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UPDATE ON HORMONAL CONTRACEPTION

- Hormonal methods of contraception are used by 32% of women in Ireland aged 15-44 years.
- Available methods of contraception have a low risk of failure if they are used correctly and consistently.
- Hormonal methods are available by a variety of routes and have both short and long term duration of action.
- Sufficient options are available to individualise contraceptive choices for women with concurrent medical conditions.

INTRODUCTION

The World Health Organisation (WHO) estimates that there are over 100 million women using some form of hormonal contraception worldwide.[1] Available hormonal methods of contraception include combined contraceptives (CCs), i.e. a combination of an oestrogen and a progestogen, available as tablets, transdermal patch or vaginal ring; progestogen-only contraceptives which are available as tablets, injectables, implants and intra-uterine systems. Available non-hormonal methods include barrier methods (diaphragm / cap with spermicide, male and female condoms), natural family planning or fertility awareness, intra-uterine devices (IUDs) and male (vasectomy) and female (tubal ligation) sterilisation. Emergency contraception is also available in hormonal and non-hormonal forms. Hormonal methods are used by 32% of women in Ireland aged 15-44 years who require contraception.[2] Most women opt for combined oral contraceptives (19%). Fewer women choose progestogen-only contraception in the forms of the levonorgestrel intrauterine system (8.7%) or as injectables / implants (3.4%).[2] This bulletin reviews recent developments and frequently asked questions on hormonal contraceptives, and is an update on the previous NMIC contraception bulletin published in 1998.

COMBINED CONTRACEPTIVES (CCs)

What is new in combined oral contraceptives (COCs)?

The reduction in the oestrogen content (to an average of 20-35 micrograms ethinylestradiol) and the introduction of more selective progestogens has led to an improved safety profile. They are given cyclically (3 weeks of active pills followed by a 7-day pill-free interval [PFI]). A newer option available in the USA is that of an extended cycle regimen (12 weeks of active pills followed by a 7-day PFI).[3,4]

Recent evidence suggests that the COC and the combined contraceptive patch may have reduced contraceptive effectiveness in overweight women. When compared with women weighing ≤ 75kg, consistent users weighing ≥ 86kg carried an almost doubled risk of pregnancy (OR 1.95, 95% CI 1.06-3.67). [5,6]

What is the current advice regarding missed COC pills?

The WHO issued updated recommendations and guidance in 2004 on this topic.[7] COCs act by inhibiting ovulation and seven consecutive pills are sufficient to do this. The remaining pills in a pack maintain anovulation. Seven consecutive pills are regularly missed in the pill-free interval (PFI) and while follicular activity is evident in the PFI, ovulation does not occur. When pills are missed outside of the PFI, the inhibitory effects may be lifted sufficiently for ovulation to occur and thus intercourse following missed pills may result in pregnancy.

When pills are missed, the chance that pregnancy will occur depends not only on **how many** pills were missed, but also on **when** those pills were missed. The risk of pregnancy is greatest when pills are missed at the beginning or at the end of the packet, i.e. when the PFI is extended. The WHO Expert Working Group has determined that missing three or more COCs containing 30-35 micrograms of ethinylestradiol (or two or more COCs containing 20 micrograms ethinylestradiol) at any time during the cycle warrants additional precautions. Flowcharts and tables outlining the recommendations are available from the WHO website (www.who.int) and the UK Faculty of Family Planning and Reproductive Health Care website (www.ffprhc.org.uk).[7,8]

The following statements serve as useful *aides memoire* for the new "missed pills rules":

- When a woman realises she has missed a **single pill**, she should take a pill as soon as possible and continue taking pills daily and additional contraceptive protection is not required.
- In the event of the **following numbers of pills** being missed: 'Two for Twenty' (i.e. if two or more 20 micrograms ethinylestradiol are missed) or 'Three for Thirty' (i.e. if three or more 30-35 micrograms

ethinylestradiol are missed), a back-up method (condoms / abstinence) should be used during the following seven days. In addition -

- If the pills are missed in the first week and unprotected intercourse has occurred (during the PFI or during the first week), the use of emergency contraception should be considered.
- If the missed pills are during week three, she should finish the pills in the current pack, commence a new pack and omit the PFI.

What is the current status of venous thromboembolism (VTE) and CCs?

The Royal College of Obstetricians and Gynaecologists (www.rcog.org.uk) recently issued a guideline on this topic.[9] VTE encompasses deep-vein thrombosis, pulmonary embolism and cerebral venous sinus thrombosis. For most women, COCs are a safe method of contraception and while the relative risk of VTE is increased, the absolute risk remains very small, as outlined in Table 1. **The increased risk of VTE is apparent by the fourth month of COC use, does not increase further with duration of use, and disappears by the third month after COC discontinuation.**[9,10] Heavy smoking, obesity and underlying thrombophilia increase the risk of VTE and these factors should be taken into account when making contraceptive choices. For the newer CCs - *Evra*® (transdermal patch) and *NuvaRing*® (intravaginal ring), it should be noted that long-term data on VTE is as yet unavailable.[9,11]

Table 1 Risk* of venous thromoembolism for combined oral contraceptive (COC) users[9]

	Relative risk	Absolute risk**
Healthy non-pregnant non-COC User		5 in 100 000
COC containing levonorgestrel / norethisterone	3-fold increase	15 in 100 000
COC containing gestodene / desogestrel / drospirenone	5-fold increase	25 in 100 000
Pregnancy	12-fold increase	60 in 100 000

*figures based on epidemiological data

**Absolute risk – refers to absolute risk per 100,000 woman-years with a 1 in 100 000 risk generally considered to be a 'minimal risk'.

What do you do with hypertension (HTN) and the COC?

HTN is an independent risk factor for myocardial infarction (MI) and stroke. COCs can increase both systolic and diastolic blood pressure (BP) by 4-9mmHg from baseline.[12] Approximately 1% of women develop HTN on COCs with the rate increasing with age and duration of use. Women with HTN who use COCs have a three-fold increase in MI and ischaemic stroke, and a ten-fold increase in haemorrhagic stroke (note: increased risk of an event refers to *relative risk* while the absolute risk remains low). Women with BP consistently greater than 140mmHg systolic or 90mmHg diastolic should be advised against use of COC.[13,14] If HTN develops while taking a COC, it should be discontinued; the BP usually returns to pre-treatment levels within 3-6 months.[12,13] Progestogen-only contraceptives are a suitable alternative for a woman who has or who develops HTN as no significant association of elevated BP with their use has been documented to date.[15]

How do COCs affect one's risk of cancer?

COCs are associated with a 50% reduction in the risk of ovarian and endometrial carcinoma.[16,17] The reduction in risk occurs after relatively short-term use (5 years) and persists for 10-20 years after use has been discontinued. The suggested mechanisms for these effects are ovulation suppression (for ovarian cancer) and suppression of oestrogen-induced endometrial cell proliferation (for endometrial cancer). There is also growing epidemiologic evidence that COCs may protect women from developing colorectal cancer.[16,17]

The data with regard to breast cancer is less clear. A meta-analysis of case-control studies showed a small increase in the risk of breast cancer with current use; beyond 10 years after discontinuation there was no detectable increase in breast cancer risk.[18] A more recent population-based case-control study found no increased risk of breast cancer in current users, women who had ever used COCs or women who were long-term COC users.[3,19] Any excess risk of breast cancer associated with COC use appears to come about quickly after starting, does not increase with duration of use and is gone ten years after discontinuation of COC use. Any excess risk does not appear to be influenced by family history, age at first use, dose or type of COC used.[16,19]

What are the new routes of administration of CCs?

Two new routes for the administration of CCs are available in Ireland – Evra® (transdermal patch) and *NuvaRing*® (intravaginal ring). Both products inhibit ovulation, with additional contraceptive benefits of thickened cervical mucus and reduced endometrial receptiveness, and have data demonstrating similar efficacy to COCs. Benefits, risks and contraindications are broadly similar to those of COCs. General advice regarding commencement / switching from a different form of contraception and advice on what to do in the event of patch detachment / ring expulsion are available to prescribers (on www.medicines.ie.)[20] and to users (patient information leaflet within each package).

Evra® is a transdermal patch which is worn for 7 days, for three consecutive weeks of each four week cycle, allowing for a withdrawal bleed during the fourth (patch free) week. Each patch releases 20 micrograms ethinylestradiol and 150 micrograms norelgestromin (active metabolite of norgestimate) daily and can be applied to the buttocks, abdomen, upper arm or torso.[20,21] Limited evidence suggests its effectiveness may decline for women weighing over 90kg.[5,6] Vomiting or diarrhoea does not affect hormone absorption. Patch detachment is uncommon – 1.8% (complete) and 2.9% (partial).

NuvaRing® is worn intravaginally for three weeks of each four-week cycle, allowing for a withdrawal bleed during the fourth week. It delivers 15 micrograms ethinylestradiol and 120 micrograms etonogestrel daily.[11,20]

PROGESTOGEN-ONLY CONTRACEPTION (POC)

What POCs are available here?

POC is available by a variety of routes including orally (*Noriday*®), injectable (*Depo-Provera*®), implantable (*Implanon*®) and intrauterine (the levonorgestrel-releasing intrauterine system: LNG-IUS / *Mirena*®). There is no increase in the risk of stroke, acute myocardial infarction, or venous thromboembolic events in women receiving oral, injectable or intrauterine POCs.

What is new with the progestogen-only pill (POP)?

The importance of taking the dose at the same time every day should be emphasised to all users as the effectiveness is reduced if pills are taken over three hours late.[20] A new POP available in the UK has the advantage of having a 12-hour window before effectiveness is reduced.[22] POPs are indicated for women who are i) lactating, ii) over 35 years of age and smoke, iii) obese, or those who have iv) oestrogen-linked contraindications or side-effects on the COC, v) diabetes, vi) hypertension and vii) migraine.

What is the link between Depo-Provera® and bone health?

Depot medroxyprogesterone acetate (*Depo-Provera*®) given by deep intramuscular injection every 12 weeks provides effective contraception for three months. *Depo-Provera*® is associated with an increase in bone resorption and a reduction in bone mineral density (BMD) as a result of suppression of oestradiol levels.[3,23] While published data suggests that the bone loss is reversible, it is not known if *Depo-Provera* use leads to a reduced peak bone mass and an increase in the risk of osteoporotic fracture in later life.[23-26] The Irish Medicines Board (IMB) and the Committee on Safety of Medicines (CSM) in the UK advise that a) in adolescents, *Depo-Provera*® may be used as first-line contraception once other methods are considered to be unsuitable or unacceptable, b) in women of all ages, re-evaluation of the risks and benefits of treatment should be carried out in those who wish to continue use for more than two years and c) other methods of contraception should be considered in women with significant lifestyle and/or medical risk factors for osteoporosis.[28] For all women, particularly users of *Depo-Provera*®, recommended strategies for optimising BMD include adequate calcium intake, weight-bearing and muscle-strengthening exercise, and cessation of smoking.[23]

Readers are also reminded that on discontinuation of *Depo-Provera*®, fertility returns within 6-9 months, though a delay of up to 18 months may be experienced.[23]

Is there a connection between the POCs and vascular disease or breast cancer? The POCs are not linked with an increase in vascular events (i.e. stroke, acute myocardial infarction, or venous thromboembolic events) although readers are reminded that there is little long-term evidence available with the newer POCs – *Implanon*® or *Mirena*®.[9,15] Recent publications affirm that POCs are not linked with an increased risk of breast cancer.[3,29]

What are the newer preparations of POCs?

Implanon® is a subdermal implant (inserted in the inner aspect of the upper nondominant arm), which releases 60-70 micrograms etonogestrel daily and provides contraception for up to three years.[20] The product SPC advises earlier replacement may be considered for women weighing ≥75kg.[20] Serum concentrations of etonogestrel high enough to inhibit ovulation are reached within one day of insertion. While well tolerated and effective, irregular bleeding (amenorrhoea in 30-40%, infrequent bleeding in 30%, prolonged bleeding in 10-20% and frequent bleeding in <10%) is the principal reason for discontinuation.[13] Counselling on the likely bleeding problems prior to insertion and the use of short-term additional oestrogen treatment, in the form of a low-dose COC may reduce these bleeding problems and reduce the rate of early removal.

Mirena® is a levonorgestrel (LNG) releasing T-shaped intra-uterine system (IUS) which releases 20 micrograms of LNG daily and provides contraception for five years.[20,30] It acts by endometrial suppression with additive effects on cervical mucus. It has minimal effect on the hypothalamo-pituitary-ovarian axis and most women (75%) continue to ovulate. Potential users should be advised that initial irregular spotting or bleeding is common after the insertion. Discontinuation / requests for removal are primarily due to menstrual bleeding abnormalities, particularly amenorrhoea. LNG-IUS users are more likely to experience amenorrhoea than IUD users. The LNG-IUS is also licensed as a therapeutic option for the treatment of menorrhagia, and for endometrial protection during oestrogen replacement therapy.[20]

EMERGENCY CONTRACEPTION (EC)

What is the risk of pregnancy following unprotected sexual intercourse and what impact does EC have on that risk?

Sperm can survive in the female genital tract for 5-6 days, and therefore fertilisation may occur days after sexual activity. A prospective study of couples seeking pregnancy found that a single act of unprotected sexual intercourse (UPSI) occurring around the time of ovulation was associated with an 8% risk of pregnancy.[31,32] Among women 19-26 years of age (the age group in which fertility is greatest), the risk of pregnancy may be as high as 50%.[31] Use of hormonal emergency contraception (EC) reduces the risk of pregnancy following UPSI to 1-2% and the use of a non-hormonal method (i.e. a copper-T IUD) reduces the risk to <1%.[31-34]

What methods are available and have there been any recent developments? The mechanism of action of EC is poorly understood. It can delay ovulation and decrease the probability of fertilisation after ovulation. The

licensed hormonal method is ***Levonelle***® - two tablets (each containing 0.75 milligrams of levonorgestrel) should be taken together within 72 hours of UPSI.[20] Taking the dose as soon as possible after UPSI increases its efficacy. Observational studies[36,37] indicate that *Levonelle*® taken 72-120 hours after intercourse may result in pregnancy rates similar to those in studies of earlier treatment (unlicensed for this use in Ireland). While available as an over-the-counter medication in the some countries, a prescription is required in Ireland.

The nonhormonal EC is the insertion of a copper-containing intrauterine device (IUD). It can be placed up to five days after UPSI and has the added benefit of providing continued contraception.[31,33,34] Clinical data indicate that it is effective for up to 12 years.

SPECIFIC SCENARIOS

Hormonal contraceptive choice for older women: The perimenopause refers to the transition from normal ovulatory menstrual cycles to the cessation of ovulation and menstruation. Its average age of onset is 46 years (range 39-51 years) and it lasts an average of 5 years (range 2-8 years).[16] Most women (93%) aged 40-55 years with regular cycles seem to ovulate each cycle.[13] No contraceptive method is contraindicated by age alone.[15] Contraceptive choice is influenced by many factors: frequency of intercourse, natural decline in fertility, sexual function, menstrual dysfunction, the presence of concurrent medical conditions or a family history of vascular disease and whether or not she is a smoker. **For sexually active women, contraception should be continued for 1 year after the last menstrual period if over 50 years, and for 2 years after the last menstrual period if under 50 years of age.**[13,16] UK data reveals that older women (≥40 years) use primarily non-hormonal methods of contraception: vasectomy (45%), female sterilisation (42%), male condoms (29%), IUDs (9%) and others (6%). Hormonal methods that are used include: COCs (8%), POPs (7%), progestogen-only injectables and implants (2%) and the LNS-IUS (2%).[16] While Irish data is much more limited, recent figures indicate that approximately 70% of prescribed *Mirena*® (used by 8.7% of Irish women aged 15-44 years) is for women over 30 years.[2]

Hormonal contraceptive advice for women over 40 years using HRT:[12,16] HRT does not suppress ovulation and cannot be used to provide contraceptive cover. The diagnosis of menopause is difficult in HRT users, as FSH measurements are unreliable and the duration of the perimenopausal period varies. POPs or *Mirena*® can be used with HRT to provide effective hormonal contraception. Effective non-hormonal methods of contraception include barrier methods and IUDs.

Hormonal contraceptive choice during lactation:[38] Fertility is reduced by breastfeeding, as a result any contraceptive method is more effective when used while lactating. COCs are generally not recommended in the first 6 months postpartum, unless other methods are deemed to be unacceptable and breastfeeding is well established. **COCs may be used** without restriction **from 6 months postpartum. POCs can be used** without restriction **from 6 weeks postpartum.**

Is there a link between hormonal contraceptives and weight gain? Contraceptive users frequently cite weight gain as a reason for quitting the use of hormonal contraception. In contrast with popular perception, randomised clinical trial data confirm that oral contraceptive use does not cause weight gain.[3,39] While evidence from observational studies suggests *Depo-Provera*® causes weight gain, the only randomised clinical trial that addressed the issue found that *Depo-Provera*® had no impact on appetite or weight.[23] Given the increasing prevalence of obesity, advice regarding diet, exercise and weight control is appropriate for all contraceptive users.

Obesity: (BMI ≥30 kg/m^2) is an independent risk factor for cardiovascular disease and VTE. Recent evidence has found that the risk of pregnancy is higher in obese women using CCs – oral and patch - and POCs – oral and implant.[5,6,13,] The SPC for *Evra*® mentions that efficacy may be reduced in women ≥90kg and the SPC for *Implanon*® advises that doctors may consider earlier replacement in heavier women.[20]

SUMMARY

The varied range of effective hormonal contraceptives available means that every woman who requires contraception should have access to information on all the methods so that she can make a fully informed decision. The benefits and risks of contraception, plans for future pregnancies, presence and treatment of concurrent medical conditions, the duration of desired contraceptive cover and a woman's preference should all be considered. If a hormonal method is preferred, consider whether oestrogen is suitable or acceptable. If appropriate, consider a COC or the alternative CCs (transdermal or intravaginal preparations). If oestrogen is deemed to be inappropriate, the progestogen-only methods – pills / injectable / implant or the LNG-IUS are available.

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