

Contraception in perimenopausal women

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Summary

During perimenopause, i. e. immediately prior to menopause until the end of the first year after a woman's last menstruation, fertility has not entirely ceased. Ovulation may occur spontaneously thus effective contraception is still necessary especially if a pregnancy is not desired. No contraceptive method is contraindicated only because of the advanced age. Therefore, perimenopausal women can choose between various contraceptive methods including oral contraceptives containing low-dose ethinylestradiol, transdermal patches, vaginal rings, progestins – pills, injectables, implants, the levonorgestrel intrauterine system, natural estrogen (estradiol) – progestin combinations, copper based intrauterine devices, barrier methods and tubal ligation. However, women should receive accurate individualized advice concerning the risks and benefits of each contraceptive method. Up to one or two years beyond menopause, the combined oral contraceptive pill (COCP) is a safe option for healthy non-smokers without contraindications and normal blood pressure but suffering from climacteric symptoms. The use of low dose oral contraceptives offers many benefits. Therefore, women having cardiovascular risk factors or active smokers should opt for progesteron-only products (pills, injectables, implants), the levonorgestrel intrauterine system (IUS), intrauterine devices (IUD), barrier methods or sterilization. For smokers, all combined oral contraceptive products are contraindicated because of the significant risk for cardiovascular disease.

Definitions

Perimenopause

Perimenopause is defined as the phase in a woman's life immediately before menopause and the first year following menopause in which the endocrinological, biological and clinical changes of the approaching menopause become apparent. Falsely, the term "menopausal transition" has been used as a synonym for perimenopause in the past few years. According to the WHO definition, menopausal transition describes the time before the last menstruation, e. g. before menopause, when the menstrual cycle starts becoming irregular. As this term is rather confusing, the WHO has recommended the abolition of the expression.

Menopause

Lately, also the term menopause has not been uniformly used.

! According to the WHO, natural menopause is defined as the permanent cessation of the menstrual cycle, resulting from the loss of ovarian functions. Diagnosis is confirmed after a 12-month long lasting amenorrhea, provided that other pathological or physiological causes can be excluded. Thus, the onset of menopause is the last menstrual cycle, followed by at least one year without menstruation. There is no known adequate and independent biological marker for this event. **!**

In this recent definition, menopause includes the last menstruation as well as the subsequent year. Until the end of the 1920s however, menopause was used to describe the years after the last menstrual cycle, today known as postmenopause, a period in life which was followed by the senium beginning at the age of 70. Until now, the time span after the last menstruation is designated as the menopause. In contrast, the expression senium was abolished because of the new definition of age developed by the WHO in 2002 (Tab. 1).

Table 1: Categorization of age (WHO 2002)

Age	Category
45-60	Aging human being
60-75	Elderly human being
75-90	Old human being
> 90	Very old human being

However, following the official definition, menopause includes the woman's last menstruation, usually at the age of 50, and the subsequent year without any menstrual cycles (Fig. 1).

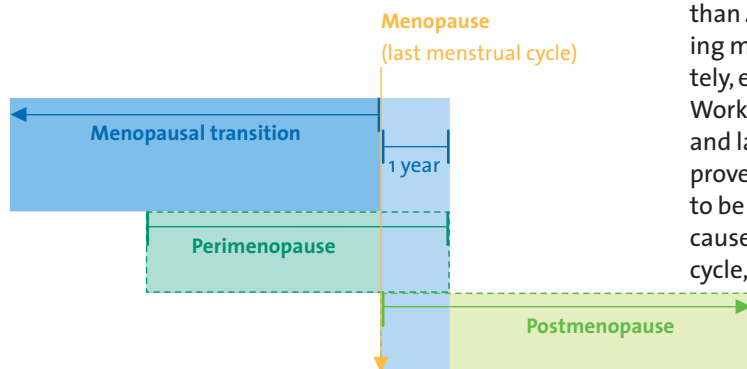


Figure 1: Progression of menopause, menopausal transition, perimenopause and postmenopause

Unfortunately, the WHO includes the first year after the last menstruation not only in the definition of perimenopause but also in the definition of menopause and postmenopause. This very often leads to difficulties and misunderstandings.

In pluriparous women, the onset of perimenopause occurs later than in nulliparous. An early perimenopause has been observed in women with polymenorrhea and unilateral oophorectomy. The use of oral hormonal contraceptives does not influence the onset of perimenopause (Hardy and Kuh 1999).

Endocrinological aspects to be considered during perimenopause

Endocrinologically, perimenopause is characterized by the decrease and then cessation of initially the generative, followed by the vegetative ovarian functions. In the typical hormonal constellation, FSH and LH increase, while the Anti-Müllerian hormone as well as Inhibin A and B decrease. During this transitional period, it is very typical to detect normal or increased FSH and LH levels with simultaneously reduced Anti-Müllerian hormone and Inhibin A and B levels combined with estradiol levels permanently altering from high down to normal or low levels. Progesterone can, depending on the cycle, remain unchanged or decrease to very low levels. Most women already experience changes in their menstrual cycle before reaching the perimenopausal period. The selection and development of the dominant follicle as well as its ovulation can occur earlier in the cycle despite the maintained ovarian steroid secretion. Consequently, this reduced follicular phase often leads to shortened menstrual cycles (Klein and Soules 1998). Neither climacteric symptoms such as hot flashes, night sweats or vaginal dryness nor laboratory diagnosis, e.g. elevated FSH and lower Inhibin A and B levels, are precise enough to include or exclude the diagnosis of perimenopause. Clinically, the diagnosis can only be confirmed by using the patient's history concerning her menstruation as well as her age (Bastian et al. 2003). The cycles in women older than 45 are prolonged, typically exceeding 35 days. Just before menopause, the length can increase to more than 42 days, which is the limit that indicates the approaching menopause (Taffe and Dennerstein 2002). Unfortunately, efforts of the STRAW (Stages of Reproductive Aging Workshop) to divide menopausal transition into an early and late phase on the basis of cycle characteristics have proven insufficient (Soules et al. 2001). This division seems to be more of theoretical and educational interest, but because of the notable individual variances in the female cycle, we can draw no practical benefits from this division.

The variability of the menstrual cycle as well as hormone levels also explain why it has so far not been possible to define a specific endocrinological marker that characterizes early or late menopause (Burger et al. 2008). Also a hormonal analysis performed during perimenopause is not capable of predicting the exact onset of menopause. Because of this existing insecurity, it is necessary to use effective and secure contraceptives.

Menstrual cycle dysfunction

During perimenopause, there is a cumulative incidence of poly- and oligomenorrhea as well as metrorrhagia, hypermenorrhea and menorrhagia with either dysfunctional or organ-derived causes.

Climacteric symptoms

Apart from the common neurovegetative symptoms such as hot flashes and night sweats, another frequent symptom is depression.

Fertility

Fertility continuously decreases after the age of 30 to 35 until above the age of 45, approximately 80% of the women are sterile (Gray 1979). However, especially during menopause, ovulation and pregnancy can occur without previous signs, particularly in women that have never been pregnant. Almost 100 years ago, R. Schröder repeatedly drew attention to the fact that ovulation can sporadically occur up to two years after the onset of menopause.

However, pregnancy at the age of 40 and older automatically implies various risks for mother and child. Chromosomal anomalies, congenital deformities, abortion as well as the infant's and mother's morbidity and mortality increase with age. In order to avoid unwanted pregnancies and thus abortions, it is important to recommend safe contraceptives while at the same time considering risks and benefits of the individual methods.

Contraception

We do not possess sufficient data on contraceptive habits of perimenopausal women. Nevertheless, all available techniques such as natural, mechanical, chemical, hormonal and operative are recommended and used. Age alone is not a sufficient contraindication for any of the contraceptive methods, however they differ in cardiovascular risk (Tab. 2). Which contraceptive method the patient uses mainly depends on personal preferences. However, we have to take into account the indications and contraindications at this stage in life. The incidence of cardiovascular diseases as well as thromboembolism increases and the risk for acquiring metabolic syndrome or diabetes mellitus

rises steadily. However, the higher risk for developing cardiovascular diseases is more likely due to smoking than to age. During perimenopause, the BMI rises steadily, even if the lifestyle or nutritional intake remains the same.

In addition, the incidence of hormone-derived gynaecological diseases such as disorders in menstruation like metrorrhagia, menorrhagia or hypermenorrhea, endometriosis (including adenomyosis), myomas, endometrial hyperplasia and carcinomas, ovarian cysts, ovarian carcinomas as well as benign breast diseases increases.

Table 2: Cardiovascular risks of different contraceptives used during perimenopause (modified on the basis of the contraception and family planning guidelines of the DGGG and DGGEF 2008)

Risk	Factor contraceptive
None	<ul style="list-style-type: none"> • Copper-based IUD • Barrier methods • Natural methods
Low:	Hormonal IUD
Medium	<ul style="list-style-type: none"> • Estrogen-free contraceptives • Progestin-only long acting reversible hormonal contraceptives: injections or implants
Increased:	Intravaginal rings
Significantly increased:	<ul style="list-style-type: none"> • COCP: combined oral contraceptive pill • Unwanted pregnancy
Strong increase:	Pregnancy with birth and puerperium

Duration of contraception

Contraception should be continued during the whole period of perimenopause, at least up to 6 months (Sparrow 1992). In the absence of classical climacteric symptoms it should even be continued up to one or two years after the last menstruation (Colls 1984; Shaaban 1996). The difficulties here lie in determining the exact date of the last period.

Hormonal contraception

Apart from the existing patient's risk factors that can constitute contraindications, all hormonal contraceptives can theoretically be prescribed. Application can be cyclic or continued either as an extended cycle or continuous use (Fig. 2)

Oral hormonal contraceptives

The combined oral contraceptive pill (COCP) that is composed of an estrogen-progestin combination is a safe option for all healthy and normotensive women suffering from perimenopausal symptoms. The COCP guarantees a safe and reliable contraception in all non-smoking women that do not have any contraindications. However, the low-dose micropill containing ethinylestradiol at a dosage of only $\leq 30 \mu\text{g}$ should be preferred considering the increased cardiovascular risk at advanced age.

! For smokers, all COCPs are strictly contraindicated because of the increased risk for stroke and myocardial infarction. !

For healthy and normotensive women in perimenopause, COCPs offer multiple benefits. Cyclic use not only prevents cycle disorders, such as dysfunctional bleeding (metrorrhagia, menorrhagia, hypermenorrhea) but also makes uterine operations such as hysterectomy irrelevant and reduces the risk to develop iron deficiency anemia.

In addition, it decreases dysmenorrhea and prevents chronic lower quadrant abdominal discomfort and midpain. Advantages for patients suffering from PCO syndrome are the interruption of menstrual disorders, the improved metabolic situation as well as the reduced androgenic appearances such as seborrhea, acne vulgaris, and hirsutism. The long-term risk for ovarian and endometrial carcinoma as well as endometrial hyperplasia are reduced. Data on ovarian carcinoma are rather convincing so that the intake of oral hormonal contraceptives is highly recommended, especially in women with a family history and a positive carrier status (Jensen and Speroff 2000). Additionally, the

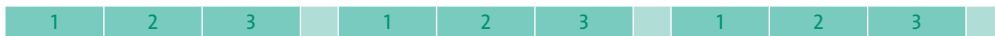
risk for postmenopausal hip fracture is reduced by the potential bone-protective effect of COCPs as additional bone tissue is built during its use (Connell 1993; Kaunitz 2001). Vasomotoric symptoms that increasingly develop during this stage in life are also reduced. Various hormone-dependent gynaecologic diseases such as leiomyomas, endometriosis, ovarian cysts, infections of the genital tract, benign diseases of the mammae and ectopic pregnancy are prevented or at least reduced in frequency. In women with endometriosis, cyclic intake of a COCPs during perimenopause very often leads to a significant pain ease while maintaining a regular menstrual cycle. The benefit can be even greater in patients suffering from endometriosis, PCO syndrome and leiomyomas if instead of the conventional cyclic intake, the oral contraceptives are administered in either an extended cycle of a 84/7 day rhythm or even more effective, a continuous regimen without interruption.

In women with Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia) it might be necessary to take COCPs not only as a means of contraception but also continuous use as a therapy after menopause. There are no contraindications for COCPs, on the contrary, they even are indicated because of the included ethinylestradiol that is superior at sealing the blood vessels compared to the natural estradiol. If, during a cyclic intake with a regular menstruation, bleeding from nose and gastrointestinal tract is observed, the application method should be changed from a cyclic intake to a continued intake without interruption beyond perimenopause, i. e. also during postmenopause. The oral contraceptives of the combination type can reduce frequency and severity of gastrointestinal bleeding and thus prevent blood transfusion (Klingenmaier 1992).

Cyclic use with 13 scheduled bleedings per year



Extended regimen in a 63/7 day rhythm with 5 scheduled bleedings per year



Extended regimen in a 84/7 day rhythm with 4 scheduled bleedings per year



Extended regimen in a 126/7 day rhythm with 2 scheduled bleedings per year



continuous use



One 21 pill-packet

7-day interval with withdrawal bleeding

Figure 2: Possible application of oral hormonal contraceptives during perimenopause

Diabetes mellitus

According to the recommendations of the WHO, normotensive diabetics without angiopathies or cardiovascular diseases can be prescribed a low dose COCP during perimenopause, provided they are non-smokers and their HbA_{1c} stays, after repeated check-ups, below 7.5%. Micropills containing 20 µg ethinylestradiol and a metabolically neutral progestins should be selected.

Micropills containing ≤ 30 µg ethinylestradiol combined with various progestins do not have any influence on glycosylated haemoglobin and only little influence on insulin usage. If anything, the course of diabetes is determined by lifestyle and a strict metabolic control by the diabetic herself not so much by the type or dosage of steroid hormones (Grigoryan et al. 2006). Another aspect that favours the prescription of low-dose micropills is that glucose homeostasis is more strongly affected by high-dose COCPs. The decision for the adequate hormonal contraceptive should therefore always depend on the risk calculation. However, because of the limited incidence of micro- and macrovascular diseases in patients with diabetes type 1 and type 2, randomized controlled studies are not the adequate method to calculate the risk of progestins or estrogen-progestin combinations (Visser et al. 2006).

Natural estrogens

For contraception in perimenopause, sometimes a combination containing a natural micronized estradiol or estradiolvalerate plus a progestin is used. The daily progestin dose should at least attain a dose inhibiting ovulation. These estradiol-progestin combinations are safe and effective oral contraceptives during perimenopause (L'Hermite et al. 1988; Rudolf 1994). However, data concerning this frequently employed method is scarce. In 2008, for the first time significant results for a four-phase combined oral hormonal contraceptive composed of the estrogen estradiolvalerate and the progestin dienogest were presented (Parke et al. 2008). Its Pearl Index for Europe is 0.73, thus representing a safe contraceptive method while at the same time maintaining cycle stability. Referring to personal observations, we indeed managed safe contraception during perimenopause with those combined preparations indicated for postmenopause containing dienogest as well as other combined preparations.

Climacteric symptoms

The prescription of hormone replacement therapy (HRT) in order to treat climacteric symptoms during perimenopause is not a first-line therapy for women desiring a safe contraceptive method.

Those still recommended sequentially combined HRTs, used during pre- and perimenopause, do not effectively protect (Kaunitz 2001). In the first phase, these sequentially combined HRTs contain merely a natural or equine estrogen that does not sufficiently suppress follicle maturation or ovulation. However, during the second phase, composed of an estrogen-progestin combination, a contraceptive effect is indeed given when used in a 21-day cycle.

Transdermal patches, vaginal ring

The transdermal (Evra transdermal contraception patch®) or the vaginal application methods (NuvaRing hormone releasing system®) are other contraceptives that can be used during perimenopause. However, because these preparations bear the same risks as the hormonal combination preparations, the above mentioned criteria by the DGGG (German Society for Gynecology and Obstetrics) and the DGGEF (German Society for gynaecologic endocrinology and reproductive medicine) for the estrogen-progestin combinations apply here.

We have to especially beware of the fact that the application of the transdermal contraceptive patch during perimenopause is combined with an increased risk to develop thrombosis (Cole et al. 2007) and that procoagulatory mechanisms are enhanced when using the vaginal ring instead of oral estrogen-progestin combinations (Magnusdottir et al. 2004). Steroid concentrations in the serum are higher when using the contraceptive transdermal patch compared to the oral intake of the same steroid components (van den Heuvel et al. 2005). Thus, steroid overload in the liver is increased. (Wiegatz and Kuhl 2007).

Independent of these findings, the WHO considers the risks and contraindications for the contraceptive transdermal patch as well as the vaginal ring to be equal to those of oral estrogen-progestin combinations.

Progestins

Progestin only pills (Cerazette®) minipills (Microlut®, 28 mini®) as well as depot formulations (Depo-Clinovir®, Implanon®, Noristerat®) not only are alternatives for smokers from the age of 35 onwards (Shaaban 1996), but also for women in whom estrogen-progestin combinations are contraindicated (Buttarelli et al. 2001; Shabaan 1996), e.g. because of cardiovascular risk factors (Gebbie 2003). Due to their low effectiveness, especially when not precisely taken, minipills should not be prescribed to women with cardiac insufficiency of WHO grade 3 or 4. However, progestin-only ovulatory inhibitors, depot formulations and levonogestrel as an emergency contraceptive pill can all be used without reservations in patients suffering from cardiac diseases (Hudsmith and Thorne 2007).

In diabetics with atherosclerosis and in women suffering from systemic lupus erythematosus, the depot formulation containing medroxyprogesterone acetate (Depo-Clinovir®) does not increase the risk for thrombosis in contrast to the estrogen-progestin combinations (Frederiksen 1996). Additionally, this progestin reduces epileptic seizure frequency (Singh 2006). The increased bone marrow degradation caused by depot-medroxyprogesterone acetate is reversible and does not bear an additional risk for fractures in elderly women (Kaunitz et al. 2008).

Hormone releasing intrauterine device containing Levonorgestrel

The levonorgestrel intrauterine system is the most effective way of contraception during perimenopause for women with cycle disorders and women that before presented with contraindications for hormonal contraceptive methods (Buttarelli et al. 2001). Blood loss and the number of bleeding days are reduced. This prevents anemia as well as the relatively frequent dysfunctional bleedings (metrorrhagia, menorrhagia, hypermenorrhea) and endometrial hyperplasia (Sitruk-Ware 2007). Small surgeries but also hysterectomy are thus prevented by the intrauterine system. While being an effective contraceptive method, treatment of menorrhagias mainly in smokers with a higher risk profile is improved in comparison to an oral or parenteral progestin therapy (Kücük and Ertan 2008). Reducing the dosage of levonorgestrel by the factor two to only 14 µg/day also accomplishes safe contraception and reduces blood loss in women with medium or big leiomyomas (Wildemeersch et al. 2005).

Termination of hormonal contraceptives and change to HRT during postmenopause

The issue of when to discontinue hormonal contraceptive and the subsequent change from hormonal therapy to hormone replacement therapy (HRT) during postmenopause is controversially being discussed: Kaunitz (2000) recommends to perform the change age-dependent in the middle of the 5th decade independent of FSH determination in the 7-day-interval because

1. a single, maybe even increased, FSH value does not reflect whether or not the woman has already entered postmenopause
2. determining FSH on the 5th to the 7th day of pill interval is not reasonable, as oral hormonal contraceptives (estrogen-progestin-combinations) can suppress the FSH level for more than 7 days
3. in addition, more than 50 % of 52-year-old women haven't had their menopause yet.

Sperroff (2000) recommends performing the change depending on age in combination with FSH levels. Of women

aged 50 and older, blood samples should be taken in the last days of the pill-free interval. If the FSH level reaches ≥ 20 IU/l, the intake of oral hormonal contraceptives can be discontinued and if necessary, HRT with designated preparations can be begun in order to treat climacteric symptoms. If applying the contraceptive transdermal patch or a vaginal ring, the procedure of changing to an oral contraceptive remains the same. In a long-term cycle FSH determination is also possible during the last days of the pill-free interval. With continuous intake or different progestin-applications, intake should be paused depending on the expected age of menopause onset in order to determine FSH levels.

Natural methods

By using natural family planning methods such as temperature, Billings' method or the symptothermal method (STM), contraceptive safety in perimenopause is not provided, because exact judging of the cervical mucus and of basal body temperature is very complex during perimenopause. This is due to physiological changes caused by a decreasing ovarian function.

Barrier methods

Barrier methods such as condoms, vaginal foam and diaphragms alone or in combination with a rhythm method are preferentially used during this period in life.

Intrauterine device

Intrauterine devices (IUD) are a possible alternative contraceptive method, especially for women with a high cardiovascular risk profile that do not have any menstruation problems (Bhathena 2006) or disorders (Colls 1984). However, these effective copper based IUDs can increase the incidence of undesired bleeding and lower quadrat pain (Rudolf 1994).

Tubal ligation

After having completed family planning, tubal ligation of both tubes is a very safe alternative contraceptive method especially for women bearing contraindications for hormonal contraceptive methods. Despite the bilateral tubal ligation, hormone levels during perimenopause are comparable to those of women who did not have this intervention. Climacteric symptoms also have a similar incidence and severity in those two populations (Nelson et al. 2005).

Keywords

Perimenopause, contraception, oral contraceptives, vaginal ring, intrauterine devices

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Conflict of interest

The author declares that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org).

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Contraception in perimenopausal women

Question 1

Which of the statements concerning perimenopause are *wrong*?

- Perimenopause includes the time directly before menopause and the following first year.
- Perimenopause is merely a synonym for menopausal transition.
- During perimenopause, ovulation is possible.
- During perimenopause, pregnancy is theoretically possible.
- Perimenopause ends one year after the last menstruation, the menopause.

Question 2

Which statement is correct?

- During perimenopause, there is no change in gonadotropin levels.
- During perimenopause, gonadotropin levels are no longer produced.
- During perimenopause, gonadotropin levels increase, the Anti-müllerian hormone and Inhibin A and B decrease.
- During perimenopause, progesteron is highly increased.
- During perimenopause, estradiol levels range at constantly low levels, approximately ≤ 20 pg/ml.

Question 3

Which statement is correct?

During perimenopause, a safe and effective contraception is

- at least necessary up to one year following menopause,
- only necessary until reaching menopause,
- not necessary,
- compulsive up to five years following menopause,
- not necessary after the first episode of hot flashes.

Question 4

Which statement is correct? Low dose oral contraceptives can be prescribed during perimenopause

- to heavy smokers,
- after a current stroke,
- after myocardial infarction,
- in malignant hypertension,
- to normotensive healthy non-smokers.

Question 5

Which statement is *wrong*?

Oral hormonal contraceptives can be prescribed during perimenopause

- in a cyclic application,
- for use in long-term cycle, with a 84/7 rhythm,
- for long-term use without interruption for several years,
- for courtesy treatment of women-to-men transsexuals after having completed gender reassignment,
- for treatment of Osler-Weber-Rendu syndrome.

Question 6

Which statement is *wrong*?

Diabetics can take oral hormonal contraceptives during perimenopause:

- micropills containing 30 μ g ethinylestradiol,
- micropills containing 20 μ g ethinylestradiol,
- only when the HbA_{1c} value is above 7.5 %,
- only if they are non-smokers,
- only if they are normotensive.

Question 7

Which statement is *wrong*?

During perimenopause, the contraceptive transdermal patch is

- contraindicated in all women,
- is fraught with an increased risk for thrombosis,
- correlated with increased hormone levels,
- connected to an increased liver overload,
- a safe contraceptive method up to a BMI of 28.5 kg/m².

Question 8

Which statement is *wrong*?

During perimenopause, progestins are contraindicated as hormonal contraceptives

- in smokers,
- in patients with an increased cardiovascular risk,
- in all patients suffering from cardiac diseases,
- in emergency contraception,
- because of its insufficient contraceptive effect.

Question 9

Which statement is correct? The levonorgestrel intrauterine system

- does not have a local effect on the endometrium,
- is an ineffective contraceptive with an unfavourably modified Pearl Index,
- does not reduce blood loss,
- is not contraindicated in smokers,
- prevents menorrhagias.

Frage 10

Which statement is *wrong*? The change from a hormonal contraceptive to hormonal replacement therapy has to be performed

- a. at the age of 50,
- b. at the age of 55,
- c. if, in the long-term cycle with a 74/7 day rhythm the withdrawal bleeding does not take place,
- d. when proving increased FSH levels at the time of menopause,
- e. at a FSH level of ≥ 20 IU/l.