Contraception in women with medical problems

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Summary: Women with medical disease have a higher incidence of maternal mortality compared with healthy women, with cardiac disease now being the most common cause of maternal death in the UK. A handful of medical conditions exist where pregnancy is not recommended due to mortality rates approaching 50%. It is imperative that such women have the most reliable methods of contraception available. Contraceptive agents may themselves affect medical disease, or may interact with medications used by such women. There may be a range of contraceptive agents suitable for each medical condition. The contraceptive selected should be tailored to suit the individual. The following points should be considered when deciding on the most appropriate contraceptive agent: efficacy, thrombotic risk (oestrogen containing contraceptives), arterial risks (oestrogen containing contraceptives), infective risk (e.g. insertion of intrauterine device [IUD]), vagal stimulation (e.g. insertion of IUD, ESSURE®), bleeding risks with patients on anticoagulants, interaction with concomitant drugs, effects of anaesthesia and ease of use. This review aims to cover the different contraceptive agents available and the best ones to use for certain medical illnesses.

Keywords: contraception, general medicine, high-risk pregnancy

INTRODUCTION

Maternal medicine specialists and obstetric physicians should have an understanding of methods of pregnancy prevention that will both be effective and safe for a given individual with a medical illness. It is a disastrous, preventable situation when a woman who has been advised not to get pregnant does so because suitable contraception was not discussed with her. It is the duty of the physician seeing a woman for pre-pregnancy and postpartum counselling to discuss contraception or to refer her to another health professional who can.

Women with medical disease have a higher incidence of maternal mortality compared with healthy women, with cardiac disease now being the most common cause of maternal death in the UK.¹ A handful of medical conditions exist where pregnancy is not recommended due to mortality rates approaching 50%. It is imperative that such women have the most reliable methods of contraception available. Contraceptive agents may themselves affect medical disease or may interact with medications used by such women.

This review aims to cover the different contraceptive agents available and the best ones to use for certain medical illnesses.

The World Health Organisation (WHO) has classified contraceptive agents into the following four classes, depending on how suitable their use is in medical diseases:²

- Class 1. A condition for which there is no restriction for the use of the contraceptive method (always usable);
- Class 2. A condition where the advantages of using the method generally outweigh the theoretical or proven risks (broadly usable);

- Class 3. A condition where the theoretical or proven risks generally outweigh advantages of using the method (caution/counselling);
- Class 4. A condition which represents an unacceptable health risk if the contraceptive method is used (do not use).

The WHO classification for an individual contraceptive agent varies according to the circumstances (e.g. age, smoking history) and pre-existing medical illness (e.g. cardiac disease, hypertension and diabetes). For example, a woman considering using the combined oral contraceptive pill who has a family history of venothromboembolism (VTE) is:

- WHO 1: if she has a second-degree relative (e.g. maternal aunt) with VTE (always usable);
- WHO 2: if she has a first-degree relative who is ≥ 45 years with VTE (broadly usable);
- WHO 3: if she has a first-degree relative who is < 45 years with VTE (caution with use);
- WHO 4: if she herself has had a VTE (do not use).

There are a plethora of different contraceptive agents in the market. They can be divided into hormonal and non-hormonal methods (Table 1).

PRE-PREGNANCY COUNSELLING

Contraception should be discussed with all women who attend for pre-pregnancy counselling if it is decided that they should never conceive or should delay pregnancy. A discussion should also be held with adolescent teenagers between the ages of 12 and 15 years who have significant medical disease, such as complex congenital heart disease, depending on their

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Table 1 Contraceptive agents

Hormonal contraceptives

Combined hormonal contraceptives (CHC) contain oestrogen and progestogen	Combined oral contraceptive pill (COC)
	Second generation (norethisterone, LNG)
	Third generation (e.g. desogestrel, gestodene)
	Anti-androgenic and anti-mineralocorticoid (drospirenone: Yasmin [®] , Bayers PLC, Berks, UK)
	Anti-androgenic (cyproterone acetate: Dianette [®] , Bayers PLC, Berks, UK)
Progesterone-only contraceptives (POC)	Combined hormonal skin patch (EE and Norelgestromin: Evra [®])
	Combined hormonal vaginal ring (EE and etonogestrel: NuvaRing [®])*
	Combined injectable (estradiol cypionate and MPA: Lunelle [®] , Bayers PLC, Berks, UK)*
	POP:
	Second-generation POP (mini-pill)
Non-hormonal contraceptives	Third-generation POP (desogestrel: Cerazette [®])
	Injectables:
	DMPA (Depo-Provera [®])
	NET-En*
	LNG-IUS (Mirena [®])
Sterilization	Subdermal etonogestrel implant (Implanon [®])
	Male
	Female:
	Laparoscopic
	Mini-laparotomy
Copper IUD	At caesarean section
	Hysteroscopic (ESSURE [®])
	Male and female condoms
	Cap
	Diaphragm
Barrier methods	Sponge
Spermicides	

LNG, levonogestrel; EE, ethinylloestradiol; MPA, medroxyprogesterone acetate; POP, progesterone-only pill; DMPA, depot medroxyprogesterone acetate; NET-En, norethisterone-enanthate; LNG-IUS, levonogestrel intrauterine system; IUD, intrauterine device
*licensed in some countries

level of maturity. This is justified by the fact that 17% of girls admit to having had sex before the age of 16 years. In the western world, teenage pregnancy rates are highest in the USA. The UK has the highest rates in Western Europe, where 7.7/1000 girls under the age of 16 get pregnant.³

CONTRACEPTIVE AGENTS

There may be a range of contraceptive agents suitable for each medical condition. The contraceptive selected should be tailored to suit the individual. The following points should be considered when deciding on the most appropriate contraceptive agent:

- Efficacy;
- Thrombotic risk (oestrogen containing contraceptives);
- Arterial risks (oestrogen containing contraceptives);
- Infective risk (e.g. insertion of IUD);

- Vagal stimulation (e.g. insertion of IUD, ESSURE[®] [Conceptus, Inc., California, USA]);
- Bleeding risks with patients on anticoagulants;
- Interaction with concomitant drugs;
- Effects of anaesthesia;
- Ease of use.

Contraceptive efficacy

Few women use a contraceptive agent perfectly and consistently, exactly in accordance with the manufacturer's instructions. Most women are 'typical users', where they may be inconsistent with correct use of the method.² Pregnancy rates for typical users are a better reflection of the efficacy that can be expected from a contraceptive and are shown in Table 2, which is based on USA studies.² The most reliable contraceptive methods should be recommended for those with WHO class 3 or 4 risk.

The contraceptive methods that will be considered in detail are those where less than 10% of women conceive in the first year of typical use.

Table 2 Failure rates of contraceptives

Contraceptive method	Percentage of women experiencing an unintended pregnancy within first year of use	
	Typical use	Perfect use
No method	85	85
Spermicides	29	18
Withdrawal	27	4
Periodic abstinence	25	
Calendar		9
Ovulation method		3
Sympto-thermal		2
Post-ovulation		1
Cap		
Parous women	32	26
Nulliparous women	16	9
Sponge		
Parous women	32	20
Nulliparous women	16	9
Diaphragm	16	6
Condom		
Female	21	5
Male	15	2
COC and POP	8	0.3
Combined hormonal patch (Evra [®])	8	0.3
Combined hormonal (NuvaRing [®] , Organon Pharmaceuticals, Inc., USA)	8	0.3
DMPA (Depo-Provera [®] , Pharmacia, Pfizer Ltd, Surrey, UK)	3	0.3
Combined injectable (Lunelle TM)	3	0.05
IUD		
Copper T	0.8	0.6
Mirena [®] (Bayer PLC, Berks, UK) (LNG-IUS)	0.1	0.1
Female sterilization	0.5	0.5
Male sterilization	0.15	0.15
Implant (Implanon [®])	0.05	0.05

COC, combined oral contraceptive; POP, progesterone-only pill; DMPA, depot medroxyprogesterone acetate; IUD, intrauterine device; LNG-IUS, levonogestrel intrauterine system

Poor efficacy	Good efficacy	High efficacy
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Female sterilization

Sterilization, although highly effective, is not the most effective form of contraception (Table 2).² It carries a 10-year failure rate of 2–3/1000 when performed laparoscopically with Filshie clips.⁴ The lifetime risk of failure is estimated to be 0.5%.⁵ The 10-year failure rate is higher (0.75%) if performed at the same time as caesarean section.⁶ There is a higher risk of ectopic pregnancies in the failures, which can rupture, resulting in severe haemorrhage and pain. Bilateral salpingectomy is a more secure method of contraception which cannot be reversed. There may be regret following sterilization, as it is intended to be permanent, although can be reversed in some circumstances.⁵

Laparoscopic sterilization is usually performed under general anaesthesia. Instrumentation of the cervix can result in a vaso-vagal response, which may not be tolerated in those with pulmonary vascular disease. A carbon dioxide (CO₂) pneumoperitoneum is created which reduces venous return and has the potential of CO₂ being absorbed systemically. This can result in paradoxical emboli in women with the right to left shunts.⁷ Regional anaesthesia and a reduced amount of CO₂ may combat some of these problems, but requires skilled operators.⁸ Alternatively, a mini-laparotomy can be performed under regional block.

ESSURE[®] is a new sterilization method in which intra-tubal stents are inserted into the proximal section of the fallopian tube hysteroscopically using oral analgesia or sedation.⁹ Tubal occlusion occurs by three months due to mechanical obstruction and inflammation causing fibrosis. The incidence of vaso-vagal attacks from the insertion of the hysteroscope is 1.85%.¹⁰

Male sterilization

Vasectomy is more efficacious than female sterilization and, of course, involves no risk to the woman.⁵ It is performed under local anaesthetic but should be a very considered choice if it is to be used as contraception in the partner of a woman with severe medical disease. Her lifespan may be significantly reduced and he may wish to father children in the future with a new partner.

Combined hormonal contraceptives

These are combinations of oestradiol (an oestrogen) and a progestogen (synthetic progesterone) which inhibit ovulation and are therefore very effective contraceptives (Table 1).

The main risks due to the oestrogen component are venous thrombosis, hypertension, ischaemic stroke and ischaemic heart disease (IHD). Data are limited as to the risks with the non-oral combined hormonal contraceptives (CHC). Tables 3 and 4 show relative (WHO class 3) and absolute (WHO class 4) contraindications to CHC.² The recommendations have recently been updated by the UK Faculty of Family Planning and Reproductive Health Care.¹¹

Liver metabolism

Both oestrogens and progestogens are metabolized by the liver and their use may adversely affect women whose liver function is compromised. They both interact with warfarin metabolism, necessitating more frequent monitoring of international normalized ratio (INR) when initiating treatment and adjustment of dose.¹²

Liver enzyme inducers such as rifampicin, rifabutin, griseofulvin, phenytoin, carbamazepine, barbiturates, primidone,

Table 3 Relative contraindications for using combined hormonal contraception (WHO class 3/UK category 3)^{2,11}

System	Disease
Arterial	Adequately controlled hypertension Moderate hypertension untreated: SBP < 160 mmHg or DBP < 95 mmHg
Venous	Multiple risk factors for arterial disease First-degree relative age <45 years with VTE Immobility unrelated to surgery
Endocrine	Diabetes mellitus with mild/moderate vascular disease/nephropathy/retinopathy/neuropathy
Breast	Not breastfeeding <3 weeks postpartum Fully breastfeeding ≥6 weeks to 6 months postpartum Breast cancer >5 years ago without recurrence Carriers of known gene mutations associated with breast cancer (e.g. BRCA1 and BRCA2)
Metabolic	Some known hyperlipidaemias* Obesity 35–39 kg/m ² BMI
Neurological	Previous migraine with aura at any age Migraine without aura age ≤35 years (C) Migraine without aura age ≥35 years (I)
Liver	Current or medically treated gallbladder disease Previous cholestasis due to combined oral contraceptives Obstetric cholestasis Mild cirrhosis (compensated)
Drugs	Liver enzyme inducers† Smoking <15 cigarettes/day and age ≥35 years Stopped smoking <1 year ago

VTE, venothromboembolism; BMI, body mass index; C, continuation of contraceptive; I, initiation of contraceptive; DBP, diastolic blood pressure; SBP, Systolic blood pressure

*e.g. familial hypercholesterolaemia

†reduces contraceptive effectiveness

Table 4 Absolute contraindications for using combined hormonal contraception (WHO class 4/UK category 4)^{2,11}

System	Disease
Arterial	Severe hypertension untreated: SBP ≥ 160 mmHg or DBP ≥ 95 mmHg Hypertension with vascular disease* IHD CVA Complicated valvular and congenital heart disease† Multiple risk factors for cardiovascular disease‡
Venous	Thrombosis (deep vein thrombosis, pulmonary embolism or cerebral venous thrombosis) Major surgery with prolonged immobilization Known thrombophilia
Endocrine	Diabetes mellitus >20 years Diabetes mellitus with severe vascular disease or severe nephropathy, retinopathy or neuropathy
Breast	Breastfeeding <6 weeks postpartum Current breast cancer
Metabolic	Obesity ≥40 kg/m ² BMI
Neurological	Migraine with aura Migraine without aura and age ≥35 years (C)
Liver	Active viral hepatitis Severe (decompensated) cirrhosis Benign or malignant liver tumours
Connective Tissue	Systemic lupus erythematosus with anticardiolipin antibodies/ lupus anticoagulant
Drugs	Smoking ≥15 cigarettes/day and age ≥35 years

DBP, diastolic blood pressure; IHD, ischaemic heart disease; CVA, cerebrovascular accident; BMI, body mass index; C, continuation of contraceptive

*coronary heart disease, peripheral vascular disease, hypertensive retinopathy, transient ischaemic attacks

†e.g. with pulmonary hypertension, atrial fibrillation, history of bacterial endocarditis

‡age, smoking, diabetes mellitus, hypertension, hyperlipidaemia

topiramate, oxcarbazepine and even St John's Wort may result in reduced contraceptive efficacy of CHC. Griseofulvin and St John's Wort are less potent enzyme inducers than rifampicin. If continuing with CHC, the preparation used should contain at least 50 µg ethinyl oestradiol and additional contraception such as barrier methods should be used for up to four weeks following discontinuation of the liver enzyme inducer.^{11,12}

Progestogen-only contraceptives

Progestogen-only contraceptives (POC) can often be used in diseases where oestrogens are contraindicated such as in women at risk of thromboses. The newer long-acting progestogen-only methods (levonorgestrel intrauterine system [LNG-IUS] and Implanon®, Organon Laboratories Ltd, Cambridge, UK) are the most efficacious contraceptives available and have few medical contraindications.²

The main side-effect with progestogens is unscheduled light vaginal bleeding. This is due to inconsistent ovulation with low-dose progesterone-only methods such as second-generation POP and implants, and may not improve. With the LNG-IUS, unpredictable bleeding is due to endometrial shedding, which usually settles after a few months when there is a thin or absent endometrium. This leads to light or absent periods, which is particularly advantageous to those with cyanotic heart disease who would not tolerate anaemia from heavy periods and those on warfarin, which may itself cause menorrhagia.

Like oestrogens, progestogens are metabolized by the liver and interact with warfarin.¹² Concomitant use of liver enzyme inhibitors reduces the contraceptive efficacy of POP and implants. If these methods are to be used, an increased dose is advisable.¹² LNG-IUS and injectable progestogens remain effective.^{2,12}

Progestogens lead to a variable fluid retention and simple ovarian cysts. Androgenic progestogens can result in acne. All POC cause alterations in the lipid profile, but injectables, POP and Implanon® have a greater effect than LNG-IUS.^{2,13-15}

Relative contraindications to POC are shown in Table 5.^{2,11} These relate in many instances to the use of injectables. Injectables and Implanon® are WHO class 3 in the context of current venous thromboses because of the theoretical risk of haematomas occurring with their use at the site of injection/insertion in a fully anticoagulated patient. Similarly, the concern with LNG-IUS relates to the potential risk of bleeding during insertion. POC should not be used in women with current breast cancer.^{2,11}

Progestogen-only pills

Second generation mini-pills do not inhibit ovulation and hence there is only a three-hour window period for missed pills. It is a less reliable method than other POC.

The third generation progesterone-only pill (POP), Cerazette® (Organon Laboratories Ltd, Cambridge, UK) (desogestrel 75 µg) is a newer anovulatory contraceptive with similar efficacy as combined oral contraceptives (COC) and 12-hour window period for missed pills. It is a pro-drug for etonogestrel found in Implanon® and can be tried before inserting the implant to assess tolerability. It can also be given with Implanon® if a liver enzyme-inducing drug is necessary.

Table 5 Relative contraindications for using progestogen-only methods of contraception (WHO class 3/UK category 3): all methods unless specified

System	Disease
Arterial	Hypertension with vascular disease (injectables) Multiple risk factors for cardiovascular disease* (injectables) IHD (injectables; POP/IMP I/C) CVA (injectables; POP/IMP I/C)
Venous	Current thrombosis on anticoagulation (deep vein thrombosis, pulmonary embolism or cerebral venous thrombosis) (injectables/IMP)
Endocrine	Diabetes mellitus >20 years (injectables) Diabetes mellitus with vascular disease i.e. nephropathy, retinopathy or neuropathy (injectables)
Breast	Breastfeeding <6 weeks postpartum Breast cancer >5 years ago without recurrence
Neurological	Migraine with aura (all methods: C)
Liver	Active viral hepatitis Severe (decompensated) liver cirrhosis Tumours: benign/malignant liver tumours
Drugs	Liver enzyme inducers (POP/IMP)

IHD, ischaemic heart disease; CVA, cerebrovascular accident; POP, progesterone-only pill; I, initiation of contraceptive; C, continuation of contraceptive; IMP, implant

*age, smoking, diabetes mellitus, hypertension, hyperlipidaemia

Norethisterone-enanthate and depot medroxyprogesterone acetate (Depo-Provera®)

These are highly effective deep intramuscular injectable contraceptives lasting for eight or 12 weeks respectively. Their use is limited in anticoagulated women who may develop haematomas at the injection site.^{2,11} Injectables result in a hypo-oestrogen status with long-term use, which may have implications for women with, or women at risk of, vascular disease, IHD or osteoporosis.¹⁶⁻¹⁸ The effects of injectables may persist for some time after discontinuation.²

Levonorgestrel intrauterine system (Mirena®)

This is an IUD which is inserted into the uterus after cervical dilatation. It is more effective than sterilization and requires replacement after five years.² It releases 20 µg per day of levonorgestrel directly into the uterus, causing endometrial shedding and subsequent light periods. Progestogenic side effects are minimal as only a small amount of the hormone is absorbed systemically.¹⁹ LNG-IUS insertion can induce a vagal bradycardia, which may not be tolerated by those with pulmonary hypertension or a Fontan's circulation.²⁰

Women should be screened for sexually transmitted infections (STIs) or empirically covered with antibiotics. Those at risk of bacterial endocarditis should be given appropriate antibiotic prophylaxis for insertion. Progestogens thicken cervical mucus, which tends to prevent infections with long-term use of LNG-IUS unlike the copper coil. Absolute contraindications to LNG-IUS insertion include patients with puerperal sepsis, following a septic abortion or with current pelvic inflammatory disease (PID).²¹

Implanon®

This subdermal rod is the most effective female contraceptive.² It is inserted by trained operators into the subdermal tissue of the non-dominant arm under local anaesthetic. There is a lesser risk of haematoma formation than with injectables. Firm pressure

following the use, for five minutes, is usually sufficient to prevent this complication. Blood levels are also steadier than with depot medroxyprogesterone acetate (DMPA) and there are less progestogenic side effects. Twenty percent of women are rendered amenorrhoeic after two years, but irregular menstrual bleeding can be problematic after insertion and is often the reason why women request removal.²² It requires removal and replacement in the other arm after three years. The effects of Implanon® may persist for some time after removal.²

Copper intrauterine contraceptive device

Copper containing coils are an effective form of contraception and are inserted into the uterus after cervical dilatation. A major advantage lies in banded copper IUDs, which require replacement after 5–10 years. The risks include infection at the time of insertion and with long-term use, vaso-vagal response with insertion (less than with LNG-IUS) and heavy periods.^{20,21}

They should be avoided in those with pulmonary vascular disease or previous bacterial endocarditis. Women should be screened for STIs prior to insertion or empirically treated. Copper IUDs should be used with caution in those with complicated valvular disease, where if used, the insertion should be covered with antibiotics. Caution is also necessary in those who are anticoagulated. They should not be used in cases of puerperal sepsis, following septic abortion or with current PID.^{2,11,21}

Emergency contraception

Women who failed to take appropriate precautions against pregnancy can use Levonorgestrel (1.5 mg Levonelle One Step®; 0.75 mg, 2 tablets Levonelle-2, Bayer PLC, Berks, UK), or the combined oestrogen–progestogen (Yuzpe) regimen (available in some countries) within 72 hours of unprotected sexual intercourse (UPSI). This is not intended to be used as a regular form of contraception due to its high annual failure rate. Within five days of UPSI, they can have a copper IUD fitted.²³

Levonorgestrel is a progestogen which is better tolerated and more effective than the combined Yuzpe regimen. There are no medical contraindications to its use. It has 1% failure rate if used within 72 hours of UPSI. Common side effects are nausea (14%) and vomiting (1%).²³ There is a reported interaction between warfarin and levonorgestrel, resulting in an increase in the INR of up to four-fold. The Yuzpe regimen may be more appropriate in patients anticoagulated with warfarin.²⁴

The preferred option for women using liver enzyme inducers is the copper IUD. If progestogens are to be used, the single dose should be increased to three tablets of Levonelle-2® (2.25 mg) or two tablets of Levonelle One Step® (3 mg).²³

Barrier methods

Use of male and female condoms is not a very effective method for prevention of pregnancy, but should be used to prevent STIs in combination with a more secure contraceptive method.

Termination of pregnancy²⁵

Urgent termination of pregnancy facilities should be readily available and accessible for women with medical conditions where pregnancy places their lives at risk.

Medical termination of pregnancy

This can be performed throughout gestation. Mifepristone is given orally and usually followed one to two days later with a prostaglandin (misoprostol or gemprost).

Surgical termination of pregnancy

This can be performed by suction or dilatation and evacuation at more advanced gestations up to 24 weeks. It may require cervical priming with a prostaglandin.

INDIVIDUAL DISEASES

Hypertension

POC do not increase blood pressure (BP) and there is no convincing evidence that they increase cardiovascular events.^{26,27} These and the copper IUD are considered as safe contraceptives in hypertensive women. A study of 140 women using DMPA for three to five years showed no significant difference in BP compared with controls.²⁸ In another study of 100 women using either DMPA or the copper IUD, no difference in BP occurred over 10 years of its use.²⁹ Two large multinational case-control studies showed no increased risk of cardiovascular disease with the use of POP²⁶ or with the use of POP or injectable methods.²⁷ The latter study did show that among women with hypertension, there was a small increase in the incidence of stroke in current POC users compared with non-users; however, numbers were small with wide confidence intervals. Little data exist on the LNG-IUS. One follow-up study of 82 women using LNG-IUS over 12 years showed a small increase in BP, but there were no comparative controls and the effect may have been due to age.¹⁹

Combined oral contraceptive pills with modern low-dose formulations increase ambulatory BP in normotensives and mild hypertensives by 6–8 mmHg compared with users of the copper IUD in small non-randomized and cross-sectional studies.^{30,31} A large prospective cohort study of female nurses in the USA confirmed that current users of COC have an increased risk of developing hypertension (multivariate RR = 1.8; 95% confidence interval [CI] 1.5–2.3) compared with women who had never used them. The risk is highest among long-term users (≥6 years) and decreases shortly after COC is stopped.³²

Arterial events

The absolute risk of arterial disease and ischaemic stroke is very small in women of reproductive age even if they have known risk factors, but the effects of these conditions can be devastating.

There is no evidence for an increase in the risk of stroke or myocardial infarction (MI) in association with the POC.^{2,26,27} There are moderately unfavourable alterations in lipid metabolism (a surrogate marker for vascular disease) with some POC particularly injectables. Injectable progestogens should

be used with caution in those with IHD and stroke. A multicentre study comparing 50 women on DMPA with 120 controls using the copper IUD for three to nine years found reductions in high-density lipoprotein (HDL) and an increase in low-density lipoprotein (LDL) in those on DMPA.¹³ Implanon® has been shown to cause a reduction in HDL and LDL levels and increase triglyceride levels over a two-year follow-up of 40 women.¹⁵ If a woman using Implanon®, DMPA or the POP develops IHD or a stroke, she should consider changing to LNG-IUS, which, in a recent one-year follow-up study of 48 premenopausal women, has been shown to have a better lipid profile with an increase in HDL levels.¹⁴ Alternatively, she could use the copper IUD.

CHC should not be used in women with a history of IHD or ischaemic stroke.² Current users of COC had an increased risk of MI with an adjusted odds ratio (OR) of 2.48 (95% CI 1.91–3.22) compared with never-users in a meta-analysis of 23 studies.³³ This meta-analysis consisted of 19 case-control studies and four cohort studies, spanning from 1968 to 2001. There was a dose-related increase in MI in users taking between 30 and 50 µg oestradiol. The risk of MI was not increased in users of 20 µg oestradiol preparations, users of third-generation COC and past users of COC. The risks of MI were further increased by 9- to 10-fold in smokers, hypertensives and those with hypercholesterolaemia.

COC use increases the risk of ischaemic stroke by two to three-fold.^{34–36} However, this risk appears mainly to be due to high-dose COC. A pooled analysis of two USA population-based case-control studies showed that women using low-dose COC did not have an increased risk of CVA.³⁷ Two large national³⁵ and multinational³⁶ case-control studies have shown that the risk of stroke with COC is oestrogen dose-related. Low-dose COC users had a lower OR of 1.5–1.7 for stroke compared with higher OR of 4.5–5.3 with oestradiol doses of 50 µg.^{35,36} Users of low-dose COC with second-generation progestogens had a higher risk of stroke than third-generation progestogens (OR 2.2 vs. 1.4).³⁵ Smoking and hypertension further increase the risk of stroke in COC users by three to 10 times.^{35,36}

Thrombosis

Oestrogen is prothrombotic due to increases in hepatic production of some clotting factors. There is a three- to five-fold increased risk of VTE with COC users compared with non-users and a 12-fold increase with pregnancy.³⁸ Third-generation progestogens desogestrel and gestodene are twice as thrombotic than second-generation progestogens (Table 6).^{39,40} The risk greatly increases with age and obesity. The risk of an event is greatest during the first year of use,

which may be due to unmasking of a previously unidentified thrombophilia.⁴¹

WHO recommends that CHC should not be used in women who have had an idiopathic VTE or a VTE associated with a high oestrogen state, such as pregnancy or previous CHC use, unless they are adequately anticoagulated.²

Women with known thrombophilias should not use CHC as they have an increased risk of VTE which is further increased by two- to 20-fold if they start COC.^{2,11,42} A recent meta-analysis showed that COC users with either Factor V Leiden or antithrombin III deficiency had the highest odds ratio (OR) of developing VTE compared with non-users with no thrombophilia (OR 16 and 13, respectively) and non-users with differing thrombophilias.⁴² This meta-analysis was unsurprisingly over-represented by studies on women with the most common mutations (Factor V Leiden and prothrombin gene mutation). Data from the Leiden thrombophilia study showed that among women with any thrombophilia, there was a 19-fold increased risk of developing a VTE in the first six months and an 11-fold increased risk in the first year of COC use.⁴³ Screening low risk populations for thrombophilias prior to commencement of CHC has not been shown to be cost-beneficial due to the cost of the laboratory tests and the low prevalence of thrombophilias. Selective thrombophilia screening based on previous personal and/or family history of VTE has been shown to be more cost-effective than universal screening in the UK.⁴²

There are few data regarding VTE and combined hormonal contraception administered transdermally, vaginally or via injectables. These non-oral routes avoid first pass metabolism and theoretically would have less effect on clotting factors. However, two out of three epidemiological studies sponsored by the drug company producing the Ortho Evra® (Ortho-McNeil-Janssen Pharmaceuticals, Inc., USA) contraceptive patch using data from electronic health care systems have shown that the Ortho Evra® contraceptive patch is associated with an approximately two-fold increase risk in the risk of medically verified VTE events compared with the users of COCs containing either 35 µg of oestradiol and norgestimate⁴⁴ or 30 µg of oestradiol and levonorgestrel.⁴⁵ This may be due to mean serum oestrogen levels being 60% higher in users of the patch compared with users of COCs containing 35 µg of oestradiol.⁴⁶

The third study is conflicting and found that non-fatal VTE events are similar in incidence in users of the Ortho Evra patch and those on the COC containing 35 µg of oestradiol and norgestimate, even with a further 17 months of new case data analysis.^{47,48}

The copper IUD and progesterone-only methods are safer than CHC for women at risk of VTE⁴⁹ and should be used in preference, although there is some concern of haematoma formation with injectables or Implanon®, and with bleeding at the time of insertion of LNG-IUS in the anticoagulated patient (see earlier).

Table 6 Risks of venothromboembolic events with COC

	Risk of VTE per 100,000 women
Healthy non-pregnant, non-users of COC	5
Second-generation COC	15
Third-generation COC*	25
Pregnancy	60

COC, combined oral contraceptive
*desogestrel and gestodene

Pulmonary hypertension

Any form of pulmonary arterial hypertension (PAH) is associated with maternal mortality rates of up to 50%.⁵⁰ The mechanism of the disease includes pulmonary vasoconstriction, pulmonary vascular remodelling and *in situ* thrombosis, resulting in an increased pulmonary vascular resistance. Pregnancy is not advisable as pulmonary blood flow cannot increase and

even mild pulmonary hypertension is associated with substantial maternal mortality rates. Fetal risks include the possibility of teratogenicity with women on the pulmonary vasodilator bosentan and the effects of chronic hypoxia.^{51,52} The most efficacious non-thrombogenic contraceptives should be used.

As most patients are anticoagulated with warfarin, injectable progestogens are unsuitable. Coil insertion (copper or LNG-IUS) results in a vaso-vagal episode in at least 1.2% of women due to cervical dilatation. The incidence is greater with IUS insertion than with copper IUDs due to the larger width of the LNG-IUS.²⁰ Bradycardias are poorly tolerated in pulmonary hypertensives and can lead to circulatory collapse. If IUD use is considered necessary, it should be inserted in hospital with an anaesthetist present and the availability of atropine.

Implanon[®] is the most suitable method of contraception in women with pulmonary hypertension as it is highly efficacious and avoids the complications of injectables and coils. The slightly less efficacious Cerazette[®] can also be used. Increased doses of both are required if the patient is on bosentan, which is a liver enzyme inducer that reduces the efficacy of some progestogens.^{12,82}

CHCs are contraindicated due to their thrombotic risk. Female sterilization may be performed without instrumenting the uterus, but vasectomy should not be recommended as the male will usually outlive his partner.

Migraines

Migraine in women of childbearing age doubles the risk of ischaemic stroke but does not affect the incidence of haemorrhagic stroke.⁵³⁻⁵⁶ Several studies have shown that women with migraine who use COC have a two- to four-fold increased risk of stroke compared with non-users with migraine.^{37,56,57} This equates to an eight-fold increase in the risk of stroke in COC users with migraine compared with non-users without migraine as evidenced in a recent meta-analysis of observational studies.⁵⁵ However, these studies are limited by their case-controlled design with small numbers of cases and the fact they do not distinguish between users of high or low-dose oestrogen or consider the influence of age, or presence of aura, on the incidence of stroke in COC users. An aura occurs before the headache and specifically relates to focal symptoms indicating ischaemia and includes unilateral sensory or motor symptoms and speech disturbance. The visual symptoms of aura include homonymous hemianopia, fortification spectra (a star-shaped figure near the point of fixation with scintillating edges) and scotoma. Aura does not include flashing lights, blurred vision, photophobia, nausea or vomiting.¹¹ Most studies (all case-controlled) show that women who suffer from migraines with aura have a higher risk of stroke than those without aura.^{53-55,58} The mechanism is considered to be due to a reduction in cerebral blood flow to certain areas and increased platelet activity. However, numbers in these studies are small and hemiplegic migraine can be erroneously classified as a stroke case.

Based on this evidence, COC use is WHO class 3 in women with migraine without aura, but is WHO class 4 with aura.² The risk of stroke also increases with age, smoking and hypertension, which would all need to be taken into consideration before using CHC. Absolute risks of stroke are small, but can be so devastating that consideration should be given to using POCs or the copper IUD in this setting. WHO

cautiously recommends that women on POC who subsequently develop migraine with aura should consider discontinuing (class 3).²

Diabetes

A planned diabetic pregnancy allows optimization of glucose control around conception, which reduces congenital anomalies in the fetus. Effective contraception for diabetics is therefore important. WHO advises the copper IUD for women with diabetes mellitus with or without further co-morbidity, although there is a risk of infection with this method.²

Hormonal contraceptives have been reported to influence carbohydrate and lipid metabolism. Small randomized studies show that glucose metabolism remains stable in diabetic women using copper IUD, LNG-IUS, POP and low-dose combined oral contraceptives, but is slightly impaired with high-dose combined oral contraceptives.⁵⁹ There are conflicting results as to lipid metabolism in diabetics with hormonal contraception, but overall, COC appear to have a minor adverse effect, whereas POC slightly improve lipid metabolism.⁵⁹ There is concern regarding injectable progestogens in diabetics. In a small prospective comparative study of DMPA, norplant (subdermal rod) and COC, DMPA was shown to increase total lipids and LDL, and decrease HDL.⁶⁰ Hence, those with vascular disease should avoid long-term use of progestogen injectables. There are no long-term studies in vascular progression in diabetics on hormonal contraceptives, but the threat of arterial events confines the use of CHC to non-smokers under the age of 35 who are normotensive and without vascular complications.

Systemic lupus erythematosus

CHC can be used in women with inactive, moderately active, stable disease but should be avoided in those with any evidence of vascular disease, lupus nephritis or antiphospholipid antibodies, due to an increase in disease activity and thrombosis. The OC-SELENA study, a double blind trial of 183 premenopausal women with mild SLE, showed no difference in disease activity in women randomly assigned to COC or placebo.⁶¹ A single blind uncontrolled study of 162 women with moderate lupus randomly assigned to COC, POP or copper IUD also found a similar rate of flares in each group. However, they found that thromboses occurred in patients on hormonal contraception in the presence of low titre of antiphospholipid antibodies.⁶² An older retrospective, uncontrolled study including women with active lupus nephritis showed a flare rate of 43% with COC.⁶³

POC and the copper IUD are suitable and effective contraceptives in women with varying lupus disease severity, but POC should probably be avoided in those with antiphospholipid antibodies.⁶²

Sickle cell disease

DMPA reduces the incidence of painful crises in women with sickle cell disease, making it an attractive contraceptive.⁶⁴

In a small study of 25 patients randomized to DMPA or intramuscular saline injections in a crossover design, women on DMPA were less likely to experience a painful sickle episode

(OR 0.23).⁶⁵ CHC use in women with homozygous sickle cell disease remains unresolved with theoretical concerns of promoting thromboses.⁶⁵

Liver

Women with a history of obstetric cholestasis or with previous cholestasis while using CHC may develop cholestasis with subsequent CHC use. This is theoretically possible with POC use. If hormonal contraception is used, the patient should be monitored for pruritis and abnormal liver function tests.⁶⁶

Oestrogens and progestogens are metabolized by the liver, and their use may adversely affect those with active viral hepatitis, severe cirrhosis and liver tumours where liver function is compromised.^{67–69} CHC use is regarded as WHO class 4 in these circumstances.² The concern with POC use is similar, but less than that of CHC use, and is graded WHO class 3.² CHC may also enhance the growth of liver tumours, although the evidence is inconclusive to establishing a relation between COC use and the risk of hepatocellular carcinoma.⁶⁹ The copper IUD can be safely used in women with liver disease.

Inflammatory bowel disease⁷⁰

The copper IUD provides a good choice for long-term contraception in women with inflammatory bowel disease (IBD). Absorption of hormonal oral methods of contraception may be reduced by small bowel involvement or malabsorption.

COC undergo an enterohepatic circulation where inactive metabolites are broken down by gut bacteria to ethinyloestradiol, which is reabsorbed. Broad spectrum non-enzyme-inducing antibiotics may reduce contraceptive efficacy of COC by altering gut flora. CHC should be stopped at least four weeks before a major surgery due to the increased risk of VTE.

Laparoscopic sterilization is inappropriate in women with IBD who have had previous pelvic or abdominal surgery due to the increased risk of complications.

Osteoporosis

DMPA suppresses pituitary production of gonadotrophins, which results in the inhibition of both oestrogen production by the ovary and ovulation. Hypo-oestrogenaemia results in a loss of bone mineral density (BMD). Two prospective studies in women aged 12–21 years have confirmed that DMPA results in a progressive and sustained loss in BMD over two years, compared with Norplant and the COC, which both resulted in equivalent increases in BMD as controls.^{17,18} There has only been one study examining fracture risk in DMPA users.⁷¹ This case-controlled study of 3758 female USA Army recruits found that non-Hispanic white DMPA users had an increased risk of stress fractures following eight weeks of basic training (RR 1.17, CI 1.01–2.90; $P = 0.04$). There was no significant difference following adjustment for baseline BMD.

Although there has been concern regarding adolescents not achieving peak bone mass due to DMPA use and women over 40 not regaining bone mass following the discontinuation of DMPA, available evidence suggests that the decline in BMD is substantially reversed after the discontinuation of DMPA. Data on fracture risk are sparse.

A prospective cohort study of 170 adolescents showed that DMPA use resulted in significant loss of BMD at the hip and spine, which reversed within a year of discontinuation to control levels.⁷² Five studies (1 large cross-sectional⁷³ and 4 prospective^{74–77}) in premenopausal women showed that spine BMD improved faster than hip BMD following cessation of DMPA,^{74–77} the rate of improvement was faster in those who had used DMPA for longer⁷⁶ and that the effects were reversible^{73,75–77} by 30 months of cessation as compared with non-users.⁷⁴ Two studies on postmenopausal women showed that those who had used DMPA up to the menopause lost less bone after the menopause than non-users, such that by the age of 60 ± 5 years the BMD measurements between the users and the non-users were equivalent.^{78,79}

Women on long-term steroids or those who have required low molecular weight heparin throughout gestation are at risk of osteoporosis. DMPA should be avoided in such patients particularly if they are breast feeding. Lactation is known to cause a further 4–6% decrease in BMD over six months, which is fully reversible on restoration of ovarian function.⁸⁰ DMPA can be used in adolescent and perimenopausal women as the effects on BMD are reversible. Those on long-term DMPA (e.g. with sickle cell disease) may benefit from supplemental menopausal doses of oral or transdermal oestrogen, which have been shown to cause similar recovery in BMD as DMPA cessation.⁸¹

CONCLUSION

The wide array of contraceptive methods available should be tailored for each individual medical disease and individual circumstance. Contraceptives vary widely in efficacy. The most efficacious should be used for those in whom pregnancy is not recommended.

Contraceptives themselves can affect the course of medical diseases. Good amount of data exist for older contraceptives such as the high-dose combined oral contraceptive pill, showing that it has significant effects on arterial disease and thrombosis, which has coloured many recommendations against their use in IHD, ischaemic stroke and vascular disease. Meta-analyses of studies on lower dose combined contraceptive pills are emerging, showing that they convey little or no risk of arterial disease. The associated progestogens in COC are important determinators of risk, with third-generation progestogens being associated with more venous thromboses but less arterial thromboses than second-generation progestogens. COC also increase the risk of stroke in women with migraine, particularly migraine with aura. However, data on the effect of oestrogen dose is lacking.

Progestogens can confer risk by virtue of their liver metabolism, which can be altered by liver-enzyme-inducing drugs and warfarin. Their metabolism can affect active liver disease, but the effect is less than that of oestrogens which are metabolized the same way. Injectable progestogens have an adverse effect on the surrogate markers of diseases such as BMD and lipid profile. However, data on clinical outcomes of fracture risk and vascular disease are lacking. There are no convincing data that POC increase cardiovascular events and injectable progestogens have been shown to reduce the incidence of crises in women with sickle cell disease. Studies on the newest forms of CHC and long-acting progestogens are awaited.

The copper IUD appears to be safe to use when hormonal contraceptives are best avoided. The risks of a vaso-vagal attack and infection limit its use in those with pulmonary hypertension and previous bacterial endocarditis.

Women should be aware that emergency contraception is readily available and should be used in the event of contraceptive failure or non-use within 72 hours with the progestogen method and within five days with the copper IUD. Failing this, termination of pregnancy can be considered if it is warranted by the severity of the medical disease.

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