Hormonal contraception

Combined hormonal contraceptives

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Summary

In the past years, hormonal contraception underwent substantial development. The dose of ethinylestradiol (EE) has continuously been decreased to reduce the risk of venous thromboembolism. Estradiol valerate (E2V), a "natural" estrogen, is now contained in a novel combined oral contraceptive (E2V/DNG). Recently developed progestins have been introduced to market for instance as progestin-only preparations. New progestins exert antimineralocorticoid and antiandrogenic activity (beneficial for mastodynia or edemas and skin and hair issues, respectively). The traditional schedule of administration of oral hormonal contraceptives is being challenged and for several preparations, the hormone-free interval has been reduced to four or two days. Extended-cycle birth control has become common practice. It provides an opportunity for the alleviation of side effects associated with menstruation (PMS/PMDD, i. e. menstrual migraine). In this context, also the non-oral hormonal contraceptive methods, the vaginal ring and the hormone patch, are discussed.

Introduction

Birth control consultation is part of a gynecologist's daily routine and thus easily underestimated. Upon closer inspection, considerable progress has been made in the past few years, whereby hormonal contraceptive methods have surpassed the initially simple intention of birth control.

In addition, patients have become more demanding, as they usually possess thorough knowledge and experience with contraceptives and seek the gynecologist's advice with specific expectations.

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Nowadays, the prescription of a contraceptive encompasses more than merely birth control due to considerable progress in the non-contraceptive properties. Recent investigations and clinical experience provide insight into the potential of hormonal contraceptives to reduce gynecological symptoms (e. g. dysmenorrhea, hypermenorrhea, mastodynia, premenstrual syndrome), avoid side effects commonly associated with menstruation (menstrual migraine, abdominal pain) or treat androgen-related health conditions (e. g. blemished skin, seborrhea, acne).

Due to recent scientific data and a wider range of preparations, contraceptives can nowadays be prescribed to patients with severe health risks such as hereditary thrombophilia or to those who have suffered from thrombosis, heart attack or hypertension.

This continuous progress in hormone-based as well as non-hormonal birth control methods demands specialized knowledge in order to individually consult our patients in selecting the adequate contraceptive.

The following developments were seminal during the last years:

1. Estrogens
   - Continuous reduction of ethinylestradiol doses
   - Introduction of estradiol valerate
2. Progestins
   - Reduction of synthetic progestin doses
   - Development of new synthetic progestins
   - Progestin-only-preparations
3. Shortened hormone-free interval
   - From a seven-day to a four-day or two-day hormone-free interval
   - Continuous-cycle regimen (Off-label-use)
4. New routes of administration of hormonal contraceptives
   - intrauterine, vaginal, transdermal, subdermal
5. Broadened spectrum of non-hormonal contraceptive methods

In Germany, 86% of women between 20 and 29 years and 68% between 30 and 44 years actively and consciously make use of birth control. Hormonal contraceptives are still the most commonly used method (Fig.1) (BZgA 2007).

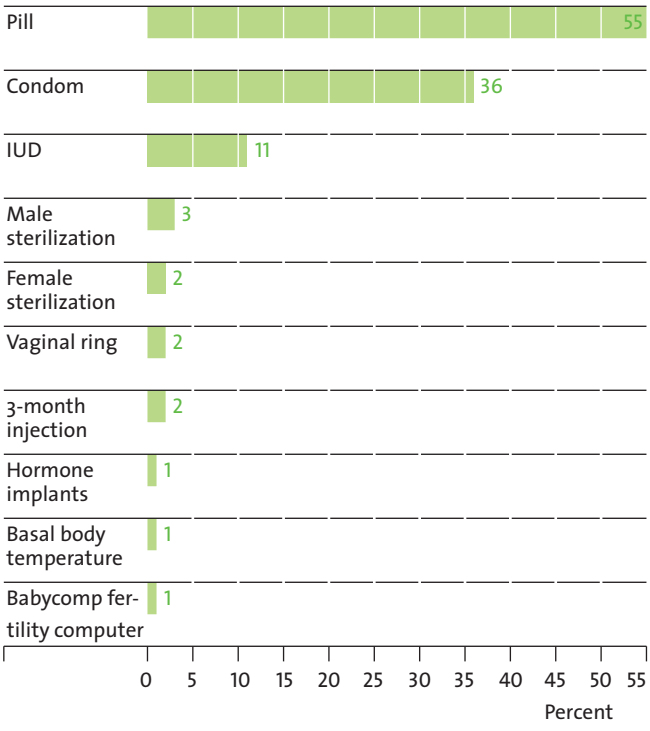

Figure 1: Application of contraceptives in percent (BZgA 2007; n = 1501)

Hormonal Contraception

In 1959, the first oral hormonal contraceptive, Enovid® was approved in the USA. It contained 75 µg ethinylestradiol and 5 mg norethynodrel. The first oral contraceptive introduced in Germany was Anovlar® in 1961 (50 µg ethinylestradiol and 4 mg norethisterone acetate).

Mode of action and contraceptive safety

The two primary mechanisms of action (Table 1) of combined hormonal contraceptives are the central inhibition of the hypothalamic-pituitary-ovary axis (inhibition of ovulation) and the functional inhibition of the three peripheral components cervix, endometrium and fallopian tube exerted by the synthetic progestins.

Table 1: Mode of action of contraceptives

Target	Effect
Hypothalamus	Inhibition of GnRH
Anterior pituitary	Inhibition of LH and FSH
Ovary	Inhibition of follicle maturation and ovulation
Fallopian tube	Disturbance of ovum transport
Endometrium	Inhibition of nidation
Cervical mucus	Cervical mucus thickening

The contraceptive safety is calculated with the internationally comparable Pearl Index (PI): The number of unintended pregnancies in 100 woman-years of exposure divided by the number of menstrual cycles. A "safe" contraceptive method has a PI of 1. If a healthy and fertile couple does not make use of contraceptives, the PI lies at approximately 80, meaning that 80% of the women turn pregnant within one year.

$$PI = \frac{\text{Number of unintended pregnancies x 100x 12}}{\text{Number of menstrual cycles}}$$

Furthermore, the "perfect use PI" excludes any pregnancies caused by the incorrect use of the method. Thus, a method bearing a high risk for incorrect use is characterized by a great discrepancy in the PI and the perfect PI. Both PIs are relevant for assessing the method: If a patient is interested in the safety of a method provided it is correctly used (i. e. the pill when regularly taken), the perfect PI applies.

Composition of hormonal contraceptives

The "classical" pill is a combined oral contraceptive consisting of an estrogen and a progestin. However, alternatives are oral and non-oral estrogen-free preparations, also known as progestin-only preparations.

Estrogens

Until now, 17α-ethinylestradiol (EE) was the most frequent estrogen contained in oral contraceptives (Table 2, Fig. 2). In the past decades, the dose was continuously reduced from an initial 75 µg to 50 µg, 35 µg and 30 µg, down to eventually 20 µg and 15 µg in order to minimize unintended side effects, especially the risk for thromboembolism.

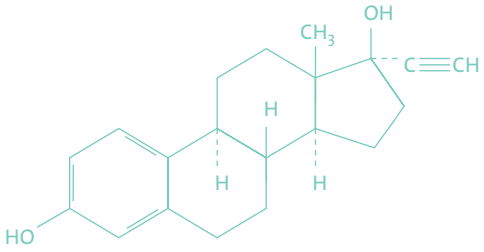

Figure 2: Structure of ethinylestradiol

In contrast to estradiol valerate, degradation is inhibited by the 17α-ethinyl residue. Furthermore, this residue prevents conversion to estrone (E1). EE does not bind to the sex hormone-binding globulin (SHBG) and has a more pronounced effect on the endometrium than estradiol. However, EE and estradiol (E2) increase the concentration of SHBG, which binds free testosterone making it biologically inactive (Timmer and Geurts 1999).

In 2009, the first preparation containing estradiol valerate (E2V, Fig. 3) was introduced to the market.

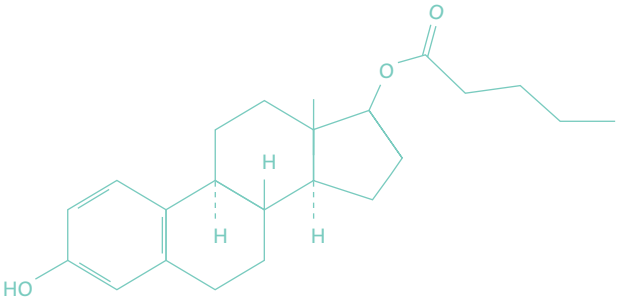

Figure 3: Structure of estradiol valerate

Estradiol valerate is quickly absorbed, hydrolyzed and, within a few minutes, converted to estradiol, whereby exerting the same estrogenic effects. 1 mg E2V is equivalent to 0.76 mg E2.

However, depending on the target organ, E2V differs in its effectiveness on the receptor. Thus, 2 mg E2V can have the same biological effect than 4 to 20 µg ethinylestradiol. Regarding its inhibitory effect on the follicle-stimulating hormone (FSH) and the stimulation of the endometrium, the dose corresponds to 20 µg EE, while it is equivalent to more than 20 µg EE concerning its effect on cell maturation of vaginal epithelial cells and less than 20 µg EE concerning protein synthesis in the liver (SHBG, angiotensinogen and hemostasis parameters (Data on file (B709); Endrikat et al. 2008; Helgason 1982; Lindberg et al. 1989; Mashchak et al. 1982; Wiegratz et al. 2004).

Progestins

Progestins included in hormonal contraceptive pills not only ensure contraceptive safety but also have additional properties (see Table 4).

The different progestin groups are shown in Figure 4.

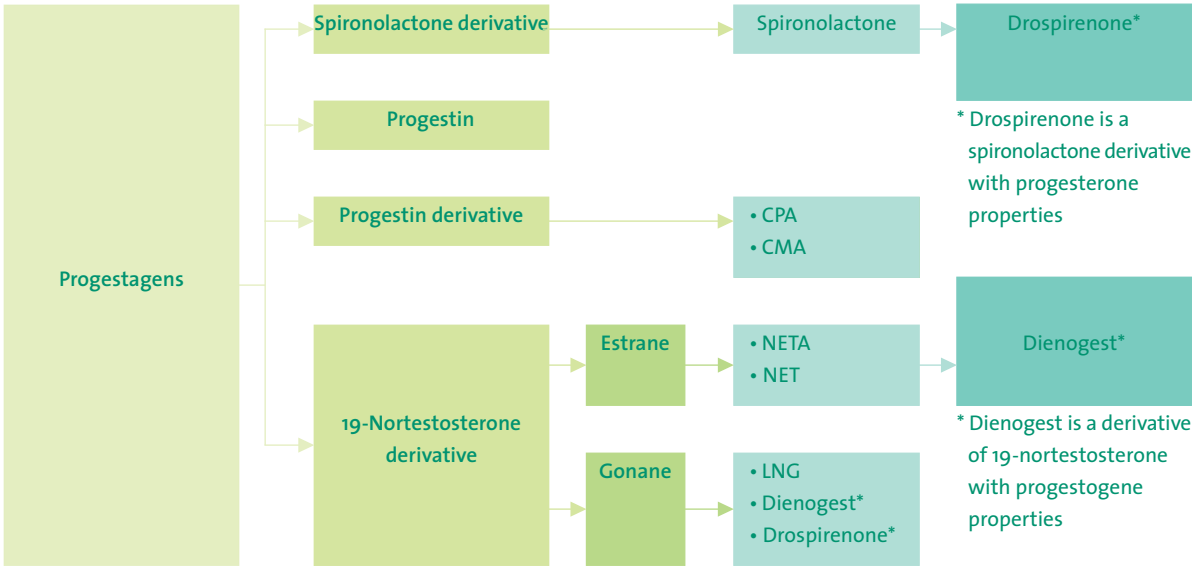

Figure 4: Classification of progestins
CMA: Chlormadinone acetate; CPA: Cyproterone acetate; LNG: Levonorgestrel; NET: Norethisterone; NETA: Norethisterone acetate

The synthetic progestins suppress preovulatory LH increase and thus impair ovulation. The preparations usually contain a 1,5- to 2-fold ovulation inhibition dose (Table 2). Additionally, they exert contraceptive activity by their peripheral effect on the cervix, the endometrium and the fallopian tubes.

Table 2: Ovulation inhibition dose (per day) and half-time of different oral progestins (Kuhl and Jung-Hoffmann 1999)

Progestin	Ovulation inhibition dose (mg/day)	Half-life (hours)
Chlormadinone acetate	1.7	34 to 84
Cyproterone acetate	1.0	48 ± 10
Desogestrel	0.06	21
Dienogest	1.0	9
Drospirenone	2	25 to 33
Dydrogesterone	30.0	
Gestodene	0.03	18
Levonorgestrel	0.06	21 to 26
Lynestrenol	2.0	26
Medroxyprogesterone acetate	10.1	45
Norethisterone	0.4	
Norethisterone acetate	0.5	8
Norgestimate	0.2	58

To a great extent, the partial activities of the synthetic progestins (Tab. 3) determine the non-contraceptive benefits of a preparation

Tabelle 3: Partial action profile of progestins (Kuhl and Jung-Hoffmann 1999)

	G	E	Anti-E	A	Anti-A	Gluc	Anti-Min
Chlormadinone acetate	+	–	+	–	+	+	–
Cyproterone acetate	+	–	+	–	+	+	–
Desogestrel	+	–	+	+	–	–	–
Dienogest	+	–	–	–	+	–	–
Drospirenone	+	–	+	–	+	–	+
Dydrogesterone	+	–	+	-	(+)	–	–
Gestodene	+	–	+	+	–	(+)	–
Levonorgestrel	+	–	+	+	–	–	–
Medroxyprogesterone acetate	+	–	+	(+)	–	+	–
Norethisterone	+	+	+	+	–	–	–
Norethisterone acetate	+	+	+	+	–	–	–
Norgestimate	+	–	+	+	–	–	–

G = progesterone activity; E = estrogenic activity; Anti-E = anti-estrogenic activity; A = androgenic activity; Anti-A = antiandrogenic activity; Gluc = glucocorticoid activity; Anti-Min = antimineralocorticoid activity

When selecting a preparation, the additional properties of the progestins play a pivotal role, especially the androgenic (libido impairment), the antiandrogenic (blemished skin or acne) as well as the antimineralocorticoid activities (tendency for water retention).

Combined oral contraceptives containing estrogen and progestin

Oral contraception (OC) is the most frequently used method of hormonal contraception. The following formulations are available:

- Combined methods containing an estrogen and a progestin
  - Monophasic preparations: same amount of estrogen and progestin in each active pill in a pack
  - Biphasic preparations: altering hormone levels once during the menstrual cycle
  - Triphasic preparations: three different doses of estrogens and progestins in one pack
  - Multiphasic preparations: Estrogens and progestins in varying doses
- Sequential preparations
  - First phase: estrogens
  - Second phase: estrogens and progestins
  - Progestin-only pills
  - Mini-pills: Progestin without ovulation inhibition
  - Progestin-only pill: Progestin with complete ovulation inhibition and a 12-hour window of effectiveness
- Post-coital contraception: high-dose progestin

Preparations with antiandrogenic activity

Patients presenting with signs for hyperandrogenemia (blemished skin, seborrhoea, acne and hirsutism) should receive a combined oral contraceptive pill that contains a progestin with antiandrogenic activity (Table 4). In more severe cases, continuous-cycle use without a hormone-free interval is recommended.

Table 4: Hormonal contraceptives with antiandrogenic activity

Active substance	Preparations
Cyproterone acetate*	Diane 35® Juliette®, BellaHexal®, Attempta ratio35®, Cyproderm®, Morea®, Ergalea®, Clevia®, Jennifer®
Dienogest	Valette®**, Qlaira®
Drospirenone	Petibelle®, Yasmin®, Yasminelle®, Aida®, YAZ®
Chlormadinone acetate	Belara®, Balanca®

* All preparations containing cyproterone are not officially approved for hormonal contraceptive use despite their contraceptive activity by ovulation inhibition. Approved indications are: therapy of androgenization symptoms in women (acne, mild hirsutism, androgenic alopecia)

** Valette®, containing the progestin dienogest (DNG), is approved as a hormonal contraceptive as well as for the treatment of mild and moderately severe androgenization: blemished skin, mild to moderately severe acne

Preparations with antimineralocorticoid activity

Apart from their antiandrogenic activity, all preparations containing drospirenone (see Table 4) also exert antimineralocorticoid activity. Thus, they are not only suitable for patients with skin and hair problems, but also for patients that tend to suffer from water-retention-related weight gain and mastodynia. Various studies could show that weight gain is not as pronounced in preparations containing drospirenone compared to other progestins and, if present, rather reflects the physiological age-dependent weight gain.

Extended– and continuous-cycle oral contraceptives

Extended-cycle use is defined as the consecutive administration of combined oral contraceptive pills for several cycles (3, 4, 6 or 9 cycles), followed by a 7-day hormone-free

interval. In continuous-cycle use, the preparation is taken for more than a year without a break (see Fig. 5). However, in the near future, only those preparations with a flexible extended-cycle scheme will prove successful. Here, the patient decides if and when to include the hormone-free interval. In general, withdrawal bleeding should be induced if the patient experiences the side effects of the extended-cycle use, such as severe mastodynia, long-lasting breakthrough bleedings or spotting. The ideal length of the hormone-free interval is four days (Göretzlehner et al. 2009).

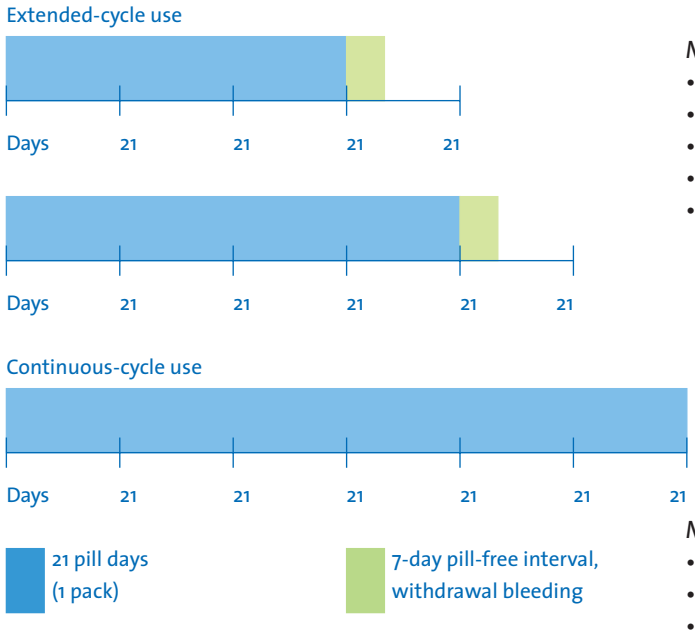

Figure 5: Diagram to illustrate the duration of administration

The extended-cycle administration regimens have been developed by practicing gynecologists on the basis of their clinical experience. An extended-cycle scheme eliminates withdrawal bleeding thus providing a means to reduce menstrual-related symptoms such as dysmenorrhea and irregular bleedings as well as alleviate endometriosis-related symptoms or menstrual migraine.

A study carried out in Germany in 2007 (BZgA 2007) discovered that 57% of the women prefer an extended-cycle administration scheme. 26% of the participants wish to have fewer periods and an additional 31% would appreciate a possibility to postpone menstruation on special occasions, for instance when on holiday. Meanwhile, data from two randomized studies of preparations approved in Germany (30 µg EE/2 mg DNG, Valette®, EE/DSG, NuvaRing®) have been published (Miller et al. 2005) that exclusively investigate bleeding response in extended-cycle regimens. However, so far no preparation has officially been approved for extended-cycle use by the BfArM.

Several observational studies with various preparations (30 µg EE/2 mg DNG, EE/CMA, EE/DRSP) have also proven positive effects on cycle-dependent complaints. Nevertheless, the following listed indications have still got to be considered as off-label-use.

Indications for continuous-cycle use are (referring to Göretzlehner, 2009):

Menstruation-dependent complaints:
- Bleeding disorders
  - Hypermenorrhea
  - Menorrhagia
  - Metrorrhagia
  - Irregular bleedings
- Dysmenorrhea
- Premenstrual syndrome (PMS)

Menstrual cycle-dependent gynecologic diseases
- Uterine fibroids
- Endometriosis
- Polycystic ovaries (PCO)
- Functional cysts
- Androgenization (Acne, seborrhea, hirsutism)

Menstrual cycle-dependent systemic symptoms
- Menstrual migraine
- Iron deficiency – anaemia
- Depressions
- Genital herpes
- Diabetes mellitus
- Multiple sclerosis
- Psychosis
- Asthma

Delay or suppression of menstruation (lifestyle)
- Sports
- Holidays
- Hygienic factors

Extensive practical experience has been gained with the extended-cycle use of Valette® (0,03 mg EE and 2,0 mg dienogest). The acquired data suggest that contraceptive safety is acceptable due to the continuous administration regimen. Missed tablets do not impair contraceptive activity, as this period is too short for the onset of endogenous estradiol production or follicle maturation. Contraceptive protection is considered to last for at least seven days, equivalent to the omission of seven active tablets during the pill-free week.

If present, irregular bleeding occurs more frequently during the first two blister packs and thereafter only in 8% of the women. Irregular bleeding patterns can be found more often in smokers and in patients that had previously experienced irregular bleedings.

Apart from the irregular bleedings, mastodynia is a habitual side effect. In general, compliance is good in a continuous-cycle administration regimen. Which of the available combination preparations are suitable for extended-cycle use/continuous-cycle use has only been confirmed for three preparations that have already been part of clinical trials (Valette®, Yasmin® und Nuva-Ring®). However, several other preparations have proven successful for this purpose in clinical practice.

Abridgement of hormone-free interval: four-day hormone-free interval in combined oral contraceptive pills (EE 20 µg and DRSP 3 mg)

For the last 50 years, the rigid administration scheme of 21 days of active tablets followed by a seven-day hormone-free interval (Fig. 6) has proven successful. This seven-day interval was necessary in order to eliminate the initially high doses of estrogens and progestins (originally 75 µg EE and 5 mg norethynodrel). However, a long interval bears a potential risk for contraception, as there is a possibility for the onset of endogenous estradiol production and follicle maturation. A shorter pill-free interval is thus beneficial and nowadays feasible due to the substantial reduction in estrogen and progestin doses. Furthermore, shortening the interval alleviates menstrual cycle-dependent complaints such as dysmenorrhea, premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD) as well as menstrual migraine that persist in a 21+7-day administration scheme.

The oral contraceptive YAZ® containing 20 mg EE and 3 mg drospirenone, similar to Yasminelle® and Aida®, only includes a 4-day interval (Fig. 6). Consequently, hormonal fluctuation and withdrawal symptoms are reduced. Clearance of drospirenone extends into the hormone-free interval, as its half-life is 31 hours. This additionally reduces menstrual cycle-dependent symptoms and enhances the antiandrogenic and antimineralocorticoid activity.

In general, the dose regimen 24+4 has the benefits of continuous-cycle use, but withdrawal bleedings remain. This is of importance for those women who prefer the reassurance of monthly withdrawal bleedings (42%) but want to benefit from the advantages of the continuous-cycle use.

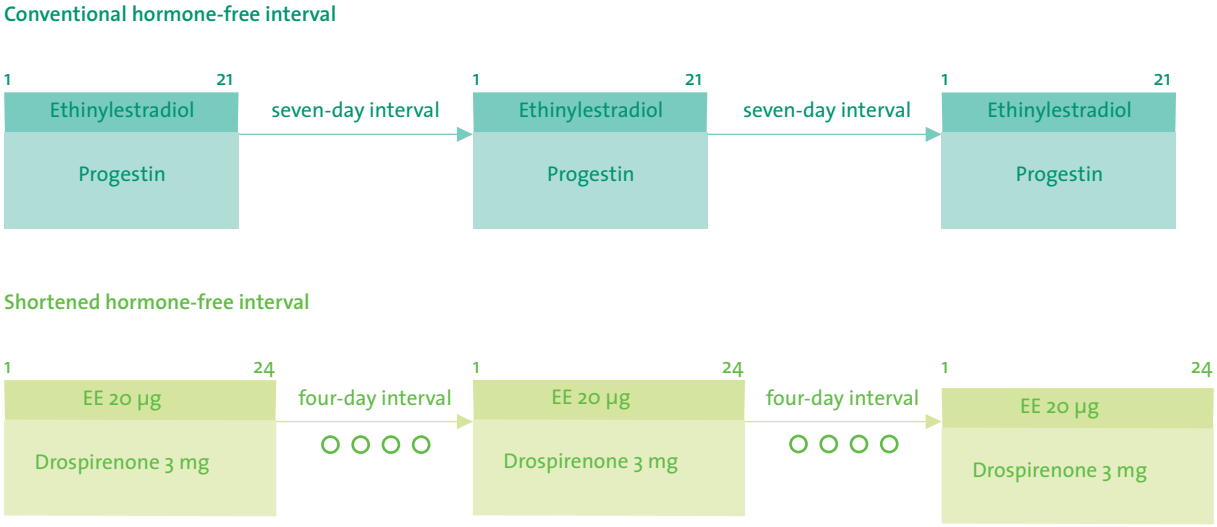

Figure 6: Administration schemes of oral contraceptives

Withdrawal bleeding

Bleeding regularity and the intensity of the withdrawal bleeding was analogous to the equivalent preparation levonorgestrel (LNG), which includes a seven-day hormone-free interval. Likewise, there was no significant difference in irregular bleedings (Bachmann and Sulak 2004; Gruber et al. 2006).

Additionally, the non-contraceptive properties have proven effective:

- Acne: In two placebo-controlled studies a total of 1072 women aged 14 to 45 years with a moderately severe facial acne were treated with six cycles of YAZ®. Mean reduction of inflammatory lesion count was 55% com pared to 32% in the placebo group (Koltun et al. 2006; Lucky et al. 2006).
- PMS/PMDD: Premenstrual disorders are prevalent in up to 80% of women (Hylan et al. 1999; Ramcharan et al. 1992; Wittchen et al. 2002; Woods et al. 1932) between 30 years and onset of menopause. Thus, 25% of all women suffer from severe distress associated with PMS (Angst et al. 2001; Wittchen et al. 2002). In approximately 5% of cases, symptoms are severe, also known as PMDD (American Psychiatric Association 1994; Angst et al. 2001; Andersch et al. 1986; Cohen et al. 2002; Johnson et al. 1988; Ramcharan et al. 1992; Rivera-Tovar and Frank 1990; Sveindottir and Bäckström 2000; Wittchen et al. 2002; Woods et al. 1982).
- In a crossover comparison of YAZ® versus placebo, the symptom scores of patients with PMDD were reduced by almost 50%.
- YAZ® is the only oral contraceptive with clinically proven effect on emotional and physical symptoms in PMDD, the most severe form of PMS (Pearlstein et al. 2005).

"Natural" estrogen: oral combined contraceptives containing estradiol valerate

For the first time, a combined oral contraceptive containing estradiol valerate (E2V) and dienogest (Qlaira®) was introduced to the market, a preparation that is characterized by its cycle stability. E2V is quickly absorbed, hydrolyzed and then converted to estradiol (E2), the active substance. However, the only available preparation so far was Femilar® (E2V, CPA; Finland), which has proven unacceptable in terms of bleeding patterns (Astedt et al. 1977; Astedt et al. 1979; Kivinen and Saure 1996; Serup et al. 1979; World Health Organization 1980). E2-based oral combination preparations lead to an increase in bleeding disorders, as the 17µ-hydroxy steroid dehydrogenase type 2 (stimulated by progestins) quickly converts E2 into E1 (estrone). E1, however, does not show any proliferative effect on the endometrium.

By applying a dynamic dose regimen, the rate of unscheduled bleeding has been adapted to that of the EE pills. The dose regimen illustrated in Figure 7 has proven successful.

Figure 8 shows that serum-estradiol levels are constant and low.

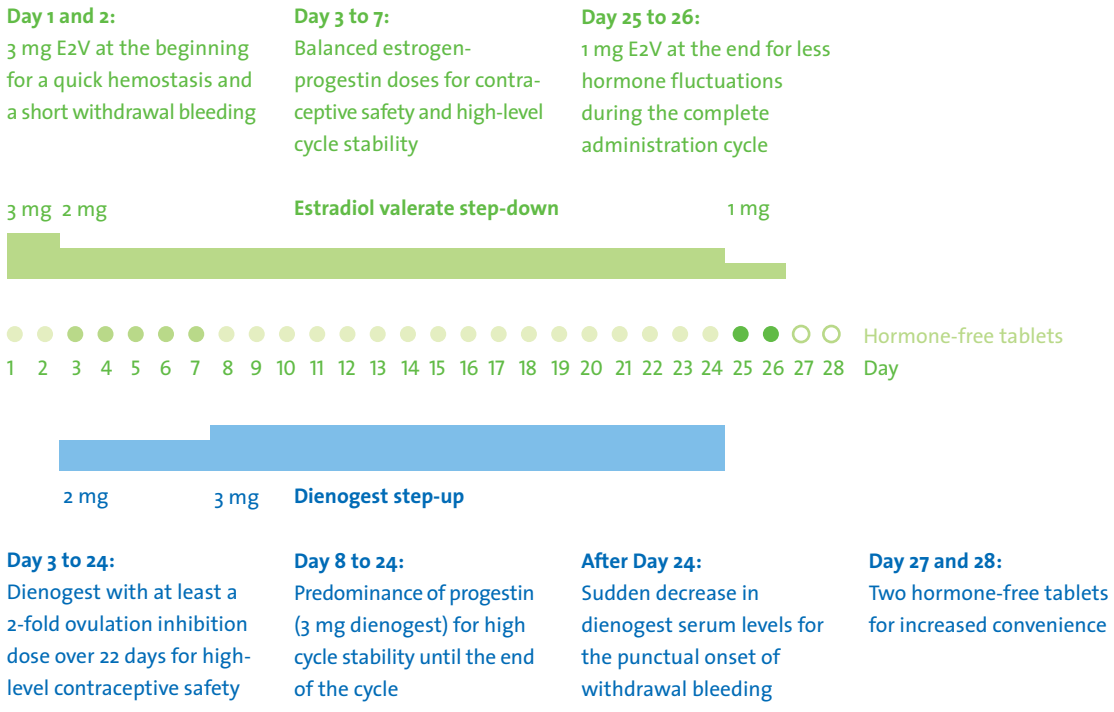

Figure 7: Dynamic dose regimen (Lu et al. 2007)

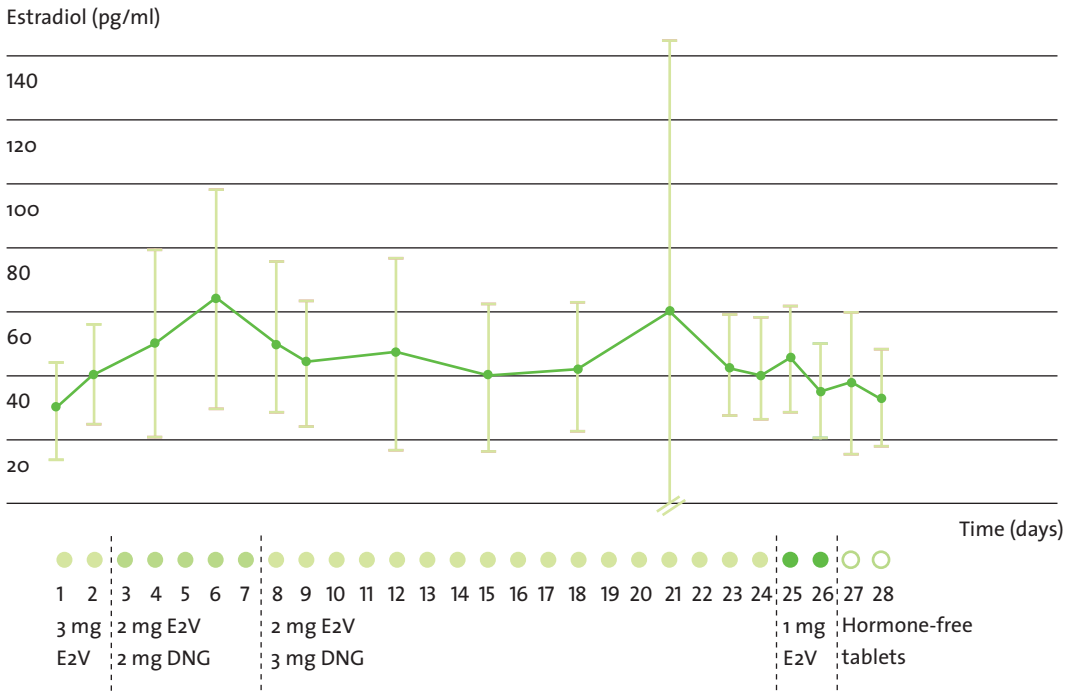

Figure 8: E2-Concentration during a 28-day administration regimen (Lu et al. 2007); average E2-level ("through-level") in daily oral administration

In this case, cycle control is acceptable because:

1. Estrogens dominate in the early menstrual cycle, which causes early endometrial proliferation and an increase in sensitivity for progestin activity during mid-cycle.
2. Progestins dominate from mid-cycle onwards. This guarantees stability of the endometrial stroma (Hirvonen et al. 1990; Kivinen and Saure 1996; Schubert and Cullberg 1987; Serup et al. 1979).

A multicentred, randomized, double-blind study (E2V/DNG und EE/LNG) monitoring 7 menstrual cycles in 798 women aged 18 to 35 years showed the following acceptable bleeding pattern:

- shorter and weaker withdrawal bleedings with E2V/DNG compared to EE/LNG
- 20% of women per cycle without withdrawal bleedings with E2V/DNG, only 8% with EE/LNG
- Number of irregular bleedings similar to a pill containing 20 µg EE/100 µg LNG (Ahrendt 2009; Ahrendt et al. 2009; Parke et al. 2008)

Studies concerning the influence on metabolic and rheological activity demonstrated a positive effect on surrogate parameters. However, clinical evaluation especially concerning thromboembolic events has to be interpreted as follows:

- The risk for thomboembolic events due to E2V/DNG is still unknown, as only limited data from clinical trials is available.
- Rare side effects of E2V/DNG such as venous (VTE) or arterial thromboembolism (ATE) will have to be reasses sed in a large-scale studies following the introduction of the preparation to the market.

Consequently, the same contraindications for other combined oral contraceptive pills apply for E2V/DNG. E2V/DNG is therefore suitable for women of all age groups, but particularly for those who:

- prefer natural estrogens
- wish to benefit from the antiandrogenic activity of dienogest (i.e. blemished skin, seborrhoea, acne)
- wish to reduce the hormone-free interval (patients with menstrual cycle -dependent complaints such as dysmenorrhea, pelvipathia spastica, menstrual migraine

Non-oral combined formulations

Transdermal contraception

Transdermal contraception is available as the Evra® transdermal contraceptive patch. The patch has a size of 4.5x4.5 cm and is applied to the skin once a week (always on the same weekday), preferably on the upper arm, the trunk or the gluteus maximus. Three patches are followed by a one-week interval.

Evra® contains the progestin norelgestromin and the estrogen ethinylestradiol. Norelgestromin is the main metabolite of norgestimate.

Pharmacology

A daily dose of 150 µg norelgestromin and 20 µg ethinylestradiol is released, which leads to a constant serum hormone level that causes complete ovulation inhibition. Contraceptive safety is good (Pearl-Index: 0.70). Sauna, whirlpool or cold water do not alter the rate of hormonal absorption.

In terms of pharmacological interaction, the concurrent administration of tetracyclines does not reduce contraceptive safety of the patch. However, recent studies could prove that the risk for thromboembolic complications is 2-fold higher than in the oral combined contraceptive pill (x instead of y/10 000 years of application), while it is reduced in hormone-replacement patches. The underlying reason is likely to be the continuous release of ethinylestradiol and its effect on the liver.

Menstrual cycle

Three patches are followed by a patch-free week with withdrawal bleeding. Unscheduled bleedings within the first cycles occur more frequently compared to oral contraceptives. After three cycles, the occurrence corresponds to that of the pill.

Acceptance

Handling of the patch is user-friendly and it adheres reliably. In approximately 2% of cases, detachment occurs. Compliance can sometimes be impaired by the occurring dirty edges. One adverse effect is skin irritation that can be found in 17.2% of cases. 94.5% of these local skin reactions are mild to moderate. For 2% of the patients, this adverse effect is a reason to discontinue treatment.

Vaginal contraception

For vaginal contraception, a hormone-containing vaginal ring, NuvaRing®, is available. The ring has a diameter of 54 mm and a cross-section of 4 mm. It consists of the synthetic medical material ethylene vinyl acetate (EVA). The ring contains the progestin etonogestrel and the estrogen ethinylestradiol. Etonogestrel is the active metabolite of desogestrel. The ring remains in the vagina for a period of three weeks, which is followed by a one-week ring-free interval that induces withdrawal bleeding. After the ring-free interval, a new ring is inserted.

Pharmacology

In the vagina, a daily dose of 15 µg ethinylstradiol and 120 µg etonogestrel are released. After five days, the maximum serum hormone level is attained, which then persists for the next three weeks.

The NuvaRing® has a high contraceptive safety (Pearl-Index: 0.65). Its mode of action is based on complete ovulation inhibition.

After discontinuation, ovulation quickly reenters.

The concurrent vaginal administration of spermicides and antimycotics has no proven negative effect on the contraceptive safety of the vaginal ring, neither does the concurrent oral administration of doxycyclin or amoxicillin.

Menstrual cycle pattern

Cycle control is excellent. The withdrawal bleedings occur regularly in every ring-free week.

With an average of 5%, irregular bleeding is seldom compared to the oral contraceptives. In contrast to the oral contraceptives, the irregular bleedings do not occur within the first three cycles. The ring is recommended for patients experiencing recurrent irregular bleedings with oral contraceptives.

Acceptance

Acceptance of the ring is high. The patient inserts and removes the ring herself without difficulties.

Disturbing influence on sexuality are exceptions. Usually, women using the NuvaRing® and their partners are content.

Per day, the ring may remain three hours outside of the vagina without impairing contraceptive safety. The ring can also remain in the vagina for an additional week without losing its effect. This can be important for the individual consultation of the women.

The NuvaRing® is suitable for long-term use, especially for three or four months. This has been proven by a randomized study (Barreiros et al. 2007; Miller et al. 2005).

The ring is well tolerated. Undesired side effects such as mastodynia, vaginitis, nausea or headaches are rare. The ring has a neutral effect on weight gain (Ahrendt et al. 2006; Barreiros et al. 2007; Miller et al. 2005).

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Keywords
Hormonal contraception, estrogen-progestin-combinations, pills containing »natural« estrogens, dose regimen including only four hormone-free days, non-contraceptive benefits

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- Advisory council for the German society for women's health (Deutsche Gesellschaft für Frauengesundheit)
- Society for sexology (Gesellschaft für Sexualwissenschaft)
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CME-Continuing Medical Education

Hormonal contraception
Combined hormonal contraceptives

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

Question 2
The high contraceptive safety of oral hormonal contraceptives is *not* based on:
a. Inhibition of sperm ascent
b. Impaired ovum transport in the fallopian tube
c. Increased FSH- and LH release
d. Inhibition of follicle maturation and ovulation
e. Inhibition of nidation in the endometrium

Question 3
Which of the following statements concerning the NuvaRing® is correct?
a. It contains the estrogen ethinylestradiol and the progestin etonogestrel.
b. It is a progestin-only preparation.
c. Its effect is exclusively due to a complete ovulation inhibition.
d. Hormone withdrawal bleeding regularly occurs in every ring-free interval.
e. The ring can be outside of the vagina for up to three days without impairing its effectiveness.

Question 4
Which of the following is *not* an indication for an extended-cycle regimen?
a. Hypermenorrhea
b. Iron deficiency anaemia
c. Breast cancer
d. Premenstrual syndrome
e. Functional ovary cysts

Question 5
Which of the following side effects of hormonal contraceptives is estrogen-derived?
a. Hypermenorrhea
b. Uterine fibroid growth
c. Mastodynia
d. Depressive disorder
e. Headaches

Question 6
How many mg estradiol (E2) are equivalent to 1 mg estradiol valerate (E2V)?
a. 1.00
b. 0.94
c. 0.83
d. 0.76
e. 0.62

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

Question 8
The 17α-ethinyl residue in ethinylestradiol causes:
a. rapid metabolization
b. slow metabolization
c. a short half-life
d. a reduced effect on the endometrium
e. poor cycle stability

Question 9
The "dynamic" dose regimen in the combination preparations containing E2V and DNG is responsible for
a. superior cycle stability
b. frequently occurring irregular bleedings
c. hypermenorrhea
d. dysmenorrhea
e. premenstrual syndrome

Question 10
Abridgement of the hormone-free interval to only four days causes:
a. more severe menstrual migraine
b. exacerbation of skin manifestations (seborrhoea, acne)
c. increased frequency of irregular bleedings
d. improvement of the premenstrual syndrome
e. exacerbation of dysmenorrhea