Estrogen free contraception: progestin-only systems

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Summary

To reduce side effects of estrogen-progestin combination preparations, the dose of estrogen has continuously been reduced in the pill. As an alternative, estrogen-free preparations are increasingly used and are now available as oral, subdermal, intrauterine and intramuscular applications. The benefits of estrogen-free contraceptives are the prevention of estrogen-related side effects (nausea, edema, weight gain, mastodynia) and of cycle-dependent side effects (dysmenorrhea, pelvic pain, premenstrual syndrome [PMS], hypermenorrhea, menstrual migraine). Furthermore, they can be used in women with risk factors, in whom estrogens are contraindicated. These include hypertension, thrombophilia, status post thrombosis, myocardial infarction, stroke, liver tumors, cholelithiasis and during lactation. In the following sections, the available preparations are being discussed.

Introduction

Apart from combination preparations, which contain estrogens and progestins, various estrogen-free systems are now available in different applications (oral, subdermal, intrauterine, intramuscular).

The reduction in ethinyl estradiol dosage from an initial 75 µg to 50 µg and further down to 20 µg and 15 µg in combination preparations (combined oral contraceptives, COCs), the introduction of estradiol valerate in the COCs and particularly the absence of estrogens in hormonal contraceptives are recent developments that are thought to avoid estrogen-dependent side effects and, in particular, reduce the risk for thrombosis (Jick et al. 1978; Thorogood and Vessey 1990).

The dosage regimen of combination preparations is usually 21 to 26 days of active therapy, followed by a two- to seven-day interval in order to induce withdrawal bleeding.

However, progestin contraceptives (progestin-only systems) are taken continuously without pill-free intervals and progestin-only devices continuously release equal hormone doses. This, in turn, avoids hormonal fluctuation and cycle-dependent complaints.

The progestins greatly account for the high contraceptive efficacy of combined hormonal contraceptives. Important mechanisms of action are the central inhibition of the hypothalamic-pituitary-ovarian axis (inhibition of ovulation) as well as the inhibition of the three peripheral parameters cervix, endometrium and tube function (Table 1).

Table 1: Mechanism of action of progestin only pills (POPs)

	Cervical mucus	Endometrium	Fallopian tube	Ovulation inhibition
Mini-pill (0.03 mg levonorgestrel)	x	x	x	–
Estrogen-free pill (0.075 mg desogestrel)	x	x	x	x
Depot injections (medroxyprogesterone acetate, norethisterone enanthate)	x	x	x	x
Etonogestrel implant	x	x	x	x
Intrauterine devices (levonorgestrel)	x	x	x	–

Advantages of progestin-only preparations

Referring to Ahrendt (2009a) and Rabe et al. (2009), the progestin-only preparations have the following advantages:

- No estrogen-dependent side effects
  - Nausea
  - Edema
  - Weight gain
  - Mastodynia
  - Estrogen-dependent headache
- No cycle-dependent complaints
  - Dysmenorrhea
  - Pelvic pain, premenstrual syndrome (PMS)
  - Hypermenorrhea
  - Menstrual migraine

The following estrogen-free preparations are currently available:

- Oral progestin preparations (Progestin-only Pills, POPs)
  - incomplete ovulation inhibition: 28 mini®, Microlut®, Micro-30 Wyeth®, containing 0.03 mg levonorgestrel (LNG) each
  - complete ovulation inhibition: Cerazette® containing 0.075 mg desogestrel
- Depot injections
  - DepoClinovir® with 150 mg medroxyprogesterone acetate (MPA)
  - Noristerat® containing 200 mg norethisterone enanthate
- Subdermal implants: Implanon®, containing etonogestrel
- Intrauterine devices: Mirena® containing levonorgestrel
- Postcoital contraception containing levonorgestrel (Unofem® and Levogynonl®) and Ulipristal (ellaOne®)
- Compared to combined oral contraceptives reduced risk for
  - Stroke
  - Myocardial infarction
  - Thrombosis
- Reduced risk for endometrial cancer
- Applicable in patients with contraindications for combined estrogen-progestin preparations
  - Hypertension (provided that treatment is initiated)
  - Thombophilia
  - Status post thrombosis
  - Myocardial infarction
  - Stroke
  - Liver tumors
  - Cholelithiasis
- Suitable during lactation
- Further benefits of non-oral progestin-only systems (subdermal implants, intrauterine devices, depot injections)
  - Bypassing of gastrointestinal tract and the first-pass effect

- No continuous tablet intake, thus also suitable for patients with low compliance
- High contraceptive efficacy
- Safe use in patients with contraindications for estrogen-progestin combination preparations

Advantages of estrogen-free contraception

The most commonly listed estrogen-dependent side effects of estrogen-progestin combination preparations are mastodynia, fullness, nausea and mood swings as well as headaches during pill intake (Hatcher and Guillebaud 1998; Oddens et al. 1990, 1993; Kuhl and Jung-Hoffmann 1999).

A multicentric observational trial in Germany investigated the situation of 403 patients that presented with estrogen-dependent complaints such as nausea, mastodynia, headaches and edemas due to the intake of combined oral contraceptives. After changing to the continuous progestin intake of desogestrel 75 µg/day (Cerazette®), the estrogen-dependent side effects ameliorated significantly after three cycles. Nausea was the most frequent symptom (92% of women), followed by mastodynia (90% of women), headaches (84% of women) and edemas (74% of women) (Ahrendt et al. 2007). These results were confirmed by an observational study in the Czech republic (n = 484) (Ahrendt and Apetauer 2008; Fig. 1).

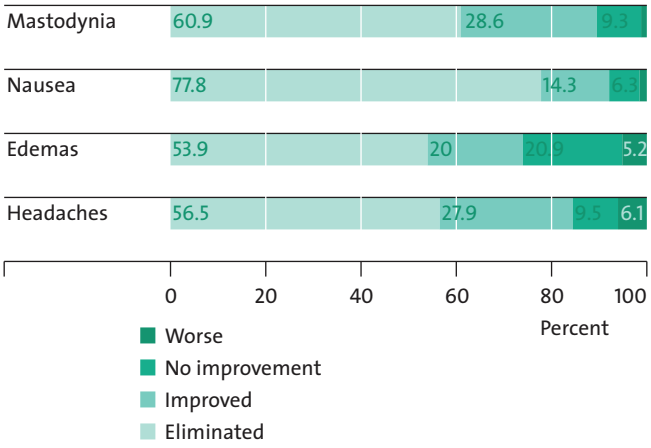

Figure 1: Change of estrogen-dependent side effects after a three month treatment with estrogen-free pills (0.75 mg Desogestrel), n = 406

Elimination of cycle-dependent complaints

Primary dysmenorrhea

Menstrual pain or dysmenorrhea affects approximately 50% of all women (Dawood 2006), which, in turn, has a great impact on the women's daily routine and their ability to attend school or work.

Menstruation-associated pain results from prostaglandin-induced uterine contractions and uterine ischemia (Dawood 2006; Bieglmayer et al. 1995; Proctor et al. 2001; Rosenwaks and Seegar-Jones 1980). Estrogen-progestin combination preparations are an effective therapy for primary dysmenorrhea, as they suppress ovulation and decrease endometrial thickness (Dawood 2006; Bieglmayer et al. 1995; Proctor et al. 2001; Hendrix and Alexander 2002). However, as cyclic combination preparations induce withdrawal bleeding, some women remain with menstrual cramps.

Results from a meta-analysis of six randomized, controlled studies showed that the effectiveness of combination preparations in dysmenorrhea increases, if the pill-free interval is reduced (Edelman et al. 2005). Shortening the pillfree interval in the new combination preparations to four or two days and administration in an extended-cycle dosage regimen or even with continuous intake, is likely to further improve dysmenorrhea (Göretzlehner 2009).

Progestin only systems such as progestin only pills (POPs), intrauterine devices (IUDs), implants and depot injections, which have no scheduled pill-free interval, are even more effective in reducing the symptoms of primary dysmenorrhea.

In a multicentric observational trial, 406 women suffering from primary dysmenorrhea were treated with continuously administered desogestrel 75 µg/day (Cerazette®) over a period of three cycles. This treatment reduced the frequency of moderately severe to severe dysmenorrhea from 84% to 7% (Fig. 2).

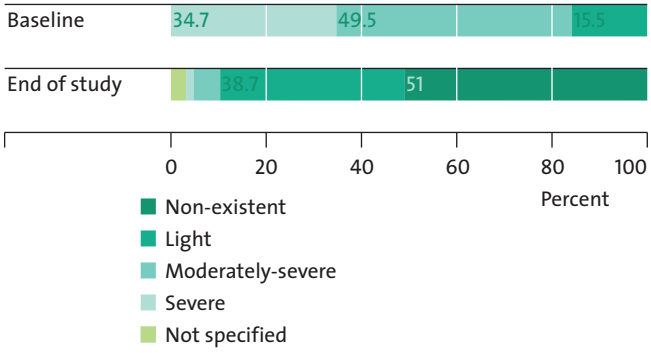

Figure 2: Severe dysmenorrhea before and after three month therapy with an estrogen-free pill (0.75 mg desogestrel; Cerazette®), n = 406

In 51% of women, the symptoms were completely abolished and 39% observed a light improvement (Ahrendt et al. 2007). These improvements are partly due to ovulation inhibition and continuous suppression of the gonadal axis.

Premenstrual syndrome (PMS)

Prevalence and symptoms

In the gynecological consultation, the treatment of women with premenstrual syndrome plays a significant role. The women affected are usually between 30 and menopausal age. Premenstrual syndrome occurs in up to 80% of women. Every fourth woman has severe symptoms in the sense of PMS. In approximately 5% of women, the symptoms disease is classified as premen-strual dysphoric disorder, PMDD, due to the severity of the symptoms. (Angst et al. 2001; Wittchen et al. 2002; Cohen et al. 2002; Hylan et al. 1999).

It refers to somatic as well as vegetative complaints symptoms (Table 2). The symptoms are diverse and the expression varies greatly.

Table 2: Symptoms of premenstrual dysphoric disorder (PMDD)

Psychological symptoms	• Depressed mood • Pronounced tension, anxiety • Pronounced mood swings • Pronounced irritability • Subjective poor concentration • Lethargy/fatigue • Sleeping disorders • Feeling overwhelmed or out of control
Somatic symptoms	• Mastodynia • Bloating • Abdominal pain • Edemas • Weight gain • Headache

In some of these patients, the complaints are so prominent that they are of clinical importance. Women are often unable to work and also feel incapable of fulfilling their daily tasks in the household and in the family.

It is likely that there is a certain disposition for this reaction to the normal fluctuations in the biphasic cycle. The physiological hormonal fluctuations after ovulation act as a trigger and lead to the disturbance of the serotonergic system. Serotonin and its various receptors in the CNS are the essential modulators of mood and emotional state. Disturbance leads to a reduced effect of serotonin and to a decreased sensitivity of the GABA-benzodiazepin receptor and the excretion of β-endorphin.

Therapeutic approaches are the inhibition of ovulation and thus, the cycle-dependent fluctuations. This is possible with any ovulation inhibitor, however, it seems to work best if taken as an extended-cycle or continuous cycle intake. This has been proven by many observational studies with combination preparations (Bachmann et al. 2004; Göretzlehner 2009; Kuhl and Jung-Hoffmann 1999).

Although the effect of estrogen-free preparations for the treatment of PMS in clinical observational studies has been proven, the only oral preparation currently available for this indication is the combination preparation YAZ® (ethinyl estradiol 20 µg and drospirenone 3 mg). It has been approved in the USA, and is taken for 24 days followed by a four-day pill-free interval (Pearlstein et al. 2005).

However, also the ovulation inhibitory progestin-only systems, which all lead to stable hormone levels, have proven successful in the prevention of PMS and PMDD.

In a placebo controlled crossover study, 43 healthy women with PMS were treated with medroxyprogesterone acetate. A significant improvement of the symptom scores ($p < 0.05$) was achieved compared to the placebo (Hellberg et al. 1991).

This was confirmed by the data of a multicentric, prospective, double-blind, randomized, parallel group study. Here, the patients received progesterone vaginally or rectally (Magill 1995). Similar results were observed by Wyatt et al. (2001). In this study, a significant clinical improvement of PMS compared to placebo occurred with the treatment with progesterone (Odds ratio [OR] = 1.05; 95% confidence interval [CI]: 1.03-1.08) and also the synthetic progestins (OR = 1.07; 95% CI: 1.03-1.11).µ

In a prospective, six month observational study with women suffering from PMS, Ahrendt compared the effectiveness of the progestin-only pill containing desogestrel 75 µg/day (Cerazette®) (n = 33) with the long-cycle intake of a combination preparation containing desogestrel 150 µg/day plus ethinyl estradiol 30 µg/day (Marvelon®) (Ahrendt 2009b). During the six months of the study, the premenstrual syndrome improved significantly with the progestin-only medication ($p < 0.001$). This result was not achieved by the combination preparation ($p = 0.054$). In average, the score results in the Cerazette® group were reduced from 1.45 points to 0.87 points, while they fell from an average of 1.00 points to 0.73 points in the Marvelon® group. The significant reduction occurred within sixth months of treatment (Screening at treatment month 3: $p = 0.531$; screening at month 6: $p = 0.002$; treatment month 3 and treatment month 6: $p = 0.005$) (Ahrendt 2009b).

Menstrual migraine

Up to 60% of all women report a time-dependent correlation between the onset of migraine and menstruation (Couturier et al. 2003; Allais and Benedetto 2004).

Definition

- Migraine without aura
- Two days before menstruation
- Up to three days after the onset of menstruation
- Pattern confirmed in 66% of all cycles

Menstrual migraine has been classified as an independent diagnosis in the headache and facial pain classification by the International Headache Society (IHS) (Headache Classification Subcommittee of the International Headache Society [IHS] 2004).

According to the definition, menstrual migraine is a paroxysmally occurring, single-sided, pulsating headache without aura, which exclusively occurs in between two days before until three days after the onset of menstrual bleeding in at least 66% of the cycles. Possible accompanying symptoms may be nausea, vomiting, phonophobia and photophobia. The headaches as well as the accompanying symptoms in menstrual migraine are usually of longer duration and more severe than in classical migraine with aura (Couturier et al. 2003; Granella et al. 2004; MacGregor 1996; Headache Classification Subcommittee of the International Headache Society [IHS] 2004). The etiology seems to be the physiological reduction in serum estrogen and serum progestin levels, which act as a trigger. Initially high estrogen levels are probably a prerequisite for the development of migraine attacks (Edelma et al. 2005; Ahrendt et al. 2007).

In a study, Ahrendt et al. (2007) compared 30 patients with menstrual migraine, who were treated with the estrogen-free pill containing 75 µg Desogestrel (Cerazette®), with 33 patients that received the combination preparation containing 150 µg desogestrel und 30 µg ethinyl estradiol (Marvelon®) in the extended-cycle intake for six months. The group studied the reduction of frequency, duration and intensity of menstrual migraine and its accompanying symptoms.

Both medications reduced all three examined parameters (Fig. 3, 4 and 5) of menstrual migraine. The frequency of headaches was significantly reduced in both medication groups ($p < 0{,}001$ each). In both groups, the onset of headaches was reduced by an average of four to 2.5 days per-cycle. Notably, the intense pain maxima occurred less frequently. This effect was more pronounced under the use of Cerazette® and occurred earlier. 25% of the patients were completely painless with the intake of Cerazette®. In 70% of patients, the migraine attacks were reduced by more than 50%.

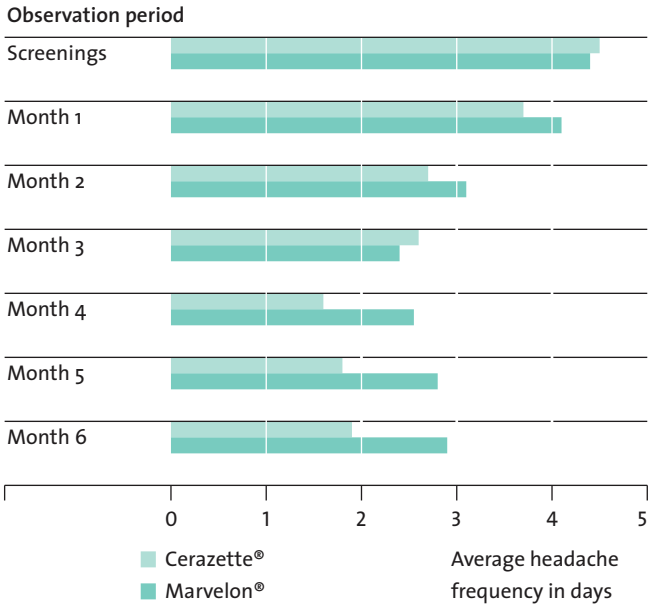

Figure 3: Reduction in headache frequency in patients treated with desogestrel (Cerazette®) and 150 µg desogestrel + 30 mg ethinyl estradiol (75 µg Marvelon®)

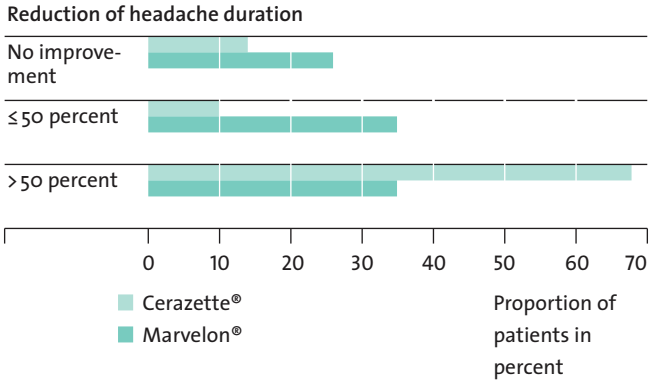

Figure 4: Reduction in headache duration in patients treated with desogestrel (Cerazette®) and 150 µg desogestrel + 30 mg ethinyl estradiol (75 µg Marvelon®)

Also the reduction in headache intensity was more pronounced with the use of Cerazette® compared with Marvelon®. In 67% of the Cerazette®-patients, pain intensity was reduced by more than 50%, however, only in 48% of the patients treated with Marvelon®.

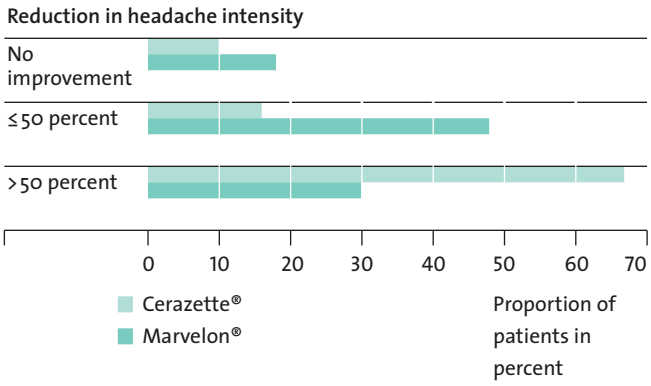

Figure 5: Reduction in headache intensity in patients treated with desogestrel (Cerazette®) and 150 µg desogestrel + 30 mg ethinyl estradiol (75 µg Marvelon®)

The average headache duration was reduced to under a third in patients treated with Cerazette®, and to 60% in patients treated with Marvelon®. The results were significant in both groups. The average headache intensity was reduced by over 60% with Cerazette® and to over 30% with Marvelon®.

Likewise, the accompanying symptoms of migraine were reduced in patients treated with the combination preparation as well as in those patients with extended-cycle treatment, but particularly in patients with estrogen-free pills. Here, the incidence reduction was 77% for nausea, 70% for vomiting, 78% for photophobia and 64% for phonophobia (Headache Classification Subcommittee of the International Headache Society [IHS] 2004).

Risks and contraindications in relation to combined oral contraceptives

In a gynecological practice, we see many patients with diseases and risk factors that represent contraindications for COCPs. Such contraindications are:

Absolute contraindications

- Acute or severe liver disease
- Previous or existent benign or malignant liver tumors
- Acute diseases of the gall bladder
- Acute diseases of the pancreas
- Estrogen-dependent tumors: breast cancer, endometrial cancer
- Previous or existent thromboembolia
- Family history of thrombosis
- Thrombophilia
- Lupus erythematodes, hyperhomocysteinemia, antiphospholipid antibodies
- Moycardial infarction and stroke
- Marfan syndrome
- Severe diabetes mellitus with artherosclerosis
- Idiopathic hyperlipidemia
- Age above 40 + hypertension + obesity + smoking

Relative contraindications

- State after hepatitis
- Cholestatic liver dysfunction
- Porphyria
- Thrombophlebitis
- Pronounced varicosis
- Hypertension
- Otosclerosis

The risk for venous thromboembolisms is particularly increased when taking estrogen-progestin combination preparations (Bauersachs et al. 1996; Koster et al. 1995; Table 3).

Table 3: Prevalence of hereditary thrombophilia

Risk factors	RR without OC	RR with OC	Prevalence in %
Clinically healthy women	1	4	0.01-0.02
Pregnancy	5		0.05
Postpartal phase	25		0.25
Family history	3	11	
APC-resistance	8	35	3-5
Protein C deficiency	9	15	0.1-0.5
Protein S deficiency	8	8	0.1-0.5
Antithrombin III deficiency	4	32	0.02-0.05
Antiphospholipid antibodies			2-9

APC: activated Protein C; OC: oral contraceptives; RR: relative risk

If a patient has any of the above-mentioned risk factors or diseases, progestin only systems are usually applicable. In any case, a sensible individual risk-benefit assessment has to be carried out together with the patient whereby providing the patient with all necessary information. Documentation is essential.

Estrogen-free pills

Of all estrogen-free preparations, the oral preparations (progestin only pills, POPs) are most frequently utilized, as they represent a non-invasive and reversible method of contraception (Ahrendt 2009a).

We differentiate between three groups of estrogen-free pills:

1. The classical mini-pill without ovulation inhibition
2. The estrogen-free pill with ovulation inhibition
3. The postcoital pill for emergency contraception

Mini-pills

Mini pills are pills containing 0.03 mg levonorgestrel that do not inhibit ovulation. This includes the preparations 28 mini®, Microlut® and Micro-30 Wyeth®.

The mechanism of action affects the three peripheral parameters: the fallopian tubes (disturbed transport of the ovum), the endometrium (inhibition of nidation) and the cervix (thickening of cervical mucus). In order to achieve high contraceptive efficacy, the mini-pill has to be taken to a strict time every day. This fact, in turn, reduces the Pearl Index. The safety window is three hours. The mini-pill is usually indicated during lactation.

Estrogen-free pills

The so-called estrogen-free pills are preparations with 0.075 mg desogestrel (Cerazette®). This pill achieves complete ovulation inhibition and, in addition, has an effect via the three peripheral parameters fallopian tube, endometrium and cervix. Contraceptive efficacy is very good and comparable to that of combination preparations. Also the intake scheme is similar to the combination preparations. The safety margin is 12 hours.

Thus, estrogen-free pills are suitable for women of all ages that desire quickly reversible oral contraceptives. In addition, they are suitable for patients with specific indications such as:

- Cycle-dependent complaints: menstrual migraine, premenstrual syndrome (PMS), pelvipathia spastica, dysmenorrhea, hypermenorrhea
- Estrogen-dependent complaints: obesity, tendency for edemas, uterine fibroids, and endometriosis
- Lactation
- Risk factors or diseases, which represent contraindications for estrogen-progestin combination preparations

The estrogen-free pill is well tolerated. Due to the partial androgenic activity of desogestrel, the pill it not suitable for women with seborrhoea, blemished skin or acne. The experience from clinical practice has shown that they are also not suitable for women with recurrent menstrual disorders (Ahrendt and Kose 2008).

Similar to other progestin preparations with continuous intake, irregular bleedings are not predictable. Some patients experience regular weak bleedings, while others suffer from intermediate bleedings, breakthrough bleedings or amenorrhea.

Even when taking the estrogen-free pill Cerazette® for several years, the endogenous estradiol production is not greatly suppressed to an extent that would favour osteoporosis.

Postcoital pills

For postcoital contraception (Fig. 6), there are two preparations with 750 µg levonorgestrel each (Unofem® and Levogynon®) and one with ulipristal (ellaOne®).

Unofem® and levogynon® (750 µg levonorgestrel each) are taken once within the first 72 hours post coitum. Effectiveness decreases linearly from 12 hours onwards. In total, pregnancy rate is reduced by 85% (74% to 93%) with 750 µg levonorgestrel (Task Force on Postovulatory Methods of Fertility Regulation 1998).

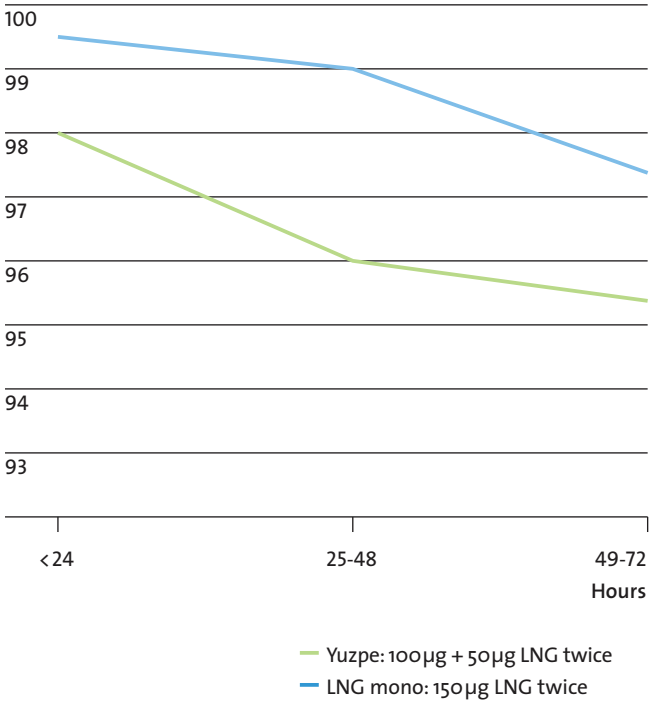

Figure 6: Postcoital contraception – intake post-GV
LNG: levonorgestrel; SI: sexual intercourse

Depending on the time point of intake within the cycle, ovulation inhibition or delay can be suspected via the impact on the hypothalamic-pituitary-ovarian axis.

EllaOne® contains Ulipristal, a progesterone receptor modulator of the second generation. Ulipristal acetate is the first approved selective progesterone receptor modulator (SPRM) for emergency contraception.

Its exclusive indication is emergency contraception for up to 120 hours (five days) after unprotected sexual intercourse or in cases of contraceptive failure.

The main mechanism of action is the inhibition or delay of ovulation, but also the effects on the endometrium. The results of two studies show that ulipristal acetate is at least as effective as levonorgestrel in emergency contraception. Both studies showed a significant improvement of the contraceptive effect compared to levonorgestrel, independent of when during the five days the pill was taken. Within the first 0 to 72 hours: 85% (Ulipristal) versus 69% (750 µg Levonorgestrel twice); on day three: 93% versus 50% (Rabe et al. 2009). This preparation was introduced to the market in October 2009.

Depot injections

Depot injections consist of progestins, which are injected i.m. and are then released protractedly.

- 150 mg medroxyprogestrone acetate (DepoClinovir®): injected every three months (plus/minus 14 days) i.m., starting on the first day of the cycle. The microcrystalline suspension forms a depot, from which continuous resorption occurs. Within the first weeks, the plasma levels range from 1000 to 6000 pg/ml and fall to 500 pg/ml in the last week.
- 200 mg norethisterone enanthate (Noristerat®): initially injected every two months, thereafter every three months i.m. It is stored in the fatty tissue. At the beginning, serum hormone levels are relatively high, and then drop continuously.

Effect

Depot progestins have a high contraceptive efficacy (Pearl Index 0.1 to 0.6). The effect is due to ovulation inhibition as well as to the effects on the cervical mucus, the endometrium and the tube motility.

Cycle

The cycle shows a very variable, unforeseeable bleeding pattern with the administration of depot progestins. Amenorrhea can exist from the beginning onwards, but also irregular or breakthrough bleedings of different severity can occur. The bleeding pattern greatly determines compliance.

If the patient still wants to conceive a child, she has to be informed that the reestablishment of a normal ovulatory cycle can take several months, in some cases up to a year.

Side effects

Side effects are acne, mastodynia (indication for POPs, see above), headaches and ,frequently, pronounced weight gain.

However, in clinical practice, the long-term intake of MPA can cause bone density loss, as the bone metabolism correlates with the serum estrogen levels. This is especially important in adolescents and young adults, as this is the predominant phase of bone growth. Bone density loss increases with intake duration. It is not known whether MPA reduces bone density in growing women (aged 12 to 18 years) and whether osteoporosis associated fractures are thus increased later in life (Noristerat® Summary of product characteristics, DepoClinovir® Summary of product characteristics).

Advantages

Depot progestins are especially indicated in patients, who desire long-term contraception and who do not want to take a daily tablet. They are also indicated in patients with contraindications for estrogens, in sickle cell anemia and during lactation.

Positive effects are also expected in patients with endometriosis, fibroid uterus, dysmenorrhea and hypermenorrhea.

Implants

As an implant, Implanon® is available. Implanon® is a little rod of 4 cm length and 2 mm diameter. It consists of the medical synthetic material Evatane® and the core contains the progestin etonogestrel (3-ketodesogestrel), the active metabolite of desogestrel. Implanon® is applied subdermally on the first day of the cycle on the upper arm and remains there for three years. Afterwards, it is removed by incision.

Pharmacokinetics

Within a few days, the serum hormone levels reach their maximum and then level out above the ovulation inhibition dose of 90 pg/ml. Within the first two years, 35 µg to 45 µg etonogestrel per day are released; in the third year 25 µg to 30 µg per day (Olsson et al. 1990).

Implanon® is a very safe method. With a Pearl Index of 0.14, it is comparable to the available oral contraceptives. Apart from ovulation inhibition, also the cervix, the endometrium and the fallopian tubes are affected.

After removal of Implanon®, the woman quickly regains fertility. Already after four days, her serum hormone levels reach normal levels.

The endogenous estradiol levels lie in the prefollicular area. Studies have shown that the bone density is not reduced with Implanon®.

Menstrual cycle
The bleeding pattern varies greatly with Implanon®. In some patients, a longer amenorrheic phase occurs immediately after implantation. In others, weak bleedings may occur regularly or with greater intervals.

Approximately 15% have additional or continuous menstrual bleeding to varying degrees, which may lower compliance. However, most irregular bleedings can be treated.

In a study by Mansour et al. (2008), the use of Implanon® resulted in the following bleeding pattern: amenorrhea (22.2%), infrequent bleeding (33.6%), frequent bleeding (6.7%) and/or prolonged bleeding (17.7%) (Hickey d'Arcangues 2002; Mansour et al. 2008).

Acceptance
The implantation as well as the subsequent removal of the implant is usually uncomplicated. The comfort for the patient is good. Migration of the implants are improbable when correctly placed. In order to correctly position the implant, application has to be learned. Once in a while, implants have been difficult to retrieve due to a too deep positioning.

In the foreseeable future, an x-ray positive implant will be introduced to the market, which will facilitate the retrieval of impalpable implants. Furthermore, a new applicator will be available, which prevents deep insertion of the implant.

If applicable, the tolerance and acceptance of the continuous treatment with desogestrel should be tested with pretreatment with Cerazette® for three months.

Also competitive athletes can use Implanon®.

Indications
Implanon® is suitable for patients who wish for a long-term contraception, in order not to have to take a daily pill. It is also indicated for patients with cycle-dependent disorders (menstrual migraine, PMS, dysmenorrhea) or estrogen-related disorders (mastodynia, tendency for edemas, endometriosis) and for patients, who lack compliance or who often transgress the time zones.

Implanon® is also approved for contraception during lactation (Reinprayoon et al. 2000).

Contraindications
Clinical practice has proven that Implanon® is not suitable for patients with acne, hypermenorrhea and recurrent breakthrough bleedings.

Intrauterine hormonal contraception
As an intrauterine hormonal contraceptive, the progestin-containing intrauterine device Mirena® is available, which contains levonorgestrel. Mirena® can remain in the uterus for as long as five years. Contraceptive efficacy is very high (Pearl Index: 0.14)

Pharmacokinetics
Not long after the insertion of Mirena®, constant serum hormone levels of 100 pg/ml to 200 pg/ml are reached.

Contraceptive efficacy of Mirena® relies on the local effects of levonorgestrel: Thickening of the cervical mucus, endometrial alterations and fallopian tube effects. Ovulation is not inhibited, as the ovulation inhibition dose in intrauterine release of levonorgestrel is 50 µg/day but Mirena® only releases 20 µg/day.

Menstrual cycle
The bleeding pattern after Mirena® implantation varies greatly. Some patients experience the immediate onset of amenorrhea, while others have regular and weak bleedings. In approximately 30% of women, irregular and breakthrough bleeding occur within the first three to six months, which are of variable duration and intensity. However, they can usually be treated by the additional administration of levonorgestrel-containing pills for two months or one tablet of ethinyl estradiol for 21 days (Busfield et al. 2006). In the majority of patients, however, bleeding intensity is greatly reduced with a positive influence on hemoglobin and ferritin and thus on the wellbeing and the performance of the patient (Allonen and Kulmala 1991; Andersson and Rybo 1990).

Advantages
Contraceptive efficacy remains for a period of five years. Mirena® is compliance-independent and acceptance is high (Mirena® Satisfaction Study 2008). This is partly explained by the fact that Mirena® causes amenorrhea lasting for several months in many patients. This, in turn, diminishes cycle-dependent disorders and the non-contraceptive additional effect concerning these cycle dependent complaints (menstrual migraine, abdominal pain, PMS but also mastodynia) is very high. Mirena® is especially indicated in patients with the wish for long term contraception, in cycle-dependent disorders, especially dysmenorrhea, hypermenorrhea and periclimacteric bleeding disorders, which has been confirmed by various studies (Busfield et al. 2006; de Jonge et al. 2007). Due to the local progestin

effect, estrogen monotherapy is indicated for menopausal complaints, which reduces the systemic effect of progestin components compared to the combination preparations. Mirena® is also indicated during lactation.

Side effects

Breakthrough bleedings can occur within the first three months of application, thereafter, they occur rather seldomly. Clinical experience shows that disturbing side effects, which are often a reason for treatment termination, are relatively rare. Amenorrhea is often seen as an advantage and is often wished for. The frequency of mastodynia, weight gain and skin alterations confer to the general population.

The risk for ascending infections is reduced compared to the general population. However, the risk is significantly lower compared to the copper IUD (Anderson et al. 1994; Römer 2009).

Treatment of irregular breakthrough bleedings with estrogen-free hormonal contraceptives

It is a disadvantage that due to a continuous use without intervals in all preparations, cycle control remains difficult. Periodic bleedings or weak bleedings may occur but also oligomenorrhea and amenorrhea. However, very often, breakthrough bleedings of varying degree, duration and frequency occur, which greatly affect the patients and sometimes even are a reason for the discontinuation of the treatment. However, these side effects are reduced with longer intake of the preparations.

For the everyday practice, it is important to know the individual characteristics of the irregular bleedings and, especially, their treatment.

Therapeutic management of bleeding disorders

As evidence based studies are not yet available on this subject, experience and opinions of expert panels are of great importance. Primarily, the following questions should be answered (according to Ahrendt et al. 2008):

- Do the irregular bleedings occur within the first three months or later?
- Is the endometrium high (more than 6 mm), low or maybe atrophic?

Within the first three months, hormonal dysregulation is to be expected. The continuous estrogen-free medication causes ovary suppression as well as a lack of proliferation and irregular secretion (Hickey et al. 2002). Here, hormonal therapy is the first choice, depending on endometrial thickness.

Irregular bleedings within the first three months

In irregular bleedings within the first three months, Ahrendt et al. (2008) suggest the following therapeutic options outlined in Table 4.

Table 4: Therapy of irregular bleedings within the first three months (according to Ahrendt et al. 2008)

Endometrial thickness	Options	Therapy
Thin (≤ 6 mm)	Option 1	One tablet ethinyl estradiol 25 µg for 21 days or 50 µg E2-patch for 4-7 days
	Option 2	Tranexam acid (Cyklokapron®) 3 x 1 tablet for 5 days
Tnick (> 6 mm)	Option 1	1 tablet norethisterone acetate 2.5-5 mg for an additional 10 days
	Option 2	Estrogen-free pills discontinuation of pill for 4 days

Irregular bleedings after more than three months of intake

Later occurring bleedings are probably due to the vascular compartment of the endometrium, i.e. angiogenetic disorders in atrophic endometrium (Römer 2007). Mechanisms that have been discussed are the suppressed development of the endometrial spiral arteries by progesterone and the subsequent altered homeostasis (Johannisson 1990). Increased vein development and dilation at the endometrial transition zone (Hickey et al. 2002; Kovacs 1996; Taubert et al. 2002) as well as an alteration of the leucocytes in the sense of an inflammatory process (Song et al. 1996; Vincent 2000). This increasingly causes microvascular fragility and thus irregular bleedings. In these cases of mostly atrophic endometrium, treatment with tranexem acid (Hickey et al. 2000) or the prostaglandin synthesis inhibitor mefenamin acid (Kaewrudee et al. 1999) has led to longer bleeding free periods in studies as well as in clinical practice. Both substances can increase vascular stability. As subclinical endometritis (Vicent et al. 2000) is also discussed as a cause for the bleedings, treatment with doxycyclin might be effective.

As an exact cause for irregular bleeding with the use of estrogen-free systems can usually not be determined, the individual therapy has to be based on hypotheses and knowledge from single studies and clinical experience.

In irregular bleedings after an intake of more than three months, the following therapies, listed in Table 5, are possible (Ahrendt et al. 2008).

Table 5: Therapy of irregular bleedings after more than three months of intake (according to Ahrendt et al. 2008)

Endometrial thickness	Options	Therapy
Thin (≤ 6 mm)	Option 1	Doxycyclin 100 mg for 10 days
	Option 2	Tranexam acid (Cyklokapron®) 3 times 1 tablet for five days
	Option 3	Ethinyl estradiol 25 µg for 21 days or 50 g E2-patches for 4-7 days
Thick (> 6 mm)	Option 1	1 tablet norethisterone acetate 2.5-5 mg for 10 days
	Option 2	Estrogen-free pill and an implant additiona tablet Cerazette® for 28 days
	Option 3	In estrogen free pills: discontinuation of estrogen free pill for 4-7 days

With a strict adherence to these therapy options, disturbing breakthrough bleedings with the use of progestin-only systems can be reduced to a minimum. This then prevents therapy discontinuation and significantly improves compliance.

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Estrogen free contraception, estrogen free pills, implants, intrauterine hormonal system, injections

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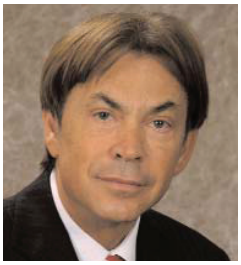

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Prof. Ahrendt works as a specialist for gynecology and obstetrics in his own practice, which has an adjacent day clinic. His focus lies on gynecologic endocrinology and sexual medicine. Apart from the clinical department, the practice also includes a department for clinical research and further education.

Prof. Ahrendt studied medicine at the medical academy (now Otto-von-Guericke-University) in Magdeburg. Afterwards, he continued working at the University Clinic for Gynecology in Magdeburg, where he completed his specialization, his doctorate and his habilitation.

His professional and scientific interest was since focused on hormonal contraception, endocrinology and sexual medicine. In his habilitation, he studied sexual behaviour and contraception in teenagers. During this time, he established further education programmes in the sexual medicine area and is a lecturer at the medical faculty of the Otto-von-Guericke-University in Magdeburg.

His scientific focus are sociological studies concerning social, sexual and contraceptive behaviour as well as clinical studies particularly with regard to the development of hormonal contraceptives, hormone replacement therapy, non-hormonal treatment of climacteric symptoms and libido.

He has published more than 100 scientific and general papers and has held more than 400 scientific presentations on symposia and congresses on the above-mentioned topics.

Prof. Ahrendt is a member of the following medical scientific associations and working groups:
- German society for gynecology and obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG))
- Society for gynecologic endocrinology and reproductive medicine (Gesellschaft für Gynäkologische Endokrinologie und Reproduktionsmedizin)

- Advisory council for the mid-German society for gynecology and obstetrics (Mitteldeutsche Gesellschaft für Gynäkologie und Geburtshilfe)
- Advisory council for the German society for women's health (Deutsche Gesellschaft für Frauengesundheit)
- Society for sexology (Gesellschaft für Sexualwissenschaft)
- Academy for sexology
- Working group for hormonal contraception
- Working group for climacteric syndrome (AG Klimakterisches Syndrom)
- Working group for hormones of the professional association of gynecologists (Berufsverband der Frauenärzte)
- Member of the panel of experts on sexual health (Expertengruppe sexuelle Gesundheit)

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Conflict of interest
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CME

Estrogen free contraception: progestin-only-systems

Question 1
Which oft he following is *not* an indication for hormonal contraceptives with partial antiandrogenic activity?
a. Hirsutism
b. Acne vulgaris
c. Seborrhea
d. Lactation
e. PCO syndrome

Question 2
The high contraceptive efficacy of oral hormonal contraceptive is *not* due to
a. Inhibition of sperm ascension
b. Disturbed transport of the oocyte in the fallopian tube
c. Increased release of FSH and LH
d. Inhibition of follicle maturation and ovulation
e. Inhibition of nidation in the endometrium

Question 3
Which statement on the NuvaRing® does *not* apply?
a. It contains the estrogen ethinyl estradiol and the progestin etonogestrel.
b. It contains progestins only.
c. Its effect is due to complete ovulation inhibition.
d. Withdrawal bleeding occurs regularly in the ring-free week.
e. The ring may be removed from the vagina for 3 hours every day without decreasing contraceptive efficacy.

Question 4
Which oft he following is not an indication for an extended-cycle dosage?
a. Hypermenorrhea
b. Iron deficiency anemia
c. Breast cancer
d. Premenstrual syndrome
e. Functional ovarian cysts

Question 5
Which of the following is an estrogen-induced side effect of hormonal contraceptives?
a. Hypermenorrhea
b. Myoma growth
c. Mastodynia
d. Depressive episodes
e. Headaches

Question 6
How many milligrams estradiol (E2) correspond to 1 mg estradiol valerate (E2)?
a. 1.00
b. 0.94
c. 0.83
d. 0.76
e. 0.62

Question 7
How many women suffer from premenstrual syndrome?
a. 45%
b. 35%
c. 25%
d. 15%
e. 5%

Question 8
The 17 α-ethinyl residue of ethinyl estradiol causes:
a. Quick metabolization
b. Slow metabolization
c. A short half-life
d. A reduction of the effect on the endometrium
e. Poor cycle stability

Question 9
The „dynamic“ dosing scheme in combination preparations containing E2V and DNG is responsible for:
a. High cycle stability
b. Recurrent irregular bleedings
c. Hypermenorrhea
d. Dysmenorrhea
e. Premenstrual syndrome

Question 10
A reduction of the pill-free interval to four days causes:
a. An increase in menstrual migraine
b. An increase of skin disorders (seborrhea, acne)
c. An increase in irregular bleedings
d. A reduction in premenstrual syndromes
e. An increase in dysmenorrhea