Female contraception: options for specific high-risk groups

Angelos Daniilidis[1], Fani Gkrozou[2], Panagiotis Papandreou[3], Orestis Tsonis[4], Anastasios Liberis[1], Anastasia Vatopoulou[5]

[1] 2nd Dept. OB-GYN, 'Hippokratio' General Hospital, Aristotle University of Thessaloniki, Greece; [2] Department of Obstetrics and Gynaecology, University Hospitals of Birmingham, UK; [3] Genesis Hospital, Thessaloniki, Greece; [4] Department of Obstetrics and Gynaecology, University Hospital of Ioannina, Greece; [5] 3rd Department of Obstetrics and Gynaecology, 'Hippokratio' General Hospital, Aristotle University of Thessaloniki, Greece

ABSTRACT

Background: Contraception and family planning are now recognized as essential in order to ensure the well-being of women, while supporting the health and development of communities. In this context, obesity, age (over 40 years or under 18 years), and interval since childbirth, abortion, miscarriage, ectopic pregnancy or gestational trophoblastic disease are some factors associated with higher a risk of adverse health issues, and maternal and infant complications, which seem to affect the safe use and effectiveness of certain types of contraceptives.

Materials and Methods: The authors examined the up-to-date literature in order to evaluate the safety and effectiveness of single contraceptive methods when used in belonging to high-risk groups such as those with obesity, over 40 years old, under 18 years old and women after childbirth, abortion, miscarriage, ectopic pregnancy or gestational trophoblastic disease.

Results: Obesity is linked to adverse health issues, such as cardiovascular disease and metabolic disorders which may affect the safe use of certain types of contraception. Women over 40 years old have an increased age-related risk of cardiovascular disease, osteoporosis, and breast, ovarian and endometrial cancer and need proper guidance in order to achieve optimal contraception safely. A young woman's decision to use contraception may be influenced by individual, familial and social factors, while the effectiveness, safety, side effects, ease of use and knowledge of the method are some of the factors that can affect her choice of contraceptive method. Finally, contraception counseling after the various possible pregnancy outcomes (childbirth, abortion, miscarriage, ectopic pregnancy, and gestational trophoblastic disease) is of great importance as short interpregnancy intervals are associated with a higher risk of maternal and infant complications.

Conclusion: Healthcare practitioners should be aware of the safety, effectiveness, possible adverse effects and also the non-contraceptive benefits of each contraceptive method before prescribing contraception, and therefore able to offer specific guidance and the most appropriate family planning solution to women in high-risk groups.

KEYWORDS

Contraception, family planning, obesity, puberty, premenopausal, childbirth, abortion, ectopic pregnancy, trophoblastic disease.

Introduction

Contraception and family planning are now recognized as essential in order to ensure the well-being of women, while supporting the health and development of communities. Globally, the use of modern contraceptive methods rose from 54% in 1990 to 57.4% in 2015 according to the World Health Organization (WHO). However, it seems that, even now, many women of reproductive age do not use a modern contraceptive method, even though they do not want to conceive. Social, economic, religious and cultural reasons may affect a woman's decision regarding contraception. Contraception is central to the prevention of unintended pregnancies and reduces the need for abortion, while some modern contraceptives protect against sexually transmitted infections. In this context, obesity, age (over 40 years or under 18 years), and the interval since childbirth, abortion, miscarriage, ectopic pregnancy or gestational trophoblastic disease are some factors associated with an increased risk of adverse health issues, and of maternal and infant complications. These same factors also seem to affect the safe use and effectiveness of certain types of contraceptives. On the contrary, certain contraceptives may offer some non-contraceptive benefits to women in these high-risk groups.

Article history
Received 27 Jan 2020 - Accepted 10 May 2020

Contact
Panagiotis Papandreou; panos1914pap@hotmail.com
Genesis Gynaecological private hospital, Thessaloniki, Greece

Materials and methods

Papers (meta-analysis and prospective studies) written in English and published in PubMed were consulted to prepare

this paper. The authors examined the up-to-date literature on the safety and effectiveness of single contraceptive methods when used in women in high-risk groups such as those with obesity, those aged over 40 years or under 18 years, and in women after childbirth, abortion, miscarriage, ectopic pregnancy or gestational trophoblastic disease. The key words used for the search were: contraception, family planning, obesity, puberty, premenopausal, childbirth, abortion, ectopic pregnancy, trophoblastic disease.

Contraception and obesity

In recent decades, obesity has become a worldwide health concern due to its repercussions [1]. According to a systematic analysis published by Marie in 2014 [2], 1.46 billion adults are overweight and 502 million are obese. Over 50% of women in the UK are overweight or obese [3,4] and levels of obesity are expected to continue rising among women of reproductive age who become pregnant [5]. Obesity and its comorbidities increase the risk of several pregnancy-related complications [5-8]. In addition, obesity is linked to various health issues, such as cardiovascular disease and metabolic disorders [9,10], which may affect the safe use of certain types of contraception. On the other hand, some contraceptive methods offer women with a raised body mass index (BMI) certain non-contraceptive benefits [1]. Finally, evidence from recent studies indicate that obese women are less likely to use contraception and are at greater risk of unintended pregnancy [11]. These considerations underlie the need for specific guidance by healthcare practitioners and targeting overweight or obese women of reproductive age, in order to promote safe and effective use of contraception. This would allow women to plan their future pregnancy safely, by optimising their pre-conception weight. This review aims to present the impact of increased weight and obesity on the effectiveness and safety of single contraceptive methods, to highlight evidence-based information relating contraception methods to weight gain and to identify the non-contraceptive health benefits, if any, for women with a raised BMI.

Intrauterine methods of contraception, including the Cu-intrauterine device (Cu-IUD) and levonorgestrel intrauterine system (LNG-IUS), are safe for women with raised BMI, even when obesity is accompanied by other risk factors for cardiovascular disease (e.g smoking, hypertension, diabetes) [12]. Recent studies suggest that the use of levonorgestrel does not increase the risk of venous thromboembolism, myocardial infarction or stroke [13-17]. In addition, obesity does not seem to impair the effectiveness of either of these types of intrauterine contraception as their mechanisms of action depend on local effects rather than systemic drug levels [18-21].

Recent studies suggest that the above intrauterine contraceptive methods reduce the risk of endometrial hyperplasia and cancer with which obesity is associated [22-27] and that there is no relationship between intrauterine contraceptive methods and weight gain [1]. Although the insertion of intrauterine contraceptive devices is more challenging in obese and overweight women, raised BMI does not seem to be a risk factor related to insertion failure or expulsion of these devices [19,28]. Progestogen-only implants, including levonorgestrel or etonogestrel implants, are a safe contraceptive method for women with increased BMI, even when other risk factors for cardiovascular disease (e.g smoking, hypertension, diabetes) coexist [12]. Indeed, recent studies suggest that there is no increase in the risk of venous thromboembolism, myocardial infraction or stroke [13-17]. Additionally, it is stated in other studies that progestogen-only implants are a highly effective contraceptive method for obese and overweight women [29-31], as raised BMI is not related to a higher risk of contraceptive failure of this method and more unintended pregnancies [21,31,32]. There is no evidence supporting a relationship between progesterone-only implants and weight gain, while the main non-contraceptive benefit is improvement of dysmenorrhoea and pain during ovulation [1]. The use of progestogen-only injectable contraceptives, including depot medroxyprogesterone and norethisterone enanthate, is not restricted in women with raised BMI, unless obesity is one of the multiple risk factors for cardiovascular disease [12]. In this case, the theoretical or proven risks outweigh the advantages of using this method [12].

Although some recent studies have shown that use of progestogen-only injectable contraceptives increases the risk of venous thromboembolism [14,15], the available evidence is limited [1]. Use of this contraceptive method is associated with weight gain, especially in women under 18 years old with a BMI over 30kg/m^2 [33-37]. As for its non-contraceptive health benefits, recent studies have proved the benefits of progestogen-only injectable contraceptives for the treatment of heavy menstrual bleeding, dysmenorrhoea and chronic pelvic pain related to endometriosis [38-39]. In addition, they offer protection against ovarian and endometrial cancer [40-43]. In obese women using progestogen-only injectable contraceptives it is strongly recommended to ensure that the muscle layer is reached during intramuscular injection, by using longer length needles or deltoid administration, otherwise subcutaneous injection should be considered [44-46].

The progestogen-only pill is also a safe contraceptive method for women with a raised BMI, even when obesity co-exists with other risk factors for cardiovascular disease [12]. Recent studies suggest that there is no increased risk of venous thromboembolism, myocardial infarction or stroke to obese women who use this contraceptive method [13-17]. Limited evidence suggests that the effectiveness of the progestogen-only pill is not affected by raised BMI [47,48]. In addition, this contraceptive method is not related to weight gain [1] and offers women some non-contraceptive benefits such as improvement of dysmenorrhoea, premenstrual syndrome symptoms and heavy menstrual bleeding [49-51]. Combined hormonal contraception, including the combined oral contraceptive pill, combined transdermal patch and combined vaginal ring, is a safe contraceptive method for women with a BMI of less than 34kg/m^2. On the contrary, the risks outweigh the benefits in women with a BMI greater than 35kg/m^2 [12]. A raised BMI over 30kg/m^2 and use of combined hormonal contraceptives are both risk factors for venous thromboembolism [52-55]. Recent studies have shown that women using oral combined hormonal contraceptives have a five to eight times higher risk of venous thromboembolism compared with obese women who are not using them.

They are also at 10 times greater risk of venous thromboembolism compared with non-users [54,56-67]. In addition, other studies report that the risk of myocardial infarction and ischaemic stroke is significantly increased in women with raised BMI who use oral combined hormonal contraceptives [68,69]. As for the transdermal patch or the vaginal ring, there are not enough data available concerning the risk of venous thromboembolism, myocardial infarction and ischaemic stroke [1]. The effectiveness of combined oral contraceptives is not affected by BMI [20,70]. Body weight does not seem to influence the effectiveness of the vaginal ring [71,72], whereas it can affect that of the transdermal patch [70,73,74]. Combined hormonal contraception is not related to weight gain when used by overweight or obese women [1]. The non-contraceptive benefits of the method include improvement of heavy menstrual bleeding, of dysmenorrhoea and of polycystic ovary syndrome symptoms. At the same time, this method decreases the risk of endometrial, ovarian and colorectal cancer [75-83].

Condoms (male and female), diaphragms, cervical caps and contraceptive sponges are the different forms of barrier contraception [1]. There are no studies in the literature regarding the use, safety and effectiveness of barrier contraception in obese women [1]. As for fertility awareness methods of contraception, raised BMI may influence their effectiveness when it is associated with irregular menstruation [1]. Female surgical sterilisation is an effective method for permanent contraception, but is associated with increased risk of technical failure and surgical or anaesthetic complications in women with obesity [84-93]. Methods used for emergency contraception are the Cu-IUD, the 1.5mg levonorgestrel pill and the 30mg ulipristal acetate pill [1]. Available evidence from a recent study shows that the Cu-IUD is the most effective method and that its effectiveness is not reduced by increased BMI [94].

Other studies have provided evidence showing that having a BMI greater than 26 kg/m^2 is associated with reduced effectiveness of the 1.5 mg levonorgestrel pill [95-100] and that having a BMI of over 30kg/m^2 may reduce the effectiveness of the 30mg ulipristal acetate pill [101].

In conclusion, when the Cu-IUD is not acceptable for emergency contraception in a woman with raised BMI, it is suggested that the ulipristal acetate pill should be offered as a first choice, or a double dose of the levonorgestrel pill can be used as a last resort [1]. Healthcare providers should inform women that medicines used for weight loss such as orlistat and laxatives can reduce the absorption and effectiveness of all oral contraceptives [1]. In addition, the effectiveness of oral contraceptives may also be reduced after bariatric surgery and non-oral contraceptive methods should be preferred by these women as they appear to be more effective [1].

Contraception for women aged over 40 years

Although fertility is naturally lower in women aged over 40 years, contraception is still required in order to avoid unplanned pregnancies [102]. Recent reviews state that women aged between 40 and 49 years have a 10-20% chance of becoming pregnant when they have unprotected intercourse. The same studies show that the chances of pregnancy are very low for women who have reached their 50s [103-108]. In addition, the number of annual live births to women aged over 40 years has increased [108,109]. The abortion rate for this population is 28.15% [110]. Pregnancy and childbirth after the age of 40 years carry a higher risk of miscarriage [111-115], ectopic pregnancy [116,117], maternal mortality [118], postpartum haemorrhage, placenta praevia, gestational diabetes, hypertension and caesarian section [109,119-125]. Furthermore, a maternal age older than 40 years is associated with a higher risk of preterm delivery [122,123,126-132], stillbirth and perinatal mortality [121,125,126-128,133], and congenital anomalies of the foetus such as Down syndrome [134,135]. It seems tha many more women over 40 years old are now likely to be enter new sexual relationships [136], and there is evidence suggesting that people over 40 years old are less likely to use condoms [137] and should be considered at high risk of sexually transmitted infections by healthcare providers [138,139]. These findings are reflected in increased rates of infections (gonorrhoea, herpes, Chlamydia, genital warts and HIV) among women over 40 years old [140,141]. On the other hand, women over 40 years old have an increased age-related risk for cardiovascular disease [142-146], osteoporosis [147], and breast, ovarian and endometrial cancer [148-150].

The above findings justify the need for guidance by healthcare providers, in order to help women obtain effective and safe contraception [102]. Healthcare providers should be properly informed and therefore able to inform women over 40 years old about the safety, effectiveness, benefits and risks of all the available contraceptive methods [102]. The very long-acting reversible contraceptive methods such as the Cu-IUD, LNG-IUS, and progestogen-only implants, are thought to be the most effective methods [102]. Data from the UK office for National Statistics published in 2008/2009 suggest that nearly 75% of women aged between 40 and 50 years use at least one contraceptive method [151].

Recent studies suggest that contraception does not affect menopausal status, but can reduce perimenopausal symptoms [152,153]. The Cu- IUD is a long-acting non-hormonal reversible contraceptive method with high effectiveness which is preferred by many women over 40 years old [103,154]. It can be used for extended periods, of 5 to 10 years until menopause, when inserted after the age of 40 years [102,155]. On the other hand, use of a Cu-IUD may be related to heavier, more painful and more prolonged bleeding, which makes it inappropriate for women with heavy and irregular periods [103,154]. The LNG-IUS is an effective choice of contraception for women over 40 years, which can also be used for endometrial protection as a part of hormonal replacement therapy [155-158], to treat abnormal bleeding patterns, and improve dysmenorrhoea and chronic pelvic pain related to endometriosis [155,159,160].

The LNG-IUS provides protection against endometrial hyperplasia and cancer [161-163]. On the other hand, some recent studies have shown that use of the LNG-IUS is associated with a higher risk of breast cancer [161,164,165]. It is also suggested that when the LNG-IUS is used after endometrial ablation its insertion should be guided by hysteroscopy, otherwise there is an increased risk of perforation of the uterus [102]. A 52 mg LNG-IUS

can be used for up to 7 years [166-168] and 13.5 mg LNG-IUS for up to 3 years [102]. The progestogen-only implant has a 0.05% failure rate. According to the literature it is the most effective type of contraception for women over 40 years old [169,170]. This method reduces menstrual and ovulatory pain [170-174]. In addition, it is not associated with an increased risk of venous thromboembolism, stroke, myocardial infarction or reduction of bone mineral density [170].

Progestogen-only injectable contraceptives, such as depot medroxyprogesterone acetate, can be used by women over 40 years old, but it is suggested that healthcare providers should regularly review these women and evaluate the benefits and risks [102]. Aside from its contraceptive use this method is also helpful in the treatment of heavy menstrual bleeding, menstrual pain and endometriosis-related symptoms [159,175]. Its use is also related to a lower risk of ovarian and endometrial cancer [175-177]. On the other hand, the use of progestogen-only injectable contraception is associated with initial reduction of bone mineral density due to hypo-oestrogenic effects [178,179]. According to studies, women over 40, with additional risk factors for osteoporosis, like smoking or family history, should be advised to avoid this contraceptive method [102].

Recent studies offer little evidence to support a connection between the use of this method and increased risk for cardiovascular disease, breast and cervical cancer [175,180]. The progestogen-only pill is also a safe and effective contraceptive method for women over 40 years old [12,102]. It helps with the symptoms of chronic pelvic pain and dysmenorrhoea, and also helps to maintain regular menstrual cycles [181-184]. Data available suggest that the above contraceptive method does not increase the risk of cardiovascular disease, reduction of bone mass density or breast cancer [175,180,185-187].

Combined hormonal contraception can be deliveres via different routes: combined oral contraceptives, transdermal patch and vaginal ring [102]. Recent studies suggest that there is no difference in the short- and long-term safety of these methods when they are uses by women over 40 years old [12]. A 2013 Cochrane review of 18 randomized controlled trials comparing the three methods showed no difference in contraceptive effectiveness between them [140]. Combined hormonal contraception is associated with management of menstrual problems and alleviation of menopausal symptoms in women over 40 years old, especially when it is used on continuous or extended dosing regimens [188-190]. A Cochrane review of 21 randomized controlled trials stated that higher doses of estrogen correlate with better cycle control, although this result can also be influenced by the type of progestogen used [191,192].

Recent studies mention that estradiol valerate/dienogest oral contraceptive is a highly effective treatment for heavy menstrual bleeding [159,192]. The use of combined oral contraceptives has been related to lower risk of ovarian and endometrial cancer [189,193-196]. A collaborative reanalysis of 45 epidemiological studies showed a 20% decrease in ovarian cancer risk after 5 years of combined oral contraception use [197]. Other studies, concluded that endometrial cancer risk decreases by 50% in women using combined oral contraception [194,198]. Additionally, many recent studies support the beneficial effect of this method on bone mineral density and on vasomotor symptoms in perimenopausal women [185,199-204]. Use of combined oral contraception and being over 40 years old are both risk factors for venous thromboembolism. The rate of venous thromboembolism is nearly 3 times greater in combined oral contraception users aged over 30 years compared with those under 30 years old [205-207]. A higher risk of venous thromboembolism is associated with higher doses of oestrogen and also depends on the type of progestogen used [208,209]. In addition, the presence of other risk factors for venous thromboembolism, such as BMI of over 35kg/m^2, hypertension, a history of venous thromboembolism, a positive family history, age over 35 years, smoking etc., reduce the safety of this method. According to the UK Medical Eligibility Criteria, if these risk factors are present, then use of this contraceptive method is more risky than beneficial for women over 40 years old [12]. The use of combined oral contraceptives has been related to small but significantrisk of breast or cervical cancer [195,210,211]. Women over 50 years old using combined hormonal contraceptives should be advised to switch to a safer contraceptive method as the risks outweigh the contraceptive benefits [102].

Barrier methods, such as condoms (male and female), diaphragms and cervical caps are safe and highly effective methods of contraception for women after the age of 40 [212]. Sterilisation is a method that some women may consider [213]. These women should be advised that a long-acting reversible contraceptive method is as effective as sterilisation [213]. They also should be advised regarding the non-contraceptive benefits [206]. In addition, couples who insist on surgical sterilisation should be informed that vasectomy is safer and quicker to perform and is associated with fewer complications than laparoscopic sterilisation [102]. Fertility awareness methods cannot be considered a safe and reliable form of contraception for women over 40 years old who, with the approach of the menopause, may be more prone to irregular menstruation and more anovulatory cycles [154,214]. Age does not affect the safety and effectiveness of the methods used for emergency contraception such as Cu-IUD, levonorgestrel and ulipristal acetate [102]. However, evidence from a recent study shows that concomitant use of progestogen-containing contraceptives or hormone replacement treatment could reduce the effectiveness of ulipristal acetate emergency contraception [97]. As regards the ceasation of contraception, the Faculty of Sexual and Reproductive Healthcare suggests that all women should stop using contraception when menopause is clinically diagnosed, i.e. after at least 12 months of amenorrhoea, or 55 years of age in women still experiencing menstrual bleeding as spontaneous conception is extremely rare after this age [102,215,216]. Faculty of Sexual and Reproductive Healthcare suggests that all contraceptive methods except for combined hormonal contraception are safe to use alongside hormonal replacement therapy [102].

Contraception choices for young people

Young people, under 18 years old, seem to have poor sexual health compared with older population groups [217]. Health issues associated with poor sexual health in young people include unintended pregnancy and sexually transmitted infections [217].

Despite the variety of contraceptive methods available nowadays, teenage pregnancy and sexually transmitted infections rates still seem to be high among young people [217-221]. Recent surveys suggest that one in three young people have had sexual intercourse by the age of 16 [217,220,221]. Early age at first sexual intercourse is related to teenage pregnancy [222]. The evidence clearly justifies the importance of providing young people with appropriate guidance and counselling regarding contraception and sexual life [217].

Recent studies indicate that a young woman's decision to use contraception during a sexual intercourse may be influenced by individual, familial, relationship and social factors [222-228]. In addition, effectiveness, discreetness, safety, side effects, invasiveness, ease of use and knowledge of the method are factors that can affect a young woman's choice of contraceptive method [229]. Contraceptive pills and condoms seem to be the most popular contraceptive methods among young women, although the last few years have seen increases in the use of long-acting reversible contraceptive methods, such as the progestogen-only implant, progestogen-only injectables, and intrauterine methods [230]. A recent survey in the USA stated that the rate of contraceptive failure among women under 20 is 16%, which is two-fold higher than the rate among women aged over 30 years [231]. Long-acting reversible contraceptives seem to have lower failure rates than contraceptive pills and condoms [217]. It has been noted that almost 70% of young women decide to discontinue contraception which results to unintended pregnancies [232-236]. Health professionals should be able to provide young people with a wide range of contraceptive methods, informing them about specific health concerns, and benefits and about the appropriate follow-up intervals [217].

Long-acting reversible contraceptive methods and their benefits should be highlighted and as regards hormonal contraception, young people should be advised to return for follow up after 3 months in order to discuss any side effects or other concerns that may lead them to discontinue use of the method [217]. The UK Medical Eligibility Criteria for Contraceptive Use suggest that, after menarche, all contraceptive methods are safe and their benefits outweigh the theoretical or proven risks [12]. For young women requiring contraception before menarche the condom is a safe method, while hormonal contraception is better avoided [217]. On the other hand, progestogen-only emergency contraception can be suggested to women before menarche if required [217]. Evidence from recent studies indicate that, for young women, immediate start of hormonal contraception is preferable to conventional start as it is related to fewer unintended pregnancies [237].

As for emergency contraception, all methods are safe and should be available to young women after unprotected sexual intercourse [217]. The possible side effects of contraceptive methods are health concerns that usually affect decisions both on starting use of contraception and on which method to choose [236,238-241]. Healthcare practitioners should be equipped to provide young people with detailed information on contraceptive methods and their association with health concerns such as weight gain, acne, bone mineral density reduction, thrombosis etc. [217]. Weight gain is often the reason for discontinuation of hormonal contraception [217].

However, limited data from recent studies indicate that there is no association between most hormonal contraceptive methods and weight gain [155,170,184,242]. Progestogen-only injectables seem to be the only hormonal contraceptives related to weight gain [243-245]. Progestogens used for hormonal contraception may have some androgenic effects and cause acne [217]. A recent study suggests that use of the LNG-IUS may increase the risk of acne, whereas the use of progestogen-only injectable contraceptives does not appear to cause acne. In addition, several other studies stated that use of progestogen-only implants can be related to improvement, worsening or onset of acne [246-249]. On the other hand, use of combined oral contraceptives has been associated with beneficial effects in the treatment of acne [250]. Mood changes and depression are other health concerns that have been linked to hormonal contraception [249,251,252].

Recent studies suggest that combined hormonal contraception and progestogen-only contraceptives may cause mood changes in young people but there is no evidence showing that hormonal contraception causes depression in young women [253-257]. The use of some contraceptive methods such as progestogen-only contraceptives and the Cu-IUD is associated with altered bleeding patterns in young women [155,170]. On the other hand, the LNG-IUS, combined oral contraceptives and progestogen-only injectable contraceptives can be used as treatment for heavy menstrual bleeding [159]. Combined oral contraceptives seem to improve primary dysmenorrhoea [258], whilst the LNG-IUS seems to improve dysmenorrhoea related to endometriosis and adenomyosis [259-261].

A Cochrane review of recent studies suggests that combined hormonal contraception does not influence the bone health of young women [262]. On the other hand, progestogen-only injectable methods may cause reduction of bone mineral density in young women [217]. The Faculty of Sexual and Reproductive Healthcare suggests that women under 18 who may not have reached their peak bone mass should initially consider other contraceptive methods [217]. As regards venous thromboembolism, combined hormonal contraceptives are known to be associated with an increased risk [263]. Nevertheless, the absolute risk of venous thromboembolism in young people remains very small [217]. Young age seems to be associated with increased rates of sexually transmitted infections such as Chlamydia, genital warts, gonorrhea etc. [221] It is important for young people to be informed about correct and consistent use of contraceptive methods such as condoms in order to reduce the risk of infections [217].

Contraception after pregnancy

Contraception after pregnancy seems to be an important issue, especially for young women who are at higher risk of unintended pregnancy [264-267]. A recent study reported that almost 85% of a sample of women having an abortion or delivery had conceived within 12 months of a previous birth [268]. Short interpregnancy intervals are associated with a higher risk of preterm birth, low birthweight, stillbirth and neonatal death [269,270]. The WHO recommends an interval of at least 24 months between pregnancies [271]. Healthcare services should offer proper con-

traceptive counselling to women after pregnancy and inform them about the full range of available contraceptive methods, in order to enable them to make safe family planning choice [272]. Clinicians should be equipped to give post-pregnancy guidance on contraception baring in mind the recommendations on contraception for each of the possible pregnancy outcomes (i.e childbirth, abortion, miscarriage, ectopic pregnancy, and gestational trophoblastic disease) [272]. Information on the safety of each contraceptive method for women after pregnancy is provided by the UK Medical Eligibility Criteria for Contraceptive Use [12].

Each woman should be properly informed abou the effectiveness of the different contraceptive methods, so that she may make a choice according to her needs and desires [272]. The effectiveness of some methods can vary widely according to women's individual characteristics [272]. On the other hand, long-acting reversible contraceptive methods, such as intrauterine devices, progestogen-only injectables and implants, seem to be highly effective methods for women after pregnancy [273]. Finally, it is important that clinicians take into account any medical or social factors that may affect the woman's choice of contraception after pregnancy [272]. The need for effective contraception after pregnancy should not be underestimated as sexual activity and fertility may return quickly [274,275]. It has been reported that almost 13% of a sample of pregnant women had another pregnancy after less than 12 months [268]. Guidance on contraception after childbirth should be provided antenatally, especially to women with pregnancy-related health conditions [12] and those vulnerabl to unintended pregnancy [264-267]. Many contraceptive methods can be provided during the first hours after delivery, including the long-acting reversible contraceptives which are associated with superior effectiveness [272,276]. Although it is generally recommended that contraception should be provided by 21 days after childbirth [277], immediate initiation of eligible contraceptives is related to reduced risk of unintended pregnancy [278].

In addition, women who delayed initiation of contraception after childbirth were more likely to fail to attend their postpartum visit [279,280]. The UK Medical Eligibility Criteria for Contraceptive Use provide all the useful evidence-based information that practitioners should be aware of in order to provide women with safe contraception after childbirth [12]. Intrauterine contraceptives, such as the Cu-IUD and LNG-IUS, are safe for insertion 48 hours after vaginal delivery or caesarian section both in breastfeeding and non-breastfeeding women; in the case of delayed insertion, it is recommended that this should be performed from 4 weeks after childbirth [12]. Combined hormonal contraception, including oral contraceptives, transdermal patch and vaginal ring, should be initiated from 6 weeks after childbirth due to increased risk of venous thromboembolism during this period [12]. Only for women with no other risk factors for venous thromboembolism and who are not breastfeeding it is suggested that the use of combined hormonal contraception has more advantages than risks after the third postapartum week [12].

Finally, progestogen-only contraceptive methods (pills, implants or injectables) can be safely used by breastfeeding or non-breastfeeding women during the first 6 postpartum weeks as they do not increase the risk of venous thromboembolism [12]. The UK Medical Eligibility Criteria for Contraceptive Use also syate that pregnancy-related conditions such as hypertension, diabetes or cholestasis do not affect the safety of contraceptive methods used in the postpartum period, although all health conditions should be taken into account by clinicians before initiating contraception after childbirth [12]. Emergency contraceptive methods, including Cu-IUD, levonorgestrel and ulipristal acetate emergency contraceptives,are safe to use after childbirth [12]. They should be provided to women having unprotected sexual intercourse from 21 days after childbirth [272]. Limited evidence from a recent study indicates that use of levonorgestrel emergency contraceptive is not related to adverse effects on breastfeeding or infant outcomes [281].

On the other hand, as ulipristal acetate is excreted in breast milk, women should be advised to express and discard milk for 7 days after use of this method [272]. Women should be advised that additional contraceptive precaution using barrier methods is required when hormonal contraception is initiated after day 21 postpartum [272]. Evidence from recent studies indicates that use of progestogen-only contraceptive methods and intrauterine devices does not affect lactation or infant growth [282,283]. In addition, a recent systematic review shows that combined hormonal contraception, initiated 6 weeks after delivery, is not associated with adverse effects on infant outcomes, although, the evidence is limited [284].

Women who wish to rely on the lactational amenorrhoea method of birth control should be advised that this method is highly effective during the first 6 postpartum weeks as long as they are amenorrhoeic and fully breastfeeding day and night [272]. When both these criteria are met, failure rates are less than 2% [285-287]. Female sterilisation is a safe and effective method of permanent contraception after childbirth [213,288]. Both partial salpingectomy and tubal occlusion, used for sterilisation of women after childbirth, are methods with a low risk of failure [289-291]. As for barrier contraceptive methods women should be informed that male and female condoms are related to low effectiveness [292] and that diaphragms are suitable 6 weeks after childbirth when uterine involution is complete [293]

Evidence from recent studies has shown that ovulation occurs within 30 days of first trimester abortions [294-297] and that more than half of women resume sexual intercourses within 15 days of abortion [298]. Clinicians should guide women about contraception very soon after an abortion, providing them with up-to-date and accurate information [272]. Long-acting reversible contraceptives (intrauterine devices, progestogen-only implants and injectables), when initiated immediately after abortion are associated with less likelihood of unintended pregnancy and another future abortion compared with other contraceptive methods [272].

The UK Medical Eligibility Criteria for Contraceptive Use [12] and the RCOG guideline on The Care of Women Requesting Induced Abortion [299] state that any contraceptive method is safe and may be initiated immediately after uncomplicated abortion. All methods of emergency contraception are safe to prescribe after an unprotected sexual intercourse from 5 days after abortion [272]. Women should be advised that additional contraceptives, such as barrier methods, are required to avoid

unintended pregnancy when hormonal contraception is initiated 5 or more days after abortion [272]. Women choosing intrauterine contraceptive methods after abortion should be advised that it is necessary to rule out an ongoing pregnancy before insertion of the device and that expulsion rates are generally low even after a second trimester abortion [272]. In addition they should be informed that the LNG-IUS is associated with less menstrual blood loss [300,301].

Women choosing progestogen-only contraception after abortion should be advised that initiation of the method is safe at any time after medical or surgical abortion [272]. Progestogen-only implants and pills can safely be used with mifepristone, administered to induce medical abortion [272]. As for the progestogen-only injectables, limited evidence from a recent study indicated an association with a higher risk of ongoing pregnancy when these are used with mifepristone [302]. Immediate use of combined hormonal contraception after abortion is safe and not linked to lower success rates of the abortion procedure, surgical or medical [303-307].

For women desiring permanent contraception after abortion, female sterilisation is safe, although tubal occlusion has shown an increased failure rate when performed at the time as abortion [272]. Before making this choice, these women should be informed about the high effectiveness and non-contraceptive benefits of long-acting reversible contraceptives [272]. The use of fertility awareness methods for contraception soon after abortion may not be easy and effective due to difficulty detecting signs of ovulation during this period [272]. After ectopic pregnancy or miscarriage, women wishing to avoid a future unintended pregnancy should start effective contraception as soon as they resume their sexual activity [272].

Evidence from recent studies indicate that ovulation can return within 1 month after treatment for ectopic pregnancy [308,309] and within 8 days of miscarriage [310,311]. Clinicians should guide women to consider contraception after ectopic pregnancy and miscarriage providing up-to-date and accurate information [272]. Evidence from a recent review suggests that pregnancy within 6 months of a miscarriage is associated with lower rates of subsequent miscarriage, abortion, ectopic pregnancy, preterm birth and low birthweigth [269]. Effective contraception can be initiated immediately after uncomplicated methotrexate administration or surgical treatment for ectopic pregnancy [272]. After methotrexate treatment of ectopic pregnancy with women should be advised to use a contraceptive method for at least 3 months in order to avoid any teratogenic effects of the medicine in a future pregnancy [312-317].

The UK Medical Eligibility Criteria for Contraceptive Use recommend that any contraceptive method is safe and may be initiated immediately after an uncomplicated miscarriage or treatment of an ectopic pregnancy [12]. Any method of emergency contraception, including Cu-IUD, levonorgestrel and ulipristal acetate oral contraceptives, is safe for use by these women if unprotected sexual intercourse takes place more than 5 days after miscarriage or treatment for ectopic pregnancy [272]. Additional contraceptive methods, such as barrier methods, are required to avoid unintended pregnancy when hormonal contraception is initiated 5 or more days after miscarriage or treatment for ectopic pregnancy [272]. Recurrent miscarriage is strongly related to thrombogenic mutations and antiphospholipid syndrome [315-317]. According to the UK Medical Eligibility Criteria for Contraceptive Use no woman with positive antiphospholipid antibodies or thrombogenic mutations should use combined hormonal contraception [12]. All the other contraceptive methods can be used as their advantages outweigh their possible risks in these women [12].

All contraceptive methods are associated with extremely low risk of intrauterine or ectopic pregnancy [272,318]. Long-acting reversible contraception methods seem to be the most effective and all women with higher risk of ectopic pregnancy should be guided to consider use of these methods [272]. Effective contraception is important for women with gestational trophoblastic disease (GTD) until monitoring is completed and serum human chorionic gonadotropin (hCG) is normal [272,319-321]. Sexual activity and ovulation may resume soon after treatment for GTD and women are at risk of subsequent pregnancy before GTD monitoring is complete [272,319-321]. For the above reasons, effective contraception should be initiated immediately in these women [272]. Clinicians should provide the right information regarding contraception and also reassurance that GTD is not associated with fertility reduction [272]. The UK Medical Eligibility Criteria for Contraceptive Use suggest that all contraceptive methods including intrauterine devices, progestogen-only methods and combined hormonal contraceptives can be used safely when levels of hCG are undetectable [12]. On the other hand, when levels of hCG are still decreasing, are persistently elevated or when malignant disease is present, intrauterine devices are not safe for use as the risks outweigh the possible advantages [12].

Emergency contraception is indicated for women with GTD who had an unprotected sexual intercourse 5 or more days after treatment [272]. Levonorgestrel and ulipristal acetate emergency contraceptive pills can safely be used by these women [12] but the Cu-IUD should be avoided as the presence of GTD increases the risk of perforation of the uterus during the insertion of the device [12]. Women should be advised that the use of additional contraceptive methods, such as barrier methods, is not required as long as hormonal contraception is initiated immediately or within 5 days after treatment for GTD [272]. Female sterilisation, barrier methods and fertility awareness methods are also safe contraceptive methods for use by women after treatment for GTD, once the menstrual cycle has returned to its previous pattern [272].

Although, female sterilisation is a safe and effective option for permanent contraception in these women, before making such a choice they should be made aware that long-acting reversible contraceptive methods are thought to have similar effectiveness and also provide some non-contraceptive benefits [272]. As for diaphragms, these should be placed at least 6 weeks after treatment for GTD as this is the time it takes the uterus to reach its normal size [272]. Fertility awareness methods may not be an effective method of contraception in women soon after treatment for GTD as it is difficult to detect signs of ovulation during this period [272]. There is no evidence indicating that any contraceptive method used by women with a history of GTD is associated with increased risk of recurrence of the disease in a future pregnancy [272].

Conclusion

Contraception and proper family planning are of great importance for women in high-risk groups (obese, adolescent, pre-menopausal, soon after pregnancy) since the presence of these risk factors is strongly associated with maternal and infant complications. However, the safety and effectiveness of some contraceptives may be affected in these groups. Healthcare practitioners, before prescribing contraception, should be aware of the safety, effectiveness, possible adverse effects and the non-contraceptive benefits of each contraceptive method, in order to be able to offer specific guidance and the most appropriate family planning to women in high risk groups. In order to achieve this goal, more carefully conducted research, in the form of well-designed studies producing evidence-based answers, is necessary in the future.

References

1. FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019;45(Suppl 2):1-69.
2. Marie Ng, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766-81.
3. Baker C. Obesity statistics. Briefing paper number 3336. London: House of Commons Library; 2019.
4. Scottish Health Survey Tables for Chapter 5: Obesity. Edinburgh, UK: The Scottish Government, 2017.
5. Public Health England. Guidance: Health matters: reproductive health and pregnancy planning. 2018. Available at: https://www.gov.uk/government/publications/health matters-reproductivehealth-and-pregnancy-planning/health-matters-reproductive-health-and-pregnancy-planning.
6. Marchi J, Berg M, Dencker A, Olander EK, Begley C. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obes Rev. 2015;16:621-38.
7. Catalano PM. Obesity, insulin resistance, and pregnancy outcome. Reproduction. 2010;140:365-71.
8. Metwally M, Li TC, Ledger WL. The impact of obesity on female reproductive function. Obes Rev. 2007;8:515-23.
9. National Heart, Lung, and Blood Institute, National Institutes of Health. Managing Overweight and Obesity in Adults: Systematic Evidence Review from the Obesity Expert Panel. Bethesda, MD: U.S. Department of Health and Human Services, 2013.
10. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda (MD): National Heart, Lung, and Blood Institute; 1998 Sep.
11. Nguyen BT, Elia JL, Ha CY, Kaneshiro BE. Pregnancy intention and contraceptive use among women by class of obesity: results from the 2006-2010 and 2011-2013 National Survey of Family Growth. Womens Health Issues. 2018;28:51-8.
12. Faculty of Sexual & Reproductive Healthcare (FSRH). UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) 2016.
13. Lidegaard O, Nielsen LH, Skovlund CW, Løkkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. Version 2. BMJ. 2012;344:e2990.
14. Mantha S, Karp R, Raghavan V, Terrin N, Bauer KA, Zwicker JI. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. Version 2. BMJ. 2012345:e4944.
15. van Hylckama Vlieg A, Helmerhorst FM, Rosendaal FR. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. Arterioscler Thromb Vasc Biol. 2010;30:2297-300.
16. Chakhtoura Z, Canonico M, Gompel A, Scarabin PY, Plu-Bureau G. Progestogen-only contraceptives and the risk of acute myocardial infarction: a meta-analysis. J Clin Endocrinol Metab. 2011;96:1169-74.
17. Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med. 2012;366:2257-66.
18) Merki-Feld GS, Skouby S, Serfaty D, et al. European Society of Contraception statement on contraception in obese women. Eur J Contracept Reprod Health Care. 2015;20:19-28.
19. Saito-Tom LY, Soon RA, Harris SC, Salcedo J, Kaneshiro BE. Levonorgestrel intrauterine device use in overweight and obese women. Hawaii J Med Public Health. 2015;74:369-74.
20. Lopez LM, Bernholc A, Chen M, et al. Hormonal contraceptives for contraception in overweight or obese women. Cochrane Database Syst Rev. 2016;8:CD008452.
21. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. Obstet Gynecol. 2012;120:21-6.
22. Brinton LA, Berman ML, Mortel R, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol. 1992;167:1317-25.
23. Varma R, Sinha D, Gupta JK. Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS)--a systematic enquiry and overview. Eur J Obstet Gynecol Reprod Biol. 2006;125:9-28.
24. Curtis KM, Marchbanks PA, Peterson HB. Neoplasia with use of intrauterine devices. Contraception. 2007;75(6 Suppl):S60-9.
25. Beining RM, Dennis LK, Smith EM, Dokras A. Meta-analysis of intrauterine device use and risk of endometrial cancer. Ann Epidemiol. 2008;18:492-9.
26. Fu Y, Zhuang Z. Long-term effects of levonorgestrel-releasing intrauterine system on tamoxifen-treated breast cancer patients: a meta-analysis. Int J Clin Exp Pathol. 2014;7:6419-29.
27. Dominick S, Hickey M, Chin J, Su HI. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database Syst Rev. 2015; 2015:CD007245.
28. Grimes DA, Shields WC. Family planning for obese women: challenges and opportunities. Contraception. 2005;72:1-4.
29. Mornar S, Chan LN, Mistretta S, Neustadt A, Martins S, Gilliam M. Pharmacokinetics of the etonogestrel contraceptive implant in obese women. Am J Obstet Gynecol. 2012;207:110.e1-6.
30. Morrell KM, Cremers S, Westhoff CL, Davis AR. Relationship between etonogestrel level and BMI in women using the contraceptive implant for more than 1 year. Contraception. 2016;93:263-5.
31. McNicholas C, Maddipati R, Zhao Q, Swor E, Peipert JF. Use of the etonogestrel implant and levonorgestrel intrauterine device beyond the U.S. Food and Drug Administration-approved duration. Obstet Gynecol. 2015;125:599-604.
32. Graesslin O, Korver T. The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. Eur J Contracept Reprod Health Care. 2008;13 Suppl 1:4-12.
33. Beksinska ME, Smit JA, Kleinschmidt I, Milford C, Farley TM. Prospective study of weight change in new adolescent users of DMPA, NET-EN, COCs, nonusers and discontinuers of hormonal contraception. Contraception. 2010;81:30-4.
34. Mangan SA, Larsen PG, Hudson S. Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. J Pediatr Adolesc Gynecol. 2002;15:79-82.
35. Risser WL, Gefter LR, Barratt MS, Risser JM. Weight change in adolescents who used hormonal contraception. J Adolesc Health. 1999;24:433-6.
36. Curtis KM, Ravi A, Gaffield ML. Progestogen-only contraceptive use in obese women. Contraception. 2009;80:346-54.
37. Bonny AE, Ziegler J, Harvey R, Debanne SM, Secic M, Cromer BA. Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal con-

traceptive method. Arch Pediatr Adolesc Med. 2006;160:40-5.
38. Dunselman GA, Vermeulen N, Becker C, et al; European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29:400-12.
39. National Institute for Health and Care Excellence (NICE). Endometriosis: diagnosis and management. NICE Guideline [NG73]. Published date: 06 September 2017. Available at: https://www.nice.org.uk/guidance/ng73.
40. Wilailak S, Vipupinyo C, Suraseranivong V, et al. Depot medroxyprogesterone acetate and epithelial ovarian cancer: a multicentre case-control study. BJOG. 2012;119:672-7.
41. Liang AP, Levenson AG, Layde PM, et al. Risk of breast, uterine corpus, and ovarian cancer in women receiving medroxyprogesterone injections. JAMA. 1983;249:2909-12.
42. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer. 1991;49:191-5.
43. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer. 1991;49:186-90.
44. electronic Medicines Compendium (eMC). Pfizer Limited. Summary of Product Characteristics: Depo-Provera 150mg/ml Injection. 29 February 2016. Available at: https://www.medicines.org.uk/emc/medicine/11121.
45. Cocoman A, Murray J. Recognizing the evidence and changing practice on injection sites. Br J Nurs. 2010;19:1170-4.
46. Small SP. Preventing sciatic nerve injury from intramuscular injections: literature review. J Adv Nurs. 2004;47:287-96.
47. Vessey M. Oral contraceptive failures and body weight: findings in a large cohort study. J Fam Plann Reprod Health Care. 2001;27:90-1.
48. Kovacs GT, Hendricks J, Summerbell D, Baker HW. A pre-coital pill? A preliminary in vitro study. Br J Fam Plann. 2000;26:165-6.
49. Ahrendt HJ, Karckt U, Pichl T, Mueller T, Ernst U. The effects of an oestrogen-free, desogestrel-containing oral contraceptive in women with cyclical symptoms: results from two studies on oestrogenrelated symptoms and dysmenorrhoea. Eur J Contracept Reprod Health Care. 2007;12:354-61.
50. Razzi S, Luisi S, Ferretti C, et al. Use of a progestogen only preparation containing desogestrel in the treatment of recurrent pelvic pain after conservative surgery for endometriosis. Eur J Obstet Gynecol Reprod Biol. 2007;135:188-90.
51. Georgantopoulou C, Field S. Treatment of premenstrual syndrome with the desogestrel-only pill (Cerazette) in an adolescent girl. J Pediatr Adolesc Gynecol. 2009;22:e1-3.
52. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation. 2010;121:1896-903.
53. Wattanakit K, Lutsey PL, Bell EJ, et al. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. Thromb Haemost. 2012;108:508-15.
54. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thromb Haemost. 2003;89:493-8.
55. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008;117:93-102.
56. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995;346:1575-82.
57. Pomp ER, le Cessie S, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. Br J Haematol. 2007;139:289-96.
58. Horton LG, Simmons KB, Curtis KM. Combined hormonal contraceptive use among obese women and risk for cardiovascular events: a systematic review. Contraception. 2016;94:590-604.
59. Nightingale AL, Lawrenson RA, Simpson EL, Williams TJ, MacRae KD, Farmer RD. The effects of age, body mass index, smoking and general health on the risk of venous thromboembolism in users of combined oral contraceptives. Eur J Contracept Reprod Health Care. 2000;5:265-74.
60. Klovaite J, Benn M, Nordestgaard BG. Obesity as a causal risk factor for deep venous thrombosis: a Mendelian randomization study. J Intern Med. 2015;277:573-84.
61. Todd J, Lawrenson R, Farmer RD, Williams TJ, Leydon GM. Venous thromboembolic disease and combined oral contraceptives: a re-analysis of the MediPlus database. Hum Reprod. 1999;14:1500-5.
62. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP Jr. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. Contraception. 2004;70:3-10.
63. Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. Version 2. BMJ. 2011;342:d2139.
64. Suchon P, Al Frouh F, Henneuse A, et al. Risk factors for venous thromboembolism in women under combined oral contraceptive. The PILl Genetic RIsk Monitoring (PILGRIM) Study. Thromb Haemost. 2016;115:135-42.
65. Kabrhel C, Varraso R, Goldhaber SZ, Rimm EB, Camargo CA. Prospective study of BMI and the risk of pulmonary embolism in women. Obesity (Silver Spring). 2009;17:2040-6.
66. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med. 2002;162:1182-9.
67. Parkin L, Sweetland S, Balkwill A, et al. Body mass index, surgery, and risk of venous thromboembolism in middle-aged women: a cohort study. Circulation. 2012;125:1897-904.
68. Tanis BC, van den Bosch MA, Kemmeren JM, et al. Oral contraceptives and the risk of myocardial infarction. N Engl J Med. 2001;345:1787-93.
69. Kemmeren JM, Tanis BC, van den Bosch MA, et al. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. Stroke. 2002;33:1202-8.
70. Dragoman MV, Simmons KB, Paulen ME, Curtis KM. Combined hormonal contraceptive (CHC) use among obese women and contraceptive effectiveness: a systematic review. Contraception. 2017;95:117-29.
71. Westhoff CL, Torgal AH, Mayeda ER, et al. Pharmacokinetics and ovarian suppression during use of a contraceptive vaginal ring in normal-weight and obese women. Am J Obstet Gynecol. 2012;207:39.e1-6.
72. Dragoman M, Petrie K, Torgal A, Thomas T, Cremers S, Westhoff CL. Contraceptive vaginal ring effectiveness is maintained during 6 weeks of use: a prospective study of normal BMI and obese women. Contraception. 2013;87:432-6.
73. Yamazaki M, Dwyer K, Sobhan M, et al. Effect of obesity on the effectiveness of hormonal contraceptives: an individual participant data meta-analysis. Contraception. 2015;92:445-52.
74. Zieman M, Guillebaud J, Weisberg E, Shangold GA, Fisher AC, Creasy GW. Contraceptive efficacy and cycle control with the Ortho Evra/Evra transdermal system: the analysis of pooled data. Fertil Steril. 2002;77(2 Suppl 2):S13-8.
75. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 2017;216:580.e1-580.e9.
76. Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013;22:1931-43.
77. Collaborative Group on Epidemiological Studies on Endometrial Cancer. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol. 2015;16:1061-70.
78. Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and

ovarian, endometrial, breast, and colorectal cancers. JAMA Oncol. 2018;4:516-21.
79. Havrilesky LJ, Moorman PG, Lowery WJ, et al. Primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet Gynecol. 2013;122:139-47.
80. Bassuk SS, Manson JE. Oral contraceptives and menopausal hormone therapy: relative and attributable risks of cardiovascular disease, cancer, and other health outcomes. Ann Epidemiol. 2015;25:193-200.
81. Wu AH, Pearce CL, Lee AW, et al. Timing of births and oral contraceptive use influences ovarian cancer risk. Int J Cancer. 2017;141:2392-9.
82. Luan NN, Wu L, Gong TT, Wang YL, Lin B, Wu QJ. Nonlinear reduction in risk for colorectal cancer by oral contraceptive use: a meta-analysis of epidemiological studies. Cancer Causes Control. 2015;26:65-78.
83. Bosetti C, Bravi F, Negri E, La Vecchia C. Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis. Hum Reprod Update. 2009;15:489-98.
84. Jamieson DJ, Hillis SD, Duerr A, Marchbanks PA, Costello C, Peterson HB. Complications of interval laparoscopic tubal sterilization: findings from the United States Collaborative Review of Sterilization. Obstet Gynecol. 2000;96:997-1002.
85. Chi IC, Wilkens L. Interval tubal sterilization in obese women -- an assessment of risks. Am J Obstet Gynecol. 1985;152:292-7.
86. Chi IC, Petta CA, McPheeters M. A review of safety, efficacy, pros and cons, and issues of puerperal tubal sterilization -- an update. Adv Contracept. 1995;11:187-206.
87. Savage UK, Masters SJ, Smid MC, Hung YY, Jacobson GF. Hysteroscopic sterilization in a large group practice: experience and effectiveness. Obstet Gynecol. 2009;114:1227-31.
88. Cooper JM, Carignan CS, Cher D, Kerin JF; Selective Tubal Occlusion Procedure 2000 Investigators Group. Microinsert nonincisional hysteroscopic sterilization. Obstet Gynecol. 2003;102:59-67.
89. Kerin JF, Cooper JM, Price T, et al. Hysteroscopic sterilization using a micro-insert device: results of a multicentre Phase II study. Hum Reprod. 2003;18:1223-30.
90. Sinha D, Kalathy V, Gupta JK, Clark TJ. The feasibility, success and patient satisfaction associated with outpatient hysteroscopic sterilisation. BJOG. 2007;114(6):676-83.
91. Andersson S, Eriksson S, Mints M. Hysteroscopic female sterilization with Essure in an outpatient setting. Acta Obstet Gynecol Scand. 2009;88:743-6.
92. Hopkins MR, Creedon DJ, Wagie AE, Williams AR, Famuyide AO. Retrospective cost analysis comparing Essure hysteroscopic sterilization and laparoscopic bilateral tubal coagulation. J Minim Invasive Gynecol. 2007;14:97-102.
93. Chi IC, Wilkens LR, Reid SE. Prolonged hospital stay after laparoscopic sterilization. IPPF Med Bull. 1984;18:3-4.
94. Turok DK, Jacobson JC, Dermish AI, et al. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014;89:222-8.
95. Kapp N, Abitbol JL, Mathé H, et al. Effect of body weight and BMI on the efficacy of levonorgestrel emergency contraception. Contraception. 2015;91:97-104.
96. Jatlaoui TC, Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception. 2016;94:605-11.
97. Faculty of Sexual & Reproductive Healthcare (FSRH). Emergency Contraception. 2017. Available at: https://www.fsrh.org/standards-and-guidance/documents/ceu-clinical-guidance-emergency-contraception-march-2017/.
98. Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet. 2010;375:555-62.
99. Creinin MD, Schlaff W, Archer DF, et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. Obstet Gynecol. 2006;108:1089-97.
100. Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception. 2016;94:52-7.
101. Moreau C, Trussell J. Results from pooled phase III studies of ulipristal acetate for emergency contraception. Contraception. 2012; 86:673-80.
102. Faculty of Sexual & Reproductive Healthcare (FSRH). Public Consultation: Contraception for Women Aged Over 40 Years (2017). Available at: https://www.fsrh.org/news/public-consultation-contraception-for-women-aged-over-40-years/.
103. Baldwin MK, Jensen JT. Contraception during the perimenopause. Maturitas. 2013;76:235-42.
104. Klein J, Sauer MV. Assessing fertility in women of advanced reproductive age. Am J Obstet Gynecol. 2001;185:758-70.
105. Nelson SM, Telfer EE, Anderson RA. The ageing ovary and uterus: new biological insights. Hum Reprod Update. 2013;19:67-83.
106. Liu K, Case A; REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY COMMITTEE. Advanced reproductive age and fertility. J Obstet Gynaecol Can. 2011;33:1165-75.
107. Sivin I. Utility and drawbacks of continuous use of a copper T IUD for 20 years. Contraception. 2007;75(6 Suppl):S70-5.
108. Office for National Statistics. Birth Summary Tables, England and Wales: 2015. 2016. Available at : https://www.ons.gov.uk/releases/birthsummarytablesinenglandandwales2015.
109. Smith GCS, Cordeaux Y, White IR, et al. The effect of delaying childbirth on primary cesarean section rates. Version 2. PLoS Med. 2008;5(7):e144.
110. Office for National Statistics. Conception Statistics, England and Wales, 2015. 2017. Available at: https://www.ons.gov.uk/releases/conceptionsinenglandandwales2017.
111. Heffner LJ. Advanced maternal age--how old is too old? N Engl J Med. 2004;351:1927-9.
112. Bulletti C, Flamigni C, Giacomucci E. Reproductive failure due to spontaneous abortion and recurrent miscarriage. Hum Reprod Update. 1996;2:118-36.
113. Gracia CR, Sammel MD, Chittams J, Hummel AC, Shaunik A, Barnhart KT. Risk factors for spontaneous abortion in early symptomatic first-trimester pregnancies. Obstet Gynecol. 2005;106(5 Pt 1):993-9.
114. Ciancimino L, Laganà AS, Chiofalo B, Granese R, Grasso R, Triolo O. Would it be too late? A retrospective case-control analysis to evaluate maternal–fetal outcomes in advanced maternal age. Arch Gynecol Obstet. 2014;290:1109-14.
115. Risch HA, Weiss NS, Clarke EA, Miller AB. Risk factors for spontaneous abortion and its recurrence. Am J Epidemiol. 1988;128:420-30.
116. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ. 2000;320:1708-12.
117. Savage PM, Sita-Lumsden A, Dickson S, et al. The relationship of maternal age to molar pregnancy incidence, risks for chemotherapy and subsequent pregnancy outcome. J Obstet Gynaecol. 2013;33:406-11.
118. Knight M, Nair M, Tuffnell D, Kenyon S, Shakespeare J, Brocklehurst P, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Surveillance of maternal deaths in the UK 2012-14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-14. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2016.
119. Antinori S, Gholami GH, Versaci C, et al. Obstetric and prenatal outcome in menopausal women: a 12-year clinical study. Reprod Biomed Online. 2003;6:257-61.
120. Dulitzki M, Soriano D, Schiff E, Chetrit A, Mashiach S, Seidman DS. Effect of very advanced maternal age on pregnancy outcome and rate of cesarean delivery. Obstet Gynecol. 1998;92:935-9.
121. Laopaiboon M, Lumbiganon P, Intarut N, et al; WHO Multicountry Survey on Maternal Newborn Health Research Network. Advanced maternal age and pregnancy outcomes: a multicountry assessment. BJOG. 2014;121 Suppl 1:49-56.
122. Shrim A, Levin I, Mallozzi A, et al. Does very advanced maternal age, with or without egg donation, really increase obstetric risk in a

large tertiary center? J Perinat Med. 2010;38:645-50.
123. Yogev Y, Melamed N, Bardin R, Tenenbaum-Gavish K, Ben-Shitrit G, Ben-Haroush A. Pregnancy outcome at extremely advanced maternal age. Am J Obstet Gynecol. 2010;203:558.e1-e7.
124. Ziadeh S, Yahaya A. Pregnancy outcome at age 40 and older. Arch Gynecol Obstet. 2001;265:30-3.
125. Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. Obstet Gynecol. 2004;104:727-33.
126. Carolan M. Maternal age ≥ 45 years and maternal and perinatal outcomes: a review of the evidence. Midwifery. 2013;29:479-89.
127. Kenny LC, Lavender T, McNamee R, O'Neill SM, Mills T, Khashan AS. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. PLoS One. 2013;8:e56583.
128. Jacquemyn Y, Martens E, Martens G. Pregnancy at late premenopausal age: outcome of pregnancies at 45 years and older in Flanders, Belgium. J Obstet Gynaecol. 2014;34:479-81.
129. S Simchen MJ, Yinon Y, Moran O, Schiff E, Sivan E. Pregnancy outcome after age 50. Obstet Gynecol. 2006;108:1084-8.
130. Glasser S, Segev-Zahav A, Fortinsky P, Gedal-Beer D, Schiff E, Lerner-Geva L. Primiparity at very advanced maternal age (≥ 45 years). Fertil Steril. 2011;95:2548-51.
131. Salihu HM, Shumpert MN, Slay M, Kirby RS, Alexander GR. Childbearing beyond maternal age 50 and fetal outcomes in the United States. Obstet Gynecol. 2003;102(5 Pt 1):1006-14.
132. Traisrisilp K, Tongsong T. Pregnancy outcomes of mothers with very advanced maternal age (40 years or more). J Med Assoc Thai. 2015;98:117-22.
133. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ. 2000;320:1708-12.
134. British Isles Network of Congenital Anomaly Registers. Congenital Anomaly Statistics 2012: England and Wales. Available at: http://www.binocar.org/content/Annual%20report%202012_FINAL_nologo.pdf.
135. Morris JK, Mutton DE, Alberman E. Revised estimates of the maternal age specific live birth prevalence of Down's syndrome. J Med Screen. 2002;9:2-6.
136. Mercer CH, Tanton C, Prah P, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet. 2013;382:1781-94.
137. Grech P, Marchant R, Samuel M. Sexual health of women aged 40 and over attending an inner city integrated sexual health clinic. Int J STD AIDS. 2017;28:404-7.
138. Gott CM. Sexual activity and risk-taking in later life. Health Soc Care Community. 2001;9:72-8.
139. Kuehn BM. Time for "the talk"--again: seniors need information on sexual health. JAMA. 2008;300:1285-7.
140. Public Health England. Sexually Transmitted Infections (STIs): Annual Data Tables. Table 2: New STI diagnoses and rates by gender, sexual risk and age group, 2012 to 2016. 2017. Available at: https://www.gov.uk/government/statistics/sexually-transmitted-infections-stis-annual-data-tables.
141. Public Health England. Sexually Transmitted Infections (STIs): Annual Data Tables. Table 8: Attendances by gender, sexual risk and age group, 2012 to 2016. 2017. Available at: https://www.gov.uk/government/statistics/sexually-transmitted-infections-stis-annual-data-tables.
142. National Collaborating Centre for Women's and Children's Health (UK). Menopause: Full Guideline. London: National Institute for Health and Care Excellence (UK); 2015.
143. Hoyt LT, Falconi AM. Puberty and perimenopause: reproductive transitions and their implications for women's health. Soc Sci Med. 2015;132:103-12.
144. Worsley R, Bell R, Kulkarni J, Davis SR. The association between vasomotor symptoms and depression during perimenopause: a systematic review. Maturitas. 2014;77:111-7.
145. Scottish Intercollegiate Guidelines Network. Prevention and Management of Venous Thromboembolism. 2014. Available at: http://www.sign.ac.uk/sign-122-prevention-and-management-of-venousthromboembolism.html.
146. Sealy-Jefferson S, Wing JJ, Sánchez BN, et al. Age- and ethnic-specific sex differences in stroke risk. Gend Med. 2012;9:121-8.
147. NIH Osteoporosis and Related Bone Diseases National Resource Center. Osteoporosis Overview. 2015. Available at: https://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/overview.pdf.
148. Cancer Research UK. Breast Cancer (C50): 2012–2014. Available at: https://www.cancerresearchuk.org/sites/default/files/cstream-node/cases_crude_f_breast_I14.pdf.
149. Cancer Research UK. Ovarian Cancer (C56-C57.4): 2012–2014. Available at: Cancer Research UK. Ovarian Cancer (C56-C57.4): 2012–2014.
150. Cancer Research UK. Womb Cancer: Risks and Causes. 2014. Available at: https://www.cancerresearchuk.org/about-cancer/womb-cancer/risks-causes.
151. Lader D. (Office for National Statistics) (2009). Opinions Survey Report No. 41: Contraception and Sexual Health, 2008/09. London Stationery Office. Available at: http://ons.gov.uk/ons/rel/lifestyles/contraception-and-sexual-health/2008-09/index.html .
152. Dratva J, Gómez Real F, Schindler C, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. Menopause. 2009;16:385-94.
153. de Vries E, den Tonkelaar I, van Noord PA, van der Schouw YT, te Velde ER, Peeters PH. Oral contraceptive use in relation to age at menopause in the DOM cohort. Hum Reprod. 2001;16:1657-62.
154. Hardman SMR, Gebbie AE. The contraception needs of the perimenopausal woman. Best Pract Res Clin Obstet Gynaecol. 2014;28:903-15.
155. Faculty of Sexual & Reproductive Contraception. 2015. Healthcare (FSRH). Intrauterine contraception. Available at: https://www.fsrh.org/standards-and-guidance/documents/ceuguidanceintrauterinecontraception/.
156. Bayer Plc. Summary of Product Characteristics: Mirena. 2015. Available at: https://www.medicines.org.uk/emc/medicine/1829.
157. Allergan Ltd. Summary of Product Characteristics: Levosert 20 micrograms/24 hours IDS. 2017. Available at: https://www.medicines.org.uk/emc/medicine/30120.
158. Bayer Plc. Summary of Product Characteristics: Jaydess 13.5 mg intrauterine delivery system. 2016. Available at: https://www.medicines.org.uk/emc/medicine/28672.
159. National Institute for Health and Care Excellence (NICE). Heavy Menstrual Bleeding. 2007. Available at: https://www.nice.org.uk/guidance/cg44.
160. Lethaby AE, Cooke I, Rees M. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Syst Rev. 2005;CD002126.
161. Soini T, Hurskainen R, Grénman S, Mäenpää J, Paavonen J, Pukkala E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol. 2014;124(2 Pt 1):292-9.
162. Minig L, Franchi D, Boveri S, Casadio C, Bocciolone L, Sideri M. Progestin intrauterine device and GnRH analogue for uterussparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Ann Oncol. 2011;22:643-9.
163. Giannopoulos T, Butler-Manuel S, Tailor A. Levonorgestrel-releasing intrauterine system (LNGIUS) as a therapy for endometrial carcinoma. Gynecol Oncol. 2004;95:762-4.
164. Soini T, Hurskainen R, Grénman S, et al. Levonorgestrel-releasing intrauterine system and the risk of breast cancer: a nationwide cohort study. Acta Oncol. 2016;55:188-92.
165. Lyytinen HK, Dyba T, Ylikorkala O, Pukkala EI. A case-control study on hormone therapy as a risk factor for breast cancer in Finland: intrauterine system carries a risk as well. Int J Cancer. 2010;126:483-9.
166. McNicholas C, Maddipati R, Zhao Q, Swor E, Peipert JF. Use of the etonogestrel implant and levonorgestrel intrauterine device beyond the U.S. Food and Drug Administration-approved duration. Obstet Gynecol. 2015;125:599-604.
167. Sivin I, Stern J, Coutinho E, et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the Copper T380 Ag IUDS. Contraception.

1991;44:473-80.
168. Rönnerdag M, Odlind V. Health effects of long-term use of the intrauterine levonorgestrel releasing system. A follow-up study over 12 years of continuous use. Acta Obstet Gynecol Scand. 1999;78:716-21.
169. Contraceptive efficacy. In: Hatcher R, Trussell J, Nelson A, et al. (eds). Contraceptive Technology. New York, NY: Ardent Media, 2011.
170. Faculty of Sexual & Reproductive Healthcare (FSRH). Progestogen-only Implants. 2014. Available at: https://www.fsrh.org/documents/cec-ceu-guidance-implants-feb-2014/.
171. Bahamondes L, Valeria Bahamondes M, Shulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Hum Reprod Update. 2015;21:640-51.
172. Mansour D, Korver T, Marintcheva-Petrova M, Fraser IS. The effects of Implanon on menstrual bleeding patterns. Eur J Contracept Reprod Health Care. 2008;13(Suppl.1):13-28.
173. Varma R, Mascarenhas L. Endometrial effects of etonogestrel (Implanon) contraceptive implant. Curr Opin Obstet Gynecol. 2001; 13:335-41.
174. Walch K, Unfried G, Huber J, et al. Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis--a pilot study. Contraception. 2009;79:29-34.
175. Faculty of Sexual & Reproductive Healthcare (FSRH). Progestogen-only Injectable Contraception. 2014. Available at: https://www.fsrh.org/standards-and-guidance/documents/cec-ceu-guidance-injectables-dec-2014/.
176. Wilailak S, Vipupinyo C, Suraseranivong V, et al. Depot medroxyprogesterone acetate and epithelial ovarian cancer: a multicentre case-control study. BJOG. 2012;119:672-7.
177. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer. 1991;49:186-90.
178. Cundy T, Cornish J, Roberts H, Reid IR. Menopausal bone loss in long-term users of depot medroxyprogesterone acetate contraception. Am J Obstet Gynecol. 2002;186:978-83.
179. Viola AS, Castro S, Bahamondes MV, Fernandes A, Viola CF, Bahamondes L. A cross-sectional study of the forearm bone mineral density in long-term current users of the injectable contraceptive depot medroxyprogesterone acetate. Contraception. 2011;84:e31-7.
180. Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: a systematic review. Contraception. 2016;94:678-700.
181. Rice C, Killick S, Hickling D, Coelingh Bennink H. Ovarian activity and vaginal bleeding patterns with a desogestrel-only preparation at three different doses. Hum Reprod. 1996;11:737-40.
182. Rice CF, Killick SR, Dieben T, Coelingh Bennink H. A comparison of the inhibition of ovulation achieved by desogestrel 75 micrograms and levonorgestrel 30 micrograms daily. Hum Reprod. 1999;14:982-5.
183. Casper RF. Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. Fertil Steril. 2017;107:533-6.
184. Faculty of Sexual & Reproductive Healthcare (FSRH). Progestogen-only Pills. 2015. Available at: https://www.fsrh.org/standards-and-guidance/fsrh-guidelines-and-statements/method-specific/progestogen-only-pills/.
185. Nappi C, Bifulco G, Tommaselli GA, Gargano V, Di Carlo C. Hormonal contraception and bone metabolism: a systematic review. Contraception. 2012;86:606-21.
186. Curtis KM, Martins SL. Progestogen-only contraception and bone mineral density: a systematic review. Contraception. 2006;73:470-87.
187. Samson M, Porter N, Orekoya O, et al. Progestin and breast cancer risk: a systematic review. Breast Cancer Res Treat. 2016;155:3-12.
188. Lopez LM, Grimes DA, Gallo MF, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2010;CD003552.
189. Faculty of Sexual & Reproductive Healthcare (FSRH). Combined Hormonal Contraception. 2019. Available at: https://www.fsrh.org/standards-and-guidance/documents/combined-hormonal-contraception/.
190. Edelman A, Micks E, Gallo MF, Jensen JT, Grimes DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. Cochrane Database Syst Rev. 2014:CD004695.
191. Gallo MF, Nanda K, Grimes DA, Lopez LM, Schulz KF. 20 µg versus >20 µg estrogen combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2013:CD003989.
192. Bayer Plc. Summary of Product Characteristics: Qlaira. 2016. Available at: https://www.medicines.org.uk/emc/product/6536/smpc.
193. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 2017;216:580.e1-580.e9.
194. Hannaford PC, Iversen L, Macfarlane TV, Elliott AM, Angus V, Lee AJ. Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. Version 2. BMJ. 2010 Mar 11;340:c927.
195. Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical,colorectal, and endometrial cancers: a systematic review. Cancer Epidemiol Biomarkers Prev. 2013;22:1931-43.
196. Vessey M, Yeates D. Oral contraceptive use and cancer: final report from the Oxford-Family Planning Association contraceptive study. Contraception 2013;88:678-83.
197. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;371:303-14.
198. Cibula D, Gompel A, Mueck AO, et al. Hormonal contraception and risk of cancer. Hum Reprod Update. 2010;16:631-50.
199. Martins SL, Curtis KM, Glasier AF. Combined hormonal contraception and bone health: a systematic review. Contraception. 2006; 73:445-69.
200. Trémollieres F. Impact of oral contraceptive on bone metabolism. Best Pract Res Clin Endocrinol Metab. 2013;27:47-53.
201. Isley MM, Kaunitz AM. Update on hormonal contraception and bone density. Rev Endocr Metab Disord. 2011;12:93-106.
202. B Blümel JE, Castelo-Branco C, Binfa L, Aparicio R, Mamani L. A scheme of combined oral contraceptives for women more than 40 years old. Menopause. 2001;8:286-9.
203. Bachmann GA, Schaefers M, Uddin A, Utian WH. Lowest effective transdermal 17 beta-estradiol dose for relief of hot flushes in postmenopausal women: a randomized controlled trial. Obstet Gynecol. 2007;110:771-9.
204. Shargil AA. Hormone replacement therapy in perimenopausal women with a triphasic contraceptive compound: a three-year prospective study. Int J Fertil. 1985;30:15,18-28.
205. Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. Version 2. BMJ. 2011;343:d6423.
206. Roach RE, Lijfering WM, Helmerhorst FM, et al. The risk of venous thrombosis in women over 50years old using oral contraception or postmenopausal hormone therapy. J Thromb Haemost. 2013;11:124-31.
207. Sugiura K, Kobayashi T, Ojima T. Risks of thromboembolism associated with hormonal contraceptives related to body mass index and aging in Japanese women. Thromb Res. 2016;137:11-6.
208. Faculty of Sexual & Reproductive Healthcare (FSRH). Statement from the Clinical Effectiveness Unit: Combined Hormonal Contraception and Venous Thromboembolism. 2016. Available at: https://www.fsrh.org/news/statement-from-the-clinical-effectiveness-unit-combined/.
209. Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. BMJ. 2016;353:i2002.
210. Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. Obstet Gynecol. 2013;122:139-47.
211. Zhu H, Lei X, Feng J, Wang Y. Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. Eur J Contracept Reprod Health Care. 2012;17:402-14.

212. Faculty of Sexual & Reproductive Healthcare (FSRH). Barrier Methods: Contraception and STI Prevention. 2012. Available at: https://www.fsrh.org/standards-and guidance/documents/ceuguidancebarriermethodscontraceptionsdi/.
213. Faculty of Sexual & Reproductive Healthcare (FSRH). Male and Female Sterilisation. 2014. Available at: https://www.fsrh.org/standards-and-guidance/documents/cec-ceu-guidance-sterilisation-cpd-sep-2014/.
214. Faculty of Sexual & Reproductive Healthcare (FSRH). Fertility Awareness Methods. 2015. Available at: https://www.fsrh.org/standards-and-guidance/documents/ceuguidancefertilityawarenessmethods/.
215. Narayan H, Buckett W, McDougall W, Cullimore J. Pregnancy after fifty: profile and pregnancy outcome in a series of elderly multigravidae. Eur J Obstet Gynecol Reprod Biol. 1992;47:47-51.
216. Encyclopedia of Birth Control. Bullough VL (ed)., Santa Barbara, CA: ABC-CLIO, 2001.
217. Faculty of Sexual & Reproductive Healthcare (FSRH). Contraceptive Choices for Young People (March 2010, amended May 2019). Available at: https://www.fsrh.org/standards-and-guidance/fsrh-guidelines-and-statements/contraception-for-specific-populations/young-people/.
218. Unicef Innocenti Research Centre. Child Poverty in Perspective: An Overview of Child Well-Being in Rich Countries (Report Card 7). 2007. Available at: https://www.unicef-irc.org/publications/pdf/rc7_eng.pdf.
219. Unicef Innocenti Research Centre. A League Table of Teenage Births in Rich Nations (Report Card 3). 2001. Available at: https://www.unicef-irc.org/publications/328-a-league-table-of-teenage-births-in-rich-nations.html.
220. Sexually Transmitted Infection Epidemiology Advisory Group. Scotland's Sexual Health Information (SSHI) Report. Edinburgh, UK: Health Protection Scotland and Information Services Division, 2008. Available at: https://www.isdscotland.org/Health-Topics/Sexual-Health/Annual-Report/SSHI2008%20Digest%20Final%20Version%20v0.2%202008%2012%2012.pd.
221. HPA (Health Protection Agency). Sexually Transmitted Infections and Young People in the United Kingdom: 2008 report. London, Health Protection Agency, 2008.
222. Wellings K, Nanchahal K, Macdowall W, et al. Sexual behaviour in Britain: early heterosexual experience. Lancet 2001;358:1843-50.
223. Godeau E, Nic Gabhainn S, Vignes C, Ross J, Boyce W, Todd J. Contraceptive use by 15-year-old students at their last sexual intercourse. Arch Pediatr Adolesc Med. 2008;162:66-73.
224. Stone N, Ingham R. Factors affecting British teenager's contraceptive use at first intercourse: the importance of partner communication. Perspect Sex Reprod Health. 2002;34:191-7.
225. Manlove J, Ryan S, Franzetta K. Contraceptive use patterns across teens' sexual relationships: the role of relationships, partners and sexual histories. Demography. 2007;44:603-21.
226. Kinsella EO, Crane LA, Ogden LG, Stevens-Simon C. Characteristics of adolescent women who stop using contraception after use at first sexual intercourse J Pediatr Adolesc Gynecol. 2007;20:73-81.
227. Manlove J, Ikramullah E, Mincieli L, Holcombe E, Danish S. Trends in sexual experiences, contraceptive use and teenage childbearing: 1992–2002. J Adolesc Health. 2009;44:413-23.
228. Iuliano AD, Speizer IS, Santelli J, Kendall C. Reasons for contraceptive nonuse at first sex and unintended pregnancy. Am J Health Behav. 2006;30:92-102.
229. Say R, Mansour D. Contraceptive choice for young people. J Fam Plann Reprod Health Care. 2009;35:81-5.
230. Office for National Statistics. Contraception and Sexual Health 2008/2009. 2009. Available at: https://webarchive.nationalarchives.gov.uk/20160128155532/http://www.ons.gov.uk/ons/rel/lifestyles/contraception-and-sexual-health/2008-09/index.html
231. Fu H, Darroch JE, Haas T, Ranjit N. Contraceptive failure rates: new estimates from the 1995 National Survey of Family Growth. Fam Plann Perspect. 1999;31:56-63.
232. Vaughan B, Trussell J, Kost K, Singh S, Jones R. Discontinuation and resumption of contraceptive use: results from the 2002 National Survey of Family Growth. Contraception. 2008;78:271-83.
233. Lakha F, Glasier A. Continuation rates of Implanon in the UK: data from an observational study in a clinical setting. Contraception. 2006;74:287-9.
234. Rai K, Gupta S, Cotter S. Experience with Implanon in a north-east London family planning clinic. Eur J Contracept Reprod Health Care. 2004;9:39-46.
235. Smith A, Reuter S. An assessment of the use of Implanon in three community services. J Fam Plann Reprod Health Care. 2002;28:193-6.
236. Cheung E, Free C. Factors influencing young women's decision making regarding hormonal contraceptives: a qualitative study. Contraception. 2005;71:426-31.
237. Lopez LM, Newmann SJ, Grimes DA, Nanda K, Schulz KF. Immediate start of hormonal contraceptives for contraception. Cochrane Database Syst Rev. 2012;12:CD006260.
238. Free C, Lee RM, Ogden J. Young women's accounts of factors influencing their use and non-use of emergency contraception: in-depth interview study. BMJ. 2002;325:1393.
239. Free C, Ogden J. Emergency contraception use and non-use in young women: the application of a contextual and dynamic model. Br J Health Psychol. 2005;10(Pt 2):237-53.
240. Hamani Y, Sciaki-Tamir Y, Deri-Hasid R, Miller-Pogrund T, Milwidksy A, Haimov-Kochman R. Misconceptions about oral contraception pills among adolescents and physicians. Hum Reprod. 2007;12:3078-83.
241. Tanfer K, Wierzbicki S, Payn B. Why are U.S. women not using long-acting contraceptives? Fam Plann Perspect. 2000;32:176-83, 191.
242. Gallo MF, Lopez LM, Grimes DA, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. Cochrane Database Syst Rev 2008;CD003987.
243. National Collaborating Centre for Women's and Children's Health (UK). Long-acting Reversible Contraception: The Effective and Appropriate Use of Long-acting Reversible Contraception. RCOG Press. 2005.
244. Mangan SA, Larsen PG, Hudson S. Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. J Pediatr Adolesc Gynecol. 2002;15:79-82.
245. Risser WL, Gefter LR, Barratt MS, Risser JM. Weight changes in adolescents who use hormonal contraception. J Adolesc Health. 1999;24:433-6.
246. Funk S, Miller MM, Mishell DR Jr, et al. Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception. 2005;71:319-26.
247. Flores JB, Balderas ML, Bonilla MC, Vázquez-Estrada L. Clinical experience and acceptability of the etonogestrel subdermal contraceptive implant. Int J Gynaecol Obstet. 2005;90:228-33.
248. Bitzer J, Tschudin S, Alder J; Swiss Implanon Study Group. Acceptability and side-effects of Implanon in Switzerland: a retrospective study by the Swiss Implanon Study Group. Eur J Contracept Reprod Health Care. 2004;9:278-84.
249. Yildizbas B, Sahin GH, Kolusari A, Zeteroglu S, Kamaci M. Side effects and acceptability of Implanon: a pilot study conducted in eastern Turkey. Eur J Contracept Reprod Health Care. 2007;12:248-52.
250. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA, Garner SE. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev. 2007;CD004425.
251. British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Volume 58. September 2009.
252. Datapharm Communications Limited. electronic Medicines Compendium (eMC). Summaries of Product Characteristics (SPC). Available at: http://www.emc.medicines.org.uk. [Accessed 16 February 2010].
253. O'Connell K, Davis AR, Kerns J. Oral contraceptives: side effects and depression in adolescent girls. Contraception 2007;75:299-304.
254. Duke JM, Sibbritt DW, Young AF. Is there an association between the use of oral contraception and depressive symptoms in young Australian women? Contraception. 2007;75:27-31.

255. Rosenthal SL, Cotton S, Ready JN, Potter LS, Succop PA. Adolescents' attitudes and experiences regarding levonorgestrel 100 mcg/ethinyl estradiol 20 mcg. J Pediatr Adolesc Gynecol. 2002;15:301-5.
256. Joffe H, Cohen LS, Harlow BL. Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. Am J Obstet Gynecol. 2003;189:1523-30.
257. Gupta N, O'Brien R, Jacobsen LJ, et al. Mood changes in adolescents using depot-medroxyprogesterone acetate for contraception: a prospective study. J Pediatr Adolesc Gynecol. 2001;14:71-6.
258. Wong CL, Farquhar C, Roberts H, Proctor M. Oral contraceptive pill as treatment for primary dymenorrhoea. Cochrane Database Syst Rev. 2009;CD002120.
259. Scottish Executive. Respect and Responsibility: Strategy and Action Plan for Improving Sexual Health. Edinburgh, UK: Scottish Executive, 2005; 1–21.
260. Abou-Setta AM, Al-Inany HG, Farquhar CM. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Cochrane Database Syst Rev. 2006;CD005072.
261. Sheng J, Zhang WY, Zhang JP, Lu D. The LNG-IUS study on adenomyosis: a 3-year follow-up study on the efficacy and side effects of the use of the levonorgestrel intrauterine system for the treatment of dysmenorrhea associated with adenomyosis. Contraception. 2009;79:189-93.
262. Lopez LM, Grimes DA, Schulz KF, Curtis KM. Steroidal contraceptives: effect on bone fractures in women. Cochrane Database System Rev. 2006;CD006033.
263. European Medicines Agency. Press release: Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks - CHMP endorses PRAC recommendation. Press release 22/11/2013.
264. Department of Health. A Framework for Sexual Health Improvement in England. 2013. Available at: https://www.gov.uk/government/publications/a-framework-for-sexual-health-improvement-in-england.
265. The Scottish Government. Sexual Health and Blood Borne Virus Framework 2015-2020 Update. 2015. Available at: https://www.gov.scot/publications/sexual-health-blood-borne-virus-framework-2015-2020-update/.
266. Welsh Assembly Government. Sexual Health and Wellbeing Action Plan for Wales, 2010–2015. 2010. Available at: http://www.wales.nhs.uk/sites3/documents/485/Strategy%20(English)1.pdf.
267. The Scottish Government. Pregnancy and Parenthood in Young People Strategy. 2016. Available at: https://www.gov.scot/publications/pregnancy-parenthood-young-people-strategy/.
268. Heller R, Cameron S, Briggs R, Forson N, Glasier A. Postpartum contraception: a missed opportunity to prevent unintended pregnancy and short inter-pregnancy intervals. J Fam Plann Reprod Health Care. 2016;42:93-8.
269. Bigelow CA, Bryant AS. Short interpregnancy intervals: an evidence-based guide for clinicians. Obstet Gynecol Surv. 2015;70:458-64.
270. Smith GCS, Pell JP, Dobbie R. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study. BMJ. 2003;327:313.
271. World Health Organization, Department of Reproductive Health and Research. Report of a WHO Technical Consultation on Birth Spacing. 2007.
272. Faculty of Sexual & Reproductive Healthcare (FSRH). FSRH Clinical Guideline: Contraception After Pregnancy (January 2017). Available at: https://www.fsrh.org/standards-and-guidance/documents/contraception-after-pregnancy-guideline-january-2017/.
273. National Institute for Health and Care Excellence (NICE). Long-acting Reversible Contraception (Update). 2014. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/long-acting-reversible-contraception-update-nice-clinical-guideline-30/.
274. Cameron S. Postabortal and postpartum contraception. Best Pract Res Clin Obstet Gynaecol. 2014;28:871-80.
275. Aiken AR, Aiken CE, Trussell J, Guthrie KA. Immediate postpartum provision of highly effective reversible contraception. BJOG. 2015;122:1050-1.
276. Glasier AF, Logan J, McGlew TJ. Who gives advice about postpartum contraception? Contraception. 1996;53:217-20.
277. Speroff L, Mishell DR Jr. The postpartum visit: it's time for a change in order to optimally initiate contraception. Contraception. 2008;78:90-8.
278. Goldthwaite LM, Shaw KA. Immediate postpartum provision of long-acting reversible contraception. Curr Opin Obstet Gynecol. 2015;27:460-4.
279. Ogburn JAT, Espey E, Stonehocker J. Barriers to intrauterine device insertion in postpartum women. Contraception. 2005;72:426-9.
280. Gurtcheff SE, Turok DK, Stoddard G, Murphy PA, Gibson M, Jones KP. Lactogenesis after early postpartum use of the contraceptive implant: a randomized controlled trial. Obstet Gynecol. 2011;117:1114-21.
281. Jatlaoui TC, Riley H, Curtis KM. Safety data for levonorgestrel, ulipristal acetate and Yuzpe regimens for emergency contraception. Contraception. 2016;93:93-112.
282. Phillips SJ, Tepper NK, Kapp N, Nanda K, Temmerman M, Curtis KM. Progestogen-only contraceptive use among breastfeeding women: a systematic review. Contraception. 2016;94:226-52.
283. Goldstuck ND, Steyn PS. Intrauterine contraception after cesarean section and during lactation: a systematic review. Int J Womens Health. 2013;5:811-8.
284. Tepper NK, Phillips SJ, Kapp N, Gaffield ME, Curtis KM. Combined hormonal contraceptive use among breastfeeding women: an updated systematic review. Contraception. 2016;94:262-74.
285. Labbok MH, Hight-Laukaran V, Peterson AE, Fletcher V, von Hertzen H, Van Look PF. Multicenter study of the Lactational Amenorrhea Method (LAM): I. Efficacy, duration, and implications for clinical application. Contraception. 1997;55:327-36.
286) The World Health Organization multinational study of breast-feeding and lactational amenorrhea. III. Pregnancy during breast-feeding. World Health Organization Task Force on Methods for the Natural Regulation of Fertility. Fertil Steril. 1999;72:431-40.
287. Pérez A, Labbok MH, Queenan JT. Clinical study of the lactational amenorrhoea method for family planning. Lancet. 1992;339:968-70.
288. Lawrie TA, Kulier R, Nardin JM. Techniques for the interruption of tubal patency for female sterilisation. Cochrane Database Syst Rev. 2015;CD003034.
289. Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. Am J Obstet Gynecol. 1996;174:1161-8; discussion 1168-70.
290. Rodriguez MI, Seuc A, Sokal DC. Comparative efficacy of postpartum sterilisation with the titanium clip versus partial salpingectomy: a randomised controlled trial. BJOG. 2013;120:108-12.
291. Hunt JL, Lynn AAA. Histologic features of surgically removed fallopian tubes. Arch Pathol Lab Med. 2002;126:951-5.
292. Contraceptive efficacy. In: Hatcher R, Trussell J, Nelson A, et al. (eds), Contraceptive Technology. New York, NY: Ardent Media, 2011.
293. Department of Reproductive Health, World Health Organization. Medical Eligibility Criteria for Contraceptive Use. Fifth edition - Executive Summary. 2015. Available at: https://www.who.int/reproductivehealth/publications/family_planning/Ex-Summ-MEC-5/en/.
294. Marrs RP, Kletzky OA, Howard WF, et al. Disappearance of human chorionic gonadotropin and resumption of ovulation following abortion. Am J Obstet Gynecol. 1979;135:731-6.
295. Lähteenmäki P, Luukkainen T. Return of ovarian function after abortion. Clin Endocrinol (Oxf). 1978;8:123-32.
296. Cameron IT, Baird DT. The return to ovulation following early abortion: a comparison between vacuum aspiration and prostaglandin. Acta Endocrinol (Copenh). 1988;118:161-7.
297. Lähteenmäki P. The disappearance of HCG and return of pituitary function after abortion. Clin Endocrinol (Oxf). 1978;9:101-12.
298. Boesen HC, Rørbye C, Nørgaard M, Nilas L. Sexual behavior during the first eight weeks after legal termination of pregnancy. Acta Obstet Gynecol Scand. 2004;83:1189-92.
299. Royal College of Obstetricians and Gynaecologists (RCOG). The Care of Women Requesting Induced Abortion (Evidence-based Guideline Number 7). 2011. Available at:https://www.rcog.org.uk/en/guidelines-research-services/guidelines/the-care-of-women-re-

questing-induced-abortion/.
300. Sääv I, Stephansson O, Gemzell-Danielsson K. Early versus delayed insertion of intrauterine contraception after medical abortion – a randomized controlled trial. PLoS One. 2012;7:e48948.
301. Bilgehan F, Dilbaz B, Karadag B, Deveci CD. Comparison of copper intrauterine device with levonorgestrel-bearing intrauterine system for post-abortion contraception. J Obstet Gynaecol Res. 2015;41:1426-32.
302. Raymond EG, Weaver MA, Louie KS, et al. Effects of depot medroxyprogesterone acetate injection timing on medical abortion efficacy and repeat pregnancy: a randomized controlled trial. Obstet Gynecol. 2016;128:739-45.
303. Tang OS, Gao PP, Cheng L, Lee SW, Ho PC. A randomized double-blind placebo-controlled study to assess the effect of oral contraceptive pills on the outcome of medical abortion with mifepristone and misoprostol. Hum Reprod. 1999;14:722-5.
304. Tang OS, Xu J, Cheng L, Lee SW, Ho PC. The effect of contraceptive pills on the measured blood loss in medical termination of pregnancy by mifepristone and misoprostol: a randomized placebo controlled trial. Hum Reprod. 2002;17:99-102.
305. Fine PM, Tryggestad J, Meyers NJ, Sangi-Haghpeykar H. Safety and acceptability with the use of a contraceptive vaginal ring after surgical or medical abortion. Contraception. 2007;75:367-71.
306. Steinauer JE, Sokoloff A, Roberts EM, Drey EA, Dehlendorf CE, Prager SW. Immediate versus delayed initiation of the contraceptive patch after abortion: a randomized trial. Contraception. 2014;89:42-7.
307. Murthy AS, Creinin MD, Harwood B, Schreiber CA. Same-day initiation of the transdermal hormonal delivery system (contraceptive patch) versus traditional initiation methods. Contraception. 2005;72:333-6.
308. Job-Spira N, Bouyer J, Pouly JL, et al. Fertility after ectopic pregnancy: first results of a population-based cohort study in france. Hum Reprod. 1996;11:99-104.
309. Fernandez H, Capmas P, Lucot JP, Resch B, Panel P, Bouyer J; GROG. Fertility after ectopic pregnancy: the DEMETER randomized trial. Hum Reprod. 2013;28:1247-53.
310. Schreiber CA, Sober S, Ratcliffe S, Creinin MD. Ovulation resumption after medical abortion with mifepristone and misoprostol. Contraception. 2011;84:230-3.
311. Ratten GJ. Resumption of ovulation after incomplete abortion. Aust N Z J Obstet Gynaecol. 1972;12:217-9.
312. Royal College of Obstetricians and Gynaecologists (RCOG). Diagnosis and Management of Ectopic Pregnancy (Green-top Guideline No. 21). 2016. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg21/.
313. Feldkamp M, Carey JC. Clinical teratology counseling and consultation case report: low dose methotrexate exposure in the early weeks of pregnancy. Teratology. 1993;47:533-9.
314. Lloyd ME, Carr M, McElhatton P, Hall GM, Hughes RA. The effects of methotrexate on pregnancy, fertility and lactation. QJM. 1999;92:551-63.
315. Rai R, Regan L. Recurrent miscarriage. Lancet. 2006;368:601-11.
316. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet. 2003;361:901-8.
317. Wong LF, Porter TF, de Jesús GR. Recurrent early pregnancy loss and antiphospholipid antibodies: where do we stand? Lupus. 2014;23:1226-8.
318. Franks AL, Beral V, Cates W Jr, Hogue CJ. Contraception and ectopic pregnancy risk. Am J Obstet Gynecol. 1990;163(4 Pt 1):1120-3.
319. Royal College of Obstetricians and Gynaecologists (RCOG). The Management of Gestational Trophoblastic Disease (Green-top Guideline No. 38). 2010. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg38/.
320. Mangili G, Lorusso D, Brown J, et al. Trophoblastic disease review for diagnosis and management: a joint report from the International Society for the Study of Trophoblastic Disease, European Organisation for the Treatment of Trophoblastic Disease, and the Gynecologic Cancer InterGroup. Int J Gynecol Cancer. 2014;24(9 Suppl 3):S109-16.
321. Bolze PA, Attia J, Massardier J, et al; EOTTD group. Formalised consensus of the European Organisation for Treatment of Trophoblastic Diseases on management of gestational trophoblastic diseases. Eur J Cancer. 2015;51:1725-31.

Conflict of interest: *the authors declare that there is no conflict of interest.*