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## HORMONAL CONTRACEPTION

-  Combined hormonal contraceptives are suitable for women with no risk factors up to 50 years of age
-  UK Medical Eligibility Criteria are a useful resource for assessing the suitability of a contraceptive method for an individual patient
-  Long-acting reversible contraceptive methods are effective options for some women
-  Emergency contraception provides women with a safe means of preventing pregnancy following unprotected sexual intercourse

### INTRODUCTION

Worldwide, hormonal contraceptives have been a part of clinical practice for 50 years. Each year family planning programmes prevent an estimated 187 million unplanned pregnancies.<sup>1</sup> A recent Irish study found that 69% of the women surveyed used contraception, of whom 55% used condoms, 30% used a contraceptive pill, 5% used an intrauterine device and 2.5% had used an injection, implant or patch.<sup>2</sup> Over the last 35 years there have been significant advances in the development of new contraceptive technologies including new types of oral contraceptives (in terms of hormone dosage and cycle lengths) and new hormone delivery systems.

This bulletin will review the hormonal contraceptives which are currently authorised in Ireland and a second bulletin will review frequently asked questions which have been received by the NMIC.

### EFFICACY OF HORMONAL CONTRACEPTION

The choice of which contraceptive to use is dependent on the effectiveness of the method in preventing an unplanned pregnancy, and the suitability of the method for the individual patient (in terms of age, choice, co-existing disease and concomitant medications). The effectiveness of a method is related to its acceptability and to compliance; “typical use” is considerably less effective than “perfect use” i.e. correct and consistent use. Table 1 compares the effectiveness of the different methods of hormonal contraception and the percentage of women continuing to use each method at the end of the first year.<sup>3</sup>

**Table 1: Percentage of women experiencing an unintended pregnancy on contraception and continuing to use the contraceptive method at 1 year<sup>3</sup>**

Method	% of women experiencing an unintended pregnancy within the 1st year of use		% of women continuing use at 1 year
	Typical use	Perfect use	
No method	85	85	
COC or POP	8	0.3	68
CHC patch	8	0.3	68
CHC vaginal ring	8	0.3	68
PO - injectable	3	0.3	56
PO - implant	0.05	0.05	84
PO – intrauterine system	0.2	0.2	80

COC – combined oral contraception, POP – progestogen-only pill, CHC – combined hormonal contraception, PO – progestogen only

**Medical Eligibility Criteria:** Most contraceptive users are medically fit and can use any available contraceptive method safely however **some medical conditions are associated with risks when certain contraceptives are used.** For example some hormonal contraceptive methods may increase the risk of a woman with diabetes developing cardiovascular complications, while some antiepileptic drugs reduce the efficacy of certain contraceptives.<sup>4</sup> The World Health Organisation (WHO) has developed a set of Medical Eligibility Criteria (MEC) to guide the prescriber on the various hormonal contraceptive methods.<sup>5</sup> The UK Medical Eligibility Criteria (UKMEC)<sup>4</sup> defined in table 2 is based on the WHO MEC and is a useful resource for prescribers (available at <http://www.ffprhc.org.uk>).

**Table 2: Definitions of UKMEC categories<sup>4</sup>**

UKMEC	Definition of category
1	<b>No restriction for the use</b>
2	A condition where <b>the advantages of using the method generally outweigh the theoretical or proven risks</b>
3	A condition where the <b>theoretical or proven risks usually outweigh the advantages</b> of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
4	A condition which represents an <b>unacceptable health risk</b> if the contraceptive method is used.

## COMBINED HORMONAL CONTRACEPTION

Combined hormonal contraceptives (CHCs) containing oestrogens and progestogens, are used by over 100 million women worldwide as combined oral contraceptives (COC)<sup>5,6</sup> however CHCs are also available in transdermal and vaginal formulations. CHCs work primarily by preventing the surge of luteinising hormone thereby preventing ovulation, but they also have effects on the cervical mucus and endometrium.<sup>7,8</sup> **Evidence supports the use of CHCs for women with no risk factors up to the age of 50 years.**<sup>5,9</sup> Since the introduction of the original pill, developments in CHC include: reduction in the oestrogen content, the use of newer progestogens, changes to the hormone-free interval and the development of different formulations (transdermal and vaginal). Non-contraceptive benefits of CHC are numerous and include reduction of menstrual symptoms, reduced duration of bleeding and reduction of lifetime risk of endometrial and ovarian cancer.<sup>5,7</sup> Return to fertility on discontinuation is immediate.<sup>1</sup>

**COMBINED ORAL CONTRACEPTION (COC)** is the most commonly used CHC,<sup>9</sup> which traditionally is taken for 21 days followed by 7 pill free days, resulting in a withdrawal bleed in most women. Currently most COCs contain 20-35 micrograms of oestrogen as ethinylestradiol (EE) in combination with a progestogen.<sup>9</sup> While contraceptive efficacy is similar for the different EE strengths,<sup>9</sup> unscheduled bleeding is more common with preparations containing 20 micrograms EE than those containing >20 micrograms EE.<sup>8,10</sup> **Progestogens** currently available in COCs include levonorgestrel, norethisterone, the “third generation” progestogens (desogestrel, gestodene and norgestimate), drospirenone (a synthetic progestogen, chemically related to spironolactone)<sup>5</sup> and dienogest (a synthetic progestogen).<sup>11</sup> Third generation progestogens have been shown to be associated with less break-through bleeding (BTB),<sup>12</sup> which is a common reason for COC discontinuation.<sup>1</sup> Third generation progestogens may also be considered for women with other side-effects including acne, headache, depression and weight gain.<sup>12,13</sup> Drospirenone has antidiuretic properties due to antiminerlocorticoid activity and also acts as an antiandrogen.<sup>7</sup> Dienogest has antiandrogenic activity<sup>11</sup> and appears to have high endometrial activity.<sup>14,15</sup> Contraceptive protection is maintained during the pill free interval as long as pills before and after are taken consistently and correctly.<sup>9</sup> **The critical time for missing pills is when a pill is omitted at the beginning or end of a cycle.**<sup>13</sup> The advice for women who miss pills varies depending on the type of COC used. The Summary of Product Characteristics (SmPC) should be consulted for the individual preparations; the advice is such that contraceptive efficacy may be reduced if there is a delay in taking the COC by more than 12 hours.<sup>16-30</sup>

**Phasic formulations:** Most COCs contain fixed amount of hormones in each tablet (monophasic); however COCs with varying amounts are available (including triphasic).<sup>7</sup> Phasic COCs are said to be useful in women who experience BTB,<sup>6,13</sup> **however two Cochrane reviews did not support any advantages of phasic over monophasic COCs.**<sup>31,32</sup> Currently there is a quadruphasic COC authorised in Ireland containing varying doses of estradiol valerate (metabolised to oestradiol) and dienogest [*Qlaira*®].<sup>16</sup> The missed pill rule for this COC differs from other COCs.<sup>13,16</sup> Current evidence suggests similar benefits and risks to other COCs.<sup>8,11,15</sup>

**Extended-cycle regimens:** Continuous use or extended cycle formulations have been developed where COCs are taken for longer than 28 days, which may improve menstrual symptoms attributed to the hormone-free interval.<sup>7,33</sup> Unscheduled bleeding/spotting is a common problem seen with these regimens and may result in discontinuation of the method.<sup>5,33</sup> Current evidence does not suggest that these regimens increase the risk of adverse outcomes,<sup>33,34</sup> however there are no data on their long-term effects. Women may be advised to run three packets of monophasic pills together for a variety of reasons, for example, to prevent or delay withdrawal bleeding, to reduce menstrual bleeding problems or to avoid withdrawal headaches. This is a recognised although unlicensed indication.<sup>9,35</sup> Extended cycle preparations are not authorised in Ireland, however there is a formulation authorised (containing drospirenone) [*Yaz*®],<sup>17</sup> where the pill-free interval is only 4 days, which is a compromise between continuous and traditional dosing.<sup>6,33</sup>

**OTHER FORMULATIONS OF CHC** including the transdermal patch and vaginal ring, may be considered for convenience or for women who are forgetful in taking COCs.<sup>7</sup>

**The contraceptive patch** which contains EE and norelgestromin (active metabolite of norgestimate) [*Evra*®],<sup>36</sup> is applied weekly for 3 weeks followed by a patch-free week. It is generally considered as effective as the COC,<sup>3,9,37</sup> however studies have shown reduced efficacy in women who are obese.<sup>7</sup> Evidence suggests that average EE levels of the patch may be higher than COC and the vaginal ring,<sup>5,38</sup> and it also suggests that patch users may experience more adverse effects.<sup>37</sup>

**The contraceptive ring** which contains EE and etonogestrel (3-keto-desogestrel)[*Nuvaring*®],<sup>39</sup> is inserted vaginally and retained for 3 weeks followed by a ring-free week.<sup>5</sup> It is considered as effective as other CHC formulations;<sup>3,9</sup> it is not affected by excess weight,<sup>7</sup> can be used concomitantly with tampons and is safe to use in latex-allergic women.<sup>5</sup> Rings can get expelled (up to 2.5% of women per year)<sup>7</sup> and women should be counselled to check for the presence of the ring after intercourse, after a large valsalva or tampon-removal.<sup>5</sup> If the ring is accidentally expelled for <3 hours, contraceptive efficacy is not reduced; it should be rinsed and reinserted as soon as possible within the 3 hours.<sup>39</sup>

**Adverse effects of CHC:** Most of the data relates to COCs however it is assumed that the risks associated with transdermal and vaginal CHCs are similar.<sup>6,7,40,41</sup> The most common side-effects are nausea, headache, breast tenderness and BTB.<sup>7</sup> A more serious but less common side-effect is **venous thromboembolism (VTE), which is reported to be 5 times more common in COC users than nonusers.**<sup>42</sup> **However the absolute risk is low: the risk is less than the risk of VTE associated with pregnancy.**<sup>7,9</sup> Studies suggest that this risk is higher for those COCs containing third generation desogestrel or gestodene than for those containing levonorgestrel.<sup>42-45</sup> While previous studies suggested a similar risk of VTE for COCs containing levonorgestrel or drospirenone,<sup>46,47</sup> more recent evidence suggests that the risk of VTE with COCs containing drospirenone might be higher, lying between the risk of second and third generation COCs.<sup>42,44,45,48</sup> There have been conflicting results from studies,<sup>5,7</sup> however it is considered that there **may be an increased risk of VTE with the CHC patch compared to second generation COCs.**<sup>5,7,36</sup> There is a small increased risk of myocardial infarction (MI) with COC use which is further increased by smoking (an independent risk factor for MI).<sup>9</sup> Any increased risk of breast cancer is likely to be small and it reduces to no increased risk 10 years after stopping COC.<sup>9</sup>

**Contraindications:** UKMEC 4 criteria (Table 2) for CHC include: <6 weeks postpartum, age ≥35 years who smoke ≥15/day, systolic ≥160 or diastolic ≥95 mmHg, history of or current VTE, thrombogenic mutation, ischaemic heart disease, stroke, complicated valvular and congenital heart disease, migraine with aura at any age, current breast cancer, diabetes with end organ disease, severe liver disease, liver cancer, autoimmune disease with lupus anticoagulant, systemic lupus erythematosus with positive antiphospholipid antibodies.<sup>4</sup> Prescribers should refer to the individual SmPC for full details of contraindications/special precautions, and UKMEC which has a comprehensive listing of all the criteria for CHC methods.<sup>4</sup>

**Drug interactions:** **Liver enzyme-inducing drugs may reduce the efficacy of CHC (UKMEC 3),**<sup>4</sup> therefore if they are to be used long-term, alternative contraceptives should be considered.<sup>9</sup> Women using CHC who are prescribed a short course of antibiotics should be advised to use additional contraceptive precautions while taking the antibiotic and for 7 days after.<sup>9</sup> This topic will be covered in more detail in the next bulletin.

## PROGESTOGEN-ONLY CONTRACEPTION

Progestogen-only (PO) contraceptive methods provide options for women with contraindications to CHC. They include: PO pills (POPs) and the long-acting reversible contraceptives (LARC) including PO injectables, PO implants and PO intrauterine system (IUS). While evidence mainly refers to POPs and PO injectables,<sup>49,50</sup> there does not appear to be a significantly increased risk of VTE with any of the PO contraceptive methods.<sup>51-54</sup> Table 3 summarises the PO contraceptive methods which are available in Ireland.

**Table 3: Summary of progestogen only methods**

Type	Description	Mode of action	Adverse Effects Include*	Contraindications <sup>4</sup>
Progestogen only pills <ul style="list-style-type: none"> <li>• Norethisterone <i>Noriday</i>®<sup>55</sup></li> <li>• Desogestrel <i>Cerazette</i>®<sup>56</sup></li> </ul>	Also known as “mini” pill Single pill taken every day <sup>51</sup> (see text for further details)	Alters cervical mucus to prevent sperm penetration, <sup>51,55</sup> inhibits ovulation in some women <sup>51</sup> (ovulation prevented in 97% of users with desogestrel) <sup>51,56</sup>	Altered bleeding patterns in up to 70% of users, may settle with time <sup>51</sup> Headaches, gastric upsets, acne, mood changes and breast pain <sup>55,56</sup> Reduced efficacy with enzyme inducing drugs – UKMEC 3 <sup>4</sup> [No delay in return of fertility on discontinuation]	UKMEC 4 – current breast cancer
Progestogen only injection <ul style="list-style-type: none"> <li>• Depot medroxy-progesterone acetate (DMPA) <i>Depo-Provera</i>®<sup>57</sup></li> </ul>	IM injection every 12 weeks	Primary mode of action is prevention of ovulation; thickening of the cervical mucus and changes to the endometrium are additional affects <sup>53</sup>	Altered bleeding patterns in up to 80% of users, may settle with time <sup>53</sup> Hypersensitivity, acne, nausea, weight change <sup>57</sup> Concerns regarding reduction in BMD <sup>53</sup> (see below) [May be delay in return of fertility up to 18 months on discontinuation] <sup>53,57</sup>	UKMEC 4 – current breast cancer
Progestogen only implant** <ul style="list-style-type: none"> <li>• Etonogestrel <i>Implanon</i> <i>NXT</i>®<sup>58</sup></li> </ul>	Single rod implanted subdermally – duration of action 3 years <sup>58,59</sup>	Primary mode of action is prevention of ovulation; thickening of the cervical mucus and changes to the endometrium are additional affects <sup>52</sup>	Altered bleeding patterns reported in 26% of users, may settle with time <sup>52</sup> Headache, acne, breast pain and weight gain <sup>58</sup> Reduced efficacy with enzyme inducing drugs <sup>52</sup> – UKMEC 2, however use of condoms recommended <sup>4</sup> [No delay in return of fertility on discontinuation]	UKMEC 4 – current breast cancer
Progesterone only intrauterine system** <ul style="list-style-type: none"> <li>• Levonorgestrel <i>Mirena</i>®<sup>60</sup></li> </ul>	Intrauterine device releases levonorgestrel directly into uterine cavity - effective for 5 years <sup>60</sup>	Effect mainly mediated via its progestogenic effect on the endometrium and in addition effects the cervical mucus reducing sperm penetration <sup>61</sup>	Altered bleeding patterns may occur initially – settles usually by 1 year <sup>61</sup> Headache, acne, weight gain, nausea and mood changes <sup>60</sup> Uterine perforation reported in up to 1 per 1,000 insertions <sup>61</sup> Risk of expulsion of 1 in 20, most common in the first year of use (more common in nulliparous women) <sup>61</sup> Increased risk of pelvic infection initially following insertion <sup>61</sup> [No delay in return of fertility on discontinuation]	UKMEC 4 – puerperal sepsis, immediate post septic abortion, unexplained vaginal bleeding, gestational trophoblastic disease with high levels of β-hCG, current breast cancer, cervical cancer, endometrial cancer, pelvic TB

\*Prescribers are advised to refer to the individual SmPC for full details of adverse effects

\*\*Physicians require training for insertion and removal<sup>52,61</sup>

It is important that norethisterone is taken at the same time every day,<sup>55</sup> while according to the SmPC for Cerazette® (desogestrel), it has to be taken at “about the same time every day”<sup>56</sup> As desogestrel inhibits ovulation in 97% of users, it may be useful for young women where CHC is contraindicated.<sup>35,54</sup> Table 4 summarises the advice for women who miss or are late taking the POP.

**Table 4: Advice for women who miss or are late taking POPs<sup>55,56</sup>**

<p><b>Women should be advised that if a traditional POP is &gt;3 HOURS LATE or a desogestrel-only pill is &gt;12 hours LATE they should:</b></p> <ul style="list-style-type: none"> <li>• Take the late or missed pill now</li> <li>• Continue pill taking as usual (may require taking 2 pills at the same time)</li> <li>• Use condoms or abstain from sex for 7 days* after the missed/late pill is taken</li> </ul>
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\*Some sources recommend 2 days<sup>51,54,62</sup>

Even though altered bleeding is common with POPs, other causes of bleeding should be considered in those with persistent bleeding or who experience a change in bleeding pattern.<sup>51</sup> **LARC are not dependent on compliance and are very effective contraceptive options for a wide range of women.**<sup>1,63,64</sup> While altered bleeding (including prolonged bleeding, irregular bleeding and oligomenorrhoea/amenorrhoea) occurs with these methods, in many women the bleeding settles with time.<sup>52,53,61</sup> DMPA reduces oestradiol levels and is **known to reduce bone mineral density (BMD)** in women of all ages, however this effect appears to be reversible on discontinuation of DMPA.<sup>57,65</sup> As DMPA causes a loss of BMD in adolescents at a time when the BMD is normally increasing, it is possible that the effects may be more important in adolescents.<sup>57,65</sup> Re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue DMPA for >2 years and for women with risk factors for osteoporosis; other methods of contraception should be considered. In addition to being an effective form of contraception, the levonorgestrel IUS (LNG-IUS) is also authorised for menorrhagia,<sup>60,66</sup> making it one of the contraceptive methods of choice for women with excessive heavy menses.<sup>66</sup>

## EMERGENCY CONTRACEPTION

The risk of pregnancy following one act of unprotected sexual intercourse (UPSI), varies throughout the menstrual cycle, increasing around the time of ovulation up to 30%.<sup>67</sup> Emergency contraception (EC) provides women with a safe means of preventing pregnancy following UPSI,<sup>68,69</sup> however women should also be initiated on a reliable form of contraception thereafter. Evidence does not suggest that facilitating access to EC leads to an increase in sexual or contraceptive risk-taking behaviour.<sup>68,69</sup>

The choice of EC includes the following:

**Levonorgestrel (LNG)** is given as a single tablet (1,500 micrograms), which should be taken orally as soon as possible but may be used up to 72 hours after UPSI.<sup>70</sup> Evidence suggests that it may continue to reduce pregnancy if taken 72-120 hours after UPSI (unlicensed indication).<sup>67</sup> The mode of action of LNG is incompletely understood, although efficacy is thought to be due primarily to inhibition of ovulation.<sup>67</sup> It is less effective than an IUD.<sup>71</sup> Women who experience vomiting within 3 hours after taking LNG should be advised to return as soon as possible for a repeat dose.<sup>70</sup> Commonly reported adverse effects include nausea, headache and irregular menses.<sup>70</sup> Existing data indicates that the use of EC does not increase the chance that a subsequent pregnancy will be ectopic.<sup>69,72</sup> **The efficacy of levonorgestrel is reduced in women taking enzyme-inducing drugs** (and for up to 4 weeks after stopping such drugs); a copper containing intrauterine device (IUD) may be offered instead or the dose of levonorgestrel may be increased to a total of 3mg as a single dose (unlicensed indication).<sup>67,71</sup>

Ulipristal acetate (*EllaOne*®) which is available in some European countries is a selective progesterone-receptor modulator, which may be taken up to 120 hours after UPSI.<sup>71,73-75</sup> It is thought to work as an EC by inhibiting or delaying ovulation and also has endometrial effects.<sup>73</sup> It has a pan European authorisation but is not currently marketed in Ireland.<sup>76,77</sup>

Copper containing IUDs are also available in Ireland and are very effective **non-hormonal methods of contraception**.<sup>64,78</sup> They can also be used for EC where they have a failure rate of no greater than 1%. They can be inserted up to 5 days after the first episode of UPSI or within 5 days of the earliest estimated date of ovulation.<sup>67</sup> Further discussion of IUDs is outside the scope of this bulletin.

### SUMMARY

There are many hormonal contraceptive options available to women today. An ideal contraceptive is one which is 100% effective, convenient, safe, reversible, maintenance free, acceptable, cheap, protective against sexually transmitted disease with other contraceptive benefits. However no available method meets all these criteria. In choosing a contraceptive method, the benefits and risks of the method, duration of desired contraception, plans for future pregnancies and presence of co-existing medical disease should be considered. UKMEC is a useful resource which can be used to assess the suitability of a contraceptive method for an individual patient.

Table 5 gives an example of the type of information that is available in UKMEC, however the prescriber should also refer to the SmPC for full prescribing information on the individual contraceptive agent.

**Table 5: Example of UK Medical Eligibility Criteria\* for various conditions<sup>†</sup>**

Condition	CHC	POP	DMPA	PO-Implant	LNG-IUS
Breastfeeding					
• <6 wks postpartum (PP)	4	1	2	1	3 (48 hrs - <4 wks PP)
• ≥6 wks to <6 mths PP (almost fully)	3	1	1	1	1 (≥4 wks PP)
• ≥6 wks to <6 mths PP (partial)	2	1	1	1	4 (puerperal sepsis)
• ≥6 mths PP	1	1	1	1	
Postpartum (non-breast feeding women)					
• <21 days	3	1	1	1	3 (48 hrs - <4 wks PP)
• ≥21 days	1	1	1	1	1 (≥4 wks PP) 4 (puerperal sepsis)
Smoking					
• Age <35 years	2	1	1	1	1
• Age ≥35 years					
○ <15 cigs/day	3	1	1	1	1
○ ≥15 cigs/day	4	1	1	1	1
○ Stopped smoking <1 year ago	3	1	1	1	1
○ Stopped smoking ≥1 year ago	2	1	1	1	1
Hypertension					
• Adequately controlled hypertension	3	1	2	1	1
• Consistently elevated blood pressure levels					
○ Systolic>140-159 mmHg or diastolic >90-94mmHg	3	1	1	1	1
○ Systolic ≥160 or diastolic ≥95 mmHg	4	1	2	1	1
• Vascular disease	4	2	3	2	2
VTE					
• History of or current VTE	4	2	2	2	2
• Family history of VTE					
○ 1st degree relative <45 years	3	1	1	1	1
○ 1st degree relative ≥45 years	2	1	1	1	1
Diabetes					
• History of gestational diabetes	1	1	1	1	1
• Non-vascular disease					
○ Non-insulin dependent	2	2	2	2	2
○ Insulin dependent	2	2	2	2	2
• Nephropathy/retinopathy/neuropathy	3/4	2	3	2	2
• Other vascular diseases	3/4	2	3	2	2

\*UKMEC 1 - A condition for which there is no restriction for the use of the contraceptive method

UKMEC 2 - A condition where the advantages of using the method generally outweigh the theoretical or proven risks

UKMEC 3 - A condition where the theoretical or proven risks usually outweigh the advantages of using the method

UKMEC 4 - A condition which represents an unacceptable health risk if the contraceptive method is used.

**List of references available on request. Date of preparation: OCTOBER 2010**

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue.

Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug

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