of >20 years' duration	3/4	3/4	3/4	<b>Clarification:</b> The category should be assessed according to the severity of the condition.
<b>THYROID DISORDERS</b>				
a) Simple goitre	1	1	1	
b) Hyperthyroid	1	1	1	
c) Hypothyroid	1	1	1	
<b>GASTROINTESTINAL CONDITIONS</b>				
<b>GALL-BLADDER DISEASE*</b>				
a) Symptomatic				
(i) treated by cholecystectomy	2	2	2	
(ii) medically treated	2	3	3	
(iii) current	2	3	3	
b) Asymptomatic	2	2	2	
<b>HISTORY OF CHOLESTASIS*</b>				
a) Pregnancy-related	2	2	2	
b) Past COC or CIC related	2	3	3	

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
<b>CONDITION</b>	<b>CATEGORY</b> I=Initiation C=Continuation			<b>CLARIFICATIONS/EVIDENCE</b>
	<b>CICs</b>	<b>P</b>	<b>R</b>	
<b>VIRAL HEPATITIS*</b>				
a) Active	3/4	4	4	<b>Clarification:</b> The category should be assessed according to the severity of the condition. <b>Clarification:</b> In women with symptomatic viral hepatitis, CICs, P and R should be withheld until liver function returns to normal or 3 months after the woman becomes asymptomatic, whichever occurs earlier.
b) Carrier	1	1	1	
<b>CIRRHOSIS*</b>				
a) Mild (compensated)	2	3	3	
b) Severe (decompensated)	3	4	4	
<b>LIVER TUMOURS*</b>				
a) Benign (adenoma)	3	4	4	
b) Malignant (hepatoma)	3/4	4	4	
<b>ANAEMIAS</b>				
<b>THALASSAEMIA</b>	1	1	1	
<b>SICKLE CELL DISEASE</b>	2	2	2	
<b>IRON-DEFICIENCY ANAEMIA*</b>	1	1	1	
<b>DRUG INTERACTIONS</b>				
<b>DRUGS WHICH AFFECT LIVER ENZYMES</b>				
a) Rifampicin	2	3	3	<b>Clarification:</b> Although the interaction of rifampicin or certain anticonvulsants with P or R use is not harmful to women, it is likely to reduce P or R effectiveness. Use of other contraceptives should be encouraged for women who are long-term users of any of these drugs.
b) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	2	3	3	
<b>ANTIBIOTICS (excluding rifampicin)</b>				
a) Griseofulvin	1	2	2	
b) Other antibiotics	1	1	1	

\* See also additional comments at end of table

<b>COMBINED INJECTABLE CONTRACEPTIVES (CICs), PATCH (P), RING (R)</b>	<b>CICs, patch, and ring do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.</b>			
<b>CONDITION</b>	<b>CATEGORY</b> I=Initiation C=Continuation			<b>CLARIFICATIONS/EVIDENCE</b>
	<b>CICs</b>	<b>P</b>	<b>R</b>	
<b>ANTIRETROVIRAL THERAPY</b>	2	2	2	<b>Clarification:</b> It is important to note that antiretroviral drugs (ARV) have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. The limited data available (outlined in Annex 1) suggest that potential drug interactions between many ARVs (particularly some non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)) and hormonal contraceptives may alter safety and effectiveness of both the hormonal contraceptives and the ARVs. It is not known whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medroxyprogesterone acetate and norethisterone enantate) would be compromised, as these methods provide higher blood hormone levels than other progestogen-only hormonal contraceptives, as well as than combined oral contraceptives. Studies are underway to evaluate potential interactions between depot medroxyprogesterone acetate and selected PI and NNRTI drugs. Thus, if a woman on ARV treatment decides to initiate or continue hormonal contraceptive use, the consistent use of condoms is recommended for preventing HIV transmission and may also compensate for any possible reduction in the effectiveness of the hormonal contraceptive.

\* See also additional comments at end of table

## **Additional comments**

### **AGE**

**Menarche to < 40 years:** Theoretical concerns about the use of combined hormonal contraceptives among young adolescents have not been substantiated.

**≥ 40 years:** The risk of cardiovascular disease increases with age and may also increase with combined hormonal contraceptive use. In the absence of other adverse clinical conditions, combined hormonal contraceptives can be used until menopause.

### **BREASTFEEDING**

**< 6 weeks postpartum:** There is some theoretical concern that the neonate may be at risk due to exposure to steroid hormones during the first 6 weeks postpartum.

**≥ 6 weeks to < 6 months (primarily breastfeeding):** Use of combined hormonal contraceptives during breastfeeding diminishes the quantity of breast milk, decreases the duration of lactation, and may thereby adversely affect the growth of the infant.

### **POSTPARTUM**

**< 21 days:** There is some theoretical concern regarding the association between combined hormonal contraceptive use up to 3 weeks postpartum and risk of thrombosis in the mother. Blood coagulation and fibrinolysis are essentially normalized by 3 weeks postpartum.

### **PAST ECTOPIC PREGNANCY**

The risk of future ectopic pregnancy is increased among women who have had an ectopic pregnancy in the past. Combined hormonal contraceptives provide protection against pregnancy in general, including ectopic gestation.

### **HYPERTENSION**

**Vascular disease:** Among women with underlying vascular disease, the increased risk of arterial thrombosis associated with combined hormonal contraceptive use should be avoided.

### **DEEP VEIN THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)**

**Family history of DVT/PE (first-degree relatives):** Some conditions which increase the risk of DVT/PE are heritable.

**Major surgery:** The degree of risk of DVT/PE associated with major surgery varies depending on the length of time that a woman is immobilized. There is no need to stop combined hormonal contraceptives prior to female surgical sterilization.

### **SUPERFICIAL VEIN THROMBOSIS**

**Varicose veins:** Varicose veins are not risk factors for DVT/PE.

### **CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE**

Among women with underlying vascular disease, the increased risk of arterial thrombosis associated with combined hormonal contraceptive use should be avoided.

### **STROKE**

Among women with underlying vascular disease, the increased risk of arterial thrombosis associated with combined hormonal contraceptive use should be avoided.

### **VALVULAR HEART DISEASE**

Among women with valvular heart disease, combined hormonal contraceptive use may further increase the risk of arterial thrombosis; women with complicated valvular heart disease are at greatest risk.

### **HEADACHES**

Aura is a specific focal neurologic symptom. For more information on this and other diagnostic criteria, see: Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2<sup>nd</sup> Edition. Cephalalgia. 2004; 24 (Suppl 1): 1- 150.

[http://216.25.100.131/ihsccommon/guidelines/pdfs/ihc\\_II\\_main\\_no\\_print.pdf](http://216.25.100.131/ihsccommon/guidelines/pdfs/ihc_II_main_no_print.pdf)

### **VAGINAL BLEEDING PATTERNS**

Irregular menstrual bleeding patterns are common among healthy women.

### **UNEXPLAINED VAGINAL BLEEDING**

There are no conditions that cause vaginal bleeding that will be worsened in the short term by use of combined hormonal contraceptives.

### **ENDOMETRIOSIS**

Combined hormonal contraceptives do not worsen, and may alleviate, the symptoms of endometriosis.

### **CERVICAL ECTROPION**

Cervical ectropion is not a risk factor for cervical cancer, and there is no need for restriction of combined hormonal contraceptive use.

### **CERVICAL CANCER (awaiting treatment)**

There is some theoretical concern that combined hormonal contraceptive use may affect prognosis of the existing disease. While awaiting treatment, women may use combined hormonal contraceptives. In general, treatment of this condition renders a woman sterile.

### **BREAST DISEASE**

**Family history of cancer:** Women with BRCA1 or BRCA2 mutations have a much higher baseline risk of breast cancer than women who do not have these mutations. Most women with a family history of breast cancer do not have these mutations.

**Breast cancer:** Breast cancer is a hormonally sensitive tumour, and the prognosis of women with current or recent breast cancer may worsen with combined hormonal contraceptive use.

### **ENDOMETRIAL CANCER**

It is not known whether CIC, P, or R use reduces the risk of developing endometrial cancer, as is the case with COCs. While awaiting treatment, women may use CICs, P or R. In general, treatment of this condition renders a woman sterile.

### **OVARIAN CANCER**

It is not known whether CIC, P, or R use reduces the risk of developing ovarian cancer, as is the case with COCs. While awaiting treatment, women may use CICs, P, or R. In general, treatment of this condition renders a woman sterile.

### **UTERINE FIBROIDS**

COCs do not appear to cause growth of uterine fibroids and CICs, P, or R are not expected to do either.

### **PELVIC INFLAMMATORY DISEASE (PID)**

COCs may reduce the risk of PID among women with STIs, but do not protect against HIV or lower genital tract STIs. Whether CICs, P or R reduce the risk of PID among women with STIs is unknown, but they do not protect against HIV or lower genital tract STIs.

### **STIs**

COCs may reduce the risk of PID among women with STIs, but do not protect against HIV or lower genital tract STIs. Whether CICs, P or R reduce the risk of PID among women with STIs is unknown, but they do not protect against HIV or lower genital tract STIs.

### **HIGH RISK OF HIV**

COCs may reduce the risk of PID among women with STIs, but do not protect against HIV or lower genital tract STIs. Whether CICs, P or R reduce the risk of PID among women with STIs is unknown, but they do not protect against HIV or lower genital tract STIs.

### **DIABETES**

Although carbohydrate tolerance may change with combined hormonal contraceptive use, the major concerns are vascular disease due to diabetes and additional risk of arterial thrombosis due to combined hormonal contraceptive use.

### **GALL-BLADDER DISEASE**

P or R, like COCs, may cause a small increased risk of gall-bladder disease. There is also concern that they may worsen existing gall-bladder disease. However, unlike COCs, CICs have been shown to have a minimal effect on liver function in healthy women, and have no first-pass effect on the liver.

### **HISTORY OF CHOLESTASIS**

**Pregnancy-related:** History of pregnancy-related cholestasis may predict an increased risk of developing cholestasis associated with combined hormone therapy.

**Past COC or CIC related:** History of COC- or CIC-related cholestasis predicts an increased risk associated with P or R use. Unlike COCs, CICs have been shown to have a minimal effect on liver function in healthy women and have no first-pass effect on the liver.

### **VIRAL HEPATITIS**

**Active:** Unlike COCs, CICs have been shown to have a minimal effect on liver function in healthy women and have no first-pass effect on the liver. However, because CICs are metabolized by the liver, they could, in theory, lead to adverse effects in women whose liver function is already compromised.

### **CIRRHOSIS**

Unlike COCs, CICs have been shown to have a minimal effect on liver function in healthy women and have no first-pass effect on the liver. However, because CICs are metabolized by the liver, they could, in theory, lead to adverse effects in women whose liver function is already compromised

**LIVER TUMOURS**

Unlike COCs, CICs have been shown to have a minimal effect on liver function in healthy women and have no first-pass effect on the liver. However, because CICs are metabolized by the liver, they could, in theory, lead to adverse effects in women whose liver function is already compromised.

**IRON-DEFICIENCY ANAEMIA**

Combined hormonal contraceptive use may decrease menstrual blood loss.

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