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Review

## Contraception during the perimenopause



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### ABSTRACT

Although the absolute risk of pregnancy is lower during the perimenopause due to decreased fertility and decreased coital frequency, unintended pregnancy occurs at ratios similar to those observed in young women, and pregnancies that do occur are at high risk for maternal complications and poor outcomes such as miscarriage or chromosomal abnormalities. Therefore all premenopausal women should receive counselling that includes discussion of sexual habits and contraception during routine health care encounters. The majority of US women in this age group use permanent contraception, but other methods can be safe and effective and can have non-contraceptive benefits.

No contraceptive method is contraindicated based on age alone. However, estrogen-containing methods should be reserved for women without cardiovascular or thrombotic risk factors. The levonorgestrel intrauterine system (LNG-IUS, Mirena®) has particular benefits during perimenopause and is safe for use in nearly all women. The LNG-IUS is approved for treatment of heavy menstrual bleeding, a common concern during the perimenopause. A substantial literature supports the use of the LNG-IUS for endometrial protection during transition from contraception to hormone therapy, although this is off-label in the United States.

Reliable contraception should be used until menopause is confirmed either by cessation of menses for 2 years prior to age 50, for 1 year after age 50, or by two elevated follicle-stimulating hormone (FSH) values  $\geq 20$ –30 IU/l while off hormonal methods for at least 2 weeks. Sterility cannot be assumed until at least age 60 because spontaneous pregnancies have been reported in women up to age 59.

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## 1. Introduction

Continuing contraception through menopause allows heterosexually-active women to exit their reproductive years having completed childbearing to their ideal family size. At all ages, the most appropriate contraceptive method is one with minimal side effects and maximal non-contraceptive benefits. The ideal contraceptive method for a particular woman might change over time in response to diminished need for efficacy with decreasing biologic fertility, the emergence of age-related comorbidities, the increasing need for management of side effects related to perimenopause, and the development of new contraceptive technology.

Perimenopause is defined as the time just before and after menopause, until there has been amenorrhea for 12 months [1]. For most clinicians and patients, it represents a period of transitional symptoms that culminates with menstrual cessation. From cohort studies, we know that perimenopause begins on average at age 47.5 and lasts for a mean duration of 3.8 years [2,3].

Many women experience no significant symptoms or menstrual changes despite a dramatic decrease in fertility during perimenopause. Decreased coital frequency and male infertility explain part of this decline, but infecundability in women in this age group is primarily due to a decrease in oocyte quality and ovulation [4,5]. However, even women with irregular menses who ovulate occasionally and unpredictably can become unexpectedly pregnant. Pregnancies to women over age 40 are far more likely to result in miscarriage than in younger women, an experience that can be particularly upsetting, even in the setting of an unplanned pregnancy [6]. Therefore continuing contraception counselling through menopause is an important health care intervention that allows heterosexually-active women to exit their reproductive years having completed childbearing to their ideal family size.

Despite more life experience with preventing mistimed pregnancy, women in the later reproductive years have a similar proportion of unintended pregnancies as younger women [7]. In 2006, 48% of pregnancies to women age 40 or greater were unintended, compared to 41% of those to women age 25–29. In both age groups, approximately 46% of unintended pregnancies resulted in abortion. Though many fewer pregnancies occur in the older reproductive age group, the overall proportion of pregnancies that results in abortion is similar to women age 20–24 [7,8]. These pregnancies are also more likely to result in miscarriage or fetal anomaly.

Since most reproductive databases only include women until age 44, the number and outcomes of pregnancies that occur to women in perimenopause is largely under-reported and unstudied. Much of the literature around fertility in women above age 40 is based on data from women who desire fertility, some of whom have never been pregnant. The downside is that our counselling and understanding of the relative chance of unintended pregnancy in this age group is based on few data. Additionally, knowledge deficits exist about the relative effectiveness of various contraceptive methods in women with subfertility or decreased coital frequency. Here we provide some age-related estimates of risk for unintended pregnancy, describe contraceptive options, and discuss relative risks and benefits of hormonal contraceptive options compared to hormone therapy.

## 2. How likely is pregnancy in perimenopause?

The chance of pregnancy occurring among married or cohabitating women not doing anything to prevent pregnancy can be estimated as about 30% per year at age 40–44 and about 10% per year for age 45–49 [9–12]. The fecundability of women in this age group is dependent on ovulation, coital frequency, efficacy of contraceptive method used, continuation and adherence to a contraceptive method, and male partner fertility.

Among infertile women attempting pregnancy at age 41–43 who undergo an in vitro fertilization oocyte retrieval, only 12% achieve pregnancy and between 2% and 7% give birth [13]. Both the low overall rate and high proportion of failed pregnancies are thought to be a result of poor oocyte quality. Further evidence for poor oocyte quality comes from the higher rates of spontaneous abortion and chromosomal anomalies detected in pregnancies during the 5th decade of life [14]. Miscarriage can occur in up to 34% of pregnancies at age 40 and 53% at age 45; most are chromosomally abnormal [6].

Factors other than poor oocyte quality and diminished ovarian reserve contribute toward decreased fertility in older reproductive women [11]. As women age, they have a higher chance of having had tubal scarring due to either PID or prior surgery [10]. Their partners may be more likely to develop factors leading to low sperm count or poor motility [4]. Relationship status may change, or erectile dysfunction may result in decreased coital frequency [15]. Alternatively, an increased risk of pregnancy can result from exposure to a new partner after several years or decades of decreased risk for pregnancy with a sub fertile or infertile partner. Women experiencing a new need for contraception during the latter reproductive years may not have access to contraceptive services or information since these services are typically targeted toward younger women.

The effectiveness of contraception is established for younger reproductive women with various methods, but has not been specifically studied in perimenopausal women. Coital frequency and ovarian reserve factor highly into the probability of pregnancy at any age and the quality of the embryo is related to the success of implantation. Given this, methods with lower inherent efficacy may be suitable for some perimenopausal women at low risk for pregnancy, but this depends on both the predictability of ovarian reserve and on coital frequency with a partner of normal fertility.

## 3. Are there risks associated with pregnancy during the perimenopause?

The risks associated with pregnancy and terminations of pregnancy are higher in women during the late reproductive years. Though these elevated risks can be related to medical comorbidities such as hypertension, obesity, or diabetes, a large Swedish cohort study identified age as an independent risk factor [16,17]. For healthy women, adverse outcomes can be minimal, but they can be significant for some high risk women. Therefore, it is important to discuss the relative risk of pregnancy and use of contraception among women of older reproductive age who are at risk for pregnancy. In general, the risks associated with pregnancy greatly outweigh the risk of contraception, and this is especially true among women with significant medical co-morbidities.

#### 4. What are the options for contraception during perimenopause?

There is no contraceptive method which is contraindicated solely on the basis of age; therefore, all methods available to younger women can be used in women over age 45. Although the relative risks associated with use of hormonal methods may increase based on underlying medical issues, such as hypertension, obesity, smoking, or other cardiovascular risk factors, the potential health effects of a high risk pregnancy must be considered as an alternative. Unfortunately, non-hormonal methods which rely on knowledge of the timing of ovulation, (fertility-awareness based methods) are not reliable during the perimenopause because both ovulation and cycle length can be unpredictable.

Contraceptive methods can be separated into non-hormonal and hormonal. Typical use failure rates for younger women as well as risks and benefits for each method are outlined in [Table 1](#). The non-hormonal methods include barrier methods (diaphragm, cervical cap, and condom), withdrawal, spermicides, and the copper intrauterine device (IUD) (CuT380A, ParaGard<sup>®</sup>, Teva). Hormonal methods can be divided into combined methods that contain both an estrogen and a progestin, and progestin-only methods. The combined contraceptive methods include the pill, patch, and vaginal ring (a monthly combination shot is available in some countries). The progestin-only methods include the levonorgestrel intrauterine system (LNG-IUS, Mirena<sup>®</sup>), injectable depot medroxyprogesterone acetate (DMPA) and various pills. Permanent contraceptive methods, including tubal ligation, hysteroscopic tubal occlusion, and vasectomy are the most common methods used in this age group in the United States [18].

##### 4.1. Non-hormonal methods

###### 4.1.1. Barrier methods and spermicides

Condoms, the cervical cap, and the diaphragm are barrier methods that many perimenopausal women use with confidence and good adherence. Vaginal spermicides are also available in some regions, and can be used with or without a barrier. Since these methods require coital-dependent correct and consistent use, the typical use failure in young women is around 15–20%.

Perimenopausal women who have used these methods successfully and consistently in the past can continue to use them with some caveats. Following a pregnancy, or if these methods have not been used for several years, an exam is necessary to re-fit the cervical cap or diaphragm. Both the cervical cap and the diaphragm should be left in place for 6 h after intercourse and should not be used during menstruation. A new cervical cap that comes in 3 sizes to simplify fitting has been recently introduced ([Fig. 1](#)). If vaginal vault prolapse or urethral hypermobility are issues, it may be difficult to use the cervical cap or diaphragm correctly. Continued use of condoms can be difficult in the setting of male erectile dysfunction, which occurs more frequently at older ages. While barrier methods may be more effective in perimenopausal women than in younger women, adherence and continuation might be challenging for some women.

Spermicides containing nonoxynol-9 are available in some regions. Other spermicides are currently in development. Though spermicides have not been evaluated for efficacy compared to no method, pregnancy rates for perfect versus inconsistent use demonstrate modest effectiveness among young women who have heterosexual sex at least 4 times per month (19.8 pregnancies per 100 women for inconsistent use of nonoxynol-9 versus 6.6 per 100 for perfect use over 12 months of use) [19]. Use of post-coital spermicides is not effective. Spermicides can be recommended as an adjunct or as a less effective method, particularly among women with decreased fertility. However, among female sex workers in



**Fig. 1.** Femcap<sup>®</sup>, a cervical cap that comes in three sizes. The device is positioned over the cervix prior to intercourse and can be left in place for up to 48 h after intercourse.

a high risk area, nonoxynol-9 spermicide was associated with increased HIV transmission rate compared to placebo possibly due to vaginal micro-trauma [20]. There are ongoing campaigns to ban nonoxynol-9 from condoms and lubricants due to concern for increased rectal transmission of HIV [21]. Other spermicides are currently in development and should be tested for efficacy and side effects among perimenopausal women.

###### 4.1.2. Copper intrauterine device

The copper IUD (CuT380A, ParaGard<sup>®</sup>, Teva) offers highly-effective long-acting reversible non-hormonal contraception appropriate for many perimenopausal women. The copper IUD is associated with slightly more menstrual blood loss so women with heavy menstrual bleeding are not good candidates for the device. But for women with light or infrequent menses it can be a cost-effective contraceptive that has been demonstrated to be safe and effective far beyond its approved duration of 10 years [9]. The copper IUD has also been approved for use as emergency contraception if placed within 72 h of unprotected intercourse. When used within 120 h after unprotected intercourse in a large multicenter cohort study in China, no pregnancies resulted among nearly 2000 women up to age 44 [22].

##### 4.2. Hormonal methods

###### 4.2.1. Emergency contraception

In addition to the copper IUD, two oral emergency contraceptive options are currently available in the United States, levonorgestrel (Plan B One-Step<sup>®</sup>, Teva Pharmaceuticals) and ulipristal acetate (EllaOne<sup>®</sup>, HRA Pharma). Only Plan B One-Step<sup>®</sup> is accessible without a prescription. Both oral options delay ovulation, so can result in delayed subsequent menses as well, and neither has been studied specifically in perimenopausal women. Levonorgestrel-based emergency contraception is approved for use within 72 h of unprotected intercourse and ulipristal acetate for use within 5 days. If used within 72 h, ulipristal acetate was as effective as levonorgestrel in preventing pregnancy, with 1.8% of women becoming pregnant, compared to 2.6% (OR 0.68; 95% CI 0.35–1.31) [23].

###### 4.2.2. Combined hormonal methods

The combined oral contraceptive pill, transdermal patch, and vaginal ring constitute the combined hormonal methods that contain both an estrogen and a progestin. Almost all of these methods use the synthetic estrogen ethinyl estradiol (EE). Doses vary from 10 to 35 mcg daily in the pill, to 15 mcg daily in the vaginal ring, and 20 mcg daily in the transdermal patch [24,25].

**Table 1**  
Contraceptive method comparison citing typical use effectiveness for younger women and for older women as available.

Method	Typical use effectiveness <sup>a</sup>	Non-contraceptive benefits	Single dose duration	Other features
Implant	0.05	Menstrual suppression; ovulatory suppression	3 years	Unpredictable bleeding pattern; 22% amenorrhea by 1 year
Male sterilization	0.15	Lowest female risk	Permanent	Initial backup method needed
LNG-IUS	0.2	Management of heavy menstrual bleeding, dysmenorrhea; endometrial protection	5 years	Unpredictable bleeding pattern; 16% amenorrhea by 1 year
Female permanent contraception (tubal ligation, hysteroscopic occlusion)	0.5		Permanent	Hysteroscopic occlusion requires initial backup method
Copper IUD	0.8		10+ years	Can result in heavier or more prolonged bleeding
DMPA	6	Management of heavy menstrual bleeding, dysmenorrhea; endometrial protection; ovulatory suppression	12 weeks	Unpredictable bleeding pattern; 46% amenorrhea by 1 year
Combined hormonal methods (pill, patch, ring)	9	Menstrual suppression; ovulatory suppression	Daily to monthly	Pills and ring can be used cyclically, continuously or extended use; thrombosis risk
Progestin-only pill	9 (0.3 for age >40) <sup>b</sup>		Daily	Unpredictable bleeding pattern
Barrier methods (condom, diaphragm, cervical cap)	12–18		Coital-dependent	
Withdrawal	22		Coital-dependent	
Spermicides	28		Coital-dependent	

<sup>a</sup> Trussell J. Contraceptive failure in the United States. *Contraception* 2011;83:397–404.

<sup>b</sup> Ref. [26].

Health risks associated with these products are due to the hepatic metabolism of the estrogen component [26]. It is important to note that while EE delivered via the transdermal or vaginal route avoids first-pass metabolism through the liver, the high potency and active metabolites of EE result in net effects on coagulation similar to those observed with oral administration of similar doses [27–29]. Estradiol containing pills have been recently introduced. While estradiol is less potent than EE, a higher dose is needed for oral activity and there is no clinical evidence to date to suggest a lower risk of thrombosis [30].

The main health risk associated with estrogen is thrombosis, either venous thromboembolism (VTE) or arterial thrombosis (ATE), including stroke [31]. Medical comorbidities in women above age 35 that increase this risk include hypertension, migraine headache, obesity, diabetes, systemic lupus erythematosus, cardiac disease, current smoking, surgery requiring immobilization, and personal history of VTE [32]. Other medical comorbidities that can be exacerbated by estrogen-containing contraceptive methods include gallbladder disease without cholecystectomy, hyperlipidemia, and hepatic disease with liver function abnormalities [26]. Women with medical contraindications should not be prescribed combined hormonal contraception. It is important to stress that age is an independent risk factor for thrombosis, and the interaction of age with other risk factors may be multiplicative. Therefore, even healthy women using estrogen-containing contraceptives in the later reproductive years should be counselled regarding other modifiable risks such as long haul air travel and surgery.

Benefits of combined hormonal methods include an improved bleeding pattern, particularly in the setting of irregular or heavy menses. An estradiol valerate dienogest pill has recently received FDA approval for the treatment of heavy menstrual bleeding [33]. Additional health benefits include management of dysmenorrhea, risk reduction for ovarian and endometrial cancer, increased bone density, and possibly a decrease in functional ovarian cysts [34]. Estrogen-containing methods can provide symptomatic relief for perimenopausal women complaining of hot flashes or vaginal

dryness associated with fluctuating estrogen levels [35]. Furthermore, for symptomatic women who require contraception, contraceptive methods are often available at reduced costs compared to hormone therapy through state or federal programs or insurance plans.

Pills can be used cyclically in the traditional fashion, or continuously, and have been shown to be more effective for ovulatory suppression and have greater effectiveness with shorter pill-free intervals [36,37]. Continuous or extended-use dosing of pills also allows management of heavy menstrual bleeding, premenstrual dysphoric disorder, premenstrual syndrome, and other cycle-related symptoms including headache in some cases [38–40]. Unscheduled bleeding can be more common with continuous or extended regimens and can be improved with introduction of a short hormone-free interval as needed, up to once monthly [41].

#### 4.2.3. Progestin-only pill

Unlike combined hormonal methods that block ovulation, the progestin-only pill available in the United States is thought to work primarily by thickening cervical mucus [42]. While the progestin-only pill does not provide exogenous estrogen that could help with symptom management, it is highly effective in the perimenopausal population. In younger women, the failure rate with perfect use is 3.1 per 100 woman-years, compared to 0.3 per 100 woman-years in women over age 40 [26]. A disadvantage to the progestin-only pill is an irregular bleeding pattern that can result in high rates of discontinuation.

Not all progestin pills are equivalent in their ability to suppress ovulation, as demonstrated in a systematic review of currently marketed progestins either alone or in combination pills [43]. Cerazette® (Merck), a desogestrel-containing pill used in Europe, and levonorgestrel pills are better at suppressing ovulation than other formulations [43]. Although other progestin pills, such as oral medroxyprogesterone acetate (MPA), are used commonly for management of abnormal uterine bleeding, the evidence for efficacy is

limited, and no data exists to evaluate the use of oral MPA as a contraceptive [44].

#### 4.2.4. *Injectable progestins*

Depot medroxyprogesterone acetate (DMPA) is an injection that is approved for subcutaneous (105 mg) administration monthly or intramuscular (150 mg) administration every 12 weeks for contraception. It can provide endometrial protection in the setting of exogenous estrogen administration [45]. Despite a paucity of good evidence, it is also widely used to manage abnormal bleeding. DMPA inhibits ovulation by blocking the LH surge but also suppresses FSH-regulated ovarian estradiol production. Thus, use can be associated with symptoms of hypoestrogenism. Perimenopausal women who are taking DMPA should be aware that return to ovulation may lag after the 3 month period of active drug metabolism [46]. However, lack of return of menses is still not diagnostic for menopause. Although long term DMPA users have been shown to have decreased bone mineral density (BMD) compared to their age-matched controls, the effect is similar to that observed at the onset of menopause and does not appear to progress or be associated with fracture risk [47,48].

### 4.3. *Long-acting reversible contraception (LARC)*

#### 4.3.1. *Implants*

The 3-year contraceptive implant currently marketed in the United States, Nexplanon<sup>®</sup> (formerly Implanon<sup>®</sup>, Merck), is a highly-effective method of contraception with a lowest expected failure rates of 0.01% [49]. This flexible single-rod subdermal implant releases approximately 67 mcg of etonogestrel daily initially, decreasing gradually to a steady state of 30 mcg daily after about 2 years [50]. The mechanism of action is by suppression of ovulation as well as thickened cervical mucus. The advantage of the implant in the perimenopausal patient is the high effectiveness in the first 3 years of use, which does not vary by body weight [51]. Few contraindications exist for the etonogestrel implant, though there are notable decreases in efficacy with concomitant use of some anti-epileptic medications [32].

Disadvantages to use of the contraceptive implant include an irregular bleeding pattern, particularly in the first year of use. However, in general, women with light or infrequent bleeding at baseline are more likely to continue that trend with the etonogestrel implant [52]. Although case reports have suggested successful use of the implant to manage HMB, rigorous clinical trials have not been performed [53].

#### 4.3.2. *LNG-IUS*

The levonorgestrel intrauterine system (LNG-IUS, Mirena<sup>®</sup>, Bayer) is a popular choice for effective contraception, selected by 45% of women seeking contraception in a large prospective study when barriers such as cost and access were removed [54]. The LNG-IUS was initially approved by the FDA for use in the United States for contraception in 2000 and was approved for the indication of heavy menstrual bleeding in October 2009. The LNG-IUS has an initial release rate of 20 mcg of levonorgestrel daily and has a typical use contraceptive failure rate of 0.1% per year [55].

One of the great advantages of the LNG-IUS is that the system can be used to provide endometrial protection in menopause. While this is not an approved indication in the United States, a number of studies support use in perimenopausal and postmenopausal women seeking endometrial protection during hormone therapy [56–58]. Estrogen therapy can be started as symptoms appear. Forty perimenopausal women with climacteric symptoms treated with 2 mg oral estradiol valerate daily were randomized to receive either cyclic oral progestin (250 mcg levonorgestrel daily for the last 10 days of each 3 week cycle) versus LNG-IUS [59]. Over a 1 year study

period, symptoms were reduced in both groups and 15 of 18 women in the LNG-IUS group experienced amenorrhea, compared to no women in the oral progestin group. No endometrial proliferation was noted in either group.

The occurrence of amenorrhea while using a progestin with hormone therapy appears highly related to the dose and route of administration of the progestin. In another small trial comparing a non-cyclic oral progestin (1 mg norethisterone acetate daily) versus 20 mcg/day LNG-IUS, more spotting was seen in the LNG-IUS group initially (2/15 using LNG-IUS and 15/17 using oral progestin amenorrheic at 3 months) with no difference in amenorrhea by 1 year in each group (12/15 using LNG-IUS and 17/17 using oral LNG amenorrheic at 12 months) [60]. Lower dose LNG IUS systems releasing 5 or 10 mcg daily have been studied with the finding that lower intrauterine progestin doses generally result in more time to amenorrhea with prolonged spotting [61]. Changes to endometrial morphology are universally seen in women using IUDs with LNG doses of 10–40 mcg per day as early as three months after initiation [62].

In addition to providing highly-effective contraception and endometrial protection in the setting of estrogen therapy, the LNG-IUS has been demonstrated to treat heavy menstrual bleeding. A Cochrane review in 2009 of randomized trials revealed that the LNG-IUS is more effective than cyclic norethindrone but can be associated with more side effects such as unscheduled bleeding [63]. Total reduction in blood loss was lower than with endometrial ablation, but there was no difference in the satisfaction with treatment. A similar decrease in mean blood loss over the first three months of use was observed among women with heavy menstrual bleeding who received either an LNG-IUS or cyclic oral norethisterone in one randomized trial [64]. Reviews of LNG-IUS compared to hysterectomy have concluded that LNG-IUS is an acceptable alternative to hysterectomy for heavy menstrual bleeding during perimenopause [65,66].

The 20 mcg/day LNG-IUS (Mirena<sup>®</sup>) contains 52 mg levonorgestrel, which is enough to sustain release for up to 5 years, decreasing to approximately 10 mcg/day by the end of its approved time [67]. A recently approved smaller intrauterine system (Skyla<sup>®</sup>, Bayer) contains 13.5 mg levonorgestrel released at a rate of 14 mcg/day initially and decreasing gradually over 3 years to 5 mcg/day [68]. Given that this newer IUD is highly effective contraception over the entire approved 3 year period at a much lower dose of levonorgestrel, it is likely that Mirena<sup>®</sup> could be effective longer. Unfortunately, there are no currently published studies evaluating effectiveness of prolonged use of Mirena<sup>®</sup>. From the 1980s, Sivin and colleagues published data on prolonged use of another 20 mcg/day LNG-IUS for up to 7 years, but this prototype IUD contained 60 mg levonorgestrel and is not the same device as currently marketed [69]. Cumulative pregnancy rates at 7 years were 1.1 per 100 in users of this IUD. Women should be counselled that use of an IUD beyond the FDA-approved length might result in non-contraceptive drug levels. However, prolonged use of an LNG-IUS in perimenopausal women may be appropriate given their lower expected fertility.

## 5. **When can a perimenopausal woman reliably stop using hormonal contraception?**

The decision about when to discontinue use of hormonal contraception depends on the individual woman's risk for pregnancy, whether she is using any additional non-hormonal methods to prevent pregnancy, and whether she has developed any risk factors for continued use of estrogen. Women using combined hormonal contraception, such as the pill, patch, or the vaginal ring in standard dosing will typically experience withdrawal bleeding, but this does not rule out ovarian failure. Similarly, amenorrhea can occur in both

**Table 2**

Laboratory values suggestive of menopause among women with amenorrhea for at least 12 months or while using hormonal contraception.

Limited reproductive potential <sup>a</sup>
FSH $\geq 20$ IU/l; or
Antral follicle count <4–6
No need for contraception <sup>b</sup>
Amenorrhea for 12 months; or
FSH $\geq 30$ IU/l on two occasions 6–8 weeks apart; or
Age 60
OR, among women using combined hormonal contraceptives <sup>c</sup>
FSH $\geq 30$ IU/l on two occasions 6–8 weeks apart obtained beginning at age
50, 7–14 days after use of a pill/patch/vaginal ring while using a
non-hormonal alternative method
OR, among women using the injectable progestin, depot
medroxyprogesterone acetate <sup>d</sup>
FSH $\geq 30$ IU/l on two occasions 90 days apart obtained beginning at age 50 on
the day of an injection

<sup>a</sup> Ref. [70].

<sup>b</sup> Ref. [71].

<sup>c</sup> Ref. [72].

<sup>d</sup> Ref. [75].

standard cycles and with continuous use of combined methods, and does not indicate menopause. Table 2 summarizes expert opinion and research for how to establish menopause.

While serum FSH, estradiol, anti-Mullerian hormone, and ultrasound evaluation of basal antral follicle count are used to predict subfertility in women seeking pregnancy, they are also useful to establish a lack of need for contraception in perimenopausal women [11]. Significantly impaired reproductive potential due to diminished ovarian reserve is associated with a single FSH  $\geq 20$  IU/l or an antral follicle count of >4–6 follicles, or both [70]. Expert opinion suggests that ovarian failure can be established with continued amenorrhea and two values of FSH  $\geq 30$  IU/l measured at an interval of 6–8 weeks apart [71].

Use of serum FSH testing can be particularly helpful in cases where women are using hormonal contraception and it is not feasible or practical to discontinue the method for assessment of amenorrhea. However, serum testing is discouraged as a primary assessment for menopause when a woman is either not at risk for pregnancy or a non-hormonal backup method could be used while assessing for amenorrhea. Sterility can be assumed using amenorrhea criteria without any serum testing or by age 60. Women age 50 and younger should use contraception for 2 years of amenorrhea and older than age 50 for 1 year of amenorrhea.

There are several approaches to determine whether hormonal contraception should be continued. A perimenopausal woman who is nearing age 50 may consider discontinuing hormonal contraception for one to two months to determine if she is still menstruating, while using a non-hormonal backup method. An alternative approach is to measure FSH during the end of the hormone-free interval beginning at age 50. If the value is  $\geq 30$  IU/l, it can be assumed that ovarian failure has occurred and that contraception is not needed. However, while a false-positive elevation is not likely, false negatives can occur. In a cohort of 28 postmenopausal patients taking oral contraceptive pills, 14 taking triphasic pills and 14 taking monophasic pills, serum parameters were analyzed in the pill-free week to determine their diagnostic criteria for menopausal status. Of the 24 women who completed the study, 15 (62.5%) had a serum FSH <30 IU/l on day 7 of the pill-free interval despite being postmenopausal [72].

Serum parameters for diagnosis of menopause were also compared between a group of 12 postmenopausal women (age 48–60) who had been on extended cycle combined oral contraceptive pills, 9 perimenopausal women (age 36–47), and 31 early reproductive age women with normal menstrual cycles [73]. Serum estradiol, FSH, and LH were assayed at days 0, 7 and 14 after discontinuation

of the pill. Elevated FSH was seen more frequently in the perimenopausal women over age 40 and in the postmenopausal women. However, not all postmenopausal women experienced a rebound of elevated FSH. Eight of the 12 postmenopausal women (66%) did not experience elevated FSH to menopausal levels until 14 days after pill discontinuation. Therefore, we recommend that in order to avoid false negative diagnosis of menopause, FSH should be performed after 14 days of a pill-free interval while using a backup contraceptive method.

It can be confusing to evaluate for menopause during long-term use of DMPA. While FSH is suppressed by DMPA during the initial phase of the injection cycle, FSH should return to baseline values by at least 80 days post-injection [74]. The usefulness of FSH in diagnosing menopause in long-term users of DMPA was evaluated in a Brazilian study [75]. Women over age 40 (mean age 46, range 40–55) who were amenorrheic on DMPA ( $n=82$ ) had two serial evaluations of serum FSH, at baseline just before a subsequent injection and 90 days later. Postmenopausal FSH values (>35 IU/l) were seen in 39% of the women, but 14 of these women subsequently had FSH values in the premenopausal range. The authors concluded that FSH testing should be limited to women above age 50, that at least two serial values of FSH should be obtained 90 days apart just prior to DMPA injection, and that an FSH value of >30–35 IU/l should be used for diagnosis of menopause. Discontinuation of DMPA during evaluation of menopause is not necessary.

How long to wait before measuring FSH rests largely with the willingness of the patient to remain off hormonal contraceptives. At age 50, it is usually appropriate to simply renew a prescription for the method, and repeat an FSH in 1 year. Once a diagnosis of menopause has been made, it makes sense to switch the patient from hormonal contraception to hormone replacement therapy. Even the lowest doses of ethinyl estradiol in combined oral contraception are fourfold higher than equivalent hormone replacement therapy doses of estradiol [76]. However, it is important to remember that postmenopausal hormone therapy will not block ovulation, so a contraceptive method should be continued until a diagnosis of menopause is definitively made.

The ovulatory suppression effect of hormone replacement therapy (HRT) was evaluated in 20 women between age 42 and 52 taking Prempak-C (1.25 mg/day conjugated estrogens with cyclic norgestrel 150  $\mu$ g for 12 of 28 days) [77]. Urine samples were collected weekly for 8 weeks prior to initiation of HRT and 12 weeks following initiation. Urine was assayed for pregnanediol (PDG), a metabolite of progesterone, to indicate ovulation, which was considered to have occurred if PDG was >0.5 mmol/g creatinine. Prior to initiation of HRT, ovulation was detected in all 10 women with regular cycles, and four of 10 women with irregular cycles. Following initiation of HRT, six women with regular cycles continued to ovulate, and 4 women with irregular cycles ovulated, one of whom had ovulated prior to initiation and three of whom had not. One woman who ovulated while on HRT had an initial FSH of 67 IU/l. This limited data suggests that ovulatory suppression does not occur in perimenopausal women on HRT, even when presenting with initial elevated FSH or irregular menses. However, further research is required to understand whether other mechanisms present in some formulations of HRT (such as thickened cervical mucus with continuous progestins) might result in effective contraception in this population. In other words, ovulatory suppression might not be necessary to achieve effective contraception.

## 6. What are the risks to perimenopausal women using hormonal contraception?

Age alone is not a contraindication to any contraceptive method [32]. Until menopause, the benefits of contraception outweigh

actual or theoretical risks. Perceived risks of combined hormonal contraceptives to women over age 35 should be considered for absolute risk difference and not just relative risk. Women who are good candidates for CHC over age 35 include a need for ovarian suppression, non-smokers, no personal or family history of thromboembolic disease, and no family history of osteoporosis, early menopause, or ovarian cancer. Risks are elevated in the setting of cardiovascular risk factors though, so there is a need for a thorough history, blood pressure check, evaluation of lipids, and screening for diabetes mellitus [78]. Risk categories for use of all methods with various concomitant medical issues can be evaluated using the World Health Organization Medical Eligibility Criteria (MEC) adapted by the Centers for Disease Control (CDC) for use in the United States [32].

## 7. Conclusions

Unintended pregnancy remains a concern for women until menopause has been reached. For most women not using permanent contraceptive methods, this means that reliable contraception needs to be initiated or continued for approximately a decade more than is generally considered reproductive age. Many hormonal and non-hormonal contraceptive options exist such that even women with medical issues can utilize highly effective methods. Contraception should be continued until menopause is confirmed, or can be assumed by age 60.

Evidence for the relative effectiveness of contraceptive methods for perimenopausal women is limited. Use of methods with lower typical use effectiveness such as barriers may be appropriate for some perimenopausal women at low risk of pregnancy. Non-contraceptive benefits such as the management of irregular or heavy menstrual bleeding may require use of a hormonal method. The LNG IUS offers effective treatment of heavy menstrual bleeding, and is associated with a high rate of amenorrhea which is highly acceptable to many women. The LNG-IUS can also be used off-label for endometrial protection during the transition to HRT.

## Contributors

Dr. M. Baldwin participated in the writing and editing of this manuscript and I have seen and approved the final version. Dr. J. Jensen declares that he participated in the writing and editing of this manuscript and has seen and approved the final version.

## Competing interests

Dr. Jensen has received payments for consulting from Bayer Healthcare, Merck, Agile Pharmaceuticals, HRA Pharma, and the Population Council, and for giving talks for Bayer and Merck. He has also received research funding from Abbott Pharmaceuticals, Bayer, the Population Council, the National Institute of Health, and the Bill & Melinda Gates Foundation. These companies and organizations may have a commercial or financial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU.

## Provenance and peer review

Commissioned and externally peer reviewed.

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