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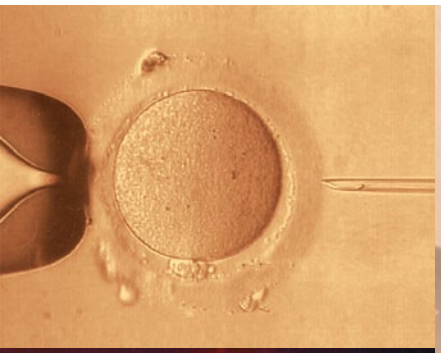

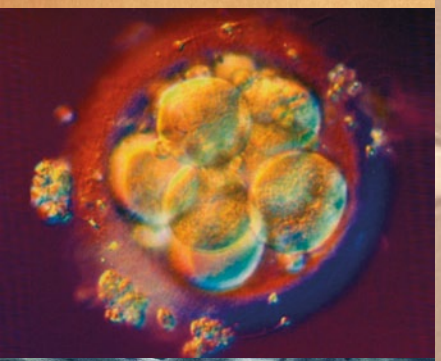

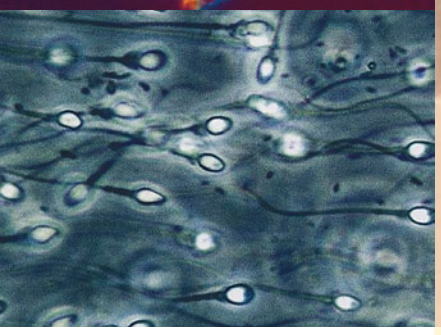

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Oral Contraceptive Pills: Combinations, Dosages and the Rationale behind 50 Years of Oral Hormonal Contraceptive Development

T. Rabe[1], M. Goeckenjan[1], H.-J. Ahrendt[2], P. G. Crosignani[3], J. C. Dinger[4], A. O. Mueck[5], P. A. Lohr[6], M. D. Creinin[6], R. Sabatini[7], T. Strowitzki[1]

The first oral hormonal contraceptive Enovid™ (9.85 mg norethynodreland 0.15 mg mestranol)(G.D.Searle, US) was approved for contraception by the FDA in the US in 1959 but was never marketed by Searle for contraception. One year later Searle got approval for a lower dose product Enovid 5mg™ (5 mg norethinodrel and 75 µg mestranol) as a contraceptive pill. On the 1st of January 1961, Bayer HealthCare (then Schering) launched its first oral contraceptive (brandname: Anovlar® by Schering) in Australia, followed a few months later by the launch in West Germany. In the beginning it was approved only on prescription for the "treatment of painful menstrual cycles" in married women until later the indication „contraception" was added.

Shortly after the introduction of the pill in Europe severe cardiovascular side effects were observed in the UK for Enovid™. The development of different formulations of oral contraceptives with less estrogen and progestins was initiated. Furthermore, highly selective derivatives of steroid hormones were investigated to find products well tolerated and with a low profile of undesired side effects. New, preferably neutral products were developed taking into consideration the metabolic profile and safety aspects of cardiovascular disease and cancer, especially breast cancer. Growing knowledge in the field of gene analysis and a deeper understanding of the regulatory changes in the coagulation system led to a discussion as to the influence of oral contraceptives on women having genetic risk factors for thrombophilia.

The development of oral hormonal contraceptives during the past 50 years has been accompanied by the continued search for new products. Specific formulas have been analyzed not only to provide data on the safety and reliability of the contraceptive method, in addition to possible non-contraceptive benefits (i.e. regular menstrual cycles, improvement of acne vulgaris, dysmenorrhea and fewer premenstrual symptoms), but also to find new compounds and formulas intended to replace those at the end of their patent lifespan. Methods of Good Clinical Practice have been established and large-scale epidemiological studies initiated (i.e. Study of the Royal College of General Practitioners, 1974) **[566].**

Several general approaches to OC development can be followed. Synthetic or natural estrogens provide a reliable cycle control and prevent estrogen deficiency symptoms due to the decreased secretion of endogenous estrogen from growth follicles. More selective, highly specific progestins have been developed with pharmacological properties similar to natural progesterone, some with antiandrogenic properties and suitable for transvaginal, transdermal, subdermal or intrauterine application. Furthermore, these new progestins produce fewer undesired effects on the breast and other reproductive organs and exhibit low carcinogenicity. Various additives have been tested for their additional non-contraceptive benefits (i.e. iron, folate, DHEA) either by preventing certain undesired side effects of estrogens and progestins or by improving the general health status. Combinations of estrogen and progestin have evolved from monophasic to multiphasic formulations. Combination products require lower doses of steroids and provide a clinical profile similar to the normal menstrual cycle. New regimens (21 + 7, 22 + 6, 24 + 4, 84 + 7) with and without placebo pills or continuous administration have been used to maintain the contraceptive efficacy of the higher dose products and to achieve a stable bleeding pattern at lower doses. To date only Ortho-McNeil, Bayer HealthCare, MSD and Pfizer have been able to afford scientific research in the field of contraception and develop new products. The loss of patent lawsuits on their part, however, has allowed for the production of generic alternatives of oral contraceptives by other companies thus making it difficult for them to continue research in this specific area due to lack of money.

In this comprehensive review the development of oral hormonal contraceptive therapy is analyzed step-by-step considering the rationale behind the development of individual substances, combinations, and the regimens developed for their application. **J Reproduktionsmed Endokrinol 2011 (Special Issue 1): 58–128.**

Key words: oral hormonal contraception, side effects, non-contraceptive benefits, dose reduction, cancer, ethinyl estradiol, progestins, regimen

Please refer to the local summary of product characteristics and prescribing information.

1. Introduction

Combined oral hormonal contraceptives – a combination of an oral active progestin necessary for ovulation inhibition and an estrogen to guarantee cycle control – often referred to as the **birth-control pill** or simply "**the Pill**", were introduced into general clinical use in the early 1960s. The development of the pill would not have been possible without two women: Margaret Sanger, a nurse, and Katherine McCormick, a philanthropic millionaire, interested in the women's movement. Together, Sanger and McCormick convinced Dr. **Gregory Pincus [519]** to develop the pill **[484]**.

Previous studies with continuous, gradually increasing dosages of natural progesterone (50–300 mg/day) and diethylstilbestrol (5–30 mg/day) over three months led to an anovulatory pseudo–pregnancy **[548].** The use of orally highly active progestins in combination with mestranol allowed the break–through in OC development. Norethindrone was the first orally highly active progestin synthesized by the chemists **Carl Djerassi**, **Luis Miramontes**, and **George Rosenkranz** at Syntex in Mexico City in 1951 **[157, 156].** One year later at Searle in Skokie, Illinois,

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the steroid chemist Frank B. **Colton** synthesized two more orally highly active progestins, norethynodrel (an isomer of norethindrone) in 1952, and norethandrolone in 1953 **[114].**

The first oral hormonal contraceptive **Enovid**™ containing 9.85 mg norethynodrel and 0.15 mg mestranol (G.D.Searle, US) had been approved for contraception by the FDA in the US in 1959 but was never marketed by Searle for this indication. The same product had been previously approved in 1957 for treatment of menstrual disorders.

A product with less progestin (5 mg norethindrone) and less estrogen (75 µg mestranol) named **Enovid 5mg**™ by Searle got FDA approval one year (June 23rd, 1960) later as a contraceptive pill and was available on the market by August 18th, 1960 as the first oral contraceptive pill.

On January 1st, 1961, Bayer HealthCare (then Schering) launched its first oral contraceptive (brand name: **Anovlar®** by Schering) (4 mg norethisterone acetate and 50 µg EE) in Australia, followed a few months later with the launch in West Germany. The new formulation based on the clinical trials with norethisterone acetate and varying amounts of estrogens performed by the Belgian gynecologist **Ferdinand Peeters (1960) [506]** showed a higher contraceptive efficacy and fewer side effects **[457].** Initially Anovlar® was approved only on prescription for the "treatment of painful menstrual cycles" in married women. The package insert mentioned that during the "treatment course", ovulation would not occur. Contraception was a side effect, not an indication **[484].** Contraception was a novel idea to the European woman and the pill met a market that was quite unprepared. It took some time until the indication "contraception" was finally added to Anovlar.

According to United Nations' estimates of contraceptive prevalence among women of reproductive age, the pill is being used in 2011 by approximately 9% of women worldwide **[324].** It represents the most common modern contraceptive method (including both reversible and nonreversible methods) in the developed countries and the third most common modern method in the developing countries **[669].** Usage varies widely from region to region **[668]** and according to age, education, and marital status. In some countries in Western Europe, more than 30% of the women of reproductive age are reported to be currently using an oral contraceptive method such as a COC. In Germany 53% of all women of reproductive age (16,6 million) use contraceptives, 37% of whom use hormonal contraceptives and 31,3% oral hormonal contraceptives, compared to only 1% of women in Japan using oral contraceptives **[237].**

More than 100 million women worldwide use oral hormonal contraceptives **[640].** A study by **Cogliano et al. in 2005 [104]**, showed that since the introduction of oral contraception in the early 1960s more than 300 million women were thought to have used it until that date, often for prolonged periods and without health problems.

The development of oral hormonal contraceptives during the past 50 years has been accompanied by a search for new products and regimens driven not only by the intention to provide safe and reliable contraception while offering, in addition, certain non-contraceptive benefits (i.e. regular menstrual cycles, improvement of acne vulgaris, dysmenorrhea and less premenstrual symptoms), but also to find new compounds and formulas intended to replace those at the end of their patent lifespan. Methods of Good Clinical Practice have been established and large scale epidemiological studies initiated (i.e. Study of the Royal College of General Practitioners, 1974 **[566]).**

Upon introduction of the pill in Europe severe cardiovascular side effects were observed in the UK **[356]** and the development of products with less estrogen and progestins was initiated aimed at finding more selective and neutral formulations which could be used in lower doses in order to increase the tolerance of COCs and to decrease the incidence of undesired side effects. The safety aspects with regard to cardiovascular disease and cancer, especially breast cancer, caused worldwide concerns. Growing knowledge in the field of genetics and increased understanding of the regulatory changes in the coagulation system led to discussions about a genetic risk profile for thrombophilia and the need to preselect patients at risk.

Certain aspects of OC development are to be considered:

Substances:

- **Estrogens:** synthetic or natural estrogens have been chosen which provide a good cycle control and prevent estrogen deficiency symptoms due to low secretion of endogenous estrogens as a consequence of inhibition of follicular growth.
- **Progestins:** more selective, highly specific progestins have been developed with pharmacological properties similar to natural progesterone, some with antiandrogenic properties making them highly potent and suitable for transdermal (i.e. patch), intrauterine, transvaginal or subdermal applications. Furthermore, these products should exhibit no carcinogenicity **nor** have undesired cardiovascular side effects or adverse effects on the breast and other reproductive organs.
- **Additives:** various supplements have been tested to add some additional non-contraceptive benefits and/or prevent undesired side effects of estrogens and progestins.
- **Combinations: various monophasic and multiphasic OCs have been developed combining** estrogen and progestins to the normal menstrual cycle, progestin to find combinations which allow lower effective doses of steroids and provide a similar clinical profile.
- **Regimen:** new regimens (22 + 6, 24 + 4 [with and without placebo pills]) or continuous administration have been used to maintain the contraceptive efficacy of the higher dose products and to achieve a stable bleeding pattern during the administration of low dose formulations.

To date only Ortho-McNeil, Bayer HealthCare, MSD and Pfizer have been able to afford scientific research in the field of contraception and develop new products. The loss of patent lawsuits on their part, however, has allowed for the production of generic alternatives of oral contraceptives by other companies thus making it difficult for them to continue

research in this specific area due to lack of money.
In the following paper the development of oral hormonal contraceptives is analyzed looking at the rationale behind the development of various substances, combinations applied regimens.
Reviews on the history and some aspects of the state of art of combined oral contraceptives can be also found using Wikipedia: "combined oral contraceptive pill" **[270].**

2. Combinations and Regimen Options of Oral Contraceptives in view of Efficacy and Adverse Events

In the first part of this chapter the influence of OC combinations, regimens, and dosages on contraceptive efficacy is analyzed. The second important parameter to be considered for new drug development of oral contraceptives is bleeding control. This aspect is discussed in the second part, followed by the description of the non–contraceptive benefits and mild to severe adverse events.

2.1. Contraceptive Efficacy

The effectiveness of contraception can be typically expressed by two methods:

– **Time table analysis:** calculation of a separate contraceptive effectiveness rate for each month of the study, as well as for a standard period of time (usually 12 months). Use of life table methods eliminates time-related biases (i.e. the most fertile couples getting pregnant and dropping out of the study early, and couples becoming more skilled at using the method as time goes on), and in this way is superior to the Pearl Index **[521].** Furthermore at the same time information about adverse reactions and drop-outs due to adverse reactions can be listed by time of use.
– **Pearl Index:** The Pearl Index introduced by **Raymond Pearl (1933) [505]** is often used to compare the effectiveness of various methods of contraception. It is expressed as the "number of unintended pregnancies in 100 normally fertile women over the period of one year".
  To calculate a Pearl Index for a particular study the total number of months or cycles of exposure for women in the study is needed, as well as the number of pregnancies and the reason for leaving the study (pregnancy or other reasons). The Pearl Index can be calculated using two methods:
  - the number of pregnancies in the study is divided by the number of months of exposure, and then multiplied by 1200.
  - the number of pregnancies in the study is divided by the number of menstrual cycles experienced by the women in the study, and then multiplied by 1300. 1300 instead of 1200 is used on the basis that the length of the average menstrual cycle is 28 days, or 13 cycles per year.

  Each method of birth control has two Pearl index numbers:
  - *Method effectiveness*: the Pearl index number for use under *perfect* conditions. The perfect use pregnancy rate of combined oral contraceptive users (COC) is 0.3% per year **[663].**
  - *User effectiveness* or *typical effectiveness*: the Pearl index number for use that is not consistent or always correct. The typical use pregnancy rate among COC users varies depending on the population being studied, ranging from 2–8.6% per year **[30, 196, 235, 663],** see also summary table **[220].**
– The Pearl Index calculation for studies in Europe compared to the US often shows higher values for studies performed in North America. This was recently shown again by **Dinger et al. (2011) 151],** probably due to higher rates of obesity, inadequate intake and low adherence to the medical regimens.

Parameters affecting contraceptive efficacy

Contraceptive efficacy may be impaired by **[622]:**

– **User's negligence/missing pills:** irregular use or missing more than one active pill in a packet is the most common cause of contraceptive failure: 30% (age 18–30) **[557],** 48–84% (50% during the first 3 cycles) (age 13–19) **[170, 557],** 74% (age < 14), an average of 3 pills per cycle (adolescents) **[35]**, 33% failed to take pills regularly during the first 3 cycles, adolescents forgot to take on the average 2,7 pills per cycle **[2].** One group of women neglected to resume taking the pill correctly after the pill free interval (18% forgot the first tablet; another 24% forgot a tablet during the first week) (CORALIANCE-Study) (n = 3316) **[29].**
– **User's negligence/prolonged pill–free interval:** delay in starting the next packet of active pills (i.e., extending the pill-free, inactive or placebo pill period beyond 7 days),
– **Intestinal malabsorption** of active pills due to vomiting or diarrhea,
– **Drug interactions** with active pills that decrease contraceptive estrogen or progestogen levels.

A comprehensive analysis done by **Dinger et al. (2009) [155]** as one part of the EURAS-OC-study in 112,659 women-years of exposure and 545 unplanned pregnancies showed that the potential reasons for contraceptive failure were associated with

– irregular OC intake in 230 (42.2%)
– vomiting and/or diarrhea in 100 (18.3%)
– use of antibiotics in 85 cases (15.6%).

In 99 cases of contraceptive failure (18.2%), the analysis suggested perfect OC use. The reasons for the unplanned pregnancies in 31 women (5.7%) could not be analyzed because of missing information.

Methods for evaluation of contraceptive efficacy

– **Inhibition of ovulation:** The contraceptive potency of an oral hormonal contraceptive can also be evaluated by observing follicular growth, ovulation and corpus luteum formation via hormone assays performed on venous blood samples or serial ultrasound examinations. These tests are done to evaluate the inhibitory potency (ovulation inhibition dosage) of new progestins.
  The ovulation inhibition dose given in mg or µg per day reflects the minimum dosage of a steroid necessary for ovulation inhibition and ranges from 0.03 mg for gestodene to 4 mg for norethindrone.

Follicular Growth as Parameter of Contraceptive Efficacy

– A review by **Milsom and Korver (2008) [462]** analyzed the incidence of ovulation with available COCs, traditional progestin-only-pills (POPs)

and with a desogestrel POP (75 µg desogestrel).
– The quality and results of many trials have been impaired by inadequate ovulation criteria, i.e. the progesterone levels defining ovulation have differed among the various studies. Based on serum progesterone – threshold for exclusion of ovulation:
Spona et al. (1997) [625]: > 5 nmol/l;
Elomaa et al. (1998) [168]:
> 9.6 nmol/l;
Kuhl et al. (1985) [389] > 9.6 nmol/l.
Birtch et al. (2006)[53] observed ovulation using ultrasound evidence of corpus luteum formation as the ovulatory criterion, but the associated hormone levels were extremely low (progesterone 2.5 nmol/l). The remaining studies used a variety of other criteria to assess ovulation. In the largest study n = 209) **[641],** ultrasound measurements were scheduled during days 18–21 of the cycle, which is considered the least critical period with respect to escape ovulation. Despite substantial follicular growth (maximum follicular diameter > 10 mm in > 10% of the cycles), no ruptured follicles were observed and an absence of escape ovulation was therefore claimed.
– Ovulation rates were found to be 2% for COCs containing 30 µg to 35 µg EE and 1.1% for COCs containing 15 µg to 20 µg of EE **[462].**
– In a Cochrane Library systematic review of COCs that compared COCs with EE ≤ 20 µg to higher dose COCs with EE > 20 µg, the authors found that the effectivness of the regimens – assessed by monitoring ovulation inhibition – was comparable **[199].**
– **Various regimens:** the divergent methodology for ovulation detection in these studies make a comparison of various dose regimens difficult, but all regimens showed high levels of effectiveness **[70].**

Number of unintended pregnancies as a parameter of contraceptive efficacy
Background: Contraceptive efficacy can be measured based on the number of unintended pregnancies during OC treatment in a trial exposing a definite number of women in the reproductive age (mostly 18–40 years) (with or without proven fertility based on previous pregnancies) to a new contraceptive method without using other contraceptive methods (i.e. condoms, if a sexually transmitted infection [STI] protection in the relationship is not necessary). Using as a competitor OC a market leader as "gold standard", these trials are required for approval of a new OC.

Large clinical surveillance studies
– **Low dose EE pills with modern progestins and formulations:** Contraceptive failure in association with oral contraceptive pills has been recently reported by **Dinger et al. (2011) [151]** analysing outcome data from 52,218 U.S. participants in the International Active Surveillance Study of Women Taking Oral Contraceptives – a large, prospective, controlled, non-interventional, long-term cohort study with active surveillance of the study participants. Low rates of loss to follow-up have been ensured by a comprehensive follow-up procedure. Contraceptive failure rates are described by the Pearl Index and the life-table analysis. Inferential statistics for contraceptive failure are based on Cox regression models. Results are given in the section on contraceptive efficacy.
– **Modern regimens of COC: Dinger et al. (2011) [151]** Analyses are based on 1,634 unintended pregnancies during 73,269 woman-years of oral contraceptive pills exposure. Contraceptive failure rates adjusted for age, parity and educational level showed a slight increase with higher body mass index.

Cochrane reviews
– In **2011 Gallo et al. [200]** updated a systematic Cochrane review of trials **[201]** comparing a combination OC product containing ≤ 20 µg EE with a another containing > 20 µg EE in terms of contraceptive effectiveness, bleeding patterns, discontinuation, and side effects. The high dropout rates in many trials make the results hard to interpret. Results are given in the section on contraceptive efficacy.
– **Maitra et al. (2004) [436]** and **(2007) [437]** assessed randomized trials evaluating combined OCs with < 50 µg EE comparing
1) a third-generation progestin (desogestrel, norgestimate, gestodene) to a second-generation (levonorgestrel, norgestrel),
2) a third-generation progestin to a first-generation (norethindrone, ethynodiol),
3) a second-generation to a first-generation, or
4) various products containing a certain progestin.
The minimum duration of the trials was six cycles. Trials involving monophasic and multiphasic products were analyzed separately.
Twenty-two trials have been included in this review. The data from one trial, comparing pills containing levonorgestrel (LNG) to those containing gestodene (GSD), showed that gestodene may be associated with less intermenstrual bleeding but both products showed similar patterns of spotting, breakthrough bleeding and the absence of withdrawal bleeds. Results are given in the section on contraceptive efficacy.
Contraceptive efficacy tables: see summary of this section.

Contraceptive efficacy
– **EE dosage:** In a Cochrane review by **Gallo et al. (2011) [200]** pregnancy rates seemed to be the same between the group receiving OC containing ≤ 20 µg EE compared to those women receiving a combined OC containing >20 µg EE, but the studies may not have been large enough to have statistical significance.
In a large prospective observational study with modern COC a clinically relevant difference in the rate of contraceptive failure was not observed with respect to OC preparations that contain an ethinylestradiol dose of < 30 or ≥ 30 µg; both doses were associated with high effectiveness **[151].**
– **Progestin dosage:** all COC contain a progestin in a dosage above the ovulation inhibition dose; to date only one EE-free contraceptive, which also inhibits ovulation, is on the market, i.e. desogestrel (75 µg/day).
– **Type of progestin:**
  - Third generation progestins: In a Cochrane review by **Maitra et al. (2004) [436] and (2007) [437]** regarding contraceptive effectiveness, pills containing gestodene (GSD) were also found to be comparable to those containing desogestrel (DSG) in the standard 30 µg estrogen dosage. However, more pregnancies occurred when pills containing 20 µg EE were used. In contrast to pills containing

DSG, those with GSD render better cycle control, although the continuation rate was higher in women using DSG pills.

- **Drospirenone:** In the analysis by **Maitra et al. (2007) [437]** the characteristics of pills containing drospirenone (DRSP) were found to be similar to those with DSG with regard to pregnancy prevention, cycle control and side effects.
- **Drospirenone-, levonorgestrel-, desogestrel-, and dienogest-containing pills:** A large study by **Dinger et al. (2011) [151]** showed that there was little variation in the contraceptive effectiveness among various weight and BMI categories.
- **Chlormadinone acetate:** In contrast, there was a significant correlation between body composition and contraceptive effectiveness for OCs that contained chlormadinone acetate (CMA), which is a progestin that is not marketed in the United States; increased BMI (≥ 30 kg/m^2) and weight (≥ 75 kg) were associated with a higher rate of failure **[151].** The reduced contraceptive effectiveness of CMA–containing OCs in heavier women may reflect the fact that CMA is highly lipophilic and has been shown to accumulate in adipose tissue **[198].** In overweight and obese women, in whom adipose tissue mass is increased, this could result in an altered fat distribution and potentially lead to (temporarily) subtherapeutic levels of systemic hormone.
- **Cyproterone acetate (CPA):** an increase in contraceptive failure rate similiar to CMA is expected for 2mg cyproterone acetate (CPA) containing OCs, due to similar lipophilic affinity of CPA **[533].**

– **Modern regimens of COC: 21+7 versus 24+4**
An analysis by **Dinger et al. (2011) [151]** based on 1,634 unintended pregnancies during 73,269 woman-years of oral contraceptive pills exposure, revealed life-table estimates of contraceptive failure for a 24-day regimen of drospirenone and ethinyl estradiol and 21-day regimens of other progestogens of 2.1% and 3.5%, respectively, after the first study year, and 4.7% and 6.7%, respectively, after the third year. The adjusted hazard ratio was 0.7 (95% CI: 0.6–0.8). Direct comparisons of the 24-day and 21-day regimens of drospirenone and norethisterone, respectively, also showed lower contraceptive failure rates for 24-day regimens. Obesity seems to be associated with a slight reduction of contraceptive effectiveness.

– **Age:** The contraceptive failure by age follows a biphasic pattern, which is in line with findings that female fecundity peaks between age 20 and 30 years **[223, 408, 722].**
A lower rate of contraceptive failure was found in women who were ≥ 30 years old and in women who had used OCs for a longer duration of time.
The decrease in contraceptive failure rates with increasing age likely reflects the decline in the overall rate of fecundity with advancing age. Indeed, lower rates of planned pregnancy were observed in older women who stopped OC use during the EURAS-OC study with the specific intention of becoming pregnant **[130].**

– **Duration of use:** The reduced failure rate observed in the EURAS-study with an increasing duration of use may be related to the fact that those women who are most likely to experience contraceptive failure do so early, which results in a group of women that is increasingly dominated by the most conscientious users and/or the least fertile users **[151].**

– **Parity:** Parous women were more likely to experience a pregnancy during OC use than nulliparous women. This outcome was not unexpected; parity is associated with many factors, which include established fecundity in the past **[662].** While parous women have "proved" their fertility, nulliparous women have not; thus, among any group of nulliparous women will be some women who are infertile (or have partners who are infertile) whose inclusion in the group will reduce the overall rate of fertility **[265].** This was illustrated by **Howe et al. (1985) [265],** who showed that parity was associated strongly with fecundity. The finding that fertility is higher in parous women, compared with nulliparous women, was also observed in those women who discontinued using OCs in the EURAS-OC study with the intention of becoming pregnant **[129].**

– **Body mass**
The impact of the BMI on the contraceptive efficacy is analyzed in a review by **Burkman et al. (2009) [69]** as follows:

– **Negative effect:** Some studies have suggested that a high body weight or body mass index (BMI) may have a negative impact on the efficacy of hormonal contraceptive methods **[218, 219, 260, 262, 738].**

– **Negative trend:** Other studies have demonstrated a non-statistically significant trend toward reduced contraceptive efficacy (after adjustment for demographic characteristics) **[65, 66, 67].**

– **No association:** Others have suggested that there is no association between BMI and risk of unintended pregnancy **[362, 691].**
The EURAS-study shows little or no impact of body composition on contraceptive effectiveness of COC (exception: chlormadinone acetate containg COC – see above) in a compliant "typical use" population in Europe, the same may not be true in other populations, such as in the United States, where the rate of obesity is high **[151].** According to **Dinger et al. (2011) 151],** it is not possible, however, to assess whether the low failure rates reported in the EURAS-study for overweight and obese women would also be seen in populations associated with a substantial amount of incorrect OC use or in populations with a higher proportion of women defined by the World Health Organization to be class II or III obese (BMI ≥ 35 kg/m^2). It is probable that most OCs are dosed adequately for OC users who are overweight or who belong to the category classified by the World Health Organization as class I obesity (BMI, ≥ 30.0–34.9 kg/m^2); however, it is conceivable that many OCs are not dosed adequately for OC users who are classified as being class II or III obese.

– With the increasing use of low-dose OCs among women of different body weights or BMIs, evaluation of their contraceptive efficacy for women of higher body weight or BMI is important **[69].**

Summary tables for contraceptive efficacy of COC: The contraceptive efficacy is listed in the US patient information leaflet in a table created by **Hatcher (2004) [234]** and **Trussell and Kowal (2004) [660]** and is also published by the **IHS National Pharmacy & Therapeutics Committee Drug Class Review: Oral Contraceptives (2010) [339]** (Tab. 1).

Summary

Methods of evaluation of contraceptive efficacy:

- **Life-table analysis:** calculates a separate contraceptive effectiveness rate for each month of the study, as well as for a standard period of time (usually 12 months). Use of life table methods eliminates time–related biases.
- **Pearl Index analysis:** the number of unintended pregnancies per 100 women per year; often used to quantify effectiveness.
  - *method effectiveness*: pregnancy rate assuming perfect use of the method
  - *user effectiveness* or *typical effectiveness*: pregnancy rate considering inconsistent or negligent use of the method.

Parameters affecting contraceptive efficacy

Contraceptive efficacy may be impaired by **(Speroff & Darney, 2005) [622]**:

- **User's negligence:** missing more than one active pill in a packet or irregular use is the most important cause of contraceptive failure: delay in starting the next packet of active pills (i.e., extending the pill-free, inactive or placebo pill period beyond 7 days),
- **Intestinal malabsorption** of active pills due to vomiting or diarrhea,
- **Drug interactions** with active pills that decrease contraceptive estrogen or progestogen levels
- **Body mass index and absolute** weight had little, if any, influence on the contraceptive effectiveness of OCs that contained drospirenone, dienogest, desogestrel, and levonorgestrel, but the contraceptive efficacy of lipophilic progestins such as chlormadinone acetate (may be also true for cyproterone acetate) is impared by increased BMI ≥ 30 kg/m^2) and weight ≥ 75 kg).

Efficacy based on ovulation inhibition studies

- The overall incidence of ovulation according to a literature search by **Milsom and Korver (2008) [462]:**
  - **COCs containing 30–35 µg EE:** 2.0% (95% CI: 1.1–3.3)
  - **COCs containing 15–20 µg EE:** 1.1% (95% CI: 0.60–2.0)
  - **Phasic COCs:** 4.6% (95% CI: 2.8–6.9)
  - **Desogestrel–only pill (75 µg/day):** 1.25% (95% CI: 0.03–6.8)
  - **Traditional POPs:** 42.6% (95% CI: 33.4–52.2)
  - The findings indicate that COCs and the desogestrel POP are equally effective in suppressing ovulation, whilst the traditional POP formulations are less effective.

Efficacy based on contraceptive failures as clinical endpoints

- The perfect use pregnancy rate of COCs is 0.3% per year **[663]** and the typical use pregnancy rate varies depending on the population being studied, ranging from 2–8,6% per year **[663]** (See summary table published by **Guttmacher Institute (2010) [220].**
- The Pearl Index in COC studies done in Europe is lower than data obtained from US studies.
- The method failure rate for COC is low, but the failure rate due to patient negligence is higher and influenced i.e. by irregular intake, missing pills, drug interactions, insufficient patient instruction, concomitant medical treatment (pharmacy or over the counter drugs including herbal medicine), vomiting and diarrhea.
- Contraceptive failure rates were found to decrease substantially from 30 years of age and as the duration of OC use increased.
- OCs were associated with a high level of contraceptive effectiveness in a "typical use" setting (ie, outside of a clinical trial setting) in Europe.

Contraceptive efficacy of COC is dependent on

Socio-economic-status: Based on education and social economic status the efficacy of COCs may be lower for those in the lowest quartiles due to the poor information status of the patient with regard to COC use, missed pill management, and drug interactions.

Age of users: A lower rate of contraceptive failure was found in women who were ≥ 30 years old **[151].**

Duration of use: A lower rate of contraceptive failure was found in women with a longer duration of OC use **[151].**

Parity: Parous women were more likely to experience a pregnancy during OC use than nulliparous women **[151].**

Ethinylestradiol dosage: even for low dose formulations (< 30 or ≥ 30 µg) a high effectiveness was found **[151].**

Progestins: only chlormadinone acetate COCs show a lower contraceptive efficacy in women with increased BMI (≥ 30 kg/m^2) and weight (≥ 75 kg) **[101].**

- **Final statement:** Overall, COCs in dosages available worldwide are among the most effective contraceptive methods when used consistently and correctly **[661].**

A summary of contraceptive efficacy is given in Table 1.

2.2. Menstrual Bleeding Pattern – Normal and Pathological

The tissue damage and subsequent repair occurring during menstruation are the result of a complex interplay between the endocrine system and the local immune system **[124, 125, 126, 346].**

Progesterone is seen as a critical steroid for endometrial differentiation. Menstruation occurs in two phases: in the first phase a decrease in the progesterone level leads to vasoconstriction of the arterioles, caused by local cytokines. This phase lasts about 36 hours and is thought to be reversible. The second phase of menstruation, however, which involves the activation of lytic mechanisms, is irreversible. This phase is independent of progesterone **[369].** This means, however, that only within the first 36 hours after the progesterone drop an add-back therapy with progesterone can usually be successful **[604].**

Prominent among factors leading to discontinuation of oral contraceptives is the occurrence of side effects, including intermenstrual bleeding, headache, weight gain, and amenorrhea **[3, 618].**

Table 1. Contraceptive efficacy of various contraceptives (Pearl Index). Mod. from **Trussel 2007,** http://www.arhp.org/uploadDocs/YD_Summary_Efficacy.pdf

	% of women experiencing an unintended pregnancy within the first year of use		% of women continuing use of 1 year
Method	**Typical use**	**Perfect use**	
Chance	**85***	**85***	**–**
Spermicides	29*	18*	42*
Coitus interruptus	27*	4*	43
Fertility observation	25*	–	51*
Standard-day-method	–	5*	–
Two-day-method	–	4*	–
Ovulation method	–	3*	–
Sponge	**–**	–	
Parous	32*	20*	46*
Nulliparous	16*	9*	57*
Diaphragm	16*	6*	57*
Condom			
Female condom (Femidom®)	21*	5*	49*
Male condom	15*	2*	53*
Oral hormonal contraceptives			
Combined oral hormonal contraceptives			
Estrogen-free ovulation inhibitor			
Cerazette	0.4 (0.09–1.2) (SPC)	0.14	n. a.
OC with estradiol derivatives			
Estradiol valerate: Qlaira®	18–50 years: 0.42 (max 95% CI 0.77) (SPC)	18–50 years: 0.79 (max. 95% CI (1.23) (SPC)	n. a.
	18–35 years: 0.51 (max 95% CI 0.97) (SPC)	18–35 years: 1.01 (max. 95% CI 1.59)	n. a.
Combined contraceptive patch			
Evra®	0.90 (0.44–1.35) (SPC)	0.72 (0.31–1.13) (SPC)	68*
Combined vaginal ring			
NuvaRing®	0.96 (0.64–1.39) (SPC)	6.64 (0.35–1.07) (SPC)	68*
Progestin-only pill			
Levonorgestrel (30 µg/Tab)			
Microlut®	4.14 (SPC)		n. a.
Depoprogestins (injectables)			
Medroxyprogesterone acetate			56*
DMPA (150 mg)			
Depoclinovir®	0.3 (SPC)		
DMPA (104 mg)			
Sayana®	0 (SPC)		
Noretisteron enantate			
Noristerat 200 mg®	0–2.3 (SPC)		
Postcoital pill			
Levonorgestrel (PiDaNa®)	n. a. (SPC) Day1: 2.5% per cycle Day 1–3: 1.7% per cycle Day 4–5: 2.8% per cycle		
Ulipristal (EllaOne®)	n. a. (SPC) Day 1: 0.9% per cycle Day 1–3: 0.9% per cycle Day 4–5: 0% per cycle		
Intrauterine devices			
Nova T 380®	0.6 (SPC)		
Multiload-Cu 375®	0–1.8 (SPC)		
ParaGard™ (***)	0.8*	0.6*	78*
Intrauterine systems			
Mirena®	0.2* 1. year 0.2%; 5. year 0.7% (SPC)	0.2*	80*
Contraceptive subdermal implants			
Ketodesogestrel			
Implanon	0.05	0.05	84*
Norgestrel			
Jadelle (previous: Norplant 2)(***)	0.08–0.17 (Rx_List, USA)		
Female sterilisation)**	0.5*	0.5*	100*
Male sterilisation	0.15*	0.1*	100*

SPC = summary of product characteristics; n. a.= not available; CI = confidence interval.
*according to Trussel 2007; ** depending on operation technique, skill of doctor performing the operation, age, time intervall after operation, *** not available on german market

2.2.1. Definition of irregular bleeding

– For the purpose of performing studies the World Health Organization has classified unplanned bleeding into 2 categories **[46]:** Breakthrough bleeding, which requires sanitary protection, and spotting, which does not require sanitary protection.
– Because of the lack of uniformity in studies of cycle control, the World Health Organization has issued recommendations aimed at standardizing the collection and analysis of data, including definitions of "bleeding" (requires sanitary protection) and "spotting" (does not require protection) and a "bleeding/spotting" episode (one or more days with bleeding or spotting bordered by days without bleeding or spotting).
The WHO furthermore advises that outcomes should be measured using a reference period of at least 84–90 days to identify changes over time while still fairly assessing bleeding patterns, and the terms used to assess bleeding during the pill-free period should be defined using at least five bleeding outcomes, namely, the proportion of women with prolonged, frequent, infrequent, or irregular bleeding/spotting episodes and those with amenorrhea during the reference period **[46].**
– The various studies are difficult to compare because, despite this formal classification, clinical trials have varied in their terminology and methods of recording menstrual irregularities.
– In addition, there is wide variation among women as to their individual tolerance to bleeding abnormalities, their perceptions of heavy vs light bleeding, as well as their need for protection **[658].**

Further definitions:

– **Intermenstrual bleeding:** all bleedings that occur between the normal withdrawal bleeding periods at the end of the hormonal treatment period. Unexpected bleeding is a major problem for women.
– **Prolonged bleeding:** pre- or postmenstrual bleeding.
– **Severity of bleeding:** breakthrough bleeding normally requires sanitary protection, whereas spottings do not.
– **Absence of withdrawal bleeding ("pill amenorrhea"):** no menstrual bleeding during the pill free interval.

– **Dysmenorrhea:** pain in relation to menstruation.

Etiology of breakthrough bleedings:
– **Skipping a pill** is a common cause of breakthrough bleeding **[559].**
– Inconsistent use, **such as failure to take the pill at the same time every day,** or lack of adherence to the pill–taking instructions, often triggers breakthrough bleeding **[560].**
– **Taking some prescription and over-the-counter medications,** as well as herbal supplements, may interfere with the activity of OCs to alter bleeding patterns and contraceptive efficacy **[698].**
– **Smoking** is associated with such anti-estrogenic effects as early menopause, osteoporosis, and menstrual abnormalities **[41].**

2.2.2. Pill Amenorrhea (silent menstruations)

All women using OCs can experience some cycles without a withdrawal bleeding. The occurrence of such a menstrual abnormality, however, may increase the fear of an unwanted pregnancy in some individuals, especially those who have not adhered to the pill-taking instructions.

Amenorrhea and women's perception:
– Lack of withdrawal bleeding leads to a latent fear of pregnancy, especially in women taking OCs irregularly.
– According to the ethnic origin and religious/cultural background of the women regular monthly bleedings are a sign of good health.
– Some women appreciate the occurrence of amenorrhea while using a COC.

Incidence (total): The incidence of a pill amenorrhea ("silent menstruations") in users of COCs varies according to the regimens and the type and dosage of progestins and estrogens, ranging between 5–20% (i.e. combined OC with 30 µg EE versus 4-phasic with dienogest and estradiol valerate) **[5].** The rate is higher using progestins with longer half-lives and low EE-dose formulations.

Incidence relative to the time of use: A 20 µg dose of EE in combination with low dose levonorgestrel (100 µg) caused no withdrawal bleeding after the first cycle in 10% of those studied and in 5% during the subsequent 7 cycles **[5].**

Incidence, dosages and regimen: see also summary

Mears & Grant (1962) [457] summarized the results with the higher dose formulations used in previous years:
– **Norethisterone: Tyler et al. (1961) [665]** using 10 mg of norethisterone, reported amenorrhea in 6% of the cycles; **Pincus et al. (1959) [519],** in trials in Humacao, Puerto Rico, and Haiti, reported 2.2%
– **Norethynodrel:** Trials in the UK showed the amenorrhea rate to vary from 1 to 9% **[163, 457].**
– **Estrogen/progestin-balance:** The lowest incidence of amenorrhea with norethynodrel (2,5 mg) was found in combination with the highest estrogen content (150 µg of mestranol). When norethynodrel was used it appeared that in amenorrhoeic cycles women often had some spotting during tablet–taking and none during the gap, whereas the women on norethisterone acetate had the spotting during the gap without periods, which was therefore regarded as a menstrual flow **[457].**
– **EE ≤ 20 µg versus EE > 20 µg:** In a Cochrane Library review, 13 combinations of COCs with regard to their EE dosage were analyzed by **Gallo et al. [200].** No differences were found in contraceptive effectiveness. Compared to the higher-estrogen pills, several COCs containing 20 µg EE resulted in higher rates of early trial discontinuation (overall and due to adverse events such as irregular bleeding) as well as increased risk of bleeding disturbances (both amenorrhea or infrequent bleeding and irregular, prolonged, frequent bleeding, or breakthrough bleeding or spotting) In other words, comparing pills with 20 µg EE and 150 µg desogestrel with those containing 30 µg EE and 150 µg desogestrel showed an odds ratio (OR) of 1.49 (0.75–2.97) after cycle 3 and an OR of 1.43 (0.65–3.12) after cycle 6 thus demonstrating a higher tendency for amenorrhea in the 20 µg EE dose formulation.
– **Incidence of no withdrawal bleedings: EE 20 µg versus EE 30 µg:** In a comparison trial withdrawal bleedings of 4.2% after 6 cycles and 3.0% after 12 cycles were reported for a group receiving a combination OC preparation containing 150 µg desogestrel and 20 µg EE, while a lower rate was observed in those receiving 30 µg EE (3,0% after 6 cycles and 1,4% after 12 cycles, respectively) **[8].**

Treatment

Preconditions:
– Exclusion of an unintended pregnancy is the first step of clinical workup.
– Treatment of missing withdrawal bleedings has no medical but in most cases, rather a psychological indication – to counsel and advise those fearing a pregnancy or possible infertility, or depending on the ethnic and cultural background of the individual, expressing concern for their health in general.

Informed consent: Women should be informed that:
- post-pill fertility is not impaired by missing regular withdrawal bleedings and do not lead to health risks. In the case of regular intake no intervention is necessary.
- By changing dosages and regimens intermenstrual bleedings may occur instead of a lack of withdrawal bleedings.

Treatment options:
– Patient information (see above)
– A low dose of EE (i.e. 10 µg/day) may be added to the regimen or the patient may be switched to a pill with a higher dose of estrogen.
– If higher EE dose pills fail to increase the thickness of the endometrium sufficiently, the dose of progestin can be decreased,
– Changes in the estrogen/progestin balance as well as the regimen (i.e. biphasic or triphasic regimen) can be tried.

Summary

Incidence (total): The incidence of a pill amenorrhea ("silent menstruations") varies from 5–20% in users of COCs according to the type and dosage of progestins, estrogens and the regimen followed.

Incidence relative to time of use: The incidence of absent withdrawal bleeding is highest following the first cycles and declines with use from 10% to 5% of cycles in a study with a 20 µg EE/100 µg levonorgestrel pill performed by **Ahrendt et al. (2009) [5].** In another study 4,2% and 3,0% of a group receiving a preparation containing 150 µg desogestrel and 20 µg EE experienced no withdrawal bleed-

ings after 6 cycles and 12 cycles, respectively. In comparison, for those receiving a 30 µg OC with the same progestin, absence of withdrawal bleedings were reported in 3.0% after 6 cycles and 1.4% after 12 cycles **[8].**

Ethinyl estradiol dosage: Lowering the dosage of EE from 50 to 30 or 20 µg per day leads to a higher rate of amenorrhea:

– **EE ≤ 20 µg vs EE > 20 µg:** In a Cochrane review by **Gallo et al. (2011) [200]** OCs with EE ≤ 20 µg and EE > 20 µg were compared. Several COCs containing 20 µg EE resulted in higher rates of early trial discontinuation due to overall adverse events such as irregular bleeding, or out of concern for the increased risk of bleeding disturbances (both amenorrhea or infrequent bleeding and irregular, prolonged, frequent bleeding, or breakthrough bleeding or spotting).
– **Estrogen-free OCs:** In users of the EE-free oral contraceptive with desogestrel (75 µg/day) a pill amenorrhea was found in 5–20 % of the cycles **[111].**

Progestins: Using progestins with a longer half-life leads to higher rates of pill amenorrhea (pregnanes versus estranes) due to a slower decline of serum levels in the pill free interval.

Regimen: The importance of the regimen with respect to pill amenorrhea is pointed out by the following:

– Using a prolonged regimen, i.e. 24+4 with drospirenone, leads to a higher incidence of amenorrhea (5–10%) with higher rates at the beginning and lower rates by time of OC use **[5].**
– In users of the 26+2 regimen (four–phasic pill) with dienogest and estradiol valerate a high rate of pill amenorrhea is observed in 15–20% of all cases **[5].**

Post Pill Amenorrhea

Definition: A post pill amenorrhea is per definition the absence of bleedings for at least 6 months following the discontinuation of the pill **[165];** various definitions are used in the literature (i.e. 3 months) and for most women 6 months seems to be too long.

Incidence: According to the 6 month definition of amenorrhea a post-pill amenorrhea occurs in 2–3 % of all OC users **[165].**

Causal relationship to OC-formulation: No relationship between the regimens and the type and dosages of estrogens and progestins has been observed in view of the incidence of a post pill amenorrhea.

Irregular cycles at pretreatment: In a literature review **Hammerstein (1977) [224]** analyzed various studies with post pill amenorrhea in women using older higher dose preparations. In 10–57% of the cases the post pill amenorrhea was due to a pregnancy. In 35–71% of all cases cycle irregularities prior to OC use, and in 3–43% in combination with galactorrhea had been reported.

The incidence of pre-existing oligomenorrhea varies in different studies of post-pill amenorrhea, but about half the women who present with post-pill amenorrhea show some irregularities in menstruation before starting the treatment **[165].**

Clinical workup: As a conclusion, in cases with preexisting disturbances of the menstrual cycle the higher risk for a post pill amenorrhea due to endocrine disturbances (i.e. hyperprolactinemia and hypothyroidism; hyperandrogenism) should be evaluated at least after 3–6 months by endocrine testing (i.e. prolactin, TSH, fT3, estradiol, FSH, LH and testosterone and DHEAS if indicated by signs of hyperandrogenism).

2.2.3. Intermenstrual bleedings [428]

Prevalence: The intermenstrual bleeding that occurs in approximately 10% to 30% of women in the first month of oral contraceptive use is best managed by encouraging users to continue the regimen and reassuring them that the problem usually disappears within a few cycles **[658].**

Consequence of intermenstrual bleedings = discontinuation: About 20% of women surveyed in a nationally representative sample had discontinued oral contraceptives (OCs) on their own or at the recommendation of their physician due to bleeding or spotting **[428, 524].** Menstrual abnormalities are consistently cited as a common reason for discontinuing OCs **[191, 560].** A prospective US study of 1657 women performed in the 1990s reported that 37% of OC users had stopped taking OCs within 6 months after starting a new prescription because of side effects **[561].** Irregular bleeding was the most common cause (12%), followed by nausea, weight gain, and mood changes, which ranged from 5% to 7%. A survey of over 6,500 women who were either current or former users of oral contraceptives showed that women experiencing bleeding irregularities during the first 3 months of use were almost twice as likely to discontinue the pill within 2 years of use when compared with women who did not experience bleeding ($p < 0.001$) **[560].**

Understandable concerns about potential side effects of oral contraceptives, embarrassment about unexpected side effects and insufficient bleeding control, and annoyance lead these women to abandon OCs **[524, 561].**

Most women do not know that the incidence of breakthrough bleeding is generally greatest in the first 3 to 4 months after starting OCs **[658]** and steadily declines until it stabilizes by the end of the fourth cycle **[619].** At the time of first prescription women must be informed about the higher rate of bleeding disturbances during the first three cycles as this could enable many of these women to cope with the bleeding and stick with an effective contraceptive method. In addition, new OC users should be informed about non-contraceptive benefits of OCs: improved menstrual regularity and decreased menstrual blood loss, dysmenorrhea, and risk of ovarian and endometrial cancer.

Women who discontinue OCs on their own switch to less effective methods of birth control or use no method **[524, 561].** The consequences thereof may be unexpected pregnancies and increased abortion rates **[559].** It would be advisable to periodically ask those users whether they are satisfied with OC use.

Factors contributing to breakthrough bleeding: Breakthrough bleeding may be due to any the following factors: physiological effects of OCs on the endometrium, OC-related parameters, including dose, formulation, and regimen, patient behavior, including compliance, using concomitant medications, cigarette smoking and benign or malignant pathology of the uterus.

Estrogen and progestin effect on the endometrium:

– Progestin and estrogen in combination OCs have profound effects on the endometrium, which, though not contributing to contraception, do lead to a predictable pattern of bleeding or such problems as breakthrough bleeding or lack of withdrawal bleeding.
– **Estrogens:** normally, estrogen causes the endometrium to proliferate. Progesterone stabilizes the growing uterine lining.

Estrogen dosage (IHS 2010) [339]:

– Since the introduction of OCs in 1960, the trend in formulation has been to use the least amount of hormone necessary to inhibit ovulation. Given that progestin is primarily responsible for the contraceptive efficacy of OCs, the risk of pregnancy is not altered by decreasing the estrogen content. However, significantly lowering the estrogen in OCs may account for breakthrough bleeding. Unplanned bleeding, though, is not dependent solely on the estrogen component as variations in the progestin dose can contribute to breakthrough bleeding as well **[174].**
– As the estrogen content of OCs has declined, higher breakthrough bleeding and spotting rates have been noted, along with a possible decrease in contraceptive efficacy **[201, 200].**

Bleeding problems related to EE dosage: Gallo et al. (2011) [200] performed a systematic review of trials comparing a combined OC containing ≤ 20 µg EE with a combined OC containing > 20 µg EE in terms of contraceptive effectiveness, bleeding patterns, discontinuation, and side effects. The high dropout rates in many of these trials, however, make the results hard to interpret.

Compared to the pills containing the higher doses of estrogen, several COCs containing 20 µg EE resulted in higher rates of early trial discontinuation (overall and due to adverse events such as irregular bleeding) as well as increased risk of bleeding disturbances (both amenorrhea or infrequent bleeding and irregular, prolonged, frequent bleeding, or breakthrough bleeding or spotting).

Various factors: Low estrogen OCs may be more influenced by missed pills or the concomitant intake of drugs **[169],** and may not provide the same non–contraceptive benefits as higher estrogen products, such as reduction in risk of ovarian cancer, protection against functional ovarian cysts, and improvements in acne **[201].**

Progestin type, content & cycle control (IHS 2010) [339]:

Progestin content may also affect cycle control, because even moderately low doses of either EE or progestin can increase the incidence of breakthrough bleeding.

– **Progestin dosage**: When 3 COCs with the same type of estrogen and progestin in different dosages (50 µg EE/100 µg norethindrone; 35 µg EE/100 µg norethindrone; 35 µg EE/50 µg norethindrone) were compared in 192 women over 8 cycles, the pill containing the lowest amount of norethindrone (35 µg EE/50 µg norethisterone) caused the highest rates of breakthrough bleeding, decreasing to 50% by cycle 8 as compared with 35% for the group receiving the 35 µg EE/100 µg norethindrone pill and 25% in the 50 µg EE/100 µg norethindrone pill group **[572].**
– **Type of progestin may affect breakthrough bleeding.**

All combination OCs contain either EE or mestranol and a variety of different substances derived either from 19-nortestosterone or from progesterone to make up the progestin component. The former progestins can be further classified as gonanes or estranes **[629].**

19-nortestosterone derivatives:

– **Estranes** include norethindrone and its derivatives: norethindrone acetate, ethynodiol diacetate and lynestrenol, which must be primarily converted to norethindrone to become biologically active.
– **Gonanes** include levonorgestrel, norgestrel, desogestrel, gestodene, and norgestimate.

Dienogest (DNG) is the only nortestosterone derivative with a cyanomethyl group in position 17α instead of an ethinyl group. Unlike the other nortestosterone derivatives it has no androgenic, but even an anti–androgenic effect, which corresponds to about 40% of that of cyproterone acetate. DNG has no glucocorticoid or antimineralocorticoid properties **[394].**

Progesterone derivatives:

– Pregnanes include progestins as chlormadinone acetate*, cyproterone acetate*, medroxyprogesterone acetate (used i.e. for injectable contraceptives) (* not available in the US)

19-norpregnane derivatives developed in France, are also derived from progesterone without an angular 19-methyl group like norethindrone. They include promegestone, NOMAC, and demegeston and trimegestone. The norpregnane derivatives have similar properties to 17α-hydroxyprogesterone derivatives, but, in contrast to, for example, medroxyprogesterone acetate has no androgenic, but rather anti-androgenic properties.

NOMAC (NOMAC) has been recently approved for oral contraception in combination with estradiol in 2011.

Each progestin differs in half-life, as well as in progestinic, estrogenic or antiestrogenic, androgenic or antiandrogenic, and partial antimineralocorticoid properties. Variations of the half-life, the progestinic and (anti)-estrogenic properties may explain the differing rates of breakthrough bleeding among formulations **[619].**

As shown by **Endrikat et al. (2001) [171]** pills with the same quantity of EE but different progestins can have markedly different effects on the breakthrough bleeding rates.

In a **Cochrane review Maitra et al. (2005) [436]** evaluated randomized trials (n = 22) comparing combined OCs with < 50 µg EE and various progestins over a minimum duration of six cycles. Trials involving monophasic and multiphasic products were analyzed separately.

Gestodene (GSD) versus levonorgestrel (LNG): Based on data from one trial a COC with GSD compared to a LNG-COC caused less intermenstrual bleeding, but showed similar patterns with regard to spotting, breakthrough bleeding and the absence of withdrawal bleeds **[436].**

Gestodene (GSD) versus desogestrel (DSG): COC with GSD when compared to DSG-COC led to better cycle control, although the continuation rate was higher in women using DSG pills.

Drospirenone (DRSP) versus desogestrel (DSG): No differences have been found between COC with DRSP

and those with DSG with regard to pregnancy prevention, cycle control and side effects.
Regarding acceptability, all the indices show that third (gestodene, desogestrel, norgestimate) and second-generation (LNG) progestins are preferred over first-generation pills containing norethisterone, norethindrone, ethynodiol diacetate, lynestrenol or norethynodrel **[436].**

Duration of use

Regardless of the progestin used or the quantity of EE, breakthrough bleeding generally decreases with each successive cycle. One study that compared 2 combination OCs composed of EE/norgestimate and EE/norgestrel demonstrated reported bleeding rates of 11.3% and 10.6% during the first 6 cycles, that decreased to 5.1% and 6.3% in Cycles 13 to 24, respectively **[118].**

Estrogen-progestin balance [428]

– Most OC users worldwide take low-dose formulations, so designated because the estrogen component is < 50 µg EE. This level of estrogen in combination with a progestin provides excellent contraceptive efficacy, but may be insufficient to sustain endometrial integrity in some women **[365].**
– Studies that have compared OCs containing 20 µg EE with those containing 30 µg or 35 µg EE have not been very useful for judging breakthrough bleeding rates because the products often also vary in the phasing and type of progestin.
– Some studies show more breakthrough bleeding with 20 µg EE pills **[528, 8, 202],** but others show equal or improved cycle control with the lower EE dose.
– **Endrikat et al. (2001) [171]** conducted a study to compare different OCs with 20 or 30 µg EE:
  - **30 µg EE:** Overall, the pill containing 30 µg EE preparation (30 µg EE/150 µg levonorgestrel) was used as a standard reference preparation and showed a lower cumulative incidence of breakthrough bleeding compared with the 20 µg EE/100 µg levonorgestrel and 20 µg EE/500 µg norethisterone pills over 13 cycles (1.0% vs. 4.1% vs. 11.7%, respectively).
  - **20 µg EE:** 20 µg EE/500 µg norethisterone pills consistently had higher breakthrough bleeding rates than the 20 µg EE/100 µg levonorgestrel pill.

In conclusion, a greater cycle control may be achieved by titrating the EE component of an OC in a balanced ratio with the same progestin, but the absolute quantity of EE in a given pill may be less important than maintaining a balance between the 2 hormones or less important than the impact of different progestins on breakthrough bleeding rates **[428].**
Pathophysiological background: The balance between estrogen and progestins required for contraception may also lead to progestin-induced decidualization and endometrial atrophy, which can result in asynchronous, irregular bleeding **[174, 254].** This has been primarily studied in long-acting progestin-only contraceptives such as implants. Alterations in angiogenic factors **[609]** may play a role. Hysteroscopic studies have shown abnormalities in superficial endometrial blood vessels in terms of size, proliferation, and fragility in women using the levonorgestrel implant Norplant™ **[253, 254, 611].**
Abnormalities in endothelial cells and extracellular matrix proteins **[551],** tissue factor **[427],** and endometrial lymphoid cells **[98]** may contribute to breakthrough bleeding in progestin-dominant environments.
Furthermore, a direct effect of progestins and estrogens on endometrial steroid hormone expression and estrogen metabolism has been observed. The antiestrogenic effect of progestins is based mainly on the suppression of estrogen receptors and activation of enzymes involved in estrogen metabolism such as 17-hydroxysteroid dehydrogenase and estrogen sulfotransferase, as well as on the differentiation of the functionalis layer of the endometrium **[394].**
In the human endometrium, inactivation of 17β-estradiol to estrone is catalyzed by 17β-hydroxysteroid dehydrogenase type 2 (17βHSD2) **[375].** Estradiol-based combined oral contraceptives cause bleeding problems, because the 17βHSD2 (stimulated by progestins) rapidly converts estradiol in estrone (E1). E1, however, does not show a proliferative effect on endometrium. Using a dynamic dose it was possible to adjust the rate of additional bleeding caused by the EE pills when using estradiol valerate and dienogest in a 4-phasic regimen.

– **Comparing regimens.**
Available OC formulations, doses, and regimens: More than 30 formulations of combination OCs are available in the US, containing different doses and types of estrogen and progestin **[235]. OC regimens** are available as biphasic, triphasic, extended–cycle, and continuous use.
Biphasic and triphasic products & cycle control [339]:
  - It is not clear whether biphasic and triphasic regimens offer any clinically meaningful advantage over monophasic OCs, although the overall reduction in progestin and/or estrogen exposure should be accompanied by a lower risk of thromboembolic events.
  - As reported by **Mishell (1991) [464]** use of the older types of biphasic (two levels of progestin) products declined relative to triphasic products because of an indicated increase in breakthrough bleeding.
  - In a Cochrane review last updated in 2005, **Van Vliet et al. [677]** compared biphasic with triphasic OCs in terms of efficacy, cycle control, and discontinuation due to side effects. Only two trials met inclusion criteria. One trial found similar results with two biphasic OCs and one triphasic OC (all containing levonorgestrel/EE) **[407].** The other compared a biphasic OC containing norethindrone (Ortho 10/11™) with a triphasic OC containing levonorgestrel (Triphasil™) and another containing norethindrone (Ortho 7/7/7™) **[508].**
  - The biphasic product had inferior cycle control compared to the levonorgestrel triphasic product, based on differences in cycles with intermenstrual bleeding (OR 1.7, 95% CI: 1.3–2.2) and cycles without withdrawal bleeding (OR 6.5, 95% CI: 3.1–13).
    - On the other hand, the biphasic product had comparable results

to the triphasic product with the same progestin.
- After excluding poor-quality trials from the analysis, the authors concluded that cycle control might depend more on the choice of progestin than the phasic regimen.

Monophasic versus triphasic:
Rosenberg et al. (1992) [558] evaluated 25 studies assessing cycle control with various OCs. In general, products containing norgestrel and levonorgestrel (2nd generation products) were found to cause a lower incidence of spotting and breakthrough bleeding compared with norethindrone acetate and norethindrone (1st generation), whether triphasic or monophasic.
Two trials comparing two norethindrone-containing triphasic products vs a levonorgestrel-containing triphasic product found that the levonorgestrel product was associated with a lower rate of intermenstrual bleeding **[159, 579].**

Extended-cycle regimen:
3-month pill: Women using extended-cycle contraceptives i.e. the 3-month pill (30 µg EE/150 µg levonorgestrel) have been found to experience more breakthrough bleeding than those using a standard 28-day pill, however the total number of planned and unplanned bleeding days may still decrease from 21 days of planned bleeding in a 28-day regimen to 7 days of planned bleeding in a 3-month cycle **[15].** The number of bleeding days decreased with each cycle.
Continuous 365-day regimen: Another study examined continuous OC use (20 µg EE/100 µg levonorgestrel) over a period of 1 year, and reported a decreasing number of bleeding days over time **[461].** In the case of continuous use, all bleeding was unscheduled, and any bleeding was considered breakthrough bleeding.
Multiphasic OC regimens were developed with the intention of decreasing breakthrough bleeding by mimicking the rising and falling pattern of estrogen and progesterone in the normal menstrual cycle **[670].**
- After the introduction of the biphasic pill, an increase in breakthrough bleeding was noted, which led to the development of the triphasic pill **[464].**
- Though the multiphasic hypothesis is physiologically plausible, recent reviews of the literature have found that the evidence for its efficacy is too limited and methodologically flawed to draw any definitive conclusions about a decrease in breakthrough bleeding **[675, 676].**

Summary
- **Data base:** Studies of cycle control tend to have methodological problems, including small sample size, lack of control for other factors that may affect the incidence of bleeding (i.e., chlamydial infection, cigarette smoking, age, missed pills, interacting medications), differences in study design/analysis, and differences in definitions of bleeding and spotting **[21].**
- **Factors contributing to breakthrough bleeding:** physiological effects of OCs on the endometrium, OC-related parameters, including dose, formulation, and regimen, women behavior, including compliance, using concomitant medications, and smoking, and benign or malignant pathology.
- **Higher incidence during first three OC cycles:** Cycle problems tend to lessen within a few months of OC initiation, regardless of formulation.
  Strategies for dealing with cycle problems include: informing the women that these problems tend to decrease during the first 3 months of use and that they should not discontinue or change the formulation during this period; consideration of factors that can contribute to problems, such as missed doses, chlamydial infections, smoking, and interacting medications; changes in regimen (adding estrogen or decreasing progestin if bleeding occurs early in the cycle, adding progestin if it occurs late in the cycle, or doubling active pills until the bleeding stops or for the rest of the cycles); or providing a course of non-steroidal anti-inflammatory drugs **[21].**

- **The type of progestin may affect breakthrough bleeding.**
- **The estrogen-progestin balance is more important than the absolute level of estrogen.**
- **Comparing regimens:**
  Phasic regimen: no Cochrane-based differences among monophasic, biphasic and triphasic OCs have been reported with regard to better control of the menstrual cycle.
  Extended-cycle: Using combined pills as "off-label" or one of the three FDA-approved 3 months pills will be of interest to those women who prefer extended menstrual cycles
  A **continuous regimen:** (Lybrel™) (90 µg levonorgestrel/20 µg EE) has only been approved in the US due to its association with high rates of irregular bleeding. All extended cycle regimens are in discussion for increased steroid exposure per year because of missing pill-free intervals.

2.3. Non-contraceptive Benefits

2.3.1. Overview

In the following section various non-contraceptive benefits of combined oral contraceptives will be described and analyzed with regard to dose reduction of estrogens and progestins and the use of different regimens and new progestins. Initial data from the UK known as the **Royal College of General Practitioners Study (1974) [566]** demonstrated a significant reduction in menorrhagia (50%), benign breast tumors (20%), dysmenorrhea (60%), iron deficiency anemia (40%), premenstrual syndrome (30%), acne vulgaris (20%) and ovarian cysts (60%) for EE ≥ 50 µg/day. In reducing the dosage of estrogens and progestins, using new regimens (i.e. multiphasic pills) and developing new progestins to make products safer it must be proven at the same time that the new products do not lose the non-contraceptive benefits as described for the pills analyzed in the **Royal College of General Practitioners Study (1974) [566]**.
The following analysis of the non-contraceptives benefits of combined oral hormonal contraceptives is based on a review of The ESHRE Capri Workshop Group (2005) [649].

2.3.2 Non-contraceptive benefits in relation to dosages, combinations and new steroids used for oral hormonal contraception

2.3.2.1. Dysmenorrhea (IHS 2010) **[339]**

Definition:
- Dysmenorrhea is the occurrence of painful cramps during menstruation.

– It is defined as primary (associated with ovulatory cycles and with no organic pathology) or secondary (associated with a condition such as endometriosis or ovarian cysts).

Prevalence:

– Dysmenorrhea is the commonest form of menstrual disorder with a reported prevalence of 50–90% among young women **[12, 635].**
– 10 % of patients with dysmenorrhea suffer severely under this condition **[148].**
– According to **Schiøtz et al. (2007) [581]** dysmenorrhea is a widespread female problem that causes reduced quality of life, a need for medical treatment, and absence from school or work.
– A recent Canadian study found that 60% of menstruating women had primary dysmenorrhea with 51% reporting limitations of daily activities and 17% reporting absenteeism; 60% had moderate or severe pain **[74].**

Etiology:

– The pain of dysmenorrhea arises from the release of prostaglandins, which cause an increase in myometrial activity **[432].**

Treatment options

Non-hormonal treatment [271]

– **Non-steroidal anti-inflammatory drugs** (NSAIDs) are effective in relieving the pain of primary dysmenorrhea **[18].** NSAIDs can have side effects, i.e. nausea, dyspepsia, peptic ulcer, and diarrhea **[565].** For patients who cannot take the more common NSAIDs, or for whom they are ineffective, a COX-2 inhibitor may be prescribed **[88].** One study indicated that conventional therapy with NSAIDs „provides symptomatic relief but has increasing adverse effects with long-term use“ **[352]** another indicated that long-term use of NSAIDs has “severe adverse effects” **[497].**
– **Other treatment regimens** include acupuncture, acupressure, and Chinese and Japanese herbal medicines etc. See the following reviews **[149] [529].**

Oral hormonal contraceptives

- Combined OCs were used to treat dysmenorrhea since their introduction in 1960.
- Several studies **[432]; [236]** have documented that combined oral contraceptives (OCs) relieve dysmenorrhea by reducing menstrual prostaglandin release, thereby preventing abnormal uterine contractility leading to reduced uterine blood flow and ischemic pain **[149].**
- Several clinical trials have proven the efficacy of COC in treating dysmenorrhea:
- An open trial in 661 women (after 12 months of treatment 12% of women still experience dysmenorrhea vs 63% pretreatment) **[204].**
  - An open trial of a low dose combined OC in 100,000 women showed that 65% of first time users of oral contraceptives with pre-existing dysmenorrhea experienced relief **[60].**
  - Studies with chlormadinone acetate 2 mg/30 µg EE include the **BEDY-study (B**elara **e**valuation on **Dy**smenorrhea) **[22], CARED-study (C**hlormadinone **a**cetate/EE **r**educes **e**motional **d**ysbalance) **[54]** and **TeeNis-study (Tee**nager **n**on-**i**nterventional **s**tudy) **[251].**

Higher dose OC:

– Formerly used higher dose OCs have been reported to provide effective pain relief for 70–80% of women with primary dysmenorrhea **[432, 236, 463].**
– A Cochrane review in 2001 last updated in 2004, **[530]** concluded that medium and high dose OCs are effective in relieving dysmenorrhea, but that proof was lacking for the modern low dose OCs. In this systematic review randomized controlled trials were analyzed comparing combined OCs with other combined OCs, placebo, no treatment or treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of primary dysmenorrhea. A total of 5 trials were included; 4 of these were combined in a meta-analysis. All of the trials included combined OCs with > 35 µg of estrogen (80 µg of mestranol in two trials, 50 µg mestranol in one trial, and 50 µg of estrogen in two trials) and first- or second-generation progestins, compared to placebo:
  - Meta-analysis results showed the combined OCs to be more effective than placebo for pain relief (OR 2.01, 95% CI: 1.22–3.33), although the difference was non-significant when reanalyzed using a random effects model to compensate for significant heterogeneity within the trials (OR 1.68, 95% CI 0.29–9.81).
  - Not surprisingly, adverse effects were higher in the combined OC group, although this outcome was reported by only 2 studies.
  - One study reported a significant reduction in women reporting absences from work or school with combined OC therapy.

Low-dose OC:

– Data from randomized controlled trials (RCTs) **[248],** cross-sectional surveys **[463]** and a non-comparative trial **[409]** support the value of OCs, including those with low dosage, in reducing the pain associated with menstrual periods.
– In a Cochrane review last updated in 2004, **[530]** no conclusions could be drawn as to the efficacy of currently used combined OCs, which use lower estrogen doses.
– However, a recent study showed that low dose (20 µg) OCs are also effective **[146].**

Progestins:

– Various trials done for drug registration showed a reduction of menstrual pain for all progestins on the market when used in a combined oral contraceptive.
– Several studies using chlormadinone acetate-containing COCs (chlormadinone acetate 2 mg/EE 20 µg) have shown a high and significant reduction of dysmenorhea and restrictions at work, along with an increase in leisure and sporting activities up to 83% in 2140 women each receiving a 2 mg chlormadinone/30 µg EE COC oral contraceptive: **BEDY-study (B**elara **e**valuation on **Dy**smenorrhea) **[22], CARED-study (C**hlormadinone **a**cetate/EE **r**educes **e**motional **d**isbalance) **[54]** and **TeeNis-study (Tee**nager **n**on-**i**nterventional **s**tudy) **[251].**

Regimen:

– In a Cochrane update **Wong et al. (2009) [721]** found only limited evidence for pain improvement with the use of the OCP (both low and medium dose estrogen) in women with dysmenorrhea.
  (Note by the authors: this is in contrast to clincial evidence and all trials with chlormadinone acetate-containing OCs).

No differences among the various OC preparations were evident.
Long cycle ("off label"): A reduction of dysmenorrhea can also be achieved using COC in a long cycle.

Summary:
Disease: Dysmenorrhea often used synonymously with menstrual cramps is the commonest form of menstrual disorder.
Prevalence: 50–90% among young women.

Treatment options:
Non-hormonal treatment: Non-steroidal anti-inflammatory drugs; other treatment regimens include acupuncture, acupressure, and Chinese and Japanese herbal medicines. See reviews **[149, 529].**

Hormonal treatment with combined oral contraceptives:
– **Mode of action:** Combined oral contraceptives (COCs) alleviate dysmenorrhea by reducing menstrual prostaglandin release thereby preventing abnormal uterine contractility leading to reduced uterine blood flow and ischemic pain.
– **Estrogen dosages:**
  • **Medium and high EE dose formulations (30–50 µg):** Several studies have shown a high and significant reduction of dysmenorrhea and restrictions at work, along with an increase in leisure and sporting activities in up to 80% of all patients with dysmenorrhea for medium and high EE dose formulations.
  • **Low dose EE formulations (≤ 20 µg):** In a Cochrane review last updated in 2004, **Proctor et al. (2001) [530]** could not draw any conclusions as to the efficacy of currently used combined OCs, which use lower estrogen doses. In contrast, a study by **Davis et al. (2005) [146]** showed that low dose (20 µg) OCs were also effective.

– **Progestins:**
Various trials done for drug registration showed a reduction of menstrual pain for all progestins on the market when used in a combined oral contraceptive.
Intensive studies have been done investigating the effect of chlormadinone acetate 2mg/30 µg EE in patients with dysmenorrhea.

– **OC regimen:** A Cochrane analysis found no evidence of differences among the various OC preparations studied. The "off label" use of long cycles is also beneficial.

2.3.2.2. Menorrhagia
Prevalence: Approximately 10% of all fertile women suffer from menorrhagia, defined as a menstrual blood loss of > 80 ml. The prevalence of menorrhagia increases with increasing age.
Clinical consequences: Excessive blood loss may lead to iron deficiency anemia and ultimately necessitate hysterectomy **[222]**.

Therapeutic effect of OC:
– Menstrual blood loss has been reduced by approximately 50% in both users of high-dose OCs **[487, 488]**, and low-dose OCs **[188, 409].**
– **Larsson et al. (1992) [409]** showed a reduction of menstrual blood loss for low-dose OCs in a non-comparative trial with 20 women and in a randomized trial involving 45 women with menorrhagia who were treated during an 8-cycle crossover treatment trial with mefenamic acid or naproxen or a low-dose OC or danazol **[188]**.
In a US-american randomized controlled trial involving 201 women with menorrhagia and dysfunctional bleeding, a low dose OC containing EE 35 µg and triphasic norgestimate was found to cause a significant reduction in menstrual blood loss (87% in OC users versus 45 % in placebo users) during OC use **[145].**
– In a Cochrane review last updated in 2004, **Iyer et al.**, **[345]** reviewing available literature in an attempt to determine the effectiveness, adverse effects, and cost-effectiveness of combined OCs vs other treatments in reducing menorrhagia, found only one small cross-over study comparing mefenamic acid, naproxen, low dose danazol and a combined OC. No differences were observed among the various groups. Women taking combined OCs had a 43% reduction in menstrual blood loss, however, due to the very small number of cases (n = 6) no conclusion can be drawn from this Cochrane review **[339]**.

Summary:
Incidence: About 10% of all fertile women suffer from menorrhagia, defined as a menstrual blood loss of > 80 ml. The prevalence of menorrhagia increases with increasing age.
Clinic: Excessive blood loss may lead to iron deficiency anemia and ultimately necessitate hysterectomy
Combined oral contraceptives:
– Several studies demonstrate that low–dose OCs reduce menstrual blood loss and are effective in the treatment of menorrhagia.
– Although monthly menstruation is natural and normal, it is not necessarily beneficial for all women. When indicated, menstruation can be minimized with safe and widely available forms of hormonal contraception.
Note:
Users of the levonorgestrel-containing IUS benefit strongly from the shorter, lighter, and pain-free menstrual periods associated with this contraceptive method.

2.3.2.3. Endometriosis
Definition of the disease: Endometriosis occurs when excess endometrial tissue grows in other areas of the body (i.e., ovaries, fallopian tubes, and other organs in the pelvic region).
Symptoms: Symptoms include dysmenorrhea, dyspareunia (painful sex), and pelvic or lower abdominal pain.
Prevalence: 10–20 % of American women of childbearing age develop endometriosis (NIDCD-endometriosis); up to 2 million women in the UK **[331]**.
Treatment options:
– **Targets:** Potential targets for treatment are suppression of the growth of endometrial implants, relief of pain and restoration of fertility.
– **Surgical treatment:** Laparoscopy, surgical removal of adhesions, biopsy and removal of endometrial implants is usually the first treatment option.
– **Postoperative treatment:** Can be treated surgically and/or with hormonal drugs, including OCs or gonadotropin-releasing hormone agonists (GnRH agonists). Since symptoms terminate during pregnancy, high dose progestins are initially used. Low dose OCs and injectables with depot medroxyprogesterone acetate (DMPA) are also treatment options **[339].** Furthermore, since 2010 Dienogest has been approved for use in the treatment of endometriosis.

– **Medical treatment:** The choice of medical treatment plays a role in the therapeutic strategy when administered over a prolonged period of time. Given their good tolerability, minor metabolic effects and low cost, contraceptive steroidal preparations must therefore be considered drugs of choice and are currently the only safe and economic alternative to surgery **[653]**. Drugs used in the treatment of endometriosis are not cytoreductive **[526].** Quiescent implants have been demonstrated in nearly all women treated with danazol, gonadotrophin-releasing hormone agonists and progestins. Upon restoration of ovulation and physiological levels of estrogens, both the eutopic and ectopic endometrium resumes its metabolic activity. As a consequence, medical therapy is symptomatic and pain relapse at treatment suspension is the rule **[688]**.
– Drugs to be administered only for some months due to poor tolerability, severe metabolic side effects or high cost, do not greatly benefit women with symptomatic endometriosis **[685]**.
– Progestins and estrogen-progestins are effective in the control of pain symptoms in approximately three out of four women affected by endometriosis. Their effect does not seem to be inferior to that of other drugs used for treating the disease **[466, 525, 688]**. Different compounds can be administered by the oral **[119, 683, 687]** intramuscular **[684]**, subcutaneous, intravaginal and intrauterine route **[178, 682, 686]** with specific advantages and disadvantages.
  Contraceptive progestins alone or combined with estrogens are generally well tolerated, have a more limited metabolic impact as opposed to danazol or GnRH analogues, are inexpensive and may be used on a long–term basis **[466, 525].**
  Cyclic hormonal contraception is the only treatment for endometriosis that permits a monthly uterine bleeding. Dysmenorrhea is known as the most frequent and most severe complaint in women with this disease. The symptom may therefore not subside completely during administration of an OC.
  Women affected by dysmenorrhea during cyclic use of an OC may benefit from the shift to a continuous administration. A monophasic OC (desogestrel 0.15 mg and EE 0.02 mg) was prescribed continuously to 50 patients with dysmenorrhea relapsing after conservative surgery for endometriosis and not responding to the cyclic use of the same OC **[687].** During the 2-year study period, 38% of women reported amenorrhea, 36% spotting and 26% breakthrough bleeding. The mean score of menstrual pain, evaluated according to a 100–mm visual analogue scale, showed a reduction from 75 ± 13 to 31 ± 17. Moderate or severe side effects were reported by 14% of the women.

Progestins – pharmacological actions:
– Progestins may prevent implantation and growth of endometrium by inhibiting expression of matrix metalloproteinases and angiogenesis. Several anti-inflammatory in vitro and in vivo effects of progestins may reduce the phlogistic status generated by the metabolic activity of the ectopic endometrium and the consequent immune response.
– Moreover, anovulation, decidualisation, amenorrhoea and the establishment of a steady estrogen-progestin milieu contribute to disease quiescence.

Summary:
Disease: Endometriosis occurs when excess endometrial tissue implants in other areas of the body (i.e., ovaries, fallopian tubes, and other organs in the pelvic region) causing dysmenorrhea, dyspareunia, and pelvic or lower abdominal pain.

Prevalence: 10–20 % of American women of childbearing age develop endometriosis (NIDCD); up to 2 million women in the UK **[331].**

Treatment options:
– Potential targets for treatment are suppression of the growth of endometrial implants, relief of pain and restoration of fertility.
– Endometriosis is treated surgically and/or with hormonal drugs, including OCs or gonadotropin-releasing hormone agonists (GnRH agonists).
– Combined oral contraceptives are a treatment option.
– Since 2010 dienogest (Visanne®/Bayer HealthCare) 2 mg/day; orally) can be used in patients with endometriosis.

Combined oral contraceptives:
Oral hormonal contraceptives:
– The **efficacy** of combined OCs in the treatment of pain-related endometriosis is not conclusive. In an update **2003** of a Cochrane review by **Moore et al. (2000) [466]** clinical trials were reviewed, assessing the effectiveness, adverse effects, compliance, and cost-effectiveness of combined OCs for the treatment of painful symptoms associated with the diagnosis of endometriosis, compared to placebo, no treatment, other medical therapies, or conservative surgical treatment. However, only a single trial comparing a combined OC with a GnRH analogue met inclusion criteria **[147, 339].**
  In this trial, the combined OC was less effective in relieving dysmenorrhea; no difference was noted regarding relief of dyspareunia or non–menstrual pain. Adverse effects varied based on the treatment option. Due to the limited data available, more research is needed to support the effect of combined OCs for pain associated with endometriosis, **[339].**
– **Progestins:** Recently a mono-therapy with dienogest (2 mg/day) received approval for treatment of endometriosis. Previously, chlormadinone acetate (2 mg/day) lost its approval in Germany for endometriosis; furthermore, lynestrenol has been withdrawn from the market. Desogestrel (75 µg/day) using 1–2 tablets continuously can only be used "off-label".
– **EE-Dosage:** Low-dose OCs used in a continuous application mode in patients with dysmenorrhea relapsing after conservative surgery for endometriosis and not responding to the cyclic use of the same OC showed a reduction of the pain scores by about 50% **[687].**
– **Regimen:** no data are available as to the efficacy of different regimens in patients with endometriosis.

2.3.2.4. Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder
Premenstrual syndrome (PMS)
Definitions: PMS has been defined as 'the cyclic recurrence in the luteal phase of the menstrual cycle of a combination

of distressing physical, psychological and/or behavioral changes of sufficient severity to result in deterioration of interpersonal relationships and/or interference with normal activities **[542].** It is estimated that women with these symptoms comprise 3 to 5% of the female population in their reproductive years **[355, 547, 723].**

Prevalence:
- During the reproductive years, up to 80–90% of menstruating women will experience symptoms (breast pain, bloating, acne and constipation) that forewarn them of impending menstruation, so-called premenstrual molimina.
- Over 60% of women report swelling or bloating **[412]**, although objective documentation of weight gain is lacking in most of these women **[175].**
- Cyclic breast symptoms affect 70% of women with 22% reporting moderate to extreme discomfort **[4].**
- Available data suggest that as many as 30–40% of these women are sufficiently bothered by symptoms to seek relief.

Oral contraceptives and PMS:
- Observational studies in the 60s and 70s suggested that premenstrual complaints were reduced in many oral contraceptive users **[468]** although symptoms be exacerbated by OC use in some women.
- The first systematic studies to examine the effects of the OC on PMS found little difference in PMS symptoms between OC users and nonusers **[36],** nor were there significant differences between agents with differing progestational potencies **[13].** Monophasic and triphasic preparations showed similar rates of symptomatology **[213].**
- Until now no oral contraceptive has been approved worldwide for treatment of PMS, but the off-label use of long-cycle, combined oral contraceptives is offering some relief **[392, 709].** Nevertheless, controlled clinical trials are necessary.
- For additional information about treatment option of PMS see **[286].**

Premenstrual dysphoric disorder (PMDD)
Definition: Premenstrual dysphoric disorder (PMDD) is a form of PMS sufficiently severe to carry its own DSM-IV diagnosis; it is typically treated with antidepressants.
Oral contraceptives and PMDD:
- The progestin drospirenone is a derivative of spironolactone that binds to aldosterone receptors, causing excretion of excess sodium and water in exchange for potassium, thus reducing bloating, breast tenderness, and weight gain. Thus drospirenone-containing OCs may be expected to have a beneficial effect on the physical symptoms of PMS and PMDD.
- OC preparation containing drospirenone with diuretic properties has undergone the most rigorous testing in normal women and women with strictly defined PMDD. Though the evidence supporting a role for fluid retention as an etiologic component of PMS is lacking **[175]** many women are distressed by feelings of bloating and edema. In an RCT involving 82 women with PMDD, patients treated with the drospirenone and EE oral contraceptive had fewer luteal phase symptoms than those treated with placebo, although between group differences were statistically significant only for appetite, acne and food cravings, $p = 0.027$ **[194].** The drospirenone OC offers relief for some physical and some psychological manifestations of PMS and may improve health-related quality of life **[55, 195].** For prolonged treatment of patients with moderate symptoms, OC is preferable, more acceptable and cheaper than selective serotonin reuptake inhibitors, but in the case of severe symptoms associated with PMDD more specific treatment is required.

Summary:
Premenstrual syndrome (PMS): During the reproductive years, up to 80–90% of menstruating women will experience symptoms (breast pain, bloating, acne and constipation) that forewarn them of impending menstruation, so-called premenstrual syndrome (PMS) Available data suggest that as many as 30–40% of these women are sufficiently bothered by symptoms to seek relief.
Until now no oral contraceptive has been approved worldwide for treatment of PMS, but the off-label use of long-cycle, combined oral contraceptives is offering some relief **[395, 709].** Nevertheless, controlled clinical trials are necessary.

Premenstrual dysphoric disorder (PMDD): Premenstrual dysphoric disorder (PMDD) is a form of PMS sufficiently severe to receive its own DSM-IV classification.
The only OC with approval only in the US for treating PMDD is the 24+4 regimen with drospirenone.
For additional information about treatment options for PMS see **[286].**

2.3.2.5. Acne
Disease: Acne is a common skin condition related to an increased rate of sebum production, predominantly controlled by androgenic sex hormones.
Prevalence: Acne affects up to 40–90% of adolescents and teens **[371, 413],** 10% of adult women **[541, 655]** and can persist into adulthood in 53% of women **[112, 212].** Women are more likely to report having acne and to have it persist into later years with a mean duration in affected adult women of 20 years **[594].**
Etiology: Androgens are related to the development of acne, whereas many combined oral contraceptive pills, and in particular those which contain anti-androgens are clearly beneficial for the treatment of acne.

Treatment options:
Dermatological treatment options: According to the guidelines of the German Dermatological Society **[478],** the first choice treatments for acute acne in men and women according to acne type are as follows:

- Comedonal acne: topical retinoids.
- Mild papular/pustular acne: fixed or sequential combinations of BPO (benzoyl peroxide) and topical retinoids or topical antibiotics.
- Moderate papular/pustular acne: oral antibiotics plus BPO or topical retinoids, or in a fixed combination.
- Acne papulo-pustulosa nodosa and acne conglobata: oral antibiotics plus topical retinoids plus BPO or oral isotretinoin.
- For maintenance treatment: topical retinoids or its combination with BPO. Particular attention should be paid to compliance and quality of life.

Note: According to this guideline combined oral contraceptives, either alone or in combination, are no first line therapy for any type of acne. This, however, does not reflect the situation observed in gynecological outpatients in clinical practice.

Global guidelines for acne have been summarized by the **Geneva Medical Foundation [310]**.

Combined oral contraceptives

– Various studies have proven the efficacy of COC, especially those containing anti-androgenic progestins, for the primary treatment of acne vulgaris.
– **Mechanism:** Combined OCs may prevent acne through several mechanisms:
  - COCs suppress luteinizing hormone (LH), and cause decreased production of androgens, including free testosterone.
  - The estrogen component of COC increases SHBG (sex hormone binding globulin) levels and decreases serum free testosterone by binding more circulating testosterone.
  - Anti-androgenic progestins block androgen receptors and inhibit the enzyme 5alpha-reductase that converts testosterone to dihydrotestosterone in the hair follicles and skin **[25]**.
– **Progestins:** The effect of OCs on acne depends on their progestin activity. Theoretically progestin dominance would exacerbate acne, whereas estrogen dominance would exert an anti-androgenic effect on the sebaceous glands. Anti-androgenic progestins such as cyproterone acetate, chlormadinone acetate, diengest, and drospirenone produce the best therapeutical results as shown in comparative studies in the treatment of acne in women:
  - Cyproterone acetate **[115, 173, 197, 465]**
  - Chlormadinone acetate **[726]**
  - Dienogest **[185, 467, 502]**
  - Drospirenone **[678]**
  - Norgestimate **[541]**

  but also
  - Desogestrel **[696]**
  - Gestodene **[515]**
  - Norethindrone **[438]**
– In a Cochrane review **Arowojolu et al. (2009) [26]** searched for randomized placebo-controlled trials comparing the effects of COCs on acne with those of other therapies.
  - The search yielded 25 trials: 7 placebo-controlled trials made 4 different comparisons, 17 trials made 13 comparisons between 2 different COC regimens, and 1 additional trial compared a COC to an antibiotic. COCs reduced acne lesion counts, severity grades and self-assessed acne compared to placebo. Differences in the comparative effectiveness of COCs containing varying progestin types and dosages, were less clear, however.
  - COCs that contained chlormadinone acetate or cyproterone acetate improved acne better than levonorgestrel, although this apparent advantage was based on limited data.
  - A COC with cyproterone acetate might result in better acne outcomes than one with desogestrel; however, the three studies comparing these COCs produced conflicting results.
  - Likewise, levonorgestrel showed a slight improvement over desogestrel in treating acne in one trial, but a second trial found that the COC groups were similar.
– In conclusion the authors found that **four COCs** (levonorgegestrel **[420, 655]** norethindrone **[438]**, norgestimate **[430, 541]** drospirenone **[378, 439]** evaluated in placebo-controlled trials are effective in reducing inflammatory and non-inflammatory facial acne lesions. No significant differences were found between COC types in their effectiveness for treating acne. How COCs compare to alternative acne treatments is unknown since limited data were available regarding this question.

– **Drospirenone:**
  - **21+7 regimen:** A number of trials evaluated drospirenone-containing OCs for the treatment of acne:
    Van Vloten et al (2002) [678] compared 30 µg EE/3 mg drospirenone (Yasmin) to a combined OC containing 35 µg EE/2 mg cyproterone (not available in the U.S., but used elsewhere for contraception/acne treatment). Yasmin produced a greater decrease in median total acne lesion count after 9 cycles as compared to the latter product (63% and 59 %, respectively).

    In a double-blind study, **Thorneycroft et al. (2004) [656]** compared the efficacy and tolerability of a combined oral contraceptive containing 30 µg EE and 3 mg drospirenone (EE/DRSP; Yasmin) with a triphasic preparation containing 35 µg EE and 0.180, 0.215, 0.250 mg norgestimate (EE/NGM; Pramino, also known as Ortho Tri-Cyclen) in the treatment of acne vulgaris. The preparation containing EE/DRSP was superior to EE/NGM in reducing the total lesion count (–3.3% in favor of EE/DRSP [95% CI, –6.5 to –0.1; p = 0.020]) and for the investigators' assessment of the therapeutic effect on facial acne (+3.6% in favor of EE/DRSP [95% CI, 0.8 to 6.3; p = 0.006]). The 2 preparations were comparable in reducing the inflammatory lesion count. In conclusion, the combined oral contraceptive EE/DRSP provides an effective treatment option in women with mild to moderate acne.
  - **24+4 regimen:** According to two multicenter, double blind, randomized, placebo-controlled studies **[439],** 889 subjects, ages 14 to 45 years, with moderate acne received drospirenone/ethinyl estradiol (YAZ®) or placebo for six 28 day cycles **[322].** The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a "clear " or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) scale on day 15 of cycle 6. YAZ® was superior to placebo in the mean percent change from baseline on all 3 primary acne efficacy measures and the probability that skin was "clear" or "almost clear" on an investigator-rated global scale.

– **Dosages and regimen:** The dosage of EE (20–50 µg) in the OC and the regimen (monophasic, triphasic, 21+7, 24+4) followed are less relevant than the type of progestin used.
– **Management of acne treatment:** For management of mild to moderate acne in women, the combination of

OCs with topical medications such as retinoids and antibacterial agents in standard clinical practice is likely to be successful. Such combination therapy should lead to more rapid and greater improvement given the synergistic mechanisms of these different treatments. Future studies are needed to evaluate the outcomes of such combination therapy **[636].**

Summary:

Prevalence: Acne is a common skin condition related to an increased rate of sebum production, predominantly controlled by androgenic sex hormones. It affects up to 40–90% of adolescents and teens **[371, 413],** 10% of adult women **[541, 655]** and can persist into adulthood in 53% of women **[112, 212].** Women are more likely to report having acne and to have it persist into later years with a mean duration in affected adult women of 20 years **[594].**

Combined oral contraceptives

- **Mode of action:** COCs suppress luteinizing hormone (LH) and cause decreased production of androgens, including free testosterone. The estrogen component of COCs increases sex hormone binding globuline (SHBG) levels and decreases serum free testosterone by binding more circulating testosterone. Antiandrogenic progestins block androgen receptors and inhibit the enzyme 5a-reductase, which converts testosterone to dihydrotestosterone in the hair follicles and skin.
- **Anti-androgenic COC:** COCs with progestins with anti-androgenic activity (cyproterone acetate, chlormadinone acetate, dienogest, drosprirenone, norgestimate [only US approval for acne]) are highly effective and lead to an improvement of acne vulgaris lesions in 80% after 3 months and > 90% after 6–12 months treatment.
- A recent systematic review reported on six placebo-controlled trials (norethindrone, levonorgestrel, norgestimate, drospirenone) that evaluated oral contraceptive treatment for women with moderate to severe acne **Arowojolu et al. (2009) [26]** showed that OCs reduced acne lesion counts and severity as assessed by clinicians and the patients themselves.
- **Dosages and regimen:** The dosage of EE (20–50 µg) in the OC and the regimen (monophasic, triphasic, 21+7, 24+4) followed are less relevant than the type of progestin used.
- **VTE–risk:** When using COC with cyproterone acetate a higher possible rate of venous thromboembolism must be considered **[422, 674].**
- For management of mild to moderate acne in women, the combination of OCs with topical medications such as retinoids and antibacterial agents in standard clinical practice is likely to be successful. Such combination therapy should lead to more rapid and greater improvement given the synergistic mechanisms of these different treatments. Future studies are needed to evaluate the outcomes of such combination therapy **[636].**

Dermatological treatment options:

- According to the guidelines of the German Dermatological Society **[478]** the first choice treatments for acne do not include oral contraceptives even with anti-androgens.
- **Global guidelines** for acne have been summarized by the **Geneva Medical Foundation [310]**.

2.3.2.6. Benign Breast Disease

Even though the use of combined oral contraceptives is associated with an increased risk of breast cancer **[647]** the risk of benign breast disease (BBD) may be reduced **[72, 366].**

There is still no consensus on the associated risk of breast cancer and benign breast diseases, exept benign tumors with atypical change.

Definition of the disease: The term benign breast disease describes a wide range of non-malignant disorders of the breast. Despite numerous attempts, there is no internationally agreed classification of these breast disorders. The only genuine point of agreement seems to be that the term excludes malignant breast pathology. The two main conditions of BBD are fibrocystic disease and fibroadenoma **[209].**

Fibrocystic breast disease is an ill-defined condition characterized by the presence of palpable lumps in the breast. They usually present with pain and tenderness of the breast. The lumps and the related symptoms fluctuate with the menstrual cycle. The maximum incidence is seen among women in their early forties, the symptoms tend to worsen until the menopause. The histological changes affect the breast epithelium, which often contains micro- or macrocysts and adenosis with the development of new lobular or ductal structures. The epithelium may display metaplasia into apocrine epithelium such as found in sweat glands, or hyperplasia, with or without atypia.

The benign breast tumor **fibroadenoma** arises from the single breast lobule, usually as a well-defined mass containing an epithelial and a stromal component. Fibroadenomas appear to result from hyperplasia and distortion originating in a single lobule involving normal epithelial components and abnormal stromal components. The age of maximum incidence is between women aged 20–25 years. The histological changes are confined to the stroma while the epithelial cells are normal.

Prevalence: The cumulative incidence of biopsy-proven BBD estimated from epidemiological studies is 10–20% **[107, 183, 354, 494].**

Treatment options:

- A number of studies published in the 1970s and 1980s **[209, 456]** suggested that OCs used in the 1970s exert a protective effect against benign breast disease. In many of these studies, however, the diagnosis of BBD was not confirmed by biopsy but based on self-reporting. The three more recent studies have demonstrated somewhat inconclusive results. One small prospective study of OC users in Greece suggested a reduced incidence of BBD diagnosed by mammography and ultrasound **[666]**. One hospital-based case-control study from France **[89]** of women with BBD confirmed by biopsy demonstrated a reduced risk among OC users. This result was restricted to non-proliferative disease and only to pill use before the first full term pregnancy. In contrast a case-cohort analysis within a large cohort of Canadian women undergoing breast screening and biopsy **[552]** showed an inverse relationship between OC use and proliferative BBD without atypical cells. In this study, there was no association between BBD with atypical cells and OC use. Modern oral contraceptive pills contain lower doses of both, estrogen and progestin, than those used in the 1970s. The risk reduction for BBD may be diminished or even lost with lower doses of steroids.

– All the research suggesting a beneficial effect of the combined pill on benign breast disease emerges from observational studies with potential bias. One form of bias may be the underestimation and underdiagnosis of the BBD. It is well known that BBD is more common among better-educated women of higher socioeconomic status leading to a selection bias **[209].** The finding that BBD is less common in obese women suggests a detection bias **[209].** At least one study demonstrated a prescribing bias **[348]** suggesting that women with a history of BBD are less likely to be prescribed oral contraceptives. In addition to the multiple problems with bias, the studies available suffer from rather poor quality, small numbers of cases, and variability in the definition of the disease itself. On the other hand there is good evidence that OC use stimulates epithelial cell proliferation in the breast **[17, 344]** casting some doubt on the biological plausibility of a protective effect on benign disease.

Summary:
Disease: BBD is a general term, which incorporates a wide spectrum of non-malignant disorders of the breast tissue.
Incidence: The cumulative incidence of biopsy-proven BBD as estimated from epidemiological studies is 10–20% **[107, 183, 354, 494].**

Combined oral contraceptives:
– Although there is some evidence that high-dose oral contraceptives may reduce the risk of BBD, there are significant problems with bias, study design and interpretation **[71].**
– An increased risk of BBD has never been demonstrated, whereas the beneficial effects of oral contraceptives on the breast tissue may be overestimated.

2.3.2.7. Uterine Fibroids/Leiomyomas of the Uterus
Definition of the disease: Uterine fibroids or leiomyomas are non-malignant tumors that originate from the myometrium. They present as single solid tumors or more often in multitude. Fibroids can cause different symptoms due to their location in the uterine wall (submucosal, intramural or subserosal).
Prevalence: In 10–20% of all women leiomyomas of the uterus can be diagnosed, i.e. 13.6 million people in the USA. (**Source statistic for calculation:** "10–20% women [NWHIC]"). Uterine leiomyomas occur in 20% to 25% of women of reproductive age and reportedly affect three times as many black women as white women. The risk of malignant transformation of a leiomyoma into a leiomyosarcoma is only 0.1% or less **[531].**

Etiology: The clear etiology of uterine leiomyomas is still unknown, but steroid hormones, including estrogen and progesterone, and several growth factors, including epidermal growth factor, have been implicated as regulators of the growth of leiomyomas. They typically develop after menarche and regress after menopause, implicating estrogen as a promoter of leiomyoma growth **[531].**
Effect of COC: It has been suggested that OC use is associated with a reduced risk of fibroids **[503, 564].** However, in these early studies, the diagnosis was limited to women with surgical confirmation of fibroids. Two large studies from the USA in which fibroids were diagnosed either at hysterectomy or by ultrasound **[451, 720]** suggest no clear pattern of association, although both report a weak association between fibroids and use of the combined pill before the age of 17. A smaller study of 335 randomly selected Swedish women aged 25–40 reported a rather low prevalence of (ultrasound detected) fibroids (5.4%; 95% CI 3.0–7.8%) in contrast to earlier studies, which suggested a prevalence of 20 to 25% in women over age 30 **[56]**. Although the sample size was too small to detect an effect of the OC on fibroids, uterine size was significantly smaller among women taking a combined oral contraceptive pill than in women with natural cycles. The authors suggest that the high prevalence of OC use might explain the low prevalence of fibroids in their study (selection bias).

Summary:
– Uterine leiomyomas occur in 20–25% of women of reproductive age and affect 3 times as many black women as white women.
– The etiology of uterine leiomyomas is unknown, but steroid hormones, including estrogen and progesterone, and several growth factors, including epidermal growth factor, have been implicated as regulators of leiomyoma growth. Leiomyomas typically develop after menarche and regress after menopause, implicating estrogen as a promoter of leiomyoma growth **[531].**
– In earlier studies it has been suggested that OC use is associated with a reduced risk of fibroids **[503, 564].** However, in these early studies, the diagnosis was limited to women with surgical confirmation of fibroids.
– The postulated beneficial effect of OC on growth inhibition of fibroids needs to be proven for modern low dose formulations and regimens.

2.3.2.8. Benign Ovarian Tumours
Definition of the disease: Benign tumors of the ovaries represent a complex entity of non-malignant ovarian tumors (e.g. functional and dysfunctional ovarian cysts, serous and mucinous adenoma, teratoma and endometrioma).
Incidence and Prevalence: [313]
– Ovarian cysts occur in 30% of females with regular menses, 50% of females with irregular menses, and 6% of postmenopausal females
– Polycystic ovary syndrome occurs in approximately10% of women in industrialized countries.
– The majority of ovarian cysts are benign (non-cancerous).
– The annual incidence of ovarian cancer is 15 cases per 100,000 women.

Treatment options:
Combined oral contraceptives:
– The use of a combined oral contraceptive is associated with a reduced risk of ovarian cancer. By analogy it has been suggested that the risk of benign ovarian tumors is also reduced.
– **Current-users:** A number of studies have shown a theoretically suspected reduced risk of functional ovarian cysts while taking oral contraceptives since ovulation is inhibited **[261].**
– **Ever-users:** However, a large case–control study from the USA demonstrated that use of the combined pill at any time was associated with a decreased risk of non-follicular benign tumors, including serous and mucinous adenoma, teratoma and endometrioma (OR 0.79, 95% CI 0.6–1.05) **[704].** The reduction in risk was associated with duration of use.
– Although OC use is associated with a lower prevalence of benign ovarian

tumors, prospective studies have failed to show that the use of OC can prevent the development of ovarian cysts or treat existing ovarian cysts **[650].**

Summary:

Disease: Various entities of benign ovarian tumors can be differentiated histologically and due to diverse etiologies.

Incidence and Prevalence [313]: Ovarian cysts occur in 30% of females with regular menses, 50% of females with irregular menses, and 6% of postmenopausal females**.** Polycystic ovary syndrome occurs in approximately 10% of women of reproductive age ("Polycystic Ovary Syndrome"). The majority of ovarian cysts are benign (non-cancerous).

Combined oral contraceptives:

– OC use has been associated with a lower prevalence of benign ovarian tumors **[566]** mainly due to an inhibition of ovulation.

– **Reduced risk in ever-users:** A large case-control study from the USA demonstrated that ever-use of the combined OC was associated with a decreased risk of non-follicular benign tumors, including serous and mucinous adenoma, teratoma and endometrioma (OR 0.79, 95% CI 0.6–1.05) **[704].** The reduction in risk was associated with duration of use.

– **No prevention or treatment of ovarian cysts:** Clinical studies have failed to show that the use of OC can prevent the development of ovarian cysts or treat existing ovarian cysts **[650].**

2.3.2.9. Sexually Transmitted Infections

Referring to an apparently increasing rate of sexually transmitted infections (STIs) **[62]** several European governments have expressed concerns about the current poor state of sexual health **[215]**.

Sexually transmitted infections include more than 25 diseases transmitted via sexual activity i.e. chlamydia, HIV-infection, hepatitis, gonorrhea, syphilis, herpes genitalis, human papilloma virus, candidiasis and trichomoniasis.

In the following passage the effect of combined OC on chlamydial infections, hospital admission and late sequelae due to pelvic inflammatory disease will be analyzed.

Chlamydia

Prevalence:

– Currently, the most prevalent infection in Western Europe is Chlamydia trachomatis (CT). The prevalence of Chlamydia trachomatis infection among asymptomatic European women ranges from 1.7 to 17%, depending on the setting **[714].**

– The difference in prevalence is determined mainly by age, rather than by clinical setting. The highest prevalence is detected in teenagers and the lowest in women over the age of 30.

– Prevalence rates may be as high in men, although not necessarily following the identical age distribution. This aspect is one of the reasons why screening initiatives solely focusing on women are questioned **[180].**

Combined oral contraceptives:

– The data in hand about Chlamydia trachomatis infection are very inhomogenous and of varying quality. Some studies were cross-sectional in design, some used inappropriate test methods for chlamydial infection and most failed to control for potential confounding factors such as sexual behavior and age. Behavior modification due to sexual education led to a steadily increasing use of contraceptives to prevent pregnancy and STIs. Nevertheless the high prevalence of chlamydial and HPV infections and the careless attitude towards risks of STI, especially HIV-infection, in young women are alarming.

– A recent observational study involving 814 women in the USA who were using different methods of contraceptives (oral contraceptives, depot gestogens, or non-hormonal methods of contraception) documented sexual behavior **[472].** The authors concluded that the use of OC was not significantly associated with an increased risk of chlamydial infection or gonorrhea after adjusting for other risk factors (HR 1.5; 0.6-3.5). No association was found between the presence of cervical ectopy and infection either with oral contraceptive or injectable contraceptive use. The risk of acquiring Chlamydia trachomatis infection during 1 year of follow-up was 1.9-fold higher in oral contraceptive users (95% CI 0.7, 4.8), compared with users of non-hormonal contraceptive methods after adjusting for sexual behavior. Although this adjusted risk is not significant, it corresponds to the risk estimates from the earlier studies and underlines the need for promoting barrier methods of contraception **[472].** This change in attitude towards prevention of pregnancy and sexual transmitted infection is promoted by the term „double dutch" – dual protection with barrier methods and hormonal contraception **[77].**

It seems to be clear that prevention of cervical infection is not a non-contraceptive benefit from OC use. The development and implementation of routine HPV-immunisation in girls and young women complements the preventive strategies.

Pelvic inflammatory disease

– Although earlier studies suggested a decrease in hospitalizations for pelvic infection, in other studies oral contraceptive use was associated with an increased risk of chlamydial infection and gonorrhea **[120].**

Summary:

– Oral hormonal contraceptives prevent pregnancy but do not directly protect against sexually transmitted diseases.

– Anyhow the cervical mucus and the cervical barrier for ascending sperms and infections is altered by OCs and the risk of pelvic inflammatory diseases is decreased.

– The epidemiological data on this aspect are not conclusive. Although earlier studies suggested a decrease in hospitalizations for pelvic infection, in other studies oral contraceptive use was associated with an increased risk of chlamydial infection and gonorrhea **[120].** The quality of studies is inhomogenous and mostly poor. An observational study involving 814 women with different contraceptive methods in the USA could not prove the risk reduction for chlamydial infection **[472].** A retrospective analysis of 563 women with diagnosed PID did not give a conclusive association either between OC use or barrier methods **[480].**

– The protective effect on the development of pelvic inflammatory disease including hospitalizations due to OC use was described in publications and seemed to be independent of the dos-

age of estrogen and type of estrogen **[495].**
– Only the condom has been shown to have a protective effect [78].

2.3.2.10. Cancer

Oral contraceptives are associated with a risk reduction for ovarian, endometrial and perhaps colorectal cancer. The inverse relation between OC use and ovarian and endometrial cancers is one of the most consistent epidemiological findings and in terms of public health, it is one of the most important examples of large-scale chemopreventive intervention **[335, 402].**

The following analysis is based on the **IARC monography (1999) [278]** and extended reviews: **Cibula et al. (2010) [96]**, **Mueck et al. (2010) [474], The ESHRE Capri Workshop Group (2005) [649]** with kind permission by the authors.

The effect of COC on breast and cervical cancer is described in section discussing serious adverse events.

2.3.2.11. Ovarian Cancer

Incidence:
– Second most frequent genital malignancy of women. The worldwide incidence for ovarian cancer is documented as 6,6/100.000, whereas the highest incidence is seen in Europe with 13/100,000, in particular in Western Europe (varying widely between 7–19/100,000 women) **[275]**.
– In high-incidence areas, the lifetime risk of developing ovarian cancer is estimated to be at 1–2%.
– **US National Cancer Institute (SEER) [284]:** From 2003–2007, the median age at diagnosis for ovarian cancer was 63 years. About 1.3% are diagnosed under the age of 20 years; 3.5% between 20 and 34; 7.4% between 35 and 44; 19.2% between 45 and 54; 22.9% between 55 and 64; 19.5% between 65 and 74; 18.4% between 75 and 84 and 7.8% at 85+ years. The age-adjusted incidence rate of ovarian cancer was 12.9 per 100,000 women per year. These rates are based on cases diagnosed in 2003–2007 from 17 SEER geographic areas.
– Successful general screening programs for ovarian cancer do not exist up to now and therapeutic options are still limited **[123].**

Histology: Histologically, ovarian cancer is divided into different subgroups such as serous, mucinous, endometrioid, clear cell carcinoma, Brenner tumor, and undifferentiated carcinomas **[587].** According to this review serous carcinoma is the most common type of ovarian cancer; it is usually associated with peritoneal metastases and poor survival except for meticulously staged patients with tumors confined to the ovaries. Endometrioid and clear cell carcinomas account for most non-serous carcinomas and more often present with low-stage disease; survival for the various cell types is similar when stratified by stage. Borderline ovarian tumors can be subdivided into benign and malignant neoplasms. Women with typical serous borderline tumors, atypical proliferative serous tumors, constitute most of these patients and have virtually 100% survival, unless invasive peritoneal implants are present. Micropapillary serous carcinomas, a less common variant, also called serous borderline tumor with a micropapillary pattern, and tumors with invasive implants behave similarly to low-grade invasive carcinomas.

Risk factors (American Cancer Society) [10] for ovarian cancer include age, obesity, reproductive history, gynecologic surgery, fertility drugs, androgens, estrogen therapy and hormone therapy, family history of ovarian cancer, breast cancer, or colorectal cancer, personal history of breast cancer, talcum powder, diet, analgesics, smoking, and alcohol use.

A high-risk situation is present in all cases with genetic predisposition, namely BRCA-1 and 2 (approx. 10% of all cases).

According to the **Holden Comprehensive Cancer Center, Cancer Information Service (2003) [257],** protective factors for the development of ovarian cancer areoral contraceptives, childbearing, breast-feeding, tubal ligation and hysterectomy.

Risk factors for ovarian cancer are summarized in the publication of **Riman et al. (2001).**

Mortality: Most cases of epithelial ovarian cancer (EOC), which constitute 80–90% of ovarian malignancies, are detected at an advanced stage. The prognosis is poor. The annual age adjusted mortality rate of ovarian cancer lies at about 9/100,000; the overall 5-year survival rate of women with ovarian cancer was 45% (1996–2003) **[349].**

For ovarian cancer, the 30–50% reduced mortality rates in countries where OC had long been extensively used correspond to 3000–5000 deaths from ovarian cancer avoided in Europe **[403, 418].**
Mortality trends: In developed countries young women showed a substantial decline in ovarian cancer mortality over the last few decades. Cohort analysis of trends in mortality from ovarian cancer showed that women born after 1920 – i.e. from the generations who had used OCs – had reduced ovarian cancer rates, and the downwards trend was greatest in countries where oral contraceptives have been more widely utilized **[335, 404].**

Combined oral contraceptives and risk of ovarian cancer

The first reports about an association between ovarian cancer and oral contraceptives were published by **Newhouse et al. (1977) [483].**

The **Collaborative Group on Epidemiological Studies of Ovarian Cancer (2008) [109]** performed a metaanalysis of data including 23,257 women with ovarian cancer and 87,303 controls from 45 epidemiological studies in 21 countries. The relative risk of ovarian cancer in relation to oral contraceptive use was estimated and stratified by study, age, parity, and hysterectomy. Overall 7,308 (31%) cases and 32,717 (37%) controls had ever used oral contraceptives, for average durations among users of 4.4 and 5.0 years, respectively. The median year of cancer diagnosis was 1993, when the patient had an average age of 56 years.

– **Risk reduction by time of OC use:** The longer the duration of oral contraceptive use, the greater the reduction in ovarian cancer risk ($p < 0.0001$).
– **Persistence of reduced risk after OC withdrawal:** This reduction in risk persisted for more than 30 years after oral contraceptive use was ceased but became attenuated over time – the proportional risk reductions per 5 years of use were:
  - 29% (95% CI 23–34%) for OC use stopped less than 10 years ago

- 19% (14–24%) for OC use stopped 10–19 years ago
- and 15% (9–21%) for use stopped 20–29 years previously.

– **Estrogen dosage:** OC use during the 1960s, 1970s, and 1980s was associated with similar proportional risk reductions, although typical estrogen doses in the 1960s were more than twice those in the 1980s and later.
– **Amount or type of hormones in OCs:** One of the studies used in the Harvard analysis, the **Cancer and Steroid Hormone Study 1997 (CASH) [646],** found that the reduction in ovarian cancer risk was the same, regardless of type or amount of estrogen or progestin in the COC**.** A more recent analysis of data from the CASH study, however, indicated that OC formulations with high levels of progestin reduced ovarian cancer risk more than preparations with low progestin levels **[578].** In another recent study, the Steroid Hormones and Reproductions study (SHARE) **[216],** researchers investigated new, lower–dose progestins that have varying androgenic properties (testosterone–like effects). They found no difference in ovarian cancer risk between androgenic and non–androgenic COC.
– **Histology:** The incidence of mucinous tumors (12% of the all ovarian cancers) is affected by oral contraceptives minimally. Apart from this entity the proportional risk reduction did not vary between different histological types **[405].**
– **Total reduction of risk and mortality:** In high-income countries, 10 years use of oral contraceptives was estimated to reduce ovarian cancer incidence before age of 75 from 1.2–0.8 per 100 users and mortality from 0.7 to 0.5 per 100; for every 5000 woman-years of use, about two ovarian cancers and one death from the disease before age 75 are prevented **[48].**
– **Interpretation:**
  - Use of oral contraceptives confers long-term protection against ovarian cancer.
  - These findings suggest that oral contraceptives have already prevented thousands of ovarian cancers and deaths from this malignancy. It can be assumed, that over the next few decades the number of cancers prevented by OC will rise to at least 30,000 cases per year **[48].**

Summary:

Incidence: Ovarian cancer is the second most frequent genital tumor entity of women. In high-incidence areas, the lifetime risk of developing ovarian cancer is about 1–2%.

Histology: Histologically, ovarian cancer is divided into different subgroups such as serous, mucinous, endometrioid, clear cell, Brenner, and undifferentiated carcinomas **[587].** Most cases of epithelial ovarian cancer (EOC), which constitute 80–90% of ovarian malignancies, are detected at an advanced stage, and the prognosis is poor**.**

Combined oral contraceptives:

– Since combined oral contraceptives were first licensed nearly 50 years ago, birth control pills containing estrogen have prevented about 200,000 cases of ovarian cancer world-wide, this estimation was published in *The Lancet*. Furthermore, without oral contraceptives, half of these women would have died of ovarian cancer **[166, 295].**
– The **Collaborative Group on Epidemiological Studies of Ovarian Cancer (2008)[109]** did a comprehensive meta–analysis based on prospective and case–control data from 45 epidemiological studies in 21 countries, mostly in Europe and the United States. According to the **National Cancer Institute, US [295]** the results are as follows:
  - **Ever-users:** Women who had taken OCs were 27% less likely to develop ovarian cancer. The studies included 23,257 women with ovarian cancer, 31% of whom had taken OCs; of the 87,303 controls, 37% had taken OCs.
  - **Duration of use:** The longer the duration of OC use, the greater is the ovarian cancer risk reduction of about 20% for each five years of use.
  - **Protective effect in past users:** After cessation of the OC intake the risk reduction for ovarian cancer endured. For each five years of OC use the risk of developing ovarian cancer was reduced by 29% in the first 10 years after cessation. The risk reduction was still significant even though smaller (19%) for years 10–20, and smaller still (15%) 20–29 years after discontinuation of the OC.
  - **Histology:** OCs seem to protect against nearly all types of epithelial and nonepithelial tumors, with the possible exception of mucinous ovarian cancer (which accounted for only 12% of cases studied in the metaanalysis).
  - **Estrogen-dosage:** The ***Lancet* editorial [166]** points out "the benefits of oral contraceptives are independent of the preparation [estrogen dose], and vary little by ethnic origin, parity, family history of breast cancer, body–mass index, and use of hormone replacement therapy."

BRCA1/2 mutations: According to a recent metaanalysis of **Iodice et al. (2010) [343]** OCs reduce the risk of ovarian cancer without any evidence that recent formulations increase the risk of breast cancer in women with a germline mutation in BRCA1 or BRCA2.

For more information see **National Cancer Institute (US) [290, 291].**

Reviews and metaanalysis:

– **IACR Monographs on the Evaluation of Carcinogenic Risks to Humans (2009) [278]**
– **Metaanalysis: Collaborative Group on Epidemiological Studies of Ovarian Cancer (2008) [109]**
– **Extended reviews: Cibula et al. (2010) [96]**

Further references:

– The ESHRE Capri Workshop Group (2005) **[649].**
– National Cancer Institute (US) **[295].**

2.3.2.12 Endometrial Cancer

Disease: Uterine Cancer with the origin in the endometrium (see histology).

Histology and hormonal dependency: Endometrial cancers are classified into two major histopathological entities, which are based upon light microscopic appearance, clinical behavior, and epidemiology **[325]**.

- **Type I endometrial cancers,** which have endometrioid histology (adenocarcinoma), are associated with chronic exposure to estrogen unopposed by a progestin, and are often preceded by premalignant disease (endometrial hyperplasia).

- **Type II endometrial cancers** have non-endometrioid histology, usually papillary serous or clear cell histology, and an aggressive clinical course. Hormonal risk factors have not been identified, and there is no identifiable premalignant phase.

Most endometrial cancers are adenocarcinomas **[294].**

Incidence:

– **US National Cancer Institute (SEER) [283]:** From 2003–2007, the median age at diagnosis for cancer of the corpus and uterus was 62 years of age. There was no diagnoses under age 20; 1.6% of patients were diagnosed between 20 and 34; 6.2% between 35 and 44; 19.2% between 45 and 54; 30.9% between 55 and 64; 22.2% between 65 and 74; 15.0% between 75 and 84; and 5.0% 85+ years of age.

– The age-adjusted incidence rate was 23.5 per 100,000 women per year. These rates are based on cases diagnosed in 2003–2007 from 17 SEER geographic areas.

– **Germany:** The local incidence of endometrial carcinoma is 24–25 cases per 100,000 women years, the mean age of occurrence is 68 years at time of diagnosis; 75% of patients are postmenopausal. Only 5% of all women are diagnosed below age 40 years **[266].**

– **Mortality:** The overall mortality of endometrial cancer is low. The annual age adjusted cancer death rates of carcinoma of the uterus (including cervix and endometrium) is estimated at about 4/100,000 **[349].**

Risk factors [671]:

– **Increased risks** for endometrial cancer are elevated steroid hormone levels, estrogen therapy, high total number of menstrual cycles, obesity, tamoxifen, ovarian tumors, polycystic ovarian syndrome, increasing age, high caloric intake, diabetes, family history, breast or ovarian cancer, prior pelvic radiation therapy, endometrial hyperplasia.

– **Decreased risks** are higher number of pregnancies, use of an intrauterine device.

Estrogens are potential carcinogens for the human endometrium: A sequential oral contraceptive with a long unopposed estrogen phase (16 tablets containing 100 µg of EE) followed by 5 days of 100 µg EE and a weak progestin (25 mg of dimethisterone) was the OC with the trade name: Oracon™ **[276].** It was removed from the consumer market in the 1970s after an association with an increased risk for endometrial cancer had been detected **[702].** In addition it became obvious that unopposed postmenopausal estrogen therapy in non–hysterectomized patients led to an endometrial cancer. Four studies (one cohort study and three large case-control studies) reported an increased risk of endometrial cancer under estrogen replacement therapy **[139, 512, 593].** Three of these studies reported strong positive associations between estrogen replacement therapy and risk of endometrial cancer with increased length of estrogen use. See also **IACR report (1999) [338].**

Combined oral contraceptives: For endometrial cancer, the absolute risk reduction by OC intake is smaller and more uncertain than for ovarian cancer. The estimated reduced risk of endometrial cancer in OC users may correspond to 1.000–3.000 deaths per year avoided in Europe **[649].**

The first reports about association of endometrial cancer and oral contraceptives by **[433, 434, 596],** showed an increased incidence of endometrial cancer in users of a sequential oral contraceptive in the US (Oracon). The first studies demonstrating a decrease of endometrial cancer incidence were published by **Horwitz & Feinstein (1979) [264], Kaufman et al., (1980) [364].**

Meta-Analysis: A meta-analysis by the **IACR (1999) [338]** included three cohort and 16 case-control studies, which addressed the relationship between use of combined oral contraceptives and the risk of endometrial cancer. These studies consistently show:

– The **risk reduction** associated with OC use for endometrial cancer, estimated at about 50%.

– **Duration of use and persistence:** The reduction in risk is generally stronger the longer the oral contraceptives are used and persists for at least 10 years after cessation of use.

Furthermore recent studies and reviews added additional information:

– **Cancer mortality:** The RR of endometrial cancer death was 0.2 in the 30 years follow-up of the Oxford-FPA study **[689].**

– **Risk reduction in current users:** More than 15 case-control studies and at least five large cohort studies demonstrated a decrease of the risk of endometrial cancer of about 50% associated with the ever-use of OC **[96, 338, 404, 474].** The limited number of elderly women who had used OCs does not allow an accurate estimation of the protection afforded after long periods.

– **Risk reduction in past users:**

Duration of use and protection after COC withdrawal: Longer duration of use is associated with an increased protective effect. This protective effect seems to persist for up to 20 years after stopping of OC use.

Selected studies:

- A reduced risk was also found as a function of longer COC use (> 5 years) in a case-control study from Washington State **[695].**
- In a multicentric US study the OR was 0.3 for 15–19 years and 0.8 for ≥ 20 years since stopping OC use **[338, 402].**
- In a Swiss study **[417]** the RR of endometrial carcinoma was 0.4 for 10–19 years after stopping use, and 0.8 for ≥ 20 years.
- In a Swedish population-based national case–control study the RR was 0.2 for ≥ 10 years of use, and the subsequent use of hormone replacement therapy did not modify the long-term protective effect of previous OC use **[700].**

– **Progestin dosage:** COCs with higher progestin potency seem to be more effective for risk reduction of endometrial cancer **[474].**

– **Low dose formulations with new progestins:** Few data are available on the more recent, low-dose formulations.

– **OC regimen:** The beneficial effect seems to be independent of the composition of COC, i.e. dosage and type of progestin, combined with EE 30–50 µg/day **[474].**

– **Cautions:** COC, POPs as well as LNG-IUS use effectively reduce endometrial hyperplasia, but should only be used in exceptional cases in patients with or after endometrial cancer **[474].**

– The mechanism for the risk reduction of endometium cancer is still under

discussion. Alternative contraceptive methods to OC mechanisms to reduce endometrium cancer are also unknown.
– **Copper-IUD (Metaanalysis by Beining et al., 2008) [44]:** Non-hormonal IUD use may be associated with a decreased risk of endometrial cancer; however, the exact mechanism for this association is unclear.
– **IUD/LNG-IUS:** Clinical studies are necessary to clarify the risk **[474].**

Summary:
Histology:
Endometrial cancers are classified into two major histological entities, also based on clinical behavior and epidemiology **[325].**
- **Type I endometrial cancers** (adenocarcinoma) account for 70 to 80% of newly diagnosed cases of endometrial cancer in the United States. They are associated with chronic exposure to estrogen unopposed by a progestin, and are often preceded by premalignant disease (endometrial hyperplasia).
- **Type II endometrial cancers** have nonendometrioid histology.

Incidence: The absolute numbers of new cases and deaths from endometrial (uterine corpus) cancer in the United States in 2010 are for new cases: 43,470 and for deaths: 7,950 **[294].**

Combined oral contraceptives:
– A historical sequential oral contraceptive with a prolonged estrogen phase and a weak progestin (Oracon) caused endometrial cancer: The OC was withdrawn from the market in the early 1970s.
– At the level of the endometrium unopposed estrogens might be carcinogenic, lead to an endometrial hyperplasia, and finally to endometrial cancer.

Current users: 15 case-controlled trials and 5 cohort studies showed a risk reduction of endometrial cancer resulting from the use of COC of about 50%.

– **Past users:** The reduced risk of endometrial cancer seems to persist for at least 15–20 years after stopping use.
– **Composition:** The beneficial effect seems to be independent of the composition of COC, i.e. dosage and type of progestin, combined with EE 30–50 µg/day **[474].** Few data are available on the more recent, low-dose formulations with new progestins.

Reviews and metaanalysis:
– **IACR Monographs on the Evaluation of Carcinogenic Risks to Humans (2009) [278]**
– **Extended reviews: Grimes & Ecomony (1995) [217]**
Cibula et al. (2010) [96], Mueck et al. (2010) [474]

Further references:
– **The ESHRE Capri Workshop Group (2005) [649].**
– **National Cancer Institute (US) [294].**

2.3.2.13. Cancer of Colon and Rectum
Disease: Cancer of the colon and rectum.
Histology:
– Tumor histology will categorize the cancer into a particular type: (95% of all colon cancers), epidermoid carcinomas (0.52–0.29 %) or other rare types of cancer.
– The overall incidence of adenocarcinoma increases with age until after age 59, whereas epidermoid carcinoma, which is rare, occurs in individuals aged 30–49.

Incidence: The contemporary incidence of colorectal carcinoma in US is published regularly by the **SEER group [282].** The latest incidence rates for colorectal carcinoma in women are 41/100,000 (US).

Combined oral contraceptives:
– **Risk reduction:** OCs may also reduce colorectal cancer risk. In fact, a role of hormonal factors in colorectal carcinogenesis has long been suggested, starting from the observation of an excess of colorectal cancer in nuns **[193].** A favorable role of hormone replacement therapy in risk reduction of colorectal carcinoma has been suggested **[338, 402].**
– **Clinical studies:** Several studies have provided information on OC use and the risk of colorectal cancer. The **IARC (1999) [338]** reviewed four cohort studies, three of which showed risk reduction for ever OC use. 11 case-control studies did not show significantly elevated risks. Whereas a tendency towards a relative risk below control was found in nine studies, a significant risk reduction was found in two.
– **Metaanalysis by Fernandez et al. 2001) [181]:** This meta-analysis considered epidemiological studies on colorectal cancer published as full papers in English up to June 2000, including quantitative information on OC use.
- **Risk reduction in current users:** The pooled RR of colorectal cancer for OC ever use from 8 case–control studies was 0.81, the pooled estimate from 4 cohort studies was 0.84, and that from all studies combined was 0.82.
- **Duration of use:** Duration of use was, however, not associated with risk, since the overall RR of colorectal cancer was 0.78 for short duration of use and 0.85 for long duration. The pattern of risk was similar for colon and rectal cancer.
- **Risk reduction in past users:** The RR was 0.8 for ever OC use in a recent Swiss case-control study **[419].** Only two studies **[49, 182]** included information on recency of use. The results indicate that the risk reduction was stronger for women who had used OCs more recently.
- **Risk and type of OCs:** Little information was available on the type of OCs, furthermore no heterogeneous or systematic pattern of trends of use was observed.
- **Open questions:** A better understanding of any potential relation between OC use and colorectal cancer may help to make an informed choice of contraception **[338, 402].** Some aspects, however, remain undefined, including the risk profile in terms of duration and recency of use and a more adequate control for confounding factors. It is therefore not possible to provide any estimate of the potential impact of OC on colorectal cancer incidence and mortality on a population level.

Summary:
Incidence: The latest incidence rates for colorectal carcinoma in the US for women are 41/100,000 **[282].**
Combined oral contraceptives:
– **Risk reduction in current users:** The pooled RR of colorectal cancer

for OC ever use from 8 case-control studies was 0.81, the pooled estimate from 4 cohort studies was 0.84, and that from all studies combined was 0.82 **[181].**

– **Duration of use:** Duration of use was, however, not associated with risk, since the overall RR of colorectal cancer was 0.78 for short duration of use and 0.85 for long duration. The pattern of risk was similar for colon and rectal cancer.
– **Progestins, regimens and dosages:** No data are available for low dose formulations and various regimens including use of modern progestins.

Reviews and metaanalysis:
– **IACR-Monography (2009) [277]**
– **Extended reviews: Cibula et al. (2010) [96]**

Further references:
– **The ESHRE Capri Workshop Group (2005) [649].**

2.4. Adverse Events and Health Risks

2.4.1. Mild and Moderate Adverse Events

Adverse events occurring in current users of combined oral contraceptives include the following categories: severity by symptoms and targets, adverse events leading to discontinuation of COC use and common OC related, treatment-emergent, adverse reactions.

Adverse reactions leading to COC discontinuation:
– Number of women discontinued from the clinical trials due to an adverse reaction.
– The most frequent adverse reactions leading to discontinuation were metrorrhagia and irregular menstruation, acne, headache,migraine and weight increase.

Common treatment-emergent adverse reactions (> 2%):
– Headache (including migraine)
– Metrorrhagia and irregular menstruation
– Breast pain, discomfort or tenderness
– Nausea or vomiting
– Acne
– Increased weight.

Mild to moderate adverse events:
– Bleeding irregularities
– Emotional disorders
– Gallbladder disease
– Interference with laboratory tests
– Drug interactions
– Other conditions.

See also Review **Sabatini et al. (2011)** in this Supplement.

Reduction of substance-specific side effects of modern combined oral contraceptives [314]:

Changes in dosage, substances and regimens of combined oral contraceptives influence the clinical side effect profile.

A. Estrogen-related side effects
– Bloating, headache, nausea, mastalgia, leukorrhea, hypertension, melasma/telangiectasia
– Can be decreased by use of 20 µg EE pills **[554],** which still have good contraceptive efficacy or estrogen-free contraceptives with ovulation inhibition (i.e. desogestrel containing POP)

B. Progestin-related side effects
– Emotional instability, cyclic mastalgia, depression, fatigue, decreased libido, weight gain
– These side effects tend to decrease with continued use
– Can be decreased by reducing the amount of progestin, increasing the amount of estrogen per pill, changing the route of administration (patch, vaginal ring) or using the "long-cycle" as an "off-label" recommendation

Androgenic side effects
- Third generation progestins such as desogestrel, and also norgestimate (a more recent 2nd generation progestin) were developed and marketed as "less androgenic" progestins than older preparations
- In fact, studies of androgenicity of progestins are based on rat models, i.e. the binding of steroids to rat ventral prostate **[113].** These artificial rankings did not take into account dose adjustments or the differential effect of steroid hormones on different target tissues in humans. Hence they are not clearly clinically fundamental **[621, 657].**

Anti-androgenic effects
- All combination OCs are mildly anti-androgenic: OCs inhibit LH and thus decrease ovarian production of testosterone; estrogen leads to increased sex hormone binding globulin (SHBG) production by the liver, progestin decreases SHBG. The overall effect of OCs is an increase of SHBG.
  - 3rd generation progestins increase SHBG more than monophasic older preparations **[620].**
  - Increased SHBG leads to a decrease in free testosterone
  - 3rd generation progestins compete less for binding with SHBG
  - Some progestins (e.g. norgestimate) inhibitis 5α-reductase, leading to decreased DHT formation. Formation of DHT is necessary for any cellular effects on skin/hair follicles **[351].**
- COC with special anti-androgenic progestins (cyproterone acetate, chlormadinone acetate, dienogest, drospirenone, norgestimate) are more effective in the treatment of acne and hirsutism.
  Norgestimate and drospirenone have only been approved for the treatment of acne in the US.

2.4.2. Severe Adverse Events

In the following the review will focus on cardiovascular risk and cancer as severe adverse events listed in modern OC in patient information leaflets **[279]** in the section warnings and precautions:
– Thrombotic and other vascular events
– Carcinoma of the breasts and reproductive organs
– Liver disease
– High blood pressure
– Carbohydrate and lipid metabolic effects
– Headache

See also Review Sabatini et al. (2011) in the Part 2 of this Supplement.

2.4.2.1. Metabolic Effects of Oral Contraceptives

Between 1970 and 1990 one main target in the development of new oral contraceptives was a low or no impact on serum lipids, carbohydrates and hemostasis in order to protect vascular health and prevent cardiovascular events.
– New progestins, low-dose formulations and regimens of OC were developed with the intention to provide oral contraceptives with as little metabolic impact as possible.
– No changes in metabolism are generally considered beneficial, whereas positive or negative changes must be individually proven to be beneficial or harmful. Changes of selective parameters must be seen in a metabolic balance of the whole functional system (i.e. hemostasis).
– The extrapolation from changes of laboratory parameters to clinical rel-

evance is difficult and delusive – especially concerning lipid metabolism and hemostasis.
– In general all new COC products currently on the market show only a small metabolic impact and are considered as safe.
Different clinical effects of various progestins on the risk for venous thromboembolism have been found but the underlying mechanisms are still under discussion.

The effect of long-term OC use on the prevention of cardiovascular events is crucial. Cardiovascular risk factors like elevated lipids, carbohydrates and blood pressure, as well as exposure to exogenous noxious factors such as cigarette smoking, nutrition, alcohol and drugs are important. Protective factors such as physical activity and lifestyle modifications should also be considered.

Today more specific molecular aspects of cardiovascular risks are shifting into the focus of research and prevention. According to a review by **Moreno et al. (2009) [470]** vascular health can be achieved by reducing vessel wall injury and promoting physiological repair. Vessel wall homeostasis requires a precise balance between injury and the defense mechanisms of repair. To promote vascular health, the destruction of the vessel wall should be reduced, whereas physiological mechanisms leading to a restoration of vessel wall function should be enhanced. Three main defense mechanisms are responsible for maintaining cardiovascular homeostasis:

- regenerative production of endothelial progenitor cells,
- vessel wall angiogenesis,
- macrophage-mediated reverse cholesterol transport.

Summary of cardiovascular effects of COC from the point of view of a cardiologist (according to Shufelt et al. 2009) [595]:

– A variety of basic science, animal, and human data suggests that contraceptive hormones have antiatheromatous effects; however, less is known regarding the impact on atherosclerosis, thrombosis, vasomotion and arrhythmogenesis.
– Newer generation OC formulations indicate no increased myocardial infarction risk for current users, but a persistently increased risk of venous thromboembolism.
– Current guidelines indicate that, similar to general medication, contraceptive hormones should be selected and prescribed on the basis of individual risks and benefits.
– Women seeking advice for oral contraception especially at the age of 35 years and older should be assessed for cardiovascular risk factors including hypertension, smoking, diabetes, nephropathy, and other vascular diseases, including migraine, prior to use.
– The existing data for OC and cardiovascular risk have to be carefully evaluated for the possible risk but also protection from atherosclerosis and cardiovascular events. Long-term cardiovascular follow-up of women with prior OC use, including subgroup information concerning ovulation, hyperandrogenism, weight, lipid und glucose metabolism, e.g. insulin resistance and the presence of prothrombotic genetic disorders is needed to address this important issue.

In the following, the known effects of estrogens and progestins as well as combinations of both in the form of combined oral contraceptives on lipids, carbohydrates and hemostasis are described in detail.

2.4.2.1.1. Lipid Metabolism

Changes in lipid metabolism might be causal for development of atherosclerosis and cardiovascular disease.

Lipid metabolism may be affected by sexual steroids in a dose- and time-dependent manner **[383, 452, 474].**

Estrogens:

– In general, treatment with potent estrogens increases the plasma concentrations of triglycerides and the components of HDL and decreases those of LDL **[575].**

Progestins:

– Decreasing HDL cholesterol levels have been reported for many progestins, especially those with androgenic activity. Less androgenic progestins (i.e. ethinodiol diacetate) affect the lipid metabolism to a lower degree than norgestrel or norethindrone **[211, 385, 732].**
– Androgens and progestins with androgenic activity counteract the estrogen-dependent effects to a certain extent.
– Progestin-only pills and injectable progestin have only minor effects on plasma lipoproteins **[132].**

Combined OC:

– **Wingrave (1982) [715]** described a correlation between serum lipids and progestin dose in older high dose combined oral contraceptives in a study investigating three brands of OC. The depression of HDL-cholesterol was strongly associated with the progestin dose.
– The net effect depends on the balance between estrogen and progestin doses and the amount and activity of the progestin.
– Changes in serum triglyceride levels have been reported with combined OC use **[311].**
– Individual progestins have specific pharmacological profiles and these findings cannot be extrapolated to all progestins. For example, use of COCs with desogestrel and drospirenone leads to an increase of HDL and a decrease of LDL **[426].**
– Among the progestins used in OCs, the progesterone derivatives possess no or only weak androgenic and partly anti-androgenic properties, whereas the nortestosterone derivatives generally have a more or less pronounced androgenic potency. Therefore, the combination of EE with higher doses of LNG may cause an increase in LDL-cholesterol and a decrease in HDL-cholesterol **132, 384, 425].**
– In contrast, when using triphasic OCs with low-dose LNG, the effect on the lipid metabolism does not appear to be unfavorable **[52, 203, 452, 672].**
– **Current users:** 1966, the Swedish group of **Aurell et al. (1966) [31]** published their findings on eight women treated with Anovlar (50 µg EE plus 4 mg norethindrone) for 1 year. These authors demonstrated increased serum levels of total cholesterol (25%, $p < 0.001$), phospholipids (27%, $p < 0.001$), and "glycerides" (mostly triglycerides), the latter increasing 64% from 0.70 to 1.15 mmol/L (70 to 102 mg/dL; $p < 0.01$). HDL cholesterol levels fell 24% from 1.6 to 1.2 mmol/L (60 to 46 mg/dL; $p < 0.001$).

Time-dependent changes: In general, changes in the lipid metabolism are fully expressed within 3 months of OC use, do not progress with contin-

ued exposure, and are fully reversible after cessation of treatment **[186].**

– **Past users:** In general, lipid changes are fully reversible when therapy ceases **[186].**
– **Dosage:**
The first detailed evaluation of the metabolic effects of OC came from the UK in 1966. **Wynn et al. (1966) [731]** compared serum lipid and lipoprotein levels in 102 women taking various OC formulations (> 80% containing 100 µg mestranol plus 0.5-2.0 mg ethynodiol diacetate) with those in 75 women not using OC. The results for the individual lipids are listed below:
– **Cholesterol:**
Lowering of the estrogen dose to 50 µg without altering the progestin content of the OC resulted in less pronounced hypertriglyceridemia and no change in serum cholesterol levels **[733].**
– **Triglycerides:**
For older high dose COC, fasting serum triglyceride levels were 70% to 80% higher in OC users than in non-users ($p < 0.001$), with one-third of these women having values exceeding the highest level of any non-user **Wynn et al. (1966)** 731].
– Hypertriglyceridemia is an estrogen-dose-dependent effect mediated by stimulation of both lipogenesis [442] and the synthesis of the apoprotein of very-low-density lipoprotein [28].

– **Lipoproteins HDL and LDL:**
– High dose norethindrone formulations can increase LDL levels and reduce those of HDL [425]. Reducing the progestin dose minimizes these changes; the increase of HDL levels was shown for 500 µg norethindrone [73, 207].
– Higher dosed levonorgestrel-containing OCs increase fasting LDL levels and reduce those of HDL.
– Reducing the levonorgestrel dose resulted in less effect on LDL and HDL
– to the extent that triphasic levonorgestrel formulations have relatively little effect on either lipoprotein.
– Progestins with androgenic profile led to a more pronounced effect of lowering HDL-cholesterol.

Regimens:
– Different formulations and regimens of OC have been intensively studied by Rabe and coworkers: studies on monophasic OCs with gestodene [534], monophasic OCs with norgestimate [537], monophasic OCs with levonorgestrel and gestodene [537] were conducted.
– See also the review by Rabe et al. (1988) [535] analyzing the impact of various monophasic and triphasic oral contraceptives on serum lipids.
– No Cochrane analysis available.

Summary:
Cardiovascular disease and lipids:
– Changes in lipid metabolism might cause atherosclerosis and cardiovascular disease (CVD). New information collected from epidemiological and interventional studies with lipid blockers led to new perspectives on the best predictive lipid markers for CVD, initially cholesterol, later on triglycerides, finally lipoproteins LDL, and a combination of the others were discussed.

Steroidal effect:
– It is presumed that the lipid metabolism is affected by sexual steroids in a dose- and time-dependent manner **[383, 390, 452].**

Combined oral contraceptives:
– **Estrogens** lead to hypertriglyceridemia in a dose-dependent manner.
– **Progestins with androgenic activity** (i.e. levonorgestrel) have a stronger negative impact on lipid metabolism than non-androgenic or antiandrogenic progestins (i.e. progesterone derivatives).
– In OC users, the following changes in serum lipids as a proportion of baseline values before OC use were observed comparing monophasic to triphasic preparations **[535]**:
– cholesterol: ± 12 %
– triglycerides: –10 % to + 50 %
– HDL-cholesterol: –13 % to + 24 %
– LDL-cholesterol: –22 % to + 15 %

Modern low dose combined oral contraceptives cause only mild changes of serum lipids. Nevertheless, monitoring of serum lipids in healthy women using COC is recommended in special circumstances.

In women with (pre-) pathological lipids and obese women especially with additional risk factors (i.e. age, smoking, hypertension, diabetes thrombophilia) special restrictions and safety recommendations have to be taken into account.

2.4.2.1.2. Carbohydrate metabolism
The increasing incidence of type 2 diabetes worldwide is a well-known fact. Considering hormonal contraception it is important to stress the association between combination oral contraceptives (OCs) and glucose intolerance. Prospective cohort studies of both high-dose estrogen-progestin formulations **[546]** and modern low-dose estrogen-progestin formulations **[90]** did not find an increased incidence of type 2 diabetes in current OC users or former OC users. However, the study populations had higher age at enrolment and were not adjusted for race. Fasting glucose or insulin levels were not documented as parameters for the effect of OCs on glucose and insulin metabolism.

The epidemic increase in the incidence of diabetes and impaired glucose tolerance is one of the leading causes of morbidity and mortality worldwide. In both disorders, tissues such as muscle, fat and liver become less responsive or resistant to insulin. Obesity, polycystic ovarian disease, hyperlipidemia, hypertension and atherosclerosis are linked with insulin resistance and diabetes. The pathophysiology of insulin resistance involves a complex network of signaling pathways, activated by the insulin receptor, which regulates intermediary metabolism and its organization in cells **[573].**

In the Walnut Creek cohort the high prevalence of OC users with impaired glucose metabolism contrasts with the low incidence of diabetes mellitus found for the entire population. After 10 years of follow–up, only 25 cases of diabetes mellitus had been documented among 16,638 women. However, after an average of 8.5 years of follow-up, the mean age of women who had ever used OCs was less than 40, too young for the study of the risk of adult-onset diabetes **[511].**

Kim et al. (2002) [373] analyzed cross-sectional associations in women (n = 1,940) in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a prospective observational study of African-Americans and whites aged

18–30 years at enrolment in 1985–1986 in view of OC use, fasting glucose, insulin and the presence of diabetes. Current use of OCs was found to be associated with lower glucose levels in young African-American and white women and probably associated with lower odds of diabetes.

The regulation of the glucose metabolism in the liver is summarized by **Saltiel and Kahn (2001) [573].**
Estrogens and progestins can change fasting serum glucose, insulin and insulin resistance.

Estrogens:
- Estradiol, estriol, and estrone may improve glucose tolerance in nondiabetic women and reduce insulin requirements in diabetics **[360].**
- Estrogens seem to have little effect on insulin resistance in muscle and adipose tissue. **Kalkhoff (1972) [360]** could demonstrate no effect on glucose tolerance in women using oral contraceptives and non-contraceptive userexamined as controls after administration of mestranol (80 µg/day) and EE (50 and 500 µg/day).
- COC containing an estrogen dose of ≥ 75 µg combined with an estrane progestin caused the greatest deterioration in glucose tolerance associated with impaired insulin secretion, hypercholesterolemia, and hypertriglyceridemia. Lowering of the oestrogen dose to 50 µg without altering the progestagen content of the COC resulted in less deterioration of glucose tolerance, increased insulin secretion, less pronounced hyper-triglyceridemia, and no change in serum-cholesterol level **[734].** These results indicate that the estrogen content of OCs should be reduced as far as is practical in order to reduce the diabetogenic and hypertriglyceridemia effects. The metabolic impact of estrogens on the carbohydrate metabolism might be different if estrogens are applied alone or in combination with progestins as well as if they are applied in continuity instead of in an intermittent or acute application mode; see data of described above **[360]**.
- With the gonane-containing COC whose estrogen content was reduced from 50 to 30 µg EE, glucose intolerance and hypertriglyceridemia were reduced **[733].**

Progestins:
- Progesterone has little effect on carbohydrate tolerance compared to synthetic progestins **[360].**
- Progestins inhibit the uptake of glucose in the muscle tissue and in fat cells by a reduction of the action of insulin. In the liver, however, progestins promote the storage of glycogen.
- The effect of progestins on the impairment of the carbohydrate metabolism depends on the androgenicity of the compound and the dosage of the OC as could be shown in the Walnut Creek cohort study **[511].**
- For 3 commonly used and structurally similar progestins (norethindrone, norethindrone acetate, and ethynodiol diacetate) regression slopes indicated a 5–10 mg% increase in serum glucose per milligram of progestin exposure, both for 1- and 2-hr test results.
- For two other progestins, norethynodrel and dimethisterone, no relationship between milligrams of exposure and serum glucose level is assumed.
- For the structurally unique compound norgestrel, the regression slopes reflected an 18–35 mg% increase per milligram.
- It can be anticipated that users of norgestrel-containing pills show the greatest decrease in glucose tolerance because OCs contain norgestrel at the same or slightly lower doses than norethindrone.
- Ethynodiol diacetate, a weak androgenic progestin, showed a lesser effect on glucose tolerance than norgestrel **[511].**
- Norethynodrel did not affect glucose tolerance **[511].**
- In general, strongly androgenic progestins seem to have the greatest capacity to adversely affect the metabolism while estrogenic progestins have the least adverse metabolic impact **[511].**
- Different progestins have been intensively studied by Spellacy et al., i.e. norethindrone **[615]**, norgestrel **[612]**, ethynodiol diacetate **[614]**, gestodene **[616]** as well as Rabe et al.**:** gestodene and levonorgestrel **[538],** norgestimate **[537],** norethisterone **[536].**

Combined OC:
- Numerous earlier studies found that older higher-dose combined oral contraceptives slightly increased the fasting glucose levels, serum glucose levels and serum insulin after an oral glucose load. After cessation of COC this effect was reversible.
- The modern combined oral contraceptives with low estrogen content (20 µg EE) containing gestodene or desogestrel cause only a slight increase in fasting blood glucose levels compared to higher doses of estrogen and progestins such as levonorgestrel (RCT with n = 36) **[741].**
- Combined OCs may decrease glucose tolerance in some users, but appear to have no effect on fasting plasma glucose in non-diabetics **[311].**
- Since estrogens administered alone do not alter glucose tolerance, the diabetogenic effect may be mainly due to the progestin. Estrogen may play a role in inhibiting the catabolism of the progestin **[486]**, thereby potentiating its effects **[733].**

Regimen: Different formulations and regimens have been intensively studied by Spellacy et al.: Triphasic with norethindrone **[613]** triphasic with levonorgestrel **[617];** triphasic with norethindrone **[613];** as well as Rabe and coworkers: monophasic with gestodene **[534],** monophasic with norgestimate **[537],** monophasic with levonorgestrel and gestodene **[537],** triphasic with norethindrone **[536].**

Summary:
A deterioration of the carbohydrate metabolism through OC use is found in diabetic women. New progestins, low dose formulations and regimens were intended to develop products with as little metabolic impact as possible.
Estrogens: Estrogens alone seem to have little effect on insulin resistance in muscle and adipose tissue.
Kalkhoff et al. (1972) [360] could demonstrate no effect of mestranol (80 µg/day) and EE (50 and 500 µg/day) on glucose tolerance in women using oral contraceptives and non-contraceptive users examined as controls.
A reduction of the estrogen dosage in combined oral contraceptives leads to a lower impact on the carbohydrate metabolism.

Progestins inhibit the uptake of glucose in muscle tissue and in fat cells by a reduction in insulin action. This effect is dose-dependent: The increase in dosage

of 1 mg norethisterone acetate leads to an increase (by about 10 mg/dl) in the 1- and 2-hour values in the oral glucose tolerance test **[511].**

Combined oral contraceptives

– According to **Kim et al. (2002) [373]** most studies with combined progestin/estrogen contraceptives indicate that OCs are associated with increased glucose and insulin levels **[207, 208, 630, 361].** However, the postulated association is not consistent throughout the studies. This inconsistency may be explained by the small number of participants and the inability to evaluate and adjust for all potential confounders, such as increased BMI, age, nonwhite race, lower education level, family history of diabetes, or health behaviors. In addition, selection bias may play a role; in particular, studies without a correlation between diabetes and OCs did not exclude women with diabetes, on the other hand women with diabetes were treated with OCs less often because of their risk profile **[127, 520].**

All low dose combined oral contraceptives currently on the market show only a slight impact on carbohydrate metabolism in healthy women.

In prediabetic and diabetic women special restrictions and safety recommendations must be considered especially if additional risk factors (i.e. age, smoking, obesity, hypertension, thrombophilia) are present.

2.4.2.1.3. Hemostasis

Hemostasis is a complex physiological process involving three mechanisms to stop the blood flow: vasoconstriction, platelet formation and clotting of blood. Intact blood vessels are central to moderating the tendency of blood to clot. The integrity of endothelial cells prevents thrombus formation by secreting tissue plasminogen activator and inactivating thrombin and adenosine diphosphate. Injury to vessels overwhelms these protective mechanisms and the coagulation cascade is activated.

Steroid hormones may influence all three mechanisms. In the following part of the paper the main focus will be on the effects of contraceptive steroids and blood coagulation as well as fibrinolysis.

Estrogens:

– **Ethinyl estradiol:** The net effect on hemostasis depends on dosage of EE.

In a 6-month, randomized, double-blind study the effects of two combined oral contraceptives containing 150 µg desogestrel and either 20 or 30 µg EE on hemostatic parameters were investigated in 1633 healthy women. A less pronounced effect on hemostasis was found with the 20 µg EE preparation compared to the 30 µg EE formulation, both in combination with the same dosage of desogestrel (150 µg) **[716].**

In the **Oral Contraceptive and Hemostasis Study Group (2003) [652],** 24 hemostatic parameters were analyzed over 6 cycles in women taking OCs with an EE dose of 50, 30 and 20 µg in combination with different progestin types (desogestrel, gestodene, levonorgestrel and norgestimate). The estradiol dose (50 vs 30 µg) significantly influenced these hemostatic parameters. No consistent EE effect was detected except for the ETP-based APC-sr and soluble fibrin, which increased to a higher degree in the 50 µg EE dose group.

– **Estradiol:** Differences between EE and estradiol on hemostasis.

Although only few data exist comparing EE vs. E2 without the addition of a progestogen, it seems plausible (based on known effects for various hepatic proteins) that all hepatic effects in terms of hemostatic factors are much stronger using EE. For example, in a cross-over study, the effect of 10 µg EE vs 2 mg E2val per day was tested during treatment of 24 postmenopausal women for six weeks, leading to a significant and much stronger increase of various hemostasic parameters during the use of EE **[424].** Although fibrinolytic factors may also be increased, on the whole, with EE a higher increase in coagulation compared to fibrinolysis with a higher risk of a venous thromboembolic event (VTE) must be expected, even if lower dosages of EE (10 µg) than in COCs (20–50 µg) are used compared to the dosages of E2V (2.000 µg), which are now used in the first COCs with E2val or E2, respectively, instead of EE.

Progestins:

– Progestins have differential effects on the intrinsic and extrinsic procoagulant activity **[249, 376, 391, 563, 571, 717].**

– An unfavorable effect of the progestin component might prevent a further reduction of the risk for VTEs when using OCs with 20 µg EE **[711].**

– Although single progestins have no or only minor effects on hemostasis, they can modify the action of EE on certain coagulation and fibrinolysis parameters, depending on their androgenic activity **[391, 571, 717].**

– In a comparative trial the effects of EE dose (50, 30 and 20 µg) and progestin type (desogestrel, gestodene, levonorgestrel and norgestimate) in oral contraceptives were investigated in 707 healthy women for 6 cycles and 24 hemostatic parameters were measured **[652].**

  - Significantly greater increases in prothrombin fragment 1+2 and factor VII (activity and antigen) were found in the DSG, NGM and GSD groups compared to the LNG group.
  - Similarly, significantly lower levels of protein S (free and total) and increased APC-sr (endogenous thrombin potential based) were found in the same groups compared with the LNG group.
  - In addition, the estradiol dose (50 vs 30 µg) significantly influenced these parameters. No consistent EE effect could be discerned except for the ETP based APC-sr and soluble fibrin, which increased more in the 50 µg EE dose group.
  - All changes were within the normal range and have not been associated with an increased risk of a venous thromboembolic event.
  - However, raised levels of these variables are associated with a prothrombotic risk situation such as pregnancy.
  - The significance of the hemostatic changes found in this study in relation to VTE risk remains to be defined. The results of this study cannot explain the differences in risk of VTE between OCs containing different progestins.

– Oral contraceptives reduce the APC sensitivity of the APT time (by about 10%) as well as the plasma concentration and activity of antithrombin (by about 10%) and protein S (by about 20%) **[45, 246, 377, 440].**

The effect appears to be more pronounced with high dose (50 µg of EE)

OC, whereas no differential impact of progestins has been described **[717].**
- Oral contraceptive use is associated with reduced anticoagulant capacity in the presence of increased coagulation activity and increased plasma concentrations of some coagulation factors. An association of these changes with the risk of VTE has not yet been firmly established **[717].**
- The changes in hemostasis parameters observed during clinical studies cannot explain the association between OC use and increased risk of VTEs. In patients with risk factors, i.e. deficiencies of coagulation inhibitors or resistance to activated protein C, OCs may enhance a preexisting imbalance in the control of coagulation **[679].**
- Such a predisposition might explain the observation that the risk is highest in the first year of OC use **[247].**
- **Winkler (1998) [717]** analyzed eighteen studies comparing second- and third-generation oral contraceptives on the basis of their effects on hemostasis. Significant changes from baseline were reported for many variables with both second- and third-generation oral contraceptives without significant between-group differences. In addition, in a combined analysis of non-significant changes, no consistent pattern of change emerged for any marker with the exception of higher factor VII levels associated with third generation oral contraceptives.

Regimen: No meta-analysis or Cochrane systematic review is available.

Summary:
- **Ethinyl estradiol:** formulations with less EE have lower impact on hemostatis.
- Estradiolvalerate and estradiol, resp., are used in a recent modification of the first COCs instead of EE in dosages of about 2 mg or 1.5 mg/day, resp., which have a much lower impact on hemostasis compared to dosages of EE used in COCs.
- **Progestins** have differential effects on the intrinsic and extrinsic pro–coagulant activity **[249, 376, 391, 571, 717].**
- Although the exclusive use of progestins has no or only minor effects on hemostasis, the action of EE on certain coagulation and fibrinolysis parameters depending on their androgenic activity can be modified in combination contraceptives **[391, 571, 717].**
- The changes in hemostasis parameters observed during clinical studies cannot sufficiently explain the association between OC use and increased risk of VTEs.
- Inherited disorders of blood coagulation determine the increased risk of VTE in OC users: i.e. factor-V Leiden, prothrombin polymorphism, antithrombin, protein C and protein S.

All low-dose combined oral contraceptives currently on the market show only a slight impact on blood coagulation.

Nevertheless in cases with a positive family history of cardiovascular disease, positive patient history of CVD, known thrombophilia and additional risk factors (i.e. age, smoking, obesity, hypertension, diabetes), special restrictions and safety recommendations must be considered.

2.4.2.2. Cardiovascular Risk

Incidence:
- An estimated 17 million people die of CVDs, particularly heart attack and stroke, every year **[329].**
- Many adults in the United States exhibit high risk factors for cardiovascular disease (CVD). Total blood cholesterol levels exceed 200 mg/dl among more than 100 million adults; approximately 70 million have diagnosed or treated high blood pressure (systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg), and over 50 million people still smoke **[327].**
- In the European Union each year there are an estimated 1.1 million diagnosed cases of venous thromboembolism including deep vein thrombosis (DVT) and pulmonary embolism, of which 150,000 are fatal **[106].** Most thromboembolisms are without symptoms and therefore not diagnosed. **Cohen et al. (2007) 106]** estimate that approximately 220,000 deaths in Europe are due to undiagnosed pulmonary embolism. Due to this fatal complication and chronic sequelae the VTE is considered a serious health problem. In the EU every year more people die from VTE than from breast cancer, HIV/AIDS and traffic accidents. However, the incidence increases exponentially in both sexes with age **[140, 141, 172, 245]** and VTE in a young, healthy woman is very rare. According to **Heit et al. (2001) [244]** hospitalized patients have a 100 times higher risk than non-hospitalized patients for VTE. One in ten patients dying in hospital or 1 percent of all patients admitted die due to pulmonary embolism **[485].**

Regional differences: Although it is a well known fact that cardiovascular disease is the predominant cause of mortality among women worldwide, the proportion of 80% of all cardiovascular deaths in women occuring in developing countries is underestimated. In China, cardiovascular disease is the major killing factor of women in both urban and rural settings, surpassing female deaths from cancer and respiratory disease **[703].**

Prevention:
- Independent of sex, race, or income, cardiovascular disease (CVD) is by far the leading cause of death in the world, with an unsustainable economic burden for societies.
- The health systems need to be revised to reduce cost and promote health. This implies a major shift of mentality: from disease treatment to promotion of health **[470].**

Key messages to protect heart health (according WHO, 2011) [328]
- Heart attacks and strokes are major, but preventable killers worldwide.
- Over 80% of cardiovascular deaths occur in low- and middle-income countries and almost equally in men and women.
- The cardiovascular risk of women is particularly high after the menopause.
- Tobacco use, unhealthy diet, and physical inactivity increase the risk of heart attacks and strokes 2–3 fold. Cessation of tobacco use reduces the risk of a heart attack or stroke.
- Engaging in physical activity for at least 30 minutes every day will help to prevent heart attacks and strokes.
- Eating at least five servings of fruit and vegetables a day and limiting your salt intake to less than one teaspoon a day also helps to prevent heart attacks and strokes.
- High blood pressure has no symptoms but can cause a sudden stroke or heart attack.

– Diabetes increases the risk of heart attacks and stroke.
– Being overweight increases the risk of heart attacks and strokes. To maintain an ideal body weight, regular physical activity and a healthy diet is necessary.
– Heart attacks and strokes can strike suddenly and be fatal if assistance is not sought immediately.

Pathomechanism:

– According to a review of **Moreno et al. (2009) [470]** atherosclerosis evolves from subendothelial retention of lipoproteins through the leaky and defective endothelium, where these plasma molecules are modified (i.e., oxidized) and become cytotoxic, proinflammatory, chemotaxic, and proatherogenic. The response-to-injury hypothesis considers inflammation as a central mechanism responsible for early atherogenesis.
– Arterial wall injury, mostly mediated by aging, diabetes, smoking, hypercholesterolemia, and hypertension, triggers an inflammatory response, a defense mechanism to restore arterial wall integrity.
– However, persistence of risk factor-mediated arterial wall injury leads to endothelial dysfunction, atheromatous plaque formation, plaque rupture, and thrombotic complications, the overall process of atherothrombosis.
– Simultaneously, inflammation also orchestrates a process of repair through three main defense mechanisms: 1) endothelial repair by progenitor cells, 2) plaque neovascularization, 3) reverse cholesterol transport.

Predictive parameters:

– **Clinical parameters:** Many previous studies have suggested significant effects of body weight, height, cholesterol, heart rate, BMI, skinfold thickness, obesity, nutrition, smoking, oral contraceptive use, menopausal status, stress and physical activity on blood pressure.
– **Laboratory parameters:** lipids (triglycerides, LDL-cholesterol, HDL-cholesterol), carbohydrates (fasting glucose, fasting insulin, insulin resistance (HOMA-index), glucose loading, HbA1c) CRP, thrombophilia and uremic acid.

2.4.2.2.1. Cardiovascular Disease (CVD) and Combined Oral Contraceptives

General considerations (according to Hannaford, 2000) [227]:

Data base: Evidence on cardiovascular risk and the use of combined oral contraceptives is based on studies conducted against a background of low cardiovascular risk in young women, changing COC composition and changing user selection and monitoring **[227].**

– **Number of subjects for clinical trials:** The inability to recruit large numbers of women exposed to any particular formulation has caused epidemiologists to rely on less specific analyses when assessing the possible influence of the hormonal content of COCs on cardiovascular risk.
– **Estrogen content:** The causal association between very high doses of estrogen and cardiovascular side effects – and in particular thromboembolism – is well established (**The Coronary Drug Project 1973**) **[648]**. In the past the impact of the estrogen component of COCs was often evaluated by breaking down the preparations into those containing > 50 µg, 50 µg, < 50 µg of EE. Such categories ignore the pharmacological effects of the accompanying progestin. Moreover, preparations containing lower doses of estrogen usually also have lower doses of progestin than those with a higher estrogen content; in addition the progestin may be different. These changes cannot be compensated for by statistical adjustments. Analyses of so-called high-dose (≥ 50 µg) versus so-called low-dose (< 50 µg) pills, therefore, are only crude comparisons between older and more recently available COCs. Comparisons between 'low-dose' preparations containing for example 30 µg and 20 µg EE are often more reliable as the progestin content of these preparations is often identical. Although generally imprecise, such comparisons have been helpful when trying to assess whether the overall risk of cardiovascular disease associated with COC use has declined over time.

In an evaluation assessing overall mortality in a study at the Royal College of Practitioners in 2010 by **Hannaford et al. (2010) [229]** the authors did not examine whether the risk of death varied with the hormonal content of the contraceptive pills used. Most (75%) of the pills used in the study contained 50 µg of estrogen, the remaining women used oral contraceptives with more than 50 µg (12%), less than 50 µg formulations (10%), and progestin only preparations (3%). Most women used preparations from more than one estrogen dose category, almost entirely in a step-down direction – for example, from a > 50 µg preparation to a 50 µg preparation. Lack of exclusive use of any particular dose category means that any associations between death and estrogen dosage may be due to the effects of the preparation used most recently before death or lingering effects from a previously used (usually higher dose) formulation.

– **Regimen:** In recent years, a number of publications have suggested material differences in the cardiovascular risk profiles of particular COC formulations. A World Health Organization (WHO) Scientific Group reviewed much of the evidence in November 1997 **[459, 725].** A more recent international consensus paper on venous thromboembolism was published by **Reid et al. 2010 543].**
– **Bias:** A number of explanations, in terms of biological plausibility, as well as bias or confounding factor, have been proposed for the rather small differences in cardiovascular risk between COCs. Clinical evidence for these explanations, however, is weak in most instances.

Case-control studies: In case-control trials with diseases that are influenced by strong prognostic factors (such as age for cardiovascular disease) a matched case-control design should be considered. It is important that the information on the outcome of interest as well as the exposure is valid and precise.

Controls: OC never-users are nowadays not available in large numbers for clinical and epidemiological trials as controls (less than 5% of the total female population in Germany, have never taken hormonal steroids – this group may also have several other risk factors leading to the decision not to use combined oral contraceptives or any hormonal contraceptive).

– **Adjustment:** for each known risk factor with a clinically relevant impact on the outcome, the analysis must be adjusted. If a new important risk factor is detected, all other studies published without the risk factor are potentially biased and their conclusions may be invalid.
– **Risk reduction of CVD (practical advice):** The risk of cardiovascular disease of any description is low in COC users. Women can minimize, and possibly eliminate entirely, their arterial risks by not smoking and by having their blood pressure checked before using a COC (in order to avoid its use if raised blood pressure is discovered). The most reliable way to minimize the risk of venous thromboembolism is to restrict the prescription of COCs to women who have no risk factor.

2.4.2.2.2 Arterial Disease
2.4.2.2.2.1 Hypertension
Incidence:
– The incidence of arterial hypertension is age-dependent. Women of reproductive age have a low incidence in comparison to the overall incidence in the population (< 20 years < 1%; age 20–39 4,6%; age 40–49 15,6% of cases per 100,000 women years) (EpiDatabase® http://pidb.khapps.com accessed August 2, 2011).
– Within several countries regional differences in the prevalence of arterial hypertension were seen, especially due to environmental and socioeconomic factors **[367, 368, 509].**

Important risk factors for the development of arterial hypertension are [582]:
– Age
– Ethnicity
– Overweight or obesity, especially in children and teenagers
– Gender
– Unhealthy lifestyle (high-calory intake, high-sodium intake, low physical activity, smoking habits, alcohol consumption, long-lasting stressors), and
– Positive family history of essential hypertension.

The superimposed risk for arterial hypertension in combination with oral contraceptive uses can be attributed to:

- **Combined oral contraceptives:** Most OCs appear to raise the blood pressure in nearly all women **[255].** Changes in systolic pressure, cardiac output and stroke volume are consistently greater than in diastolic pressure.
- Estrogens and their dose in relation to hypertension
  Theoretically the effect of estrogen as a protective factor on the vascular system has been stated; premenopausal and postmenopausal women differ as well as age-matched premenopausal women and men in blood pressure **[160].**
  Higher doses of EE induce arterial hypertension in about 5% (OC with at least 50 µg of EE), whereas OC with lower doses of EE only lead to a smaller increase of hypertension **[91].**
- In her review, **Hussain (2004) [334]** reported on three prospective control trials and one cross-sectional survey and found no significant association between high blood pressure and the use of progestin only pills (POPs) for up to 2–3 years of follow-up.
- **Qifang et al. (1994) [532]** reviewed data on blood pressure changes and hormonal contraceptives. The authors found that many cross–sectional and longitudinal studies demonstrated that the use of combined OCs containing 50 µg or more estrogen could induce a rise in blood pressure averaging 6 and 2 mmHg for systolic and diastolic pressure, respectively. Similar results were observed in a WHO multicenter trial **[638].**

– **Progestins and their dose in relation to hypertension**
- Initial data on the relationship between progestin dose and arterial hypertension have been provided by the **Royal College of General Practitioners Oral Contraceptive Study (1977) [567].** Three COC brands containing the same dose of the same estrogen (50 µg EE) and different doses of the same progestin (1 mg, 3 mg and 4 mg norethisterone acetate) were analyzed. Based on about 27,000 woman years (WY) of exposure and 294 cases of hypertension the authors were able to show a dose–dependent increase in the incidence of hypertension: 1 mg NETA, 8.2 cases/1000 WY; 3 mg NETA 12.3 cases/1000 WY; 4 mg NETA: 13.9 cases/1000 WY.
  Progestin-only OCs do not appear to increase blood pressure significantly. A 2003 systematic review by **Hussain (2004) [334]** included four studies in normotensive women treated with progestin-only OCs, three prospective control trials and one cross-sectional survey. The author reported no significant association between high blood pressure and the use of progestin-only OCs over up to 2–3 years.
  However, individual progestins have specific pharmacological profiles and these findings cannot be extrapolated to all progestins. For example, drospirenone has substantial antimineralocorticoid activity and it was demonstrated in several randomized clinical trials that drospirenone/estrogen combinations lead to a reduction of the systolic as well as diastolic blood pressure **[491, 527, 707].** In addition, the LASS study demonstrated that a substantially lower proportion of users of drospirenone containing OCs started antihypertensive treatment compared to users of other OCs **[152].**

– **Current healthy users:** According to a review of the **IHS [311],** increases in blood pressure are known to occur in women taking OCs. A 1989 **World Health Organization (WHO) study [654]** comparing 704 women younger than 35 using a combined OC (EE 50 µg/levonorgestrel 250 µg) to 703 women using a non-hormonal intra–uterine device (IUD) reported higher systolic and diastolic blood pressures among those receiving OC. Data from the **Nurses' Health Study [91]** have shown a relative risk of approximately 1.8 for the development of hypertension in women receiving low dose combined OCs. Increasing progestin doses were associated with a higher risk of hypertension; the lowest risk occurred in women receiving triphasic OCs, which have the lowest total progestin dose.
– In a systematic review, **Curtis et al. (2006) [317]** addressed the use of combined OC among women with hypertension. Based on 25 trials, the authors concluded that hypertensive users of combined OCs were at higher

risk for stroke and acute myocardial infarction (AMI) than hypertensive non-users, but that they were not at higher risk for venous thromboembolism (VTE). Data from two studies suggested that women with hypertension on combined OCs may have further increases in blood pressure, but reviewers found these studies to be of low quality. Women who did not have their blood pressure measured before starting combined OCs were at higher risk for ischemic stroke and AMI than those who had a blood pressure measurement, although the same was not true for hemorrhagic stroke or VTE.

– **Past users:** The risk of elevated blood pressure and the increased risk of arterial hypertension quickly decreases with cessation of the oral contraceptive use **[91].** A large prospective study of the same working group on the relationship between past, pregravid OC use and the risk of pregnancy-induced or -related hypertensive disorders did not show conclusive results. The RR for gestational hypertension was lower than in the control group of never-users (0.7) but for recent use of COC and preeclampsia, a RR of 1.3 was shown **[644].**

Summary:

Incidence: The incidence of arterial hypertension in young women is low and increases with age up to the highest risk for women between 40–49 years.

Risk factors: Several well known risk factors for high blood pressure have been described and are the focus of preventive measures. As a result of increasing risk factors especially in developed countries, prehypertension and hypertension are on the rise in women of reproductive age.

Estrogens: Estrogens seem to aggravate the effect of progestins in COC in a dose-dependent manner. COC with higher EE (50 µg and higher) lead to a significant and clinically relevant increase in arterial blood pressure (about 5% of women with arterial hypertension). Modern OC have a less pronounced effect **[91].**

Progestins: Progestin-only OCs do not appear to increase blood pressure significantly. Individual progestins have specific pharmacological profiles and these findings cannot be extrapolated to all progestins. For some progestins a dose-dependent effect of increasing arterial blood pressure has been shown.

Combined oral contraceptives:

In some women, the use of COC leads to a reversible increase in blood pressure. The risk of hypertension is higher for older high dose estrogen and progestin formulations. The initial assessment of arterial blood pressure (BP) before starting COC use is essential; women whose BP had not been taken were at a higher risk for ischemic stroke and myocardial infarction than those who had a BP measurement **[137].**

A regular assessment of the blood pressure is recommended throughout the period of OC use. Women with medically treated hypertension may use low dose oral contraceptives under regular blood pressure control – special recommendations and restrictions must be considered.

2.4.2.2.2.2. Myocardial Infarction (MI)

Prevalence: According to the data of the Framingham Heart Study, the incidence of a MI over a 10 year follow-up was 5.2/1000 in women between the age of 35 to 44. The incidence of MI was eight to nine times higher in men and women aged 55 to 64 years. The prevalence and detection rate of MI in women has increased in the last 30 years **[363].**

Risk factors: Studies of myocardial infarction have found inconsistent results due to confounding risk factors (particularly smoking and raised blood pressure) in the populations studied. Age is an important factor, especially for women who have a considerable increase of MI risk after menopause.

Combined oral contraceptive users:

– **Current healthy OC users:** Findings from several early case–control studies suggested that the risk of MI was two to four times greater in women who currently used COCs than in non–users **[443, 444, 445, 446, 447, 606, 626].**

Women with additional CVD risk factors [70]: COC use is associated with an increased risk of MI, particularly in women who smoke and are older than 35 years and in those who have underlying risk factors for coronary artery disease, such as hypertension, as has been shown by numerous studies **[128, 210, 513, 555, 591, 626, 743].**

Most of the excess risk of MI related to COCs is attributed to their use by smokers older than 35 years; the risk of MI is not increased with COC use in nonsmoking women without cardiovascular risk factors such as hypertension.

– **Past users:** Former users do not have an increased risk of myocardial infarction.

– **Regimen:** Evidence for important differences in the risk of myocardial infarction between different formulations of OC is weak and contradictory.

– **EE-dose:** There is little evidence that lowering the estrogen dose leads to a lower risk of arterial thrombosis **[637].**

– **Progestins:**

The progestin type in COCs as well as the estrogen dose has an impact on the risk of MI **70].**

In a community-based, case-control study, **Dunn et al. 1999 [162]** found that MI risk was similar in women who received COCs containing desogestrel or gestodene and in women who received COCs containing norethisterone or levonorgestrel.

In contrast, in another case-control study, **Tanis et al. (2001) [637]** observed an increased risk of MI with levonorgestrel-containing COCs but no significant increased risk with desogestrel- or gestodene-containing COCs in comparison to non-users.

An aggregated analysis of 22 studies **[624]** including 4 metaanalyses indicated that so-called third generation OCs might have a lower risk compared to so-called second generation OCs (OC with second generation progestins). Given the methodological limitations of the individual studies, however, it is very difficult to differentiate between causation, bias and residual confounding. This overview of seven controlled observational studies confirms that OC containing third generation progestins do not show disadvantages with regard to MI compared with non-users of OC. The odds ratio (OR) for MI with older COCs was 2.18 (95% confidence in-

terval [CI] 1.62"2.94) and 1.13 for newer COCs (95% CI 0.66- 1.92) comparing COC users with non-users. The estimated OR for MI significantly favored formulations containing desogestrel or gestodene vs. those containing norgestrel or levonorgestrel (0.62; 95% CI 0.38"0.99). The aggregate data and the continuing replication of findings allow the conclusion that there is a benefit of newer compared with older combined OC.

Data from recent studies of the cardiovascular risks associated with COCs overall and specific COC formulations are summarized by **Shufelt and Bairey Merz (2009) [595]**.

Summary:

Incidence: There is a low incidence of myocardial infarction in young healthy women. It rises with age to up to 40 cases per 100.000 woman years for women between 40–49 years of age.

Risk factors: The following important primary risk factors for the MI have been identified: age, hyperlipidemia, diabetes mellitus, hypertension, and a family history of arterial atherosclerosis. Especially several life-style habits such as smoking, high-calory diet, chronic stress also contribute to an increased risk for MI.

Combined oral contraceptives:

- **Current users:** Findings from several early case-control studies suggested that the risk of MI was two to four times higher in women who currently used COCs than in non-users.
- COC use is associated with an increased risk of MI, particularly in women who smoke and are older than 35 years and in those who have underlying risk factors for coronary artery disease, such as hypertension.
- The risk of MI is not increased by COC use in nonsmoking women without cardiovascular risk factors.
- **Past users** have no increased risk for MI.
- **Dosage:** The aggregate data and the continuing replication of findings suggest a benefit of newer compared with older combined OC **[624].**
- **Progestins:** No conclusive relevant differences between various progestins, dosages, combinations and regimens have been shown. The only clear finding is that the estimated OR for MI significantly favored formulations containing desogestrel or gestodene vs. those containing norgestrel or levonorgestrel (0.62; 95% CI 0.38–0.99).

2.4.2.2.2.3. Ischemic Stroke (Cerebrovascular accident, CVA)

Prevalence and Definition:

- The symptoms of a cerebrovascular accident (CVA) are caused by cell and tissue damage in the brain due to impaired blood supply. The causes of the impaired blood supply can be the formation of a blood clot (thromboembolic, ischemic) or the rupture of the arteries (hemorrhagic).
- A low risk for a CVA in young healthy women has been reported. According to figures from the CDC in the US in 2005, the prevalence of stroke in women and men under 45 years was 0.8% whereas in the age-group of 45–65 years, the prevalence increased to 2.7%. The overall prevalence for males and females was reported to be comparable (2.7 vs 2.5%), the incidence in whites was lower compared to multiracial and black persons **[296].**
- Increasing age, genetic thromboembolic predisposition and life-style are the predominant risk factors for atherosclerosis and CVA. Concurrent medical risk factors for ischemic stroke are diabetes and atrial fibrillation.

Special risk factors for CVA in combination with OC: Current users of low estrogen dose COCs appear to have an increased risk of ischemic stroke compared to non-users if they are 1) 35 years of age or older, 2) cigarette smokers, 3) hypertensive, and 4) have a history of migraine with aura.

Migraine itself is an outstanding risk factor for CVA. Evidence from case–control-studies and later a meta–analysis show that COC users with a history of migraine have a clearly elevated risk compared to users without migraine (Curtis) and an up to 14-fold increased risk of ischemic stroke compared to OC non–users without migraine **[87].** In combination with oral contraceptives, especially migraine with aura has an increased risk of CVA and should clearly be considered as a contraindication for COC **[87, 138, 232, 387].**

Combined oral contraceptive users (Collaborative Group for the Study of Stroke in Young Women, 1973) [108]:

- **Past users:** Former users of COCs do not have an increased risk of ischemic stroke.
- **Regimen:** There is insufficient information to determine major differences in the risk of ischemic stroke between products.
- **EE-dose:**

  Past studies suggest that the use of COCs with > 50 µg EE increases the risk of ischemic stroke more than low-dose preparations.

  A critical evaluation of 36 studies describing 20 distinct populations **[86]** found a modest association between ischemic stroke and COCs containing less than 50 µg EE. However the authors pointed out that the association is tenuous given the low magnitude of the odds ratios, severe methodological limitations, and – in contrast to the case-control studies – odd ratios of less than 1.0 in cohort studies.
- **Progestins:** No consistent differences between second and third generation progestins were found.

Summary:

Prevalence: Healthy women of reproductive age have a low prevalence of CVA.

Risk factors for CVA are, in particular, age, familial risk for thromboembolic incidents and life-style factors like cigarette smoking, hypertension as well as special diseases like migraine with aura.

Combined oral contraceptives:

- Overall, no convincing evidence has been found that the use of low–dose COCs increases the risk of ischemic stroke in women younger than 35 years of age who do not smoke or suffer from hypertension.
- Current users of low estrogen dose COCs appear to have an increased risk of ischemic stroke compared to non-users if they are 35 years of age or older, smoke, are hypertensive, and have a history of migraine with aura.

2.4.2.2.2.4. Hemorrhagic Stroke

Prevalence:

- Hemorrhagic stroke is a subcategory of CVA with intracranial bleeding after primary rupture of a vessel or secondary to an ischemic stroke. Similar to ischemic stroke, a low risk for hemorrhagic stroke has been reported for young healthy women.

Risk factors:
– In theory, similar risk factors to ischemic stroke, such as hypertension and age, apply. Additionally genetic factors determining vessel wall abnormalities in the brain and hemostatic parameters play a role in the pathogenesis of hemorrhagic stroke.
– In a prospective study, smoking and the risk of hemorrhagic stroke in women was evaluated and tobacco users had a RR of 2–3 in comparison to women who had never smoked **[401].**

OC and hemorrhagic stroke:
– However, no evidence exists that OC users with these risk factors have a higher risk of hemorrhagic stroke than non-OC users with the same risk factors.
– **EE:** No evidence of a dose-dependent risk.
– **Progestins:** No evidence of a differential risk for second and third generation progestins.

Combined oral contraceptives:
– **Current users:** The critical evaluation of 30 studies mentioned above **[86]** did not find any association between hemorrhagic stroke and use of COC.
– **Past users:** Former users of COCs do not have an increased risk of hemorrhagic stroke.

Summary:
Prevalence: Data suggest a low overall risk for hemorrhagic stroke in young healthy women.
Risk factors: There is no evidence that OC users with risk factors like hypertension, diabetes mellitus or a family history have a higher risk of hemorrhagic stroke than non-users with the same risk factors, but these risk factors must be evaluated carefully before prescribing an oral contraceptive.
Combined oral contraceptives:
– No association between hemorrhagic stroke and use of COC.
– No data on a dose-dependent risk associated with EE
– No studies showing a differential risk for second and third generation progestins.

2.4.2.2.3. Venous Disease
2.4.2.2.3.1. Venous Thromboembolism (VTE)
Venous thromboembolism is a collective term for deep venous thrombosis (DVT) and pulmonary embolism.

Incidence:
– The overall incidence of DVT in the United States is estimated to be 1.2 cases per 1000, with the risk continuously increasing with age.
– Differences in incidence of VTE have been shown for gender, ethnicity and race **[706].**

Data on VTE risk in combination with OC: Various studies have consistently found an increased risk of venous thromboembolism among current users of low estrogen dose COCs with a relative risk within the range of 3–6 **[228].**
The first report suggesting a link between use of combined oral contraceptives (COCs) and pulmonary embolism was published in 1961 **[357]**. Since then, there have been more than 70 epidemiological studies investigating the relationship between COC use and myocardial infarction, stroke or venous thromboembolism **[230].**
Risk factors: The VTE Risk is substantially elevated among women with various inherited clotting factor defects and women with a family history of VTE. In clinical practice, investigating the family history may be clinically more useful and cost-effective for risk assessment than thrombophilia testing. The risk of VTE in women with a factor V Leiden mutation increases 15-times (heterozygous) or even more than 100 times in the high risk case of a homozygous mutation.
Considering the prevalence of thrombophilia and the low prevalence of VTE in non-users of combined oral contraceptives, the absolute risk remains low. The findings from the TREATS study show that selective screening based on prior VTE history is more cost-effective than universal screening **[727].** Furthermore, the presence of several cardiovascular risk factors (such as age and obesity) leads to an over-additive increase in COC users.
Combined oral contraceptives:
– **Current users:** Current users have a 3-6-fold increased risk of DVT compared to non-users. Especially in the first year of use the risk is elevated, but continues to be increased until the OC use is stopped **[228].**
– **Past users:** The increased risk of VTE normalizes within 3 months after cessation of OC use. Former users of COCs do not have an ongoing increased risk of ischemic stroke.

Dosage of ethinyl estradiol in relation to the risk of VTE
Estrogen dose: The causal association between very high doses of estrogen and cardiovascular side effects – and in particular thromboembolism – is well established **[648]**. Furthermore, it has been demonstrated that the VTE risk is influenced by the EE dosages typically used for COCs **[423, 562].**
– **Dose reduction from 50 to 30–40 µg EE:** A risk reduction by reducing EE from 50 to 30–40 µg has been shown even if the study results have sometimes been contradictory **[423, 724].** Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in women without other risk factors for VTE using combined oral contraceptives with low estrogen content (< 50 µg EE), is 20 to 40 cases per 100,000 woman-years. However, in the typical population of OC users, the incidence is about 90 cases per 100,000 woman-years **[149].**

Dose reduction of 30–40 to 20 µg EE: The further reduction of EE to 20 µg EE can lead to a further, but only slight reduction in the risk of VTE **[149, 422].**
– **Dose reduction of 30–40 µg of EE COC vs EE free OCs:** The data of **Lidegaard et al. (2009) [422]** suggest that progestin-only pills taken by women of fertile age are not associated with an increased risk of venous thromboembolism: POP containing levonorgestrel or norethisterone: RR for VTE: 0.59 (0.33–1.03) (data base: 65.820 woman-years) or 75 µg desogestrel RR 1.12 (0.36–3.49) (Source: 9.044 woman-years). However, we must point out that although these results reflect typical use there is no hard evidence that these results can be extrapolated to women with significant risk factors.
– **Risk assessment for COC with estradiol or estradiol valerate:** Compared with EE-containing products estradiol and estradiol valerate lead to lower liver enzyme induction and reduced influence on hemostasis. At present it is unclear whether this theoretical advantage will actually lead to a lower incidence of VTE.
– **Progestins and their dose in relation to the risk of VTE:**
– The influence of different progestins on the risk of VTE is controversial.

Levonorgestrel is mostly used as the reference for comparison between different progestins relative to CVD. According to the best currently available studies **[149]** the VTE incidence of levonorgestrel-containing COCs with less than 50 µg EE is approximately 8 cases per 100,000 woman-years. This number represents the risk for the typical OC user population; however the risk in each individual case may be different due to the strong age-dependent risk.

– The incidence rates for norethisterone, norethisterone acetate and norgestimate are similar to that for levonorgestrel **[422].**

The studies published in the mid-1990s showed a higher risk for the so-called third-generation progestins, gestodene and desogestrel compared to levonorgestrel (see meta-analysis of **Kemmeren et al. 2001) [370].** Studies that adjusted for the time dependence of risk (higher risk in the first months after initially starting OC use or restarting after a break) and adjusted quantitatively correctly for differences in age showed no significant differences between the progestins of different generations. However, due to the methodological shortcomings of all the available studies, no definitive conclusions can be drawn about a causal relationship. For the time being, the discussion is ongoing **[243, 422, 590, 674].**

– **Cyproterone acetate:** The results for cyproterone acetate (CPA) are contradictory. This applies even to the results from the one and the same working group, which have been evaluated at different times and with different methodologies but using the same data source. Analysing the Danish patient registry in 2003, Lidegaard reported an incidence of 31 VTE per 100,000 woman-years with a confidence interval of 13–49 **[422].** Six years later the point estimates of the incidence rate were 71 VTE cases per 100,000 woman-years – clearly outside the confidence interval of the 2003 analysis. In the same period, the relative risk compared with levonorgestrel increased from 0.7 to 1.9. These differences are not easily explained by chance and show the major methodological difficulties in implementing and evaluating studies on VTE risk in OC-users.

– **Chlormadinone acetate:** Regarding chlormadinone acetate (CMA), there is no evidence of an increased risk of VTE compared to COC with levonorgestrel **[697]. Conard et al**. (2004) evaluated the impact of antigonadotropic doses of CMA (10 mg/day) on the recurrence of DVT in women with a previous history of DVT and/or hereditary thrombophilia **[116].** The incidence of DVT was similar in women using contraception with and without CMA. This retrospective study still needs to be confirmed by further prospective studies.
– **Dienogest:** This also applies to EE-containing COC with dienogest **[153].**
– **Drospirenone:** For drospirenone the results are also contradictory. Two large prospective cohort studies **149, 586],** and a German case-control study **[153]** showed no increased risk, whereas a retrospective cohort study in Denmark **[154]** and a Dutch case–control study found a modestly increased risk compared with levonorgestrel-containing preparations **[673].** The latter two studies have significant methodological bias **[154, 590].** The Dutch study was not statistically significant and neither the cases nor the controls were representative. In the Danish study, short–term use and long–term use had been misclassified to a significant degree and no data have been published on important risk factors. In addition, an independent validation study demonstrated that about 30% of the diagnoses that were adopted by the authors from the Danish patient registry were probably incorrect **[589].** Probably drospirenone when compared with levonorgestrel poses no increased risk, although a small increase (or theoretically, a slightly lower risk) cannot be ruled out.

In summary, the VTE risk of drospirenone- versus levonorgestrel-containing COCs cannot be conclusively ascertained. The studies with the best methodology do not indicate a higher risk for drospirenone, but these studies also have methodological limitations and cannot exclude a slight increase in risk.

This is also reflected in a statement by the PhVWP (Pharmacovigilance Working Party) of the **European Medicines Agency (EMA) [729]** (May 26th, 2011), which was based on a review of all available data, including some further re analyses and information on additional analyses regarding the risk of venous thromboembolism (VTE) associated with drospirenone containing combined oral contraceptives (COC), such as Yasmin and Yasminelle. Altogether seven epidemiological studies **[422, 674, 353, 504, 586, 150, 153]** analysed/evaluated the association between drospirenone-containing COC and VTE.

The assessment has not changed the conclusion that the risk of VTE associated with any COC (including those containing drospirenone) is very small. The PhVWP concluded that the data showed that drospirenone-containing COC are associated with a higher VTE risk than levonorgestrel containing COC and that the risk may be similar to that for COC containing desogestrel or gestodene. The PhVWP recommended that the product information for all drospirenone containing COC should be updated to reflect these conclusions. There is no reason for women to stop taking drospirenone containing COC such as Yasmin and Yasminelle or any other COC. In Germany the **BfArM (Federal Institute for Pharmaceuticals and Medical Products) (2011) [288]** published a similar statement on their homepage.

Summary:

– The incidence of VTE in the general population is about 1 /1000 (US data). Oral contraception is associated with a 3–6 fold increase of VTE risk.
– Additional risk factors for deep venous thrombosis should be taken into account when counseling on contraceptive methods. General screening of genetic thromboembolic risk factors is not recommended. A notable high-risk situation is the familial predisposition for VTE events.
– On the whole, it should be noted that the use of any combined oral hormonal contraceptive (COC) is always associated with an increased VTE risk. The risk is dependent on the estrogen dose and might be modulated by the choice of progestin. Whether a clinically relevant difference in the risk of venous thromboembolism exists for different progestins is currently the subject of debate.

Table 2 shows an evaluation of different hormonal contraceptives and ve-

Table 2. Classification of contraceptives according to the risk of VTE in healthy women of reproductive age without additional risk factors (such as obesity, immobilization, positive family history of cardiovascular disease, cigarette smoking). Rabe et al. Contraception and Thrombophilia. See this issue, page 204.

Risk	Age (Years)	Incidence (VTE/10,000 women years)	Contraceptive method/ Population group	Published Studies	Ongoing Studies
Reference	≤ 19 20–29 30–39 40–49 **15–49**	1–2 2–3 3–4 5–7 **3–4**	Healthy, non-pregnant women of child-bearing age not using a contraceptive Non-hormonal contraceptive methods – tubal sterilization – condoms, spermicides – behavioral methods – copper IUDs	Lidegaard 2009 [422]: I = 3.0 (2.9–3.2); Ex = 4813 TWY Dinger 2007 [150]: I = 4.4 (2.4–7.3); Ex = 65 TWY Review Article: Heinemann 2007	INAS-OC and INAS-SCORE (EURAS-type studies; end 2013 and 2014, respectively)
Unchanged or Slightly increased	**15–49**	**3–4**	Progestin-containing contraceptives (slight increased risk cannot completely be excluded in comparison to non-hormonal contraceptive methods; therefore non-hormonal methods should be preferred for women with a history of thrombophilia) – Levonorgestrel-IUS – Progestin-only pill – Progestin-only ovulation inhibitor – Progestin depot injections	Lidegaard 2009 [422]: Levonorgestrel-IUS I = 3.4 (2.3–4.7); Ex = 101 TWY Progestin-only pill I = 2.0 (1.1–3.3); Ex = 75 TWY	EURAS-IUD (EURAS-type study; ends 2012) LASS (EURAS-type study; ends 2011)
Moderately increased – Level 1	≤ 19 20–29 30–39 40–49 **15–49**	3–4 5–8 8–10 15–22 **6–10**	Combined oral contraceptives with < 50 µg Ethinyl estradiol and – Levonorgestrel (LNG), Norethisteron, Norethisteron acetat or Norgestimate (NGM)	Lidegaard 2009 [422]: I = 5.5 (4.7–6.3); Ex = 367 TWY (underestimation due to misclassification of current duration of use and other reasons) Dinger 2007 [150]: I = 8.0 (5.2–11.7); Ex = 31 TWY	LASS (EURAS-type study; ends 2011)
			– Chlormadinone acetate (probably no higher risk than with LNG-containing COCs; however, a slightly higher risk cannot be excluded)	Waldmann-Rex 2009: I = 2.4 (0.9–5.2); Ex = 25 TWY (underestimation due to methodological short-comings)	No EURAS-type study
			– Dienogest (probably no higher risk than with LNG-containing COCs; however a slightly higher risk cannot be excluded)	Dinger 2010 [153]: OR vs LNG: 1.0 (0.6–1.8); 95 Ca/303 Cn	INAS-SCORE (EURAS-type study; ends 2014)
			– MPA depot injection (classification is based on a methodologically limited study with a limited number of cases and controls; overestimation of risk compared to other hormonal contraceptives possible)	van Hylckama, Vlieg et al. 2010: OR* 3.6 (1.8–7.1); 20 Ca/15 Cn (*vs. non-use of hormonal contraceptives; OR vs. LNG: ~1)	No EURAS-type study
			Combined oral contraceptive pills with Estradiol valerate and Dienogest (less influence on hemostasis compared with Ethinyl estradiol/Dienogest; however, risk assessment should be based on the VTE-incidence of Ethinyl estradiol/Dienogest as long as robust data are not available)		INAS-SCORE (EURAS-type study; ends 2014)
			NuvaRing® (provisional classification based on interim results from the TASC study)		TASC (EURAS-type study; ends 2012)
– Level 2	**15–49**	**6–14**	Combined oral contraceptives with < 50 µg Ethinyl estradiol and – Drospirenone (DRSP) (inconsistent study results; in contrast to retrospective database studies 2 prospective cohort studies and 1 retrospective field study did not show an increased risk compared to LNG-containing COCs; based on currently available data a slightly increased risk is possible)	Lidegaard 2009 [422]: I = 7.8 (6.4–9.5); Ex = 131 TWY (no substantial missclassification of duration of use; potential overestimation of risk compared to LNG [see above]) Dinger 2007 [150]: I = 9.1 (5.9–13.3); Ex = 29 TWY Dinger 2010 [153]: OR vs LNG: 1.0 (0.5–1.8); 85 Ca/281 Cn Jick et al. 2011 [353]: OR 2.2 (1.5–3.4); 166 Ca/550 Cn Parkin et al. 2011 [128]: OR 2.9 (1.1–7.4); 57 Ca/176 Cn	LASS (EURAS-type study; ends 2011) INAS OC (EURAS-type study; ends 2011)
			– Desogestrel (DSG), Gestoden (GSD) or Cyproterone-acetate (CPA) (risk of VTE in comparison with LNG-containing preparations scientifically controversial, however a slightly to moderately higher risk is possible)	Lidegaard 2009 [422]: DSG/GSD I = 6.8 (6.5–7.2); Ex = 2008 TWY CPA I = 7.1 (5.7–8.7); Ex = 127 TWY (less substantial underestimate of the risk compared to LNG [see above]) Case-control studies with and without adjustment for duration of use showed ORs of ~ 2 and ~ 1. Numerous review articles available; the most balanced representation being the decision of the High Court of Justice in 2002 [132]	LASS (EURAS-type study; ends 2011)
			Evra contraceptive patch (VTE risk compared to COCs with LNG or NGM controversial; a slightly to moderately increased risk is possible)	Dore 2010: OR vs NGM: 2.0 (1.2–3.3); 102 Ca/353 Cn Jick 2010: ORs vs LNG from 2 sources 46 Ca/207 Cn & 97 Ca/382 Cn: 2.0 (0.9–4.1) & 1.3 (0.8–2.1)	No EURAS-type study
Substantially increased	**15–49**	**20–30**	Pregnancy and the first three months after childbirth; risk after cesarean section significantly higher than after spontaneous delivery	Heit 2005: I = 29.3 (23.8–35.6); Ex = 50 TWY Lidegaard 2011: RR vs 'non-pregnant non-users' 10.6 (9.4–12.0); 265 Cases	No EURAS-type study

Ex = Exposure in 1000 woman-years; Ca = Number of relevant cases in a case control study; I = Incidence of VTE/10,000 WY with 95% CI; Cn = Number of relevant controls in a case control study; OR = odds ratio; RR = relative risk; TWY = 1,000 woman-years; * cases/controls

nous thromboembolism risk in healthy women of reproductive age without additional risk factors compared to pregnancy and childbirth (see also the review by Rabe et al. "Contraception and Thrombophilia" in this supplement).

The evaluation of different hormonal contraceptives and venous thromboembolism risk in healthy women of reproductive age without additional risk factors compared to pregnancy and childbirth is published in a review by Rabe et al. on "Contraception and Thrombophilia" in this supplement.

2.4.3. Oral Contraceptives and Cancer

Cancers of the breast, lung and colon are among the top ten causes of death of older women globally. The incidence (new cases) of breast cancer is much higher in high-income countries compared to low- and middle-income countries, but mortality is similar. This is due to the availability of better treatment in the high-income countries. For lung and colon cancer, both incidence and mortality are currently higher in high-income countries. Globally, 71% of lung cancer deaths are caused by tobacco use.

According to the **WHO [330],** cervical cancer is the second most common type of cancer among women worldwide, with virtually all cases linked to genital infection with the human papillomavirus (HPV). Almost 80% of cases today and an even higher proportion of deaths from cervical cancer occur in low-income countries, where access to cervical cancer screening and treatment virtually does not exist.

Some recent reviews deal with hormonal contraception and cancer in women **[96, 231],** as well as previous reports of the **IARC monograph (1999) [278] , the IARC monograph (2007) [336], the ESHRE Capri Workshop Group (2005) [359, 608, 649, 690].**

2.4.3.1. Breast Cancer

The worldwide incidence of breast cancer is increasing; it is estimated that one out of ten women will suffer from breast cancer during their lifetime.

– **US National Cancer Institute (SEER) [280]:** From 2003–2007, the median age at diagnosis for cancer of the breast was 61 years. No breast cancer was diagnosed under the age of 20; 1.9% between 20 and 34; 10.5% between 35 and 44; 22.6% between 45 and 54; 24.1% between 55 and 64; 19.5% between 65 and 74; 15.8% between 75 and 84; and 5.6% at 85 and older.
The age-adjusted incidence was 122.9 per 100,000 women per year. These rates are based on cases diagnosed in 2003–2007 from 17 SEER geographic areas.
– **Multiple risk factors have been analyzed in various reviews [**i.e. **598]** and can be classified according to their importance and the preventive profile.

Risk factor classification according to their importance [184]:

- **Strong risk factors** are older age, family history, and previous breast cancer.
- **Moderate risk factors** are density of the breasts on mammogram, biopsy abnormalities, and exposure to radiation.
- **Other risk factors are** age at time of reproductive events, pregnancy and breastfeeding, hormone replacement therapy (HRT), height and weight, alcohol consumption, presence of other cancers, miscellaneous factors.
- **The risk is decreased** by removal of the ovaries, lifestyle changes, medication, and early detection.

Risk factors (American Cancer Society) [9]:

- **Unchangeable risk factors:** gender, aging, genetic risk factors, family history of breast cancer, personal history of breast cancer, race and ethnicity, dense breast tissue, certain benign breast conditions, lobular carcinoma in situ, menstrual periods, previous chest radiation, diethylstilbestrol exposure
- **Lifestyle-related factors and breast cancer risk:** having children, recent oral contraceptive use, hormone therapy after menopause, breast-feeding, alcohol, being overweight or obese, physical activity
- **Factors with uncertain, controversial, or unproven effect on breast cancer risk:** diet and vitamin intake, antiperspirants, bras, induced abortion, breast implants, chemicals in the environment, tobacco smoke, night work.

– **Epidemiological data [96]**
  - The first report about the association between breast cancer and oral contraceptives was published by **Pike et al. (1981) [517].**
  - **Meta-analysis and re-analysis:** In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer published a re-analysis of worldwide epidemiologic data on a possible relationship between OCs and the diagnosis of breast cancer. The re-analysis involved 54 studies (90% of all epidemiological studies), a total of 53,297 women with breast cancer and 100,239 women without breast cancer **[110],** Oxford meta-analysis **[83],** Mayo Clinic (meta-analysis) **[359].**

  Large cohort-studies: Nurses' (cohort) **[226],** RCGP (cohort) **[231],** Oxford Family Planning (cohort) **[690],** Women's CARE **[448],** Women's Lifestyle and Health study (cohort) **[398].**
  - **Definition of risk:** "Risk of having breast cancer diagnosed" is different from "life–time risk" for breast cancer. The question why OC-users have a higher detection rate of breast cancer (earlier detection of preexisting tumors) or a higher lifetime risk (additional new tumors in OC users) has not been answered until now. A stimulation of preexisting breast cancer is assumed, rather than the induction of mutagenesis and new tumors (latency between toxic exposure and clinically detectable carcinoma: 10–15 years).

– **Current users [96]:**
  - In the majority of studies there has been no increase in the risk of breast cancer reported in current OC users.
  - Long duration of OC use at a young age before the first full-term pregnancy seems to be the most important risk factor, as hormones act on a less differentiated tissue.
  - The number of events attributable to OC use remains below 1% of the total number of breast cancers and

7% for premenopausal breast cancer. This risk calculation is based on the RR of the fraction of breast cancer attributable to OC in France **[82].**

– **Risk in past users:** The risk decreases progressively after cessation of OC use.
– **First generation of OC formulations.** The increase in the RR is low, heterogeneous and may be linked to high dose first generation of OC formulations. Variations may be due to study design and disease heterogeneity. Screening or recall bias cannot be excluded **[448, 556, 592].**
– **OC-regimen:** None of these studies provided evidence for any relevance of the OC composition on breast cancer risk.
– **BRCA1/2 mutations:** According to a recent review by **Iodice et al. (2010) [343]** oral contraceptive use has been associated with a moderately increased risk of breast cancer, which tends to decline progressively after termination of use. In addition, a reduced risk of ovarian cancer in women who had not been selected for predisposing genetic mutations was shown. The use of OCs in mutation carriers remains controversial because of their increased risk and early onset of breast cancer. For BRCA1/2 carriers, the protective effect against ovarian cancer must be taken into account. COC reduce the risk of ovarian cancer without clear evidence that recent formulations increase the risk of breast cancer in women with a germline mutation in BRCA1 or BRCA2. While these results are reassuring, further prospective studies in carriers are indicated. The open questions are possible additive effects of the usage of other hormones and specific effects of different types of OCs.

Summary:

Incidence: The incidence of breast cancer is increasing globally; one of ten women will suffer from breast cancer during their lifetime.

Hormone dependency of breast cancer: The growth of existing estrogen-sensitive breast carcinoma cells is stimulated by estrogens and inhibited by antiestrogens, withdrawal of estrogens by aromatase inhibitors and ovariectomy. Breast carcinoma cells express steroid hormone receptors and human epidermal growth hormone receptors. Tumor growth, treatment options and prognosis are linked to the expression of these receptors.

In postmenopausal women, the lower incidence of HRT use recently led to a lower rate of diagnosed breast cancer cases.

Oral contraceptives:

The conclusions below are based on multiple meta–analyses (e.g. **Collaborative Group on Hormonal Factors in Breast Cancer 1996**) **[110]**, Oxford meta-analysis **[83],** Mayo Clinic (meta-analysis) **[359].**

– **Current users at a young age:** Long-term OC use at a young age before the first full-term pregnancy seems to be the most important risk factor.
– **Risk:** The risk of a contemporarily diagnosed breast cancer increases, but not the lifetime-risk for breast cancer itself.
– **Risk in past users:** The RR for BC risk is increased; this effect disappears progressively after stopping OC use.
– **First generation OC formulations.** The increase in the RR is low and heterogeneous. It is likely linked to high dose first generation OC formulations. Screening or recall bias cannot be excluded **[448, 556, 592].**
– **OC regimen:** The large studies on OC and BC risk have shown no impact of the OC composition on breast cancer risk.
– **Progestins:** No specific effects of progestins currently used for oral hormonal contraception on BC risk have been found.
– **Studies clearly suggest that OC are not an initiator of breast cancer development and do not induce carcinogenicity, but might act as a promotor**. Steroid hormones might stimulate preexisting malignant cells.

BRCA1/2 mutations: According to a recent meta-analysis of **Iodice et al. (2010) 343],** the use of OCs in mutation carriers remains controversial. The meta-analysis provides evidence that OCs reduce the risk of ovarian cancer without any evidence that recent formulations increase the risk of breast cancer in women with a germ–line mutation in BRCA1 or BRCA2. For more information see **National Cancer Institute (US) [290, 291].**

Prevention: Regular cancer screening including self-examination of the breasts is strongly recommended. Special screening programs for women with BRCA1/2 have been established.

Reviews and meta-analysis:

– **IACR Monographs on the Evaluation of Carcinogenic Risks to Humans (2009) [278]**
– **Meta-analysis: Collaborative Group on Hormonal Factors in Breast Cancer (1996) [110]**.
– **Large cohort-studies:** Nurses' (cohort) **[226],** RCGP (cohort) **[231],** Oxford Family Planning (cohort) **[690],** Women's CARE **[448],** Women's Lifestyle and Health study (cohort) **[398]**.
– **Extended reviews: Cibula et al. (2010) [96]**

Further references:

– **The ESHRE Capri Workshop Group (2005) [649]**
– **National Cancer Institute (US) [292]**

2.4.3.2. Cervical Cancer

Incidence: US National Cancer Institute (SEER) [281]: From 2003–2007, the median age at diagnosis for cancer of the cervix uteri was 48 years. Approximately 0.2% were diagnosed under age 20; 14.5% between 20 and 34; 26.1% between 35 and 44; 23.7% between 45 and 54; 16.3% between 55 and 64; 10.4% between 65 and 74; 6.5% between 75 and 84; and 2.4% 85+ years of age.

The age-adjusted incidence was 8.1 per 100,000 women per year. These rates are based on cases diagnosed in 2003–2007 from 17 SEER geographic areas.

Etiology:

- **HPV-infection:** The vast majority of cervical cancers are caused by HPV infection. HPV is considered as the main and preventable risk factor. Approximately 14 types of HPV have been identified as a potential cause of this cancer. HPVs were found in 99% of cervical cancer biopsy specimens worldwide **[187].** Certain strains of HPV, most notably HPV-16 and HPV-18, are especially associated with cancer of the uterine cervix and considered as high risk (HR) strains **[57].** Long-term COC use has been identified as a possible co-factor that significantly increases the risk of cervical cancer in women who

are positive for HPV-DNA **[471].** More information about HPV and cancer is available at the US National Cancer Institute **[742].**

- **Prevention of infection:** The use of condoms prevents cervical HPV infection – but not vaginal and vulvar infections.
- **Different contraceptive methods:** An association between HPV-infection, cervical cancer and oral contraception is assumed, especially as the use of other contraceptives like IUD/IUS does not seem to be linked with a higher risk of cervical cancer:
  - **Copper-IUD [136]:** Four case–control studies found no association between IUD use and risk for cervical cancer. No trend in associations was observed with characteristics of IUD use, type of IUD and histologic type of cancer.
  - **IUD/LNG-IUS –** No specific data are available.

Co-risk factors for HPV-infection

– **Chlamydial infection [607]**
– **Cigarette smoking [342]**
– **Other risk factors (American Cancer Society) [11]:** immunosuppression, diet, oral contraceptives, multiple full-term pregnancies, young age at the first full-term pregnancy, poverty, diethylstilbestrol (DES), family history of cervical cancer

Combined oral contraceptives

The first reports about an association between cervical cancer and oral contraceptives were published by **Peritz et al. (1977) [510], Vessey et al., (1983) [692], WHO collaborative study of neoplasia and steroid contraceptives (1985) [708], Brinton et al., (1986) [61].**

Meta-analysis: Smith et al. (2003) [608]

– 28 eligible studies were identified, including a total of 12,531 women with cervical cancer.
– **Duration of use [608]:** Compared with never-users, the relative risks of cervical cancer increased with increasing duration of OC use:
  Duration of use No HPV-infection
  < 5 years 1.1 (1.1–1.2)
  5–9 years 1.1 (1.1–1.2)
  ≥ 10 years 2.2 (1.9–2.4)
  Duration of use HPV-infection
  < 5 years 0.9 (0.7–1.2)
  5–9 years 1.3 (1.0–1.9)
  ≥ 10 years 2.5 (1.6–3.9)
  In 2007, findings from another pooled analysis of data from 24 studies worldwide including 16,573 women with cervical cancer and 35,509 without cervical cancer suggested that the risk of invasive cervical cancer increased with prolonged duration of COC use (RR for use 5 years vs never-use, 1.90; 95% CI 1.69–2.13) **[23].**
– **Histology:** Histological results were broadly similar for invasive and in-situ cervical cancers, for squamous cell and adenocarcinoma.
– **Confounding factors:** The results were comparable in studies that adjusted for HPV status, number of sexual partners, cervical screening, smoking, or use of barrier contraceptives.
– **Past users:** The risk decreased in the meta-analysis of **Appleby et al. 2007 [23]** after discontinuation of COC use, returning to that of never-users 10 or more years after discontinuation. Consequently long-term users of OC should be screened for cervical cancer in specific programs.
  Bias: However, study designs showed a remarkable variety and heterogeneity between different studies.

Screening programs: Improved screening programs and initiation of vaccination against HPV infection during adolescence have created a new paradigm in cervical cancer control.

Summary:

Incidence: Estimated new cases and deaths from cervical (uterine cervix) cancer in the United States in 2010: New cases: 12,200, Deaths: 4,210 **[293]**

Histology: The World Health Organization (WHO) recognizes two main histological types of invasive cancer: **Squamous carcinoma** (about 85% of all cases) and **adenocarcinoma** (about 10–12% of all cases) **[307].**

Etiology: Cervical cancer is almost always caused by human papillomavirus (HPV) infection **[293]**

Combined oral contraceptives:

– **Metaanalysis: [608]:** 28 eligible studies were identified, including a total of 12,531 women with cervical cancer.
– **Current users [608]:** Compared with never–users of oral contraceptives, the relative risks of cervical cancer increased with increasing duration of use **[23].**
– **Past users:** The risk decreased in the meta–analysis of **Appleby et al. (2007) [23]** after discontinuation of COC use, returning to that of never-users 10 or more years after discontinuation.
– **Bias:** Study designs varied and the results showed big heterogeneity.

Reviews and meta-analysis:

– **IACR Monographs on the Evaluation of Carcinogenic Risks to Humans (2009) [278]**
– **Meta-analysis: Smith et al. (2003) [608]**

Further references:

– The ESHRE Capri Workshop Group (2005) [649]
– **National Cancer Institute (US) [293], National Cancer Institute, US [479]**.

2.4.3.3. Benign Liver Tumors and Hepatic Cancer

– **Liver cancer:** Current, but not past OC use is associated with an increased risk of benign liver tumors and a modestly increased relative risk of liver cancer.

OC use and liver diseases (benign tumor and hepatic cancer)

– Several studies have found that OCs increase the risk of liver cancer in populations usually considered low risk, such as white women in the United States and Europe who do not suffer from liver disease. In these studies, women who had used OCs for longer periods of time were found to be at an increased risk of liver cancer **[728].** However, OCs did not increase the risk of liver cancer for women in Asia and Africa, which are high risk areas for this disease. The most probable explanation for this is the fact that predominant risk factors, such as hepatitis infection, outweigh the effect of OCs **[735].**

2.4.3.4. Various benign tumors and carcinoma [311]

– There was no evidence of an association between OC use and lung or digestive tract neoplasms, cutaneous malignant melanoma, thyroid cancer and any other neoplasms investigated **[337]**
– The data for colorectal cancer are suggestive of a favorable, protective

effect of OC albeit in the absence of any consistent duration or recency risk relation. A better understanding of any potential link between OC use and colorectal cancer may therefore help making an informed choice about contraception **[337, 402].**

2.5. Serious Adverse Events/ Contraindications [339]

Use of combined OCs is associated with an increased risk of several serious conditions, including e.g. myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease. The absolute risk of these events is very low in women without risk factors. The epidemiological data have mainly been obtained from studies using oral contraceptive formulations containing higher estrogen and progestin doses than currently used. The effect of long-term, low dose OC use has yet to be determined.
See also **Sabatini et al. (2011)** in the same supplement.

2.5.1. Absolute Contraindications to the use of Combined OCs Include

- Previous thromboembolic event or stroke, cerebral vascular or coronary artery disease, and valvular heart disease with complications
- Major surgery with prolonged immobilization
- Severe hypertension
- Headaches with focal neurologic symptoms
- Known or suspected estrogen-dependent tumor (i.e., endometrial, breast cancer)
- Liver disease
- Cholestatic jaundice of pregnancy or jaundice with prior hormonal contraceptive use

Relative contraindications:

- Pregnancy
- Undiagnosed abnormal uterine bleeding
- Women over the age of 35 who smoke
- Obesity – Women with a BMI > 27 are at an increased risk of pregnancy if they receive low dose estrogen formulations. However, since obesity is an independent risk factor for thromboembolism, the use of higher estrogen formulations (50 µg) is not advisable.
- Inherited thrombophilia – Combined hormonal contraceptives should be avoided, although routine screening is not recommended.
- Poorly controlled hypertension – risk of exacerbation, long term risk for stroke, myocardial infarction
- Treatment with anticonvulsants – efficacy may be reduced due to drug interactions
- Migraine headaches, especially with aura and neurological symptoms – increased risk of stroke
- Diabetes – not a contraindication if no vascular disease is present, but the insulin dose may need adjusting

3. Various Combinations of Estrogens and Progestins

3.0. Basics of Steroids Used for Hormonal Contraception
3.1. Substances

3.1.1. Estrogens

3.1.1.1. Estrogen Type

Ethinyl estradiol and mestranol
Most oral contraceptives have contained EE as the estrogen component of combined OC for more than 50 years. Initially mestranol, the 3-methylether of EE, was also used. Mestranol is metabolized in the liver into the active EE but this conversion process is highly variable und not clearly predictable. Today mestranol is used only in a few combinations still on the market.

Estradiol and its derivatives
Estradiol or its derivatives are used in combination with progestins for ovulation inhibition, to substitute estrogen deficiency, and to prevent intermenstrual bleeding, leading to regular withdrawal bleedings.

3.1.1.2. Estrogen Dosage

- Estrogen doses do not clearly influence contraceptive effectiveness, but the limiting factors are dose-dependent differences in tolerability **[70].**

- In a clinical study comparing COCs with 20 and 35 µg of EE, cycle control and discontinuation rates were comparable between the two groups. Women receiving the higher EE dose reported a 50% greater incidence of estrogenic adverse events, such as bloating, breast tenderness and nausea, compared with women receiving the lower EE dose **[554].**

- A Cochrane Library review on COCs containing ≤ 20 µg EE showed an increased risk of bleeding irregularities, including amenorrhea or infrequent bleeding, prolonged or frequent bleeding and unscheduled bleeding or spotting, and higher rates of early discontinuation, both overall and due to adverse events such as irregular bleeding compared with COCs containing more than 20 µg EE **[199].**

3.1.2. Progestins

- **Classification:** Progestins are commonly classified by "generation". These categories may be misleading because progestins of the same generation often behave differently from each other and the same progestin may be categorized differently in different studies, i.e., norgestimate has been classified as both a second-and third-generation progestin.

- **Biological action:** Progestins diminish the estrogen-related stimulating effect on the endometrium by inhibiting the expression of the estrogen receptor. All progestins bind to the progesterone receptor. They differ in their relative binding strength to this steroid receptor, as well as to the androgen, estrogen, glucocorticoid and mineralocorticoid receptors and sex hormone-binding globulin **[393, 580].** In binding to a steroid receptor, progestins may exert antagonistic, agonistic or no clinical effects. Moreover, low-or high-binding affinity does not necessarily correlate with biologic effectiveness **(Tab. 3).**

3.2. Target Organs

- **Hypothalamic and pituitarian effects:** One of the progestational effects as a basis of oral contraception is the inhibition of ovulation. The ovulation inhibition dosages vary between different progestins.

- **Endometrial effects:** At the level of the endometrium, estrogens stimulate endometrial cell division, whereas progestins block this effect. As a result of progestin action, cell proliferation ceases, despite continuous exposure to estrogen levels, comparable to the physiological cycle,i.e. the luteal phase. Progestins protect from estrogen-induced hyperplasia and changes in the proliferative status. They induce the glandular epithelial secretory activity

and decidual transformation of stromal fibroblasts; these terminally differentiated cells can no longer proliferate and are shed in withdrawal bleeding if implantation does not occur. These effects are dependent on the pharmacology of the progestins used, especially their type, dosage, pharmacokinetics **[474].**

However, multiple changes in histological features occur during hormonal contraception treatment, such as different proliferatory, secretory, and atrophic patterns, changes in the glando-stromal ratio, stromal factors (i.e. growth factors), architectural structures (i.e. cribriform and/or papillary patterns), glandular cellularity, cytoplasmic changes, mitotic activity, (tumor-) angiogenesis, and increase or decrease in cytological atypia.

3.2.1. Reduction of the Dosage of Ethinylestradiol or Mestranol in Monophasic OCs in a 21-day Regimen

Monophasic pills are oral contraceptives that have the same amount of estrogen and progestin in each active pill in a blister pack. Due to the consistently high hormone level in each pill, monophasic OCs are less likely to cause side effects that may result from fluctuating hormones. Monophasic OCs are classified by their estrogen level:

- Low dose pills have the least amount of EE (15–20 µg)
- Regular dose pills contain 30–35 µg EE
- High dose pills have about 50 µg of EE.

Monophasic birth control pills are as effective in preventing pregnancies as the more expensive phasic OCs, which typically cause more side-effects. Low estrogen-containing, monophasic OCs may cause less bloating or breast tenderness but result in more bleeding complications (especially spotting). Most women prefer a monophasic OC as a first choice.

Table 3: Contraceptive progestins: pharmacological, experimental and clinical profile. According to [394, 500, 481, 482, 599, 602, 639].

Progestogens	Oral active	Used for COC	COC on the market	Halflife (hours)	Ovulation inhibition dosage per day (mg/day)	Endometrium transformation dosage per cycle (mg/cycle)	Endometrial action	Antigonadotropic action	Antiestrogenic action	Estrogenic action	Androgenic action	Antiandrogenic action	Glukocorticoid-similar action	Anti-mineralo kortikoid action
Progesterone	+	+	+	several minutes [304]	300 [394]	4200 [394]	+	+	+	–	– (±)	–	–	+
19-Nortestosterone derivatives Ethinyl-substituted														
Norethisterone	+	+	+	8 (6–12) [304]; 7 [299]	0,4 [394]	120 [394]	+	+	+	+	+	–	–	–
Norethisterone acetate	+	+	+	8 [304]	0,5 [394]	50 [394]	+	+	+	+	+	–	–	–
Lynestrenol	+	+	+	26	2 [394]	70 [394]	+	+	+	+	+	–	–	–
Norethinodrel	+	+	+	5–14	4 [394]	150 [394]	±	+	±	+	+	–	–	–
Ethynodiol diacetate	+	+	+		2 [394]	15 [394]	+	+	+	+	+	–	–	–
Levonorgestrel	+	+	+	16 (8–30) [304]	5 [394]	5 [394]	+	+	+	–	+	–	–	–
Norgestimate	+	+	+	12–30 [300]	0.2 [394]	7 [394]	+	+	+	–	(+)	(+)	–	–
Desogestrel	+	+	+	27.8 ± 7.2 [298]	0.06 [394]	2 [394]					(+)	–		
3-Keto-Desogestrel	+	–	–	38 ± 20			+	+	+	–	(+)	–	–	–
Gestoden	+	+	+	16–18 [301]	0.031	3 [394]	+	+	+	–	(+)	–	–	+
Methyl-substituted														
Dienogest	+	+	+	8–10 [492]	1 [394]	6 [394]	+	+	–**	–	–	+	–	–
19-Norprogesterone derivatives														
Nestorone *) non-oral route	–	–	–	24–72 [599, 189]	0.15 [599]	0.6	+	+	+	–	–	–	–	–
Trimegestone	+	+	+	15 [599]	0.5 [599]	0.25	+	+	+	–	–	–	–	–
Nomegestrol acetate	+	+	+	28–51 [599]	1.25–2.5 [599]	100 [394]	+	+	+	–	–	±	–	–
Promegestone	+	–	–		0.5 [394]	10 [394]	+	+	+	–	–	–	–	–
Dimegestone	+	–	–		2.5	100 [394]	+	±	±	–	–	–	–	–
17-Hydroxyprogesterone derivatives														
Chlormadinone acetate	+	+	+	25 (sd); 36–39 (md) [643]	1,7 [394]	25 [394]	+	+	+	–	–	++	+	–
Cyproterone acetate	+	+	+	40 [297]	1 [394]	25 [394]	+	+	+	–	–	++	+	–
Megestrol acetate	+	–	–	34 (13–104) [304]	n. a.	50 [394]	+	+	+	–	(+)	–	+	–
Medroxyprogesterone acetate	+	–	–	12–17; 30 [304]	n. a.	50 [394]	+	+	+	–	(+)	–	+	–
Spirolactone derivatives														
Drospirenone	+	+	+	30	2	50	+	+	+	–	–	+	–	+

sd = single dose; md = multiple dose; * depends on delivery system; ** according to Oettel et al. (1999) [493], and Taubert and Kuhl (1995) [639] dienogest possesses antiestrogen action like all progestins

High dose estrogen (150 µg mestranol or 100 µg ethinyl estradiol) and progestin (several times above ovulation inhibition dosage) pills [270]:

1951 The progestin derivative Norethindrone was the first orally active substance first synthesized by the chemists L. Miramontes, C. Djerassi, and G. Rosenkranz at Syntex in Mexico City. Norethindrone is an isomer of norethisterone.

1956 The Harvard group of physiologists, chemists, clinicians and physiologists G. Pincus, J. Rock, M.C. Chang and C.R. Garcia experimented with progestins to induce an artificial state of pregnancy. Norethynodrel and norethindrone, the progestins used, were contaminated with a small percentage of estrogen (up to 4-7% mestranol). Mestranol, a methylether and an inactive pro–drug of EE, undergoes its first metabolization in the liver. The potency of 150 µg mestranol equals 100 µg EE **[730, 308].** The suitable additional dose of Mestranol to supplement Norethynodrel in order to suppress breakthrough bleeding was found, and the first oral contraceptive as a combination of progestins and mestranol was introduced under the proprietary name **Enovid™ [518, 549].**

1957 The Food and Drug Administration (FDA) approved the first hormonal combination Enovid 10 mg™ (9.85 mg norethynodrel plus 150 µg mestranol) for menstrual disorders based on data from its use by more than 600 women. Numerous additional contraceptive trials showed *Enovid* to be highly effective at 10, 5, and 2.5 mg doses **[358].**

1959 Searle intended to add contraception as an approved indication for 10, 5, and 2.5 mg doses of Enovid™. The FDA refused the application until Searle agreed to withdraw the lower dosage forms from the application **[450, 719].**

1960 The FDA announced the approval of Enovid 10 mg™ for contraceptive use. By this time Enovid 10 mg had been in general use for three years. In a conservative estimate, at least half a million women had used it **[358, 450, 719].** Although FDA-approved for contraceptive use, Enovid 10 mg™ was not marketed by Searle as a contraceptive.

1961 On February 15, 1961, the FDA approved Enovid 5 mg™ by Searle for contraceptive use. In July 1961, Searle finally began to market Enovid 5 mg™ (5 mg norethynodrel and 75 µg mestranol) to physicians as a contraceptive **[450, 699].**

1961 The replacement of mestranol by the active substance EE was the first step of many subsequent modifications of COCs. **Anovlar®,** a drug containing 4 mg norethisterone acetate and 50 µg EE, was introduced in Germany by Bayer HealthCare, formerly Schering. This first European OC (Anovlar®) was already improved in comparison to the pioneer US version Enovid™ in that the hormone dose was reduced. The marketing of Anovlar® was the start of a continuously successful track record of innovation in contraception. The steroid dosages in Anovlar® were lower than in the original Enovid™, which contained 10 mg - the first step in minimizing the hormone dose.

1961 In the UK the first case of thrombosis and pulmonary embolism in a woman using Envid 10mg™ (formulation of Enovid™ in the UK) was published by **Jordan and Anand in 1961 [356],** four years after its approval. It took almost a decade of epidemiological studies to conclusively establish an increased risk of venous thrombosis in oral contraceptive users as well as an increased risk of stroke and myocardial infarction in risk groups **[450].**

1968 Epidemiological studies showed a high rate of pulmonary embolism in the UK linked to the use of oral contraceptives **[340].** The evaluation of transcripts of 499 death certificates relating to women aged 20–44 who died in England, Wales, and Northern Ireland during 1966 (pulmonary embolism [n = 77], coronary thrombosis [n = 205], cerebral thrombosis [n = 27]) showed a strong correlation to the use of the oral contraceptives Enavid™/Enovid™.

High dose COCs containing 75 and 150 µg estrogen led to a 6 fold increased risk for venous thromboembolism, and the progestin content of the pill was linked to the development of hypertension **[568].** These data led to the reduction of both components: the estrogen (EE or mestranol) – responsible for the increased risk of venous thrombosis – and the progestin, whose dosage of up to 6 times the ovulation inhibition dose was unnecessarily high and essentially responsible for the increased risk of arterial complications (arterial hypertension, myocardial infarction, stroke).

50 µg ethinyl estradiol containing pills

1970 Successful studies were performed with EE dosages reduced from 150 µg mestranol per tablet to 80 µg mestranol and 50 µg EE respectively.

30 µg ethinyl estradiol containing pills

1972 Development of low dose monophasic preparations called micropills containing less than 50 µg EE per pill in the United States and Germany. The first micropill was introduced in Germany by Schering Pharmaceuticals, Berlin (now Bayer HealthCare).

1973 The micropill Microgynon 21® and 28® was introduced by Schering (now Bayer HealthCare) containing 0.15 mg levonorgestrel and 30 µg EE. For the first time, an OC containing less than 50 µg EE was available, establishing a whole new class of pills called "micropills". Since then, the micropill has become the standard OC. Pills with higher estrogen doses have more or less disappeared. Microgynon® is still on the market even today, more than 35 years after its introduction and used by hundreds of millions of women worldwide. It is considered the standard product for contraception and was included in the WHO Model List of Essential Medicines.

Lowering the EE dosage per tablet from 50 to 30–35 µg led to a reduction of myocardial infarction, stroke and deep vein thrombosis (DVT).

1992 The first large-scale study including more than 60.000 women in Germany provided data about the prevalence of cardiovascular disease in the family history of OC users **[569].**

20 µg ethinyl estradiol containing pills

1992 A further reduction of the EE dosage from 30–35 to 20 µg EE per tablet became possible and was effective in preventing pregnancies. Lovelle, an ultra low dose OC containing 20 µg EE, was introduced by Organon. A **Cochrane database analysis of** the contraceptive effectiveness, side-effects and bleeding pattern under ultra-low-dose pills (20 µg) versus OCs with > 20 µg EE/tablet was published by **Gallo et al. (2005) [200].** The report stated that women taking OCs with less estrogen tend to quit the studies early due to higher rates of disrupted bleeding patterns than women using OCs with a higher EE content. This review did not show differences between the estrogen containing OCs concerning their contraceptive effectiveness.

1996 A lower dosed monophasic preparation containing 20 µg EE/100 µg levonorgestrel was developed and introduced by Schering under the name Miranova® in 1998. In this COC product, the proportions of estrogen and progestin were maintained, ensuring a balance between the components. This low dose preparation proved the concept that COCs containing less than 30 µg EE can achieve reliable contraceptive efficacy and acceptable cycle control. Later on, this led to further successful developments by Bayer HealthCare (formerly Schering), such as OCs containing drospirenone (Yasminelle® and YAZ®).

Summary:

– Lowering the EE dosage per tablet from 30–35 to 20 µg per tablet in a 21+7 regimen led to comparable contraceptive effectiveness but to often inadequate bleeding control. Regimens with a shorter hormonal withdrawal interval (24+4) showed characteristics which differed less from OCs containing 30–35 µg EE.
– The meta-analysis by Gallo did not focus on the severe adverse events like DVT. Theoretically the reduction of the EE content to 20 µg could lead to a reduction of DVT risk.
– For the ultra-low dose class of COC, non-contraceptive benefits including protection against endometrial and ovarian cancer must still be proven by epidemiological trials.
– Furthermore, additional data about bone health (i.e. BMD, fracture etc.) are necessary.

15 µg ethinyl estradiol containing OCs [501]

The amount of EE per tablet was reduced even further to 15 µg per day. Although these very low dose combinations are theoretically better tolerated by women with metabolic risk factors **[38],** they appear to be less well tolerated in terms of bleeding pattern disruption and sex life compared with a 20 µg EE containing pill or a vaginal ring delivering 15 µg of EE per day **[570].** The effect on bone mineral density of such low dose EE treatment remains to be determined.

Summary:

– Lowering the EE dosage per tablet from 30–35 to 15 µg may lead to a further reduction of DVT, but studies are lacking.
– Non–contraceptive benefits including protection against endometrial and ovarian cancer must be proven by epidemiological trials for this class of COC.
– Furthermore, new data about bone (i.e. BMD, fracture etc.) health are necessary.

3.2.2. Monophasic Oral Contraceptives Without Ethinyl Estradiol

Desogestrel-only pill (Cerazette®, MSD then Organon)

1999 Introduction of an estrogen-free oral contraceptive with desogestrel (Cerazette from MSD then Organon).

Rationale:

– A progestin-only pill with a progestin dose above the ovulation inhibition dosage achieves complete ovulation inhibition. In addition it impairs fertility based on three peripheral factors: the Fallopian tube, the endometrium and the cervix.
– Contraceptive efficacy is very good and comparable to that of combination OCs.
– The intake scheme is also similar to the combination preparations but due to continuous intake, fewer intake errors and problems with medication adherence may occur compared to conventional 21+7 COC.

Indications

Estrogen-free OCs are suitable for women of all ages who desire quickly reversible oral contraceptives. In addition, they are suitable for patients with specific indications **[6]** such as:

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

Clinical profile:

– It was recently demonstrated that the 75 µg desogestrel-only pill (Cerazette) could maintain ovulation inhibition even after a 12 h delay in tablet intake **[379].** However, regardless of the route of administration, the main drawback of progestin only contraceptives is the high incidence of irregular vaginal bleeding leading to discontinuation rates of close to 25% **[381]** Breakthrough bleeding in POP users can be related to incomplete suppression of ovarian activity or to a direct effect of progestins on the endometrium.
– The estrogen-free pill is well-tolerated. Due to the partial androgenic activity of desogestrel, this OC it not suitable for women with seborrhoea, or acne. Clinical practice has shown that they should not be used in case of recurrent menstrual disorders **[6, 7].**
– Similar to other progestin preparations with continuous intake, irregular bleeding is not predictable. Some women experience regular weak bleeding, while others suffer from intermediate bleeding, breakthrough bleeding or amenorrhea.

Safety profile:

– Even when the desogestrel estrogen-free pill is taken for several years, the

endogenous estradiol production is not suppressed to such an extent that it would favor osteoporosis.

Summary:
- Estrogen-free contraceptives with ovulation inhibition are a good choice for hormonal contraception.
- These OCs can be used when estrogens are contraindicated or not well tolerated, and in breastfeeding women.
- Lowering the EE dosage per tablet from 30–35 to 0 µg led to a further reduction of DVT **[422].**
- The safety margin for "missed pills" is 12 hours.
- Regardless of the route of administration, the main drawback of progestin only contraceptives is the high incidence of irregular vaginal bleeding leading to high discontinuation rates.
- Another solution to the tablet intake delay problem might be new non–user dependent administration routes, such as implants. They (Norplant®, Jadelle® and Implanon®) contain levonorgestel or etonogestrel. They are safe and highly effective **[205, 458].**

3.2.3. Monophasic OCs with Ethinylestradiol and Different Regimens

3.2.3.1. Shortening the pill-free interval in 28 days regimens

Rationale:
- In 2008, there was a renaissance of a shorter placebo regimen; existing patents had prevented the "new" discovery and development of OCs with a shorter hormone-free interval.
  Due to the high doses in the first- and second generation OCs and the 21/7 regimen, the hormone levels declined in the week without pill intake.
- For low-dose OCs and a 7-day hormone–free interval (HFI), **Sulak and Liu (2008) [632]** described a high incidence of hormonal withdrawal symptoms, unscheduled bleeding (i.e. breakthrough bleeding or spotting), and, finally, a high rate of breakthrough ovulations.
- The reason for these symptoms is the interaction of contraceptive steroids with follicular development during the menstrual cycle **[632].** In the normal menstrual cycle, the pituitary secretion of follicle-stimulating hormone (FSH) increases dramatically during the first 2 days of the cycle, triggering the development of up to 10 primordial follicles. As estrogen and inhibin-B levels increase and suppress FSH, only the follicle with the highest expression of FSH receptors survives this low-FSH environment to become the leading follicle.
  During the hormone–free interval of an OC regimen, FSH begins to increase in line with the physiological state of a normal menstrual cycle. When very-low-dose estrogen/progestin OCs are taken, this rebound occurs rapidly and follicles begin to develop. When follicles develop – the critical size might be as small as 14 mm – escape ovulation may occur despite the fact that active OC pills are taken and FSH is suppressed **[33].**
- According to **Sulak and Liu 2008 632],** up to 30% of women may ovulate on OCs when the hormone-free interval is extended **[33].** Studies have shown that the dramatic rise in FSH occurs around the fourth day of a 7-day hormone-free intervall, followed rapidly by the rise in 17-beta estradiol from the ovarian follicles **[634, 713].** Even in women using a 30 µg pill there may be a 500% increase in estradiol, from 10 pg/ml to almost 60 pg/ml **[713].**

- **Reduced placebo regimen by shortening the pill free interval [632]:** Starting in 1998 with the approval of Mircette, a number of modifications to the 21/7 regimen have been made. **Mircette**™ is a regimen including 21 days of 20 µg EE and 0.15 mg desogestrel, 2 placebo days, and 5 days of 10 µg EE pills. By adding 10 µg EE in the last 5 placebo pills a stronger ovarian suppression and less follicular development was achieved **[372].** This led to a bleeding profile comparable to OCs with 30 µg EE **[554, 651].** The use of a very low-dose estrogen instead of the placebo suppresses the pituitary, prevents "rebound" FSH rise and attenuates the rise of inhibin B, so that new follicles do not begin to develop **[540].** This prevents a situation where increased endogenous production interferes with the next cycle and causes breakthrough bleeding **[554, 680].**

Discussion of Sulak's opinion:
- **Breakthrough ovulations** may not be as frequent as generally assumed**:** In a literature review, **Milson and Korver (2008) [462]** demonstrated an overall ovulation incidence of 2.0% (1.1–3.3) for COCs containing 30–35 µg EE, 1.1% (0.60–2.0) for 15–20 µg EE, 4.6% (2.8–6.9) for phasic COCs, 1.25% (0.03–6.8) for a desogestrel–only pill and 42.6% (33.4–52.2) for traditional progestin-only pills.

- **Contraceptive efficacy** was not improved by a low EE dose drospirenone 24+4 regimen.

- **Estrogen withdrawal symptoms: Sulak et al. (2000) [633]** performed a study including 262 women (26 with no previous OC use, 43 prior users, and 193 current users) who kept daily records of hormone-related symptoms. Women with no prior OC use and prior users restarting were pooled for analysis as new-start OC users. Current users had patterns of symptoms that were more frequent during hormone-free intervals than during the 3 active-pill weeks. These included pelvic pain (70% versus 21%, $p < 0.001$), headaches (70% versus 53%, $p < 0.001$), use of pain medication (69% vs 43%, $p < 0.001$), bloating or swelling (58% versus 19%, $p < 0.001$), and breast tenderness (38% vs 16%, $p < 0.001$). Similar patterns were seen in new-start OC users after the first cycle. Among new-start OC users, menstrual flow patterns, headache, bloating or swelling, and breast-tenderness symptoms decreased during the three cycles to approach the levels of current users.
  It is possible that the adverse effects in the pill free interval may be specific to progestins; i.e. the antimineralocorticoid action of drospirenone counterbalancing the increased aldosterone is not opposed during the pill-free interval. This could lead to fluid retention through increased aldosterone and corresponding symptoms.

Further comments:
- The OCs that have been approved since 2003 and feature modifications of the 21/7 regimen are mainly Seasonale™ (84+7 placebos), Seasonique™ (84+7 low EE pills), Low Seasonique™ (84+7) and Yaz™ (24+4 regimen).
- Hormone withdrawal symptoms in the pill-free interval depend on the

dosages of steroids used and mainly on the half-life of the progestins. Progestins such as nomegestrol acetate (50 hours), drospirenone (40 hours), cyproterone acetate (30 hours), chlormadinone acetate (36–39 hours) have a longer half-life. In the case of these substances, declining steroid concentrations are still detectable after the withdrawal of the active tablets in the pill-free intervall. The half-life of other progestins is shorter: levonorgestrel (15 hours), gestodene (12 hours), desogestrel (12 hours), dienogest (8–10 hours) **[454]** and norethisterone (7 hours).

– A lot of excellent studies demonstrate that a shortening of the pill-free interval led to a better suppression of follicle recruitment but clinical trials prepared to obtain approval for COC with the 24+4 regimen based on drospirenone **[32, 179]** and chlormadinone acetate **[64]** did not show a better contraceptive efficacy or bleeding control compared to traditional 20 µg EE-containing combined oral contraceptives.
– The longer annual exposure time to steroids must be carefully monitored in long term trials with these formulations.
– **Patient and health care provider attitudes [315]:** Most women and health care providers are considering options other than the traditional oral contraceptives that result in a 28-day cycle and monthly withdrawal bleeding. International studies have demonstrated that each cultural context has its own beliefs **[206, 710].** Health care professionals providing care to an ethnically diverse population need to realize the influence of culture on attitudes regarding reproductive health.

  One survey of U.S. women demonstrated that 59% would be interested in menstruating less often; 56% would be interested in menstruating every 3 months or not at all, and 33% would consider using a contraceptive method that would induce amenorrhea **[20].** A more recent survey examined the attitudes and prescribing patterns of U.S. health care providers (including physicians, physicians' assistants, and nurse practitioners) regarding extended and continuous-cycle oral contraceptives **[631].** Most (87%) respondents thought that these regimens should be offered, and many (81%) had prescribed such regimens before. A small number of respondents (12%) viewed monthly withdrawal bleeding resulting from a traditional 21/7 regimen as "necessary and having health benefits." Obstetricians and gynecologists were more likely (94%) to offer extended- and continuous-cycle regimens than prescribers in other specialties (81%).

Norethindrone/EE 24+4 pill (brand name: Loestrin 24 Fe)

Product: Loestrin 24 Fe™ (EE 20 µg–norethindrone 1 mg (Loestrin 24 Fe; Warner Chilcott, Rockaway, NJ) provides a dosage regimen consisting of 24 tablets with 1 mg norethindrone acetate and 20 µg EE and 4 brown ferrous fumarate (placebo) tablets.

– **Side effects:** The most common adverse events reported by 2–6% of the 743 women using Loestrin 24 Fe™ were in order of decreasing incidence: headache, vaginal candidosis, upper respiratory infection, nausea, menstrual cramps, breast tenderness, sinusitis, vaginitis (bacterial), abnormal cervical smear, acne, urinary tract infection, mood swings, weight gain, vomiting, and metrorrhagia. Among the 743 women using Loestrin 24 Fe™, 46 women (6.2%) stopped taking the drug because of an adverse event. Adverse events occurring in 3 or more subjects leading to discontinuation of treatment were, in decreasing order: abnormal bleeding (0.9%), nausea (0.8%), menstrual cramps (0.4%), increased blood pressure (0.4%), and irregular bleeding (0.4%).
– **Contraceptive efficacy:** A 6–month, open–label, randomized, active–controlled study was conducted in the United States to determine the efficacy of this new 24/4 regimen **[476].** In addition, the frequency of breakthrough bleeding under the 24/4 regimen was compared with that of a traditional 21/7 regimen. Both preparations contained EE 20 µg/norethindrone 1 mg. Healthy women of childbearing age were included and randomized. After 6 months of treatment, the Pearl Index was 1.82 in the 24/4 group versus 2.98 in the 21/7 group. The study was not powered to detect differences in contraceptive efficacy between the two groups.
– **Bleeding pattern:** At 6 months, significantly less breakthrough bleeding was noted with the 24/4 versus the 21/7 regimen (mean number of days 0.95 vs. 1.63, $p = 0.005$). In addition, the 24/4 group had a mean withdrawal bleeding duration of 2.66 days compared with 3.88 days in the 21/7 group ($p < 0.001$).

Summary:

– The 24+4 regimen based on norethindrone and low dose estrogen provides a good contraceptive efficacy and bleeding pattern.
– The discontinuation rate due to side effects was as low as 6,2%.
– Using ferrous fumarate in the 4 placebos as iron supplementation is an additional feature of this OC. A product without iron supplementation is available, or the placebo tablets can be skipped.

Drospirenone/EE 24+4 regimen (brand name: YAZ™)

2006 The first 24+4 regime with drospirenone called YAZ™ and containing 20 µg EE and 3 mg drospirenone was introduced in the US 2006. It has been on the German market since 2009. For the US, it has been approved by the FDA for 3 indications; in Europe it has only been approved for contraception.

Contraception (rx-list) [322]

– **Indication:** YAZ™ is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.
– **Contraceptive efficacy (US trials) [32]: The pregnancy rate (Pearl Index)(PI) was 1.41 per 100 woman-years** of use based on 12 pregnancies that occurred after the onset of treatment and within 14 days after the last dose of YAZ™ in women 35 years of age or younger during cycles in which no other form of contraception was used.

According to Fenton et al. (2007) [179]: For the US trial, the PI adjusted for noncompliance was 0.72;
In the European trial **[250]** the uncorrected PI was 0.49 **[179].**
The cumulative pregnancy rates were 1.26% **[179]** and 0.5% in the international and EU trials **[179].**

– **Oral Contraceptive Clinical Trial in the US [32]:** In the primary contraceptive efficacy study of YAZ (3 mg

DRSP/20 µg EE) with a duration of up to 1 year, 1,027 subjects were enrolled and completed 11,480 28-day cycles. The age range was 17 to 36 years. The racial demographics were: 88 % Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian, and 2.1% other. Women with a BMI greater than 35 were excluded from the trial.

Premenstrual dysphoric disorder (PMDD) [322]:

- **Indication in the US:** YAZ™ is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception.
- **Effectiveness over time:** The effectiveness of YAZ™ for PMDD when used for more than three menstrual cycles has not been evaluated.
- **Definition of disease:** The essential features of PMDD according to the Diagnostic and Statistical Manual – 4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective instability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptoms assessed prospectively over at least two menstrual cycles. When making the diagnosis, care should be taken to rule out other cyclical mood disorders.
- **Clinical trials: Premenstrual Dysphoric Disorder Clinical Trials:** Two multicenter, double-blind, randomized, placebo-controlled studies were conducted to evaluate the effectiveness of YAZ in treating the symptoms of PMDD. Women aged 18–42 who met DSM-IV criteria for PMDD confirmed by prospective daily ratings of their symptoms were enrolled. Both studies measured the treatment effect of YAZ™ using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable reproductive-aged women with PMDD who were randomly assigned to receive YAZ or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrolment difficulties. A total of 64 women of reproductive age with PMDD were treated initially with YAZ™ or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.
  Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems. Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received YAZ™ had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking YAZ™, compared to 30 points in women taking placebo.
- **Manufacturer's note:** To achieve maximum contraceptive and PMDD effectiveness, the pill YAZ™ must be taken exactly as directed at intervals not exceeding 24 hours
- **Limitations:** YAZ™ has not been evaluated for the treatment of the premenstrual syndrome (PMS).

Acne vulgaris [322]:

- **Indication in the US:** YAZ™ is indicated for the treatment of **moderate acne vulgaris** in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. YAZ™ should be used for the treatment of acne **only if the patient desires an oral contraceptive for birth control.**
- **Clinical trials:** In 2 multicenter, double blind, randomized, placebo-controlled studies, 889 subjects, aged 14 to 45 years, with moderate acne received YAZ™ or placebo for six 28 day cycles. The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a "clear" or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) scale on day 15 of cycle 6 showing according to the ISGA a total success rate for the reduction (Yaz versus placebo) in the first trial of 15% (35/228) versus 4% (10/230) (35 (15%), and in the second trial of 21% (46/218) versus 9% (19/213). Data given for non-inflammatory lesions lesions have been reported **[322].**

Precautions [322]:

In addition to precautions known for all COC, there are progestin-specific precautions for drospirenone, which has an anti-mineralocorticoid activity

- including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone.
- YAZ™ should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction and adrenal insufficiency).
- Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium should have their serum potassium level checked during the first treatment cycle.
- Medications that may increase serum potassium include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDS.

Summary [179]:

- **24+4 regime:** Novel low dose oral hormonal contraceptive containing 20 µg EE combined with the innovative progestin drospirenone (3mg) in a regimen of 24 days of active tablets followed by a short hormone free interval (4 days; 24/4 regimen)(brand name: YAZ™).
- **Drospirenone**, unlike other synthetic progestogens used in COCs, is a 17α-spirolactone derivative with anti-

androgenic and antimineralocorticoid properties (leading to a significant increase in serum aldosterone).
– **US approval:** Yaz™ has been approved in the US for the prevention of pregnancy in women, for the treatment of the symptoms of premenstrual dysphoric disorder (PMDD) and for the treatment of moderate acne vulgaris in women who wish to use an oral contraceptive for contraception.
– **European approval:** only for contraception, because in Europe randomized control trials for drug approval (i.e. acne and PMDD) must be conducted against a competitor and not a placebo.
– **Contraceptive efficacy:** The contraceptive efficacy is different between US and European trials, which has also been shown for other contraceptive efficacy studies. The adjusted Pearl Index of 1.26 in the international and 0.5 in the European trials is in the range expected for low dose oral contraceptives **[179].**
– **PMDD and acne vulgaris:** The same treatment regimen over three treatment cycles also improved the emotional and physical symptoms associated with PMDD significantly as well as alleviating moderate acne vulgaris over six treatment cycles in double blind trials **[179].**
– **Side effects:** Due to the fact that OC products containing drospirenone are market leaders, even the reporting of side effects is more frequent than for other brands with other progestins.
It was generally well tolerated, with most adverse events typical of those experienced with other COCs and most likely to occur in the first few cycles **[179].**
The rate of venous thromboembolism corresponds to the rates of products containing levonorgestrel, dienogest, chlormadinone acetate, norethisterone and lynestrenol and seems to be lower than for gestodene, desogestrel or cyproterone acetate. New ongoing studies are needed to provide further proof of this. **See Table 3 [539]**
– **Precautions:** As drospirenone is a spironolactone analogue with antimineralocorticoid activity, it has the potential to induce hyperkalemia in high risk patients (those with conditions that predispose them to hyperkalemia, i.e. renal insufficiency, hepatic dysfunction and adrenal insufficiency, or those receiving other medications that may increase serum potassium) **[179].**
– **Continuous use:** new clinical trials are investigating the possibility of an extended use of Yaz under the name of Yaz flex™ similar to the principle of Lybrel™ using levonorgestrel.

3.2.2.2. Continuous Daily Regimen for 3 Months

Three different low dose combined oral contraceptive pills with different regimens are currently on the US market.

- **Seasonale™ [574] (Generics: Quasense™, Jolessa™ [305].** It was first developed by Barr Pharmaceuticals and approved in 2003 by the FDA **[177].** It is now produced by Teva Women's Health, containing 30 µg of EE and 150 µg of levonorgestrel in each active pill for 12 weeks (84 d), followed by 1 week (7 d) of placebo tablets. Seasonale™ gives the benefit of less frequent periods (from thirteen per year to four per year) with the potential drawback of breakthrough bleeding. Although Seasonale™ users have fewer scheduled menstrual cycles, data from clinical trials show that, especially in the first few cycles of use, many women had more unplanned bleeding and spotting between the expected menstrual periods than women taking a conventional 28–day cycle of an oral contraceptive **[16].**
Method failure: A parallel, randomized, multicenter open-label, 1-year study of the OC Seasonale™ (30 µg EE/150 µg levonorgestrel (LNG) (n = 397), and Nordette-28™ (30 µg EE/ 150 µg LNG) (n = 195) in sexually active, adult women (18–40 years) of childbearing potential led to method failure (Pearl Index) of 0.60 for Seasonale™ and 1.79 for Nordette™ **[15].**
According to data published in the rxlist in a 1-year controlled clinical trial 4 pregnancies occurred in women aged 18–35 during 809 completed 91-day cycles of Seasonale™ during which no backup contraception was utilized. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 1.98 per 100 woman-years of use **[320].**
- **Quasense™ [316]:** On December 13, 2007, Teva filed a patent infringement lawsuit against Watson in the United States District Court for the District of New Jersey involving Watson's Quasense™ product, which is a generic equivalent of Teva's Seasonale™. Under the terms of the settlement agreement, Teva has granted Watson a fully paid-up license to the U.S. patents covering Seasonale™, and Watson (Watson Pharmaceuticals, Inc. has announced that its subsidiary, Watson Laboratories, Inc. will continue marketing its generic equivalent product Quasense™ (levonorgestrel and EE tablets USP, 0.15 mg/0.03 mg). Watson further admits that the licensed patents are valid and enforceable. Barr Pharmaceuticals also produces the same medicine as a generic called Jolessa™.

- **Seasonique™ 333], [574] (Generic: Lynoral®):** To counteract the unplanned bleeding, a newer version of Seasonale (Seasonique) was developed by Duramed Pharmaceuticals, now Teva Women's Health. Seasonique™ has active pills and packaging identical to Seasonale™, but replaces the placebo week with a low-dosage week of estrogen (84 active pills with 30 µg of EE and 150 µg of levonorgestrel followed by 7 more active pills with 10 µg EE) instead of the traditional placebo). **Teva [289]** acquired Seasonique™, a newer version of the now-generic Seasonale™, in the 2008 purchase of Barr Laboratories. Teva Pharmaceutical Industries Ltd., the world's biggest generic-drug maker, won a court ruling that upholds the validity of the U.S. patent on its Seasonique™ birth-control tablet which will expire in 2024. The two main advantages of replacing the placebo week with a week of low-dose estrogen are a reduced incidence of unplanned bleeding and spotting and fewer or no symptoms (e.g., cramps, bloating, headaches) for women who are sensitive to the placebo week hormone fluctuations (in particular, low estrogen). A study of 1000 sexually active adult women (aged 18–40) who used Seasonique™ for one year found that, for cycles 2–4, the median number of bleeding days on a per-patient month basis was minimal (<1 d) **[14].**
Method failure: In a multicenter, open–label, 1 year study the method

failure of Seasonique™ (30 µg EE/150 µg levonorgestrel for 84 days followed by EE 10 µg for 7 days) was 0,78 (Pearl Index) and 0,64% (life table analysis) **[14].**

Adverse reactions leading to study discontinuation: 16.3% of the women dropped out of the clinical trial due to an adverse reaction; the most common adverse reactions (≥ 1% of women) leading to discontinuation were irregular and/or heavy uterine bleeding (5.9%), weight gain (2.4%), mood changes (1.5%), and acne (1.0%) **[321].**

Risk profile: The risk profile of using Seasonale™ is similar to that of other conventional combined oral contraceptives and includes an increased risk of blood clots, heart attack, and stroke. The labeling also carries the warning that cigarette smoking increases the risk of serious adverse cardiovascular effects from the use of combination estrogen and progestin-containing contraceptives. The study cited for Seasonique does not report any unexpected adverse events or thromboembolic events; the risk profile is the same as Seasonale.

- **LoSeasonique™ [332, 574]** has been produced by Teva Women's Health (previously Duramed Pharmaceuticals) since 2009. LoSeasonique™ consists of 84 orange tablets containing 0.1 mg levonorgestrel and 20 µg EE and 7 yellow tablets containing 10 µg EE.

  The risk profile is similar to Seasonale™ and Seasonique™; however, the risk of unplanned breakthrough bleeding is increased. In a clinical trial over a 12-month period, 209 of the 2185 participants (9.6%) discontinued LoSeasonique™; at least some of them due to bleeding and/or spotting. The breakthrough bleeding remained consistent over time, averaging 2–3 days of bleeding and/or spotting per 91-day cycle. The breakthrough bleeding eventually decreased over successive 91-day cycles.

  In a multicenter, open-label, single treatment phase 3 study (n=1249 completed the study) the method failure of LoSeasonique™ was 2,74 (95% confidence interval 1,92–3,78) (Pearl Index) **[386].**

Summary:

– Three different 91-days regimens with combined oral contraceptives have been developed with the aim of reducing menstrual bleeding to 4 times a year.
– The contraceptive efficacy (Pearl Index) ranges between: 1.98 for Seasonale™, 1.34 for Seasonique™ and 2,74 for LoSeasonique™.
– The products Seasonale™, Seasonique™ and LoSeasonique™ are only available in the US.
– In many European countries, extended cycles are recommended to OC users for the "off-label" use of combined oral contraceptives, vaginal rings or hormonal patches.
– An alternative is the use of a 365-day regimen Lybrel™ (containing low-dose EE (15 µg) and levonorgestrel (90 µg)).

365 days regimen = continuous daily regimen

Lybrel™ (generic: Anya™)

– **Rationale:** continuous administration of low-dose progestin and EE suppresses follicular maturation, ovulation and menstrual bleedings. This is a continuation of the idea of the Seasonale inventors or the extended cycle with classic combined oral contraceptives.
– **FDA approval [740]:** In 2007 the U.S. Food and Drug Administration (FDA) approved Lybrel™ (90 µg levonorgestrel/20 µg EE tablets) (Pfizer then Wyeth-Ayerst) for a low dose, continuous, non-cyclic combination oral contraceptive designed to be taken continuously with no placebos and withdrawal bleeding **[176].** Lybrel® is currently available at pharmacies in the US on prescription only. This drug is marketed under the name of Anya or Lybrel™. Studies have shown that after seven months, 71% of users no longer had any breakthrough bleeding, the most common side effect of going on active pills for longer periods of time without breaks **[705].** The product went on the market in 2008, and Wyeth invested more into advertising this drug than any other medicine before **[274].**
– **Clinical profile:** In clinical trials (n = 2,134) performed by the Conrad Program (US) (2006), a Pearl Index of 1,26 has been reported with absence of bleeding in 79% of cases **[24].** Nevertheless the high rate of intermenstrual bleedings and a higher Pearl Index when compared to combined oral contraceptives meant that European approval of Lybrel™ was refused.

Summary:

- Lybrel™ is a new low dose combined oral contraceptive with a 365-day regimen.
- The only pill for an "extended cycle" of up to one year approved with clinical data about efficacy and safety.
- High intermenstrual bleeding meant that the product was not approved in Europe.
- No long-term safety data are available for long term use and for a higher steroid exposure than traditional 21+7 combined OCs.

YAZ Flex™

Ongoing studies are investigating the contraceptive efficacy, clinical tolerability and control of the menstrual cycle achieved by a product called **Yaz Flex™** developed by Bayer HealthCare.

Extended regimen with combined oral contraceptives based on "off label" use outside the US

If the pill formulation is monophasic, it is possible to skip withdrawal bleeding and still remain protected against conception by skipping the placebo pills and starting directly with the next pack. Attempting this with bi- or tri-phasic pill formulations carries an increased risk of breakthrough bleeding and may be undesirable. It will not, however, increase the risk of getting pregnant. An increasing number of women are using OCs as a long cycle (3, 6 or more blisters of a continuous combined OC without an OC free interval).

– **Rationale:** continuous administration of low dose progestin and EE through the extended use of classic combined oral contraceptives shows a good contraceptive efficacy and freedom from menstrual bleeding in most users.
– **Clinical profile:** In all COCs using an extended-cycle, breakthrough bleeding is the most common side effect, although it tends to decrease over time **[16].** In a 12-month study of a continuous COC regimens, 59% of women experienced no bleeding in months six through 12 and 79% of

women experienced no bleeding in month 12 **[24].**

– **Risk profile:** Extended or continuous use of COCs or other combined hormonal contraceptives carries the same risk of side effects and medical risks as traditional COC use.
– **Safety data:** There are no available data at this time concerning the long-term effects of menstrual suppression on a woman's overall health. There is concern in the medical field that increasing the amount of hormones typically taken by a woman may have an adverse effect on her long-term health, but there is no data to confirm or disprove this.
– **Cochrane:** In a Cochrane analysis by **Edelman et al. 2005 164]** oral contraceptives taken continuously for more than 28 days compare favorably to traditional cyclic oral contraceptives. Six randomized controlled trials met the inclusion criteria. Study findings were similar between 28-day and extended cycles in regard to contraceptive efficacy (i.e., pregnancy rates) and safety profiles. When compliance was reported, no difference between 28-day and extended cycles was found. Participants reported high satisfaction with both dosing regimens, but this was not an outcome universally studied. Overall discontinuation and discontinuation for bleeding problems were not uniformly higher in either group in most studies. The few studies that reported menstrual symptoms found that the extended cycle group fared better in terms of headaches, genital irritation, tiredness, bloating, and menstrual pain. Five out of the six studies found that bleeding patterns were either equivalent between groups or improved with continuous-dosing regimens. Endometrial lining assessments by ultrasound were done in a small number of participants but all endometrial stripe measurements were less than 5 mm.

– **Summary:**
  - Extended cycles can be achieved based on the "off label" use of any brand of combined oral contraceptive, also the combined vaginal ring and the combined contraceptive patch.
  - A flexible duration of use is possible and should be based on unexpected bleedings and the intention of the user relative to the duration of use
  - No safety data are available for long-term use and for a higher steroid exposure than traditional 21+7 combined OCs
  - Women must be informed about the "off label" use.
  - Furthermore, they have to be informed about the management of breakthrough bleedings and withdrawal bleedings. If a regular control bleeding occurs, the extended cycle must be stopped, and a new extended cycle can be started after a pill-free interval.
  - Nethertheless there is great experience in Germany with extended cycles, a method highly accepted by women and doctors. Use of this regimen in Germany is "off-label" and the women must be informed accordingly.
  - According to a German study by the **Federal Centre for Health Education (BZgA)[68],** 42% of all German women prefer regular menstrual bleedings.
  - **For further information, see (http://en.wikipedia.org/wiki/Extended_cycle_combined_hormonal_contraceptive) [272]**

3.3. Multiphasic Birth Control Pills [268]

Multiphasic oral contraceptives were developed in the 1980s. Phasic birth control pills contain varied amounts of hormones designed to be taken at specific times throughout the course of each pill pack. These pills were developed to help lessen the side effects of monophasic birth control pills. When compared to monophasic oral contraceptives, some phasic birth control pills tend to lower the total hormone dosage a woman receives while using each pill pack; they are also designed to more naturally mimic the female body's natural menstrual cycle.

3.3.1. Biphasic Oral Contraceptives [268]

1963 Introduction of sequential (biphasic) oral contraception in the United States; Sequilar® was introduced in Germany in 1964.

1968 Development of multiphasic preparations (estrogens and progestins in two dose levels; origin: Australia). First introduced in Germany in 1969.

Rationale: biphasic pills were introduced to the market in 1963 with the intention to offer OCs with a better control of the bleeding pattern and the side effect profile.

Biphasic regimen: Biphasic birth control pills alter the level of hormones once during the menstrual cycle. There are two types on the market:

– **Step-up-regimen:** One type of OC delivers the same amount of estrogen each day, but the level of progestin is increased about halfway through the cycle. Although the estrogen level remains the same, during the first half of the cycle, the progestin/estrogen ratio is lower to allow the endometrium to thicken as it normally does. During the second half of the cycle, the progestin/estrogen ratio is higher to allow for the normal shedding of the lining of the uterus. The progestin concentration in the first 7 to 10 days is different from the level in the next 11 to 14 pills. The last 7 tablets (if included) are placebo pills and contain no hormone.
– **Two-phase-regimen:** The other types deliver different amounts of EE and progestin in a biphasic fashion, e.g. Biviol® (German brand name/MSD): 7 days: 250 µg desogestrel, 40 µg EE; 15 days: 125 µg desogestrel, 30 µg EE

OC-market in Germany:

– **Desogestrel** (7 days 40 µg EE & 250 µg desogestrel/15 days 30 µg EE & 125 µg desogestrel)
– **Levonorgestrel** (11 days 50 µg EE & 50 µg levonorgestrel/10 days 50 µg EE & 125 µg levonorgestrel)
– **Chlormadinone acetate** (11 days 50 µg EE & 1 mg CMA/11 days 50 µg EE & 2 mg CMA) (Note: chlormadinone acetate is not available in the US).

Summary:

– **Modern biphasic pills on the market in Germany:** see above list.
– **Modern biphasic pills on the market in Germany:** Desogestrel (7 days 40 µg EE & 250 µg desogestrel/15 days 30 µg EE & 125 µg desogestrel), levonorgestrel (11 days 50 µg EE & 50 µg levonorgestrel/10 days 50 µg EE & 125 µg levonorgestrel), chlormadinone acetate (11 days 50 µg EE & 1 mg CMA/11 days 50 µg EE & 2 mg CMA) (Note: chlormadinone acetate not available in the US).

– **Cochrane analysis by van Vliet et al. (2006) [676]: Biphasic versus monophasic oral contraceptives:** in a Cochrane analysis, **van Vliet et al. 2006a [675]** did not find enough evidence to determine if two-phase pills worked any better than one–phase types for birth control, bleeding patterns, or staying on the pill. One trial report had methodological problems and lacked data on pregnancies. Therefore, one-phase pills are the better choice, since we have much more evidence for such pills and there is no clear reason to use two-phase pills. (Comment: weak Cochrane analysis due to lack of data).

– **Cochrane analysis by van Vliet et al (2011) [676]: Biphasic versus triphasic contraceptives:** The authors found only two trials that looked at two-phase versus three-phase birth control pills. The studies had methodological defects, and not all methods had been reported. Many women dropped out of the studies, which affects what can be said about the results. One study compared two types of two-phase pills with a three-phase pill. The pills did not differ in any major way, including the number of women who stopped using the pills due to health problems. The other trial compared a two-phase pill with two different three-phase pills. The two-phase pill had worse bleeding patterns than the three-phase pill with a different hormone (levonorgestrel). In contrast, bleeding with the two-phase pill was like that of the three-phase pill with the same hormone (norethindrone). For cycle control, the type of hormone may be more important than the phases. These trials did not provide enough evidence to say if three-phase pills worked any better than two-phase types for birth control, bleeding patterns, or staying on the pill. More research would be needed to show whether three-phase pills are better than two-phase pills. However, two-phase pills are not used enough to justify further research.
– **Indications:** patients with intermenstrual bleeding, i.e. mid-cycle bleeding or therapy-resistant bleeding problems using combined oral contraceptives.
– **Limitations:** biphasic pills cannot be used for extended cycles ("off label") or in order to pre- or postpone menstruation; the regimen for "missed pills" is more difficult than for combined pills. No biphasic pills with modern antiandrogens are on the market. The VTE risk of desogestrel-containing OCs is higher than for levonorgestrel.

3.3.2. Triphasic Birth Control Pills [268]

1977 Development of the tricyclic pill (combination pill for 84 consecutive days; origin: Great Britain).

1977 Development of low dose triphasic preparations (3-phase dosing of estrogens and progestins; origin: Germany). First introduced in Germany in 1979 and abroad in 1980.

1979 Triquilar®: In 1979, Schering, Berlin, (now Bayer HealthCare) introduced the first triphasic COC, Triquilar® in an attempt to reduce the overall hormone content. The doses of the estrogen and the progestin components were altered during the cycle.

1994 Introduction of the first third-generation triphasic pill in Germany (norgestimate; Pramino® from Cilag – and Tricyclen® in the US).

2001 Introduction of a triphasic oral contraceptive with desogestrel (Novial® from Organon (now MSD) (7 days 35 µg EE & 0,05 mg desogestrel 0,05 mg, EE 0,035 mg; 7 days: 30 µg EE & 0,1 mg desogestrel 0,1 mg; 7 days: 30 µg EE and 0,15 mg desogestrel)

Rationale:
– Triphasic pills offered the lowest amount of total EE and progestin per cycle compared to other OCs containing 50 µg EE at the time of market introduction in 1970.
– At that time, further dose reduction seemed difficult without a negative effect on cycle control. Triquilar® contained EE 30 µg/LNG 50 µg on days 1–6, EE 40 µg/LNG 75 µg on days 7–11, EE 30 µg/LNG 125 µg on days 12–21. Due to the phasic formulation, the total hormone content was reduced by 40%. Moreover it was designed to better resemble the hormonal fluctuations that occur during the menstrual cycle. Triquilar achieves excellent contraceptive efficacy, good cycle control and is well tolerated.

Triphasic regimen:
– Due to different patents, various regimens in terms of different length of the 3 phases and different dosage regimens have been developed.
– Triphasic oral contraceptives contain 3 different doses of hormones in the 3 weeks of active pills, so the hormone combination changes approximately every 7 days throughout the pill pack. Depending on the brand, the amount of estrogen may change as well as the amount of progestin. In a single month's supply, triphasic pills may have a gradual estrogen increase and/or some pills may also increase the dose of progestin.

German OC market:
– **Norethisterone:** 35 µg EE/0,5; 1 mg norethisterone; 35 µg EE/0.5–1 mg norethisterone
– **Levonorgestrel:** 30; 40 µg EE/50–125 µg; 30; 40 µg EE/50;125 µg levonorgestrel
– **Norgestimate:** 35 µg EE/180; 250 µg norgestimate; (US: OrthoNovum 7/7/7™)
– **Desogestrel:** 30 µg EE/50–150 µg desogestrel

Summary:
– **Modern triphasic pills on the market in Germany:** see list above.
– **Cochrane analysis by van Vliet et al (2011) [676]:** see biphasic pills.
– **Indications:** patients with intermenstrual bleeding, i.e. mid-cycle bleeding or therapy resistant bleeding problems using combined oral contraceptives.
– **Limitations:** Triphasic pills cannot be used for extended cycles ("off label") or for pre- or postponing the menstruation; the regimen for "missed pills" is more difficult compared to combined pills. No triphasic pills with modern antiandrogens are on the market – with the exception of norgestimate (Tri-Cyclen™), which has an approval for acne in the US only – but norgestimate is only a weak antiandrogen. The VTE risk of desogestrel-containing OCs is higher compared to levonorgestrel.

4. New Oral Contraceptive Regimens

4.1. Progestin-Only Pills with Ovulation Inhibition

To date, only one desogestrel (75 µg/day) pill inhibiting ovulation due to a progestin dosage above the ovulation inhibition level has been marketed by MSD.

4.2. Ethinyl Estradiol-free Contraceptives Using Estradiol or Estradiol Esters

Over the years, development in the field of combined oral contraceptives (OCs) has focused on improving their tolerability by reducing the dose of progestins and ethinyl estradiol (EE), modifying the dosing regimen and incorporating progestins with more favorable clinical profiles.

Additional efforts to improve the acceptability of combined OCs included the replacement of EE with 17β-estradiol (E_2).

4.2.1. Dienogest/Estradiol Valerate in a Combined Oral Contraceptive

E2V/DNG has been available in multiple countries in Europe since May 2009, and is also available outside of Europe and in the USA.

On May 13, 2010, the FDA approved a new COC called **Natazia™,** manufactured by Bayer HealthCare Pharmaceuticals of Wayne, N.J., which is the first four-phase oral contraceptive to be marketed in the United States containing estradiol valerate and dienogest in a four-phasic 26+2 regimen **[319]**.

Indications: Natazia™ is indicated for use by women to prevent pregnancy. The efficacy of Natazia in women with a body mass index (BMI) of > 30 kg/m² has not been evaluated **[318]**.

Rationale:

- In several historic clinical trials, E_2-containing OCs have been found to provide effective contraception, but their association with unsatisfactory bleeding profiles has largely prevented them from being developed further **[27, 135, 256].**
- Dienogest (DNG) is an established progestin with strong endometrial effects, antiandrogenic properties and a lack of androgenic activity **[382, 492].**
- Estradiol valerate (E_2V) is promptly hydrolyzed to E_2 after oral administration, and is identical to E_2 in terms of pharmacodynamics and pharmacokinetics **[659].** An OC containing estradiol valerate (E_2V) and dienogest in a four-phasic 26+2 regimen has been the first OC on the market with a derivative of a natural estrogen providing both a good contraceptive efficacy and sufficient control of the menstrual bleeding pattern.
- Ovulation inhibition is achieved by a progestin dosage above the threshold necessary for ovulation inhibition and estrogens are used to prevent a relative estrogen deficiency and thereby achieve a good cycle control.
- E_2V/DNG utilizes dynamic dosing in a simple and continuous 1-pill-per-day format, which delivers an estrogen step-down, progestin step-up regimen over 26 days of active treatment, 2 days of placebo. This regimen was designed to ensure good cycle control by maintaining estrogen dominance in the early part of the cycle and progestin dominance in the mid-to-late part of the cycle. It also provides stable trough E_2 levels over the whole 28-day cycle, with low variability in E_2 levels over 24 hours **[737].**

Experience with clinical trials:
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Contraception Studies:
Two multicenter phase 3 clinical trials evaluated the safety and efficacy of Natazia™ for pregnancy prevention. Both were non-comparative, open-labeled, single-arm studies with a duration of up to 28 cycles. A total of 1,867 women aged 18–50 were enrolled and took at least one dose of Natazia.
The first study was conducted in North America (U.S. and Canada) as a multicenter, open-label, single-arm, unintended pregnancy study. There were 490 healthy subjects between 18 and 35 years of age (mean age: 25.1 years) who were treated for up to 28 cycles of 28 days each. The second study was conducted in Europe (Germany, Austria and Spain) as a multicenter, open-label, single-arm contraceptive reliability study. There were 1,377 healthy subjects between 18 and 50 years of age (mean age: 30.3 years) who were treated for 20 cycles of 28 days each **[318]**.

Clinical trial for the treatment of heavy menstrual bleeding: The efficacy of E_2V/DNG for the treatment of heavy, prolonged and/or frequent menstrual bleeding without an organic cause measured by the alkaline haematin method was investigated in two identically designed double-blind, randomized, placebo-controlled trials in USA/Canada **[190]** and Europe/Australia **[350].**

Adverse reactions leading to study discontinuation: 11.5% of the women dropped out of the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were metrorrhagia and irregular menstruation (1.9%), acne (1.2%), headache and migraine (1.0%), and weight increase (0.7%).

Common treatment-emergent adverse reactions (≥ 2%): headache (including migraines) (13.2%), metrorrhagia and irregular menstruation (8.0%), breast pain, discomfort or tenderness (6.6%), nausea or vomiting (6.5%), acne (3.9%) and increased weight (2.8%).

Serious adverse reactions: deep vein thrombosis, myocardial infarction, focal nodular hyperplasia of the liver, uterine leiomyoma, and ruptured ovarian cyst.

Summary:

- First OC with estradiol valerate in a four-phasic regimen.
- The 4-phasic combination allows for the use of estradiol valerate instead of EE for contraception and control of the menstrual cycle and to provide stable and sufficient serum levels of estradiol.
- Only one 4-phasic pill has been marketed until now. The 4-phasic combination of dienogest with estradiol valerate is the first oral contraceptive containing a derivative of a natural estrogen, which is converted in the human body to the natural estrogen

estradiol. Estradiol valerate is necessary to overcome an estrogen deficiency during the cycle as a consequence of ovarian suppression by dienogest to maintain constant levels of estradiol and to support the good cycle control in terms of bleeding pattern.

- Clinical trial data show that E_2V/DNG effectively inhibits ovulation **[135]** and offers women an acceptable bleeding profile, with lighter bleeding and a significant reduction in the duration of withdrawal bleeding per cycle compared with EE/LNG **[5].**
- Significantly more patients per cycle had no withdrawal bleeding, although only in a minority of cycles.
- **Treatment for heavy menstrual bleeding:** Together, the two international studies provide the first evidence from rigorous randomized trials that an oral contraceptive is an effective treatment for heavy menstrual bleeding. Study results revealed a rapid effect of E2V/DNG, with a significant reduction in menstrual blood loss seen from cycle two onwards.
- **Side-effect profile:** No long-term safety data are available demonstrating the benefit in terms of a lower rate of cardiovascular disease. Prospective multicenter trials of the EURAS type are ongoing.
- **Market overview:** Only one modern four-phasic pill is on the market in Germany and the US.

Estetrol for Contraception

According to Herjan Coelingh Bennink, Pantarhei Bioscience, The Netherlands, and Jean Michel Foidart, University of Liège, Belgium.

Estetrol (E_4) is a human steroid, produced by the fetal liver during pregnancy only. This natural hormone was discovered in urine of pregnant women by Diczfalusy and coworkers in 1965 **[221].** Based on its physical and chemical characteristics it was concluded that E_4 is identical with 15α-hydroxyestriol (15α-OHE3) or estra-1, 3, 5(10)-triene-3,15α-,16α-, 17α-tetrol **[739].** Estetrol has the structure of an estrogenic steroid with four hydroxyl groups, which explains the acronym E_4. Estetrol is synthesized by the human fetal liver during pregnancy and reaches the maternal circulation through the placenta. The fetal liver is the exclusive site of 15α- and 16α-hydroxylation **[441, 584, 585].** After birth the neonatal liver rapidly loses its capacity to synthesize E_4.

Estetrol was already detected at 9 weeks of pregnancy in maternal urine **[240, 242].** During the second trimester of pregnancy high levels were found in maternal plasma, with steadily rising concentrations of unconjugated E_4 to about 1 ng/ml (3 nmol/L) towards the end of pregnancy **[99, 259].** So far the physiological function of E4 has not been studied and is unknown.

The possible use of E_4 as a marker for fetal well-being has been studied quite extensively. However, due to the large intra- and interindividual variation of maternal E_4 plasma levels during pregnancy this appeared not to be feasible **[241, 399, 400, 490, 664].** More details on the history of E_4 and data from studies in the period from 1965 to 1984 have been summarized in two review papers **[101, 259].**

In the last 7 years E_4 has been studied extensively. High oral absorption and bioavailability with a 2–3 h elimination half-life in the rat have been established **[100].** In the human E_4 showed a high and dose-proportional oral bioavailability and a remarkably long terminal elimination half-life of about 28 h **[694].** Estetrol has a moderate affinity for both human ERα and ERβ receptors with a 4–5-fold preference for the ERα **[693].** In addition it was found that E_4 binds highly selectively to the estrogen receptors.

In rat and human hepatocytes the rate of E_4 metabolism was studied and found to be slow **[693].** In addition E_4 did not inhibit any of the major drug-metabolizing cytochrome P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 at a high concentration of 10 µM **[693].** This is in contrast with the effects of estradiol (E_2) and ethinylestradiol (EE) on these enzymes.

Contraceptives Studies

In a preclinical model the effects of E_4 on ovulation inhibition were studied in cyclic female rats. Animals (8 per group) were treated twice daily with oral E_4 (0.03, 0.1, 0.3, 1.0 or 3.0 mg/kg), or oral EE (0.0003, 0.001, 0.003, 0.01 or 0.03 mg/kg) over the 4 days period of the estrous cycle **[103].** The control group was given oral vehicle only. The primary endpoint of this study was the number of ovulated oocytes in the genital tract. All rats ovulated when treated with vehicle. The twice-daily dose of 0.3 mg/kg E_4 and the higher doses significantly inhibited ovulation ($p < 0.05$) as did twice daily administration of the comparator EE at the highest dose (0.03 mg/kg). By comparison of the ED_{50} the antiovulatory potency of E_4 was about 18 times less thanEE.

In a single rising dose study in healthy postmenopausal women pharmacokinetics and pharmacodynamics of E_4 were studied after administration of single doses of 0.1, 1, 10 and 100 mg E_4 **[694].** To investigate the antigonadotrophic potency of E_4 the effect of E_4 on the plasma levels of the gonadotrophins luteinising hormone (LH) and follicle stimulating hormone (FSH) was measured. A dose-dependent inhibition of LH levels was observed. In addition in the 100 mg dose group (FSH was not measured in the other dose groups) a profound inhibition of FSH levels was observed lasting for 7 days.The effect of E_4 on plasma LH and FSH levels was also studied in a multiple rising dose study in early postmenopausal women with oral E_4 doses of 2, 10, 20 and 40 mg/day administered for 28 days. A 2 mg/day oral E_2-valerate group served as control. In this study both FSH and LH levels decreased dose dependently after administration of E_4 for 28 days. Suppression of LH and FSH in the 2 mg E_2-valerate group was approximately similar to the inhibitory effect of the 10 mg E_4 dose group. Ovulation inhibition was further investigated in a phase IIA clinical trial in premenopausal women with proven ovulation in the previous cycle. Estetrol was administered alone in 2 different doses (10 or 20 mg/day) or in combination with either desogestrel (150 µg DSG) or progesterone (200 mg P_4). All treatments were oral and for 28 days. Ovulation was inhibited in all women in the E_4/DSG group, while in the 10 mg and 20 mg E_4-only groups, ovulation was inhibited in one third and two thirds of the cycles respectively. The E_4/P_4 group showed a poor antiovulatory efficacy and an unacceptable bleeding pattern. All other E_4 groups showed acceptable bleeding patterns albeit for just one treatment cycle. A phase 2 program for the development of an E_4 containing oral contraceptive will be completed in 2011, including E_4 dose finding and progestogen selection.

Summary:
- Estetrol is a steroid synthesized exclusively by the human fetal liver during pregnancy. After its discovery in 1965, basic research on E_4 was performed until about 1984. At that time E_4 was considered to be a weak estrogen and interest in this steroid disappeared. However, recently it has been shown that E_4 has a high and dose-related oral bioavailability in the rat **[100]** and the human **[694],** does not bind to SHBG **[225]** and has a long elimination half-life in both rats **[100]** and humans **[694],** allowing its use as an oral once-a-day drug.
- In well validated and predictive rat models, E_4 behaves as an estrogen agonist in all tissues investigated, i.e. bone **[100],** vagina **[238],** myometrium **[238],** endometrium **[238]** and brain (hot flush) **[258]** and ovulation inhibition **[238, 258]**, except for breast tumor tissue where this steroid acts as an estrogen antagonist in the presence of E_2 **[102].**
- Estetrol may be useful for a series of potential clinical applications including hormone replacement therapy in women, especially for the treatment of vaginal atrophy and hot flushes, as an estrogenic component in oral contraceptives as well as for the prevention and treatment of osteoporosis, and E_4 might even be suitable for the prevention or treatment of breast cancer. These potential applications will be further explored in clinical trials.
- Potential advantages of E_4 over EE and E_2 include fewer subjective side effects, less interaction with liver function, less venous thromboembolism and a lower incidence of cardiovascular and gallbladder disease. The antagonistic effect of E on breast tissue in the presence of E_2 may be beneficial for the breast.

4.3. New Progestins used for Hormonal Contraception

Trimegestone [602]

Pharmacological profile [600, 718],
- Trimegestone (TMG) is a 19-norprogesterone derivative with strong progestational activity.
- TMG is a weak antiandrogen and has modest antimineralocorticoid activity.
- In preclinical studies, it was demonstrated that TMG has a limited effect on the GABA-ergic (γ-aminobutyric acid) system, explaining the lack of unwanted mood effects in users **[553].**

Contraception [602]:
- Preclinical studies in the rat have demonstrated inhibition of ovulation and anti-estrogenic activity in the uterus **[718].**
- The contraceptive potential of using TMG via a transdermal system has been explored, but so far no clinical trial has been published **[435].**
- Although TMG is a potent progestin with good antiovulatory action, it has not been developed as a contraceptive so far.

Summary:

Trimegestone could be used as an oral hormonal contraceptive. In 2007, the German pharmaceutical company Gruenenthal (http://www.prnewswire.co.uk/cgi/news/relea se?id=203073) **[317]** announced its worldwide exclusive rights on trimegestone for the use in oral contraception by Aventis Pharma, SA, France, a subsidiary of Sanofi-Aventis. Trimegestone is a metabolically neutral and naturally derived progesterone agonist, thus long-term acceptance female users is expected. Due to its favorable metabolic safety profile trimegestone is already in use in hormone replacement therapy. In this respect trimegestone is an ideal progestin to be used in hormonal contraception.

Nesterone

Pharmacological profile:
- **Nesterone (NES)** is a 19-norprogesterone derivative with a high progestational activity, which may be attributed to the absence of the 19-methyl radical and the addition of the 16-methylene substitute, which promotes binding to and transactivation of the PR **[397, 627].**
- It does not bind to the androgen receptor and is therefore not androgenic.
- It does not bind to SHBG.
- NES binds to the glucocorticoid receptor but does not exert glucocorticoid activity in in vivo assays at the doses required for its contraceptive efficacy **[397].**
- As NES has the highest antiovulatory action among existing progestins, a very low dose could be used and delivered from non-oral delivery systems.
- NES has been shown to exert a high contraceptive activity when administered via different non-oral delivery routes such as vaginal rings, implants and transdermal systems.

Contraception [602]:
- **Oral contraceptives:** The oral route is not possible, because NES is not absorbed following oral application.
- **Vaginal rings:** A vaginal ring containing NES/EE releasing low doses of NES (150 μg) and EE (15 μg) is undergoing development as a contraceptive at the Population Council **[35, 36]**. At present, the ring is in its final stages of development. Second-generation vaginal rings, which include a design delivering NES together with E2, the natural estrogen, instead of EE, are in the early developmental stage. The contraceptive potential of NES delivered via the transdermal route has also been studied. The first study testing NES as a transdermal gel found it to be effective in suppressing ovulation in a high percentage of women **[601].**
- **NES-gel:** In a 3-month multicenter study carried out among 150 cycling women, NES gel was applied transdermally in three different doses of 0.3, 0.6 and 1.2 mg. The level of ovulation suppression reached 53%, 64% and 83% in the three dose groups, respectively **[134, 601].**

  Based on these promising results, higher doses of NES were combined with low doses of E2, and preliminary results indicate a high antiovulatory efficacy.

- **Metered Dose Transdermal System (MDTS):** Similarly, the Metered Dose Transdermal System (MDTS), which is in the initial stages of development, is a fast-drying liquid formulation used in a non-occlusive spray containing NES dosed via a precisely engineered system delivering the drug to the skin surface **[189].** NES is combined with a safe skin penetration enhancer – octisalate, which forms a reservoir within the skin wherein the drug is slowly absorbed into the circulation over a duration of several hours. A pharmacokinetic trial of this new transdermal delivery system has demonstrated the feasibility of achieving serum levels of NES sufficient to block ovulation and hence provide ef-

fective contraception. A spray formulation incorporating both NES and an estrogen, either E2 or EE, is undergoing clinical trials.

– **Implant:** NES has been tested in the form of a single implant releasing 100 µg of NES per day administered to lactating women in a 2-year study **[453].** No pregnancies were reported in 2195 woman-months of exposure, and implant users demonstrated significantly less irregular bleeding compared to copper-T IUD users. This progestin also has the advantage of being safe for infants as NES is not active orally and is quickly destroyed in the gastrointestinal tract. **Massai et al. (2001) [453]** followed the growth of infants who were breastfed by mothers receiving an implant of NES and found no difference in infant growth and development as compared with those who were breastfed by mothers using the IUD.

Summary:
Nesterone is not orally active and cannot be used for oral hormonal contraceptives. It can be used for vaginal rings, vaginal gel, transdermal "spray-on" contraceptives etc.

Nomegestrol acetate
The following chapter about NOMAC is mainly based on a review on Nomegestrol acetate and its pharmacology, safety profile and therapeutic efficacy **by Lello (2010) [415]** and **Mueck & Sitruk-Ware (2011) [473].**

Pharmacological profile:
– Nomegestrol acetate is a 19-norprogesterone derivative, which is also characterized by the absence of a methyl group at the 19 position **[79].**
– Absorption of NOMAC is rapid after oral administration, reaching a peak serum concentration within 4 hours, with a terminal half-life of approximately 50 hours. This long half-life especially results in the high contraceptive safety of NOMAC in case of pill-taking errors and provides a stable bleeding pattern.
– NOMAC is a potent antigonadotropic agent in women and exerts a high progestational action although it is lower than that of Nesterone and Trimegestone. As with other progestins, the antigonadotropic action of NOMAC is mediated at the hypothalamic and pituitary levels.
– In animal models some antiandrogenic effect was demonstrated **[161].**
– No androgenic, estrogenic or glucocorticoid activities could be found **[414].**
– NOMAC has been shown to be neutral on the carbohydrate and lipid metabolism **[414].**

Rationale:
– The majority of older progestogens, i.e. 19-nortestosterone derivatives, were synthesized primarily for their antigonadotropic activity as a component of hormonal contraception in combination with an estrogen. NOMAC, a 19-norprogesterone derivative was designed to show highly selective binding to the progesterone receptor; furthermore, it is relatively lacking in competitive affinity to other steroid receptors.
– NOMAC exerts strong antiestrogenic effects at the level of the endometrium and has potent antigonadotropic activity without any residual androgenic or glucocorticoid properties.

Clinical indications:
– NOMAC has been used successfully for the treatment of some gynecological disorders, such as menstrual irregularities, dysmenorrheal and premenstrual syndrome. It has been approved in Europe as a monotherapy for the treatment of the menopausal syndrome, menorrhagia, and in combination with an estrogen for the treatment of menopausal symptoms.
– In-vitro data suggest that NOMAC preserves the beneficial hemostatic effects of estrogen; furthermore NOMAC has a neutral or beneficial effect on lipid profiles, and does not adversely affect glucose metabolism or bodyweight.
– NOMAC has shown a lack of proliferative activity in normal and cancerous breast tissue, and does not have a deleterious effect on bone remodeling.
– The potent antigonadotropic properties and other beneficial metabolic and pharmacological characteristics suggest that NOMAC can also be an effective progestin for use in combination with an estrogen in oral estrogen/progestin contraceptive treatment, providing additional non-contraceptive benefits for women's health.

Contraception:
– NOMAC has been tested for its contraceptive action in the form of oral pills and subdermal implants. Clinical trials with Uniplant, a single silastic capsule containing NOMAC, have shown its efficacy in preventing pregnancy **[37, 121].**
Its mechanism of action has been attributed to a high antigonadotropic activity leading to blockade of ovulation and prevention of follicular growth, as well as changes in the cervical mucus, endometrial vascularization and endometrial architecture **[37, 39].**
– At an oral dose of 1.25 mg/day, NOMAC has been shown to suppress ovulation, while at higher doses of 2.5 or 5 mg/day, full suppression of both ovulation and follicular development is seen **[43].**
– A new OC has been developed recently combining NOMAC and E2 showing a high contraceptive efficacy and good bleeding control **84].** In the near future a new regimen with natural estrogens (estradiol) in combination with Nomegestrol acetate (NOMAC) (Organon, Schering-Plough now MSD) will be available as an oral contraceptive **[473].** NOMAC has been tested clinically in phase III trials as an oral contraceptive with 1.5 mg estradiol and 2.5 mg NOMAC (MSD) and is about to be approved by the FDA and the European authorities.

Combined oral contraceptive with NOMAC and estradiol:
Different formulations of NOMAC as an agent in oral contraceptives have been studied: as a single agent, in combination with ethinylestradiol and with natural estradiol. Modern formulations of the oral contraceptives combine different progestogens and natural estrogens with variations of the cyclic intake. Previous attempts to replace ethinylestradiol with natural estradiol resulted in an inadequate bleeding pattern.
Due to the low estrogenic effect in combination with the long half-life, NOMAC has been proven to provide good cycle control in earlier studies.
The monophasic oral contraceptive containing NOMAC 2.5 mg and 17-beta-

estradiol is administered in a 24/4-day cycle **[473].**

Contraceptive efficacy:

At a dosage of 1.25 mg, NOMAC has proven antigonadotropic activity and effectively inhibits ovulation, although follicle growth is possible.

Cyclic dosages of 2.5 to 5 mg/day lead to suppressed ovulation and follicle development **[43, 122].** The pharmacological properties of orally administered NOMAC were studied in 10 clinical trails **[415].** A subdermal implant with 55 mg NOMAC also showed the effective suppression of ovulation **[121].** NOMAC also interacts with the cervical mucus, with a proven loss of spinnability, ferning pattern and high density of the midcycle mucus having additional contraceptive potential **[95].**

Bleeding control: Nomegestrol acetate was studied as a single agent (cyclical oral intake of 5 mg) in the treatment of progesterone deficiency, i.e. menstrual irregularities, premenstrual syndrome, mastodynia, functional uterine bleedings, dysmenorrhoea and menorrhagia of fibromas. Menstrual bleeding disturbances resolved or improved in 81.3% of subjects **[105].**

Studies with NOMAC/E2 showed a good cycle control **[84, 588].**

Metabolic side effects: The oral application of NOMAC as a single agent and in combination with estradiol and ethinylestradiol has a favourable tolerability profile and neutral metabolic characteristics. This profile is achieved through the almost exclusive binding to the progestogen receptor with little interaction with other steroid receptors **[397, 473].** The effect on lipid und glucose profiles, thromboembolic risk and other markers of cardiovascular activity is low.

The potential risk of clinically significant interactions between NOMAC and modifiers of CYP3A4 such as rifampicin or ketoconazole must be taken into account.

Adverse events:

– **Metabolic side effects:** The effect on plasminogen and fibrinogen levels as well as the overall risk of venous thrombosis has been shown to be low **[42],** although there was a slight, significant increase in antithrombin levels. The relative risk of VTE and pulmonary embolism in oral combined contraception with NOMAC is doubled. The pro-thrombotic effect of progestogen derivatives in oral contraceptives may be due to nitric oxide effects, which might be induced by glucocorticoid activity. As NOMAC is a highly specific progesterone stimulator with low additional properties, it can be assumed that the relatively low VTE-risk is based on this feature of NOMAC. In premenopausal women, NOMAC did not change the glucose tolerance, fasting blood glucose and insulin levels.
– Data on **cancer** development in postmenopausal women with NOMAC as HRT suggest an antiproliferative effect in breast tissue **[93].**
– Studies also suggest a beneficial effect on bone remodelling.
– Overall, NOMAC is well-tolerated. Nausea, headache, breast tenderness or irregular bleeding were the most commonly reported adverse events.
– A randomized comparative multicentre trial to assess the contraceptive efficacy and general safety was conducted in over 4000 women **[576, 577].**

Summary:

– NOMAC shows promising properties as a contraceptive progestin.
– The highly specific binding to progestogen receptors and the lacking or minimal effect of binding to other steroid receptors contributes to the good tolerability and metabolic profile.
– Furthermore, the favourable effects on estrogen metabolism, human breast tissue and cancerous breast tissue are additional advantages.
– New contraceptives with natural estradiol have the potential for a higher safety than EE-based OCs due to the lower impact of estradiol on the synthesis of estrogen-dependent liver proteins.
– However, large safety surveillance studies are still required once the new E2-based combinations become available and it is to be hoped that preferential prescription and biased results will be avoided.

5. Special Combinations of Combined Hormonal Contraceptives

5.1. Progesterone Receptor Modulators

– **Definition:** Progesterone receptor modulators (PRMs) are defined as any molecule that binds the ligand-binding domain of the progesterone receptor (PR), leading to the tissue-specific activation and/or inhibition of the downstream hormonal response.
– **Substances and PRM profile:** In the past a variety of PRMs with antagonistic (i.e. full antagonist: mifepristone), partial agonistic as well as antagonistic (i.e. ulipristal acetate) and agonistic profile (i.e. comparator: progesterone) have been developed.
– **Indications:** PRMs have been used in contraceptive research as well as the treatment of fibroids, endometriosis and heavy or irregular menstrual bleeding **[455].** Those with progesterone antagonist activity have potential application in contraception and the treatment of uterine leiomyomata and endometriosis**.** Recently, new clinical applications of mifepristone, asoprisnil (J867), CDB-2914 and onapristone have come under development **[475].** Some PRMs (i.e. asoprisnil) exert anti-estrogenic effects, either through partial progesterone receptor agonist activity **[583, 712]** or they exert these effects independently of the progesterone receptor itself, i.e. by up-regulation of the androgen receptor response **[605, 477].** These PRM lead to a dose-dependent suppression of estrogen-induced mitotic activity and to glandular secretory changes **[712].** PRMs are also efficient in improving bleeding problems associated with contraceptive hormonal implants **[92, 701].**

– **Contraceptive trials [501]:**
  - Different trials examining the co-administration of antiprogestinic compounds (also called selective progesterone receptor modulators) with progestin-only pills have been conducted to control this adverse effect of progestins on the endometrium **[681].**
  - **Croxatto et al.** demonstrated that a sequential administration of mifepristone and nomegestrol acetate could improve irregular bleed-

ings **[133].** In this study, administration of mifepristone (5 mg/day) during the first part of the menstrual cycle inhibited ovulation without decreasing estradiol secretion and allowed endometrial growth. In the second part of the menstrual cycle, nomegestrol acetate inhibited ovulation and regular menstruation was observed at the end of the 28 days' treatment.

- Finally SPRMs administered alone in a continuous manner are currently evaluated as estrogen free contraception. Daily low doses of mifepristone (2 mg/day) inhibit ovulation, prevent secretory transformation of the endometrium and induce amenorrhea **[63, 411, 623].**
- **Pei et al. (2007) [507]** have recently demonstrated that weekly administration of mifepistone (25 and 50 mg) also inhibited ovulation. This weekly intake may contribute to improving compliance.
- The use of SPRMs alone has the very important advantage of providing ovulation inhibition without lowering estradiol levels **[628]** and may not result in estradiol deprivation symptoms or long term estrogen deprivation consequences.
- However, as the effect of estradiol is unopposed, the impact on the endometrium through long term use of SPRMs is unclear. It may result in simple hyperplasia as previously described in women treated for fibromyomas **[628]**.
- The aspects observed may also correspond to class specific modifications of the endometrium **[85, 263, 406, 712].**
- Intrauterine administration of antiprogestins has also been evaluated showing promising bleeding patterns and histological profiles **[239]**. This may overcome the previously described potentially negative endometrial effect.
  Substance-specific adverse events led to the discontinuation of the development of clinical phase III trials with asoprisnil due to endometrial changes in patients **[269].**

Summary:

– Progesterone receptor modulators (SPRMs) are defined as any molecule that binds the ligand-binding domain of the progesterone receptor (PR), leading to the tissue-specific activation and/or inhibition of the downstream hormonal response.
– Various PRMs with antagonistic (i.e. full antagonist: mifepristone), partial agonistic as well as antagonistic (i.e. ulipristal acetate) and agonistic profile (i.e. comparator: progesterone) have been developed.
– Mono-preparations have been analyzed as to whether they can suppress or postpone ovulation, act as modulators of the endometrial surface preventing implantation without disturbing the normal menstrual cycle or be used as an abortifacient.
– Mono-preparations (i.e. 30 mg ulipristal acetate) are used for emergency contraception.
– In combination with combined estrogen/progestin contraceptives, they might improve the bleeding pattern by counteracting the progestin activity at the time the withdrawal bleeding should occur.
– Weekly administration, sequential discontinuation or administration of progestins may be other options. Finally, vaginal routes of administration of SPRMs and progestins are currently under evaluation **[603]**. Furthermore, intrauterine application is a promising approach.
– Oral formulations of potent PRMs with an antagonistic profile have a high potential for illegal abuse as abortifacients. Furthermore, substance-specific adverse events must be considered.

5.2. Special COC Compositions

5.2.1. Oral Contraceptives with Folate Supplementation

Neural tube defects

Even in countries with high average incomes where pregnancies and deliveries are believed to be as safe as possible, there is a perinatal mortality of 5–7 per 1000 births, with 20% resulting from congenital malformation **[610]**.

Of all congenital anomalies, structural malformations such as heart defects or neural tube defects play the dominant role. Especially since the thalidomide catastrophe, it has been known that there are sensitive periods in embryonic development in which specific abnormalities can occur or may be prevented.

The neural tube closes by the 28th day of gestation. If this process is disturbed in the upper part of the spine, this may lead to anencephaly, while closure defects of the lower part result in spina bifida. On a global level, about 300,000 children are born each year with neural tube defects. According to a national study, the prevalence in Germany was about 5.7 per 10,000 births **[431]**.

The prevalence is particularly high in areas of the world where the folate levels are traditionally low, e.g. in the Northern part of the People's Republic of China **[421]**.

Folate and folic acid

Folic acid is a purely synthetic form of vitamin B9, which is effective only after appropriate biotransformation in the body. The naturally occurring form in food are folates, with L-5-methyl-tetrahydrofolate (L-5-MTHF) being the predominant form in humans (approx. 98%). Folates are essential for a healthy embryonic development.

Neural tube defects and folate

Andrew E. Czeizel and his group published the first randomized study showing a dramatic reduction in the expected incidence of neural tube defects after substitution with multivitamins including folic acid. Furthermore, some other malformations such as heart defects, urinary tract anomalies, and stomach stenosis were reduced **[142, 143].**

A large Chinese study also showed these results **[51].**

The Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force (USPSTF) recommend that all women of childbearing age supplement their diet with at least 400 mcg of folic acid daily to reduce the risk of a neural tube defect (NTD) **[80, 667].**

Despite multiple studies and well-designed information campaigns for the periconceptional use of folic acid, the decline in neural tube defects in countries with and without folic acid food supplementation has not met expectations. The likely reason is that the campaigns are failing to reach out especially to those women who have an increased risk of birth defects, a low standard of education as well asyounger age and who experience unplanned pregnancy **[167].** Another reason is selective adherence to the intake of medicines and nu-

tritional supplementation. The women's compliance with the folic acid supplementation is still not sufficient **[76].**

Women who plan to become pregnant, should take a daily dose of 400 µg of folic acid starting not later than four weeks before the onset of pregnancy. The folate treatment should be maintained during the first trimester of pregnancy. Folic acid is a synthetic formula that is activated after biotransformation in the body **[516].** Compared to other B-vitamins, the daily supply of folate in food in Germany is by far the lowest. The daily intake of folate by adults in Germany is about 80–90% below the reference values recommended by the German Society for Nutrition **[460, 645].** On average, the daily dietary uptake is only 250 µg whereas it should be 400 µg. Because of the importance of folate for cell division processes, the demand during pregnancy rises to 600 µg/day, whichmeans an increase of 50% **[460].**

It is not possible to ensure an adequate folate supply based on daily nutrition alone. This would require a daily vegetable and fruit consumption of 600–700 g. In fact, however, on average, the daily uptake is 260 g. In more than 50 countries around the world, food is voluntarily or mandatorily supplemented with folic acid – with remarkable success: the number of embryonic development defects caused by folate deficiency, especially neural tube defects, has decreased significantly **[50, 59].**

However, to date, there is no mandatory folic acid supplementation of food in any European country. Health authorities rely on the voluntary principle, which does not lead to the desired result. Many European countries justify this by legal regulations; in Germany, Article 2 of the Basic Law ("right to free development of one's personality") precludes such action. The discussion about food fortification and potential risks of mandatorily fortified food is ongoing **[117, 499].**

Folate supplementation should start before pregnancy (preconceptionally)

The neural tube closes at the end of the first month of pregnancy (24 to 28 days after conception), at a time when many women still have not realized that they are pregnant. Even before conception, an adequate folate status is necessary. It is too late to substitute folate or folic acid after the beginning of a pregnancy, especially since it takes 6–8 weeks until sufficiently high folate levels have been achieved **[597].**

Folate deficiency in oral contraceptive users

In the first month after discontinuing an oral contraceptive, more than 20% of women and after three months about 50% were pregnant **[131].** After 12 months, 70–90% of the former oral contraceptive users become pregnant **[40].** A survey in France showed that about one third of pregnancies are unplanned/unintended, and about two thirds of them occur while contraceptive methods including oral contraception are used **[469].** Especially long-term use of a medication like the oral contraceptive is associated with intake errors **[498].** Discontinuation of the oral contraception is often not reported to or discussed with the women's gynecologist. The chance to receive preconceptional medical advice is missed in most cases.

In women using an oral contraceptive containing folate, up to 12 weeks after withdrawal of the pill, folate levels remain at a sufficient level for protection against neural tube defects and other early embryonic defects **[34].**

The addition of folate to an oral contraceptive is an innovative, targeted approach to ensure a protective folate level in women of reproductive age before conception.

Rationale for folate supplementation in oral contraceptives

The concept of a folate-supplemented OC makes sense in many ways.

– Users of oral contraceptives benefit most from adequate folate levels compared to all other population groups.
– Women who use oral contraceptives receive regular gynecological care. Gynecologists have the opportunity to raise the awareness for the usefulness of folate supplementation.
– A woman who uses oral contraceptives is not interested in questions of folate supplementation as a preparation for pregnancy as she is actively trying to prevent a pregnancy. In fact, unintended, unplanned pregnancies occur also during the intake of oral contraceptives, mostly due to inadequate intake of one or more pills in a cycle.

The financial and social burden due to neural tube defects has been calculated in various preventive strategies, e.g. food fortification in the US **[47].** The health economic benefits of integrating oral contraception with folate supplementation has been shown by a model calculation. About 50% of neural tube defects in Germany could be prevented by this approach **[499].**

The risk of neural tube defects can be significantly reduced if women increase their folate levels. The combination of oral contraceptives with folate is an innovative and useful concept that can represent a significant advance in women's health.

New oral contraceptives with folate supplementation have received FDA approval

A new class of oral contraceptives containing folate (L-5-MTHF) has been developed, reducing the risk of neural tube defects in unintended, unplanned pregnancies or pregnancies occuring directly after the cessation of the oral contraceptive.

The first oral contraceptive containing levomefolate calcium (L-5-MTHF), a folic acid metabolite, was Beyaz™, which was approved by the FDA on September 24, 2010 **[302]**. It is manufactured by Bayer HealthCare Pharmaceuticals Inc. and is based on the previously approved oral contraceptive YAZ™. While thedoses of estrogen and progestin (ethinyl estradiol 20 µg; drospirenone 3 mg) are the same, Beyaz™ also contains 0.451 mg of levomefolate calcium. Beyaz™ shares the previously approved indications of YAZ™: pregnancy prevention, treatment of premenstrual dysphoric disorder (PMDD) symptoms in women who use OCs for contraception, and treatment of moderate acne in patients aged 14 years and older who have chosen to use an OC for birth control. Beyaz® has been approved for the secondary indication of raising folate levels to reduce the risk of neural tube defects in women who conceive while using the product or shortly after discontinuation. Users should be counseled prior to taking the drug to report whether they are taking folate supplements. Folate supplementation should be maintained after discontinuing the oral contraceptive Beyaz™ **[287].**

The other oral contraceptive used to raise the folate level in women is

Safyral™, which received FDA approval on December 16th, 2010 **[303]** (Bayer HealthCare). It is an oral contraceptive raising folate levels in women who choose an oral contraceptive for birth control. Safyral™ is based on a 21/7 day regimen containing drospirenone 3 mg, ethinyl estradiol 30 µg and levomefolate calcium 451 µg.

The FDA approval was based on data from two clinical trials **[306].** The first was a U.S. multicenter, randomized, double-blind, parallel-group study, a 24-week clinical trial involving 379 healthy women aged 18–40 years. Data showed that YAZ™ (drospirenone 3 mg, ethinyl estradiol 20 µg, Bayer HealthCare) in combination with 451 µg of levomefolate calcium (Metafolin) increases folate levels significantly from baseline compared to YAZ™ alone: RBC folate (420 ± 347 nmol/L vs. 34.3 ± 171 nmol/L, respectively) and plasma folate (15.8 ± 20.4 nmol/L vs. –2.2 ± 14.6 nmol/L, respectively).
A separate European study based on Yasmin® (drospirenone 3 mg, ethinyl estradiol 30 µg, Bayer HealthCare) in combination with either 451 µg of Metafolin or 400 µg of folic acid for 24 weeks followed by 20 weeks of treatment with Yasmin® only found that the Metafolin treatment produced the maximum mean increase in plasma folate (33.5 ± 14.5 nmol/L) and in RBC folate (782 ± 260 nmol/L) levels at 24 weeks. However, folate-containing oral contraceptives have not yet become available on the European market.

5.2.2. Lactose-Free Oral Contraceptives

Lactose intolerance

The term "lactose intolerance" refers to the partial or total inability to digest lactose. The lactose is a carbohydrate found in milk and other dairy products and may be concealed in products with special ingredients, as well as in most pharmaceuticals. Lactose is cleaved in the small intestine by the enzymatic activity of lactase. A lack of lactase or its insufficient activity results in malabsorption of the disaccharide. Malabsorption leads to a clinical syndrome with at least one digestive symptom: diarrhea, abdominal pain, nausea, flatulence and/or bloating. The severity of the symptoms depends on the total enzyme activity and on the lactose intake. In severe cases, lactose intolerance can result in malnutrition, skin rashes and depression. The symptoms may increase with age.
Lactose intolerance can have different causes. The primary type of lactose intolerance is caused by a genetic deficiency of the enzyme lactase. Secondary lactase deficiency occurs due to damage or atrophy of the epithelial layer of the small intestine. Diseases leading to secondary lactase intolerance are acute gastroenteritis, persistent diarrhea, small bowel overgrowth or chemotherapy **[252].**
About 70% of the world's population suffer from lactose intolerance in various degrees **[252]**. There are different regional prevalences of lactose intolerance worldwide. In Asia and Africa the prevalence is extremely high, whereas in Western Europe, the US and Australia, the syndrome is not so dominant, but still common. It is estimated that 15–20% of adults in Germany suffer from this condition **[642].** Genetic testing for polymorphism can be used to diagnose the primary type of lactose intolerance.

A common diagnostic test is the lactulose hydrogenbreath test. Additional genetic testing for lactase gene polymorphisms may confirm the diagnosis of a primary lactase deficiency; homozygous carriers of the polymorphism developing a manifest lactose intolerance with a likelihood of 95% are as follows:

– 13 910 TT (in 40% of all cases): no evidence of Primary Lactose Intolerance
– 13 910 TC (in 45% of all cases): no evidence of Primary Lactose Intolerance, carrier
– 13 910 CC (in 15% of all cases): predisposition to Primary Lactose Intolerance **[326].**

Clinical options in patients with lactase deficiency and contraception

After diagnosis, the treatment of lactose intolerance consists of avoiding food containing lactose **[410]** or in special cases of enzyme replacement.
Pharmaceuticals contain a small but possibly relevant amount of lactose. Users should be informed that lactose as an excipient in tablets may worsen their gastrointestinal symptoms **[514].** Women with severe symptoms after a lactose challenge should be informed about

Table 4. Lactose content of various oral contraceptives.

Oral contraceptive	Hormone	Excipients	Brand name (Germany)	Brand name (US)
progestin-only pills	levonorgestrel	lactose monohydrate 33,1 mg	Microlut®	
progestin-only pills	desogestrel	lactose 1-water 8 mg	Cerazette®	
combined oral contraceptive (20 µg EE)	EE + drospirenone	lactose 52,15 mg	YAZ®	
combined oral contraceptive (30 µg EE)	EE + drospirenone	lactose 46 mg	Yasmin®	Zarah™
combined oral contraceptive (30 µg EE)	EE + chlormadinone acetate	lactose-monodydrate 69,5 mg	Belara®	
combined oral contraceptive (30 g EE)	EE + dienogest	lactose 1-water 27 mg	Valette® (change of ingredients)	
combined oral contraceptive with estradiol	estradiol-valerate + dienogest	lactose 50 mg	Qlaira®	Natazia™

Lactose-free oral contraceptives:		**Germany**	**US**
progestin-only pill	ethynodiol diacetate	Femulen®	Femulen™
combined oral contraceptive	30 µg EE and levonorgestrel		Nordette™/ Portio™
combined oral contraceptive	chlormadinone acetate and 30 µg EE	Enriqua®	
combined oral contraceptive	30 µg EE, dienogest	Valette®, Maxim®	

the fact that lactose-free oral contraceptives are available. Alternative contraceptive methods without lactose are shown in **Table 4:**
- Injections, implants of progestogen
- Contraceptive patches
- Intrauterine devices (IUD)
- Intrauterine systems (IUS)
- Barrier methods (diaphragms, condoms and cervical caps).

Contraception in patients with lactase deficiency

Symptoms of a lactose intolerance frequently occur after taking 3–5 g lactose. It can be seen that the majority of those affected will tolerate up to 12 g of lactose per day without symptoms under a low-lactose diet **[429].** This corresponds to 240 ml of cow's milk. In most cases the intake of one tablet daily containing less than 50 mg of lactose should have little consequence **514].**

Summary:

Lactose intolerance is common, but shows high local and ethnic variability. In Germany, the incidence is relatively low, but no fewer than 15% of the women are affected by abdominal symptoms following lactose intake. Based on clinical symptoms and in some cases the results of gene tests, the elimination of lactose from the daily diet is recommended. In severe cases, the use of lactase tablets to support digestion may be necessary. Compared to the dietary intake of lactose, the lactose content per tablet is relatively low (50–70 mg/tablet versus 12 g containing in 240 ml of milk). In most cases symptoms start when 3–5 g lactose are ingested. Individual responses have been observed.

A person with lactase deficiency symptoms or lactase deficiency proven by gene tests can avoid lactose in oral contraceptives using specific brands or choosing other contraceptive methods.

5.2.3. Oral Contraceptives With Iron Supplementation

For women aged between 14 and 18, the recommended daily intake of iron is 15 mg and for 19–50 years 18 mg **[341].** In humans, iron is an essential component of proteins involved in oxygen transport **[144, 341].** It is also essential for the regulation of cell growth and differentiation **[19, 58].**

Iron deficiency
- Iron deficiency is one of the most commonly known forms of nutritional deficiency.
- In the human body, iron is present in all cells and has several vital functions – as a carrier of oxygen to the tissues from the lungs in the form of hemoglobin, as a transport medium for electrons within the cells in the form of cytochromes, and as an integral part of enzyme reactions in various tissues **[273].**
- The direct consequence of iron deficiency is iron deficiency anemia. Iron deficiency is quite common. In 1998, it was found in in 9–11% of women between 12 and 19 years, while iron deficiency anemia was present in 2–3% of all subjects in the US **[81].**

Medications such as oral contraceptives can lighten heavy menstrual flow **[312]** and prevent loss of iron during menstruation.

According to **Frassinelli-Gunderson et al. (1985)** numerous cross-sectional and some short-term longitudinal studies indicate that OCs consistently elevate serum iron,the total iron-binding capacity and serum transferrin while hemoglobin and hematocrit remain essentially unchanged **[75, 347, 374, 449, 488, 489, 522, 523, 736].**

In the US, the norethindrone-containing OCs Loestrin and Loestrin 24 Fe have iron supplements in the placebo pills.

Summary:
- Iron supplementation is only available in some brands of OC in the placebo pills.
- Oral contraceptives elevate serum iron, the total iron-binding capacity and serum transferrin, while hemoglobin and hematocrit levels remain essentially unchanged
- Oral contraceptives lighten heavy menstrual flow **[312]** and prevent loss of iron during menstruation.
- Iron supplementation is useful in special cases due to the toxicity of iron in individuals with iron store disease in the liver.

5.2.4. Vitamin D-Supplemented Oral Contraceptives

Vitamin D is classically known to protect against rickets and is a standard treatment for osteoporosis patients.

Vitamin D is a fat-soluble vitamin that plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties. In addition, recent epidemiologic studies have examined the link between low vitamin D levels and multiple disease states. Low vitamin D levels are associated with increased overall and cardiovascular mortality, cancer incidence and mortality, and autoimmune diseases such as multiple sclerosis **[142, 396].**

The majority of the general population has insufficient 25-hydroxyvitamin D (25[OH]D) levels. This is mainly a consequence of lifestyle related reductions in sunlight exposure and subsequently reduced vitamin D synthesis in the skin.

Vitamin D receptors (VDR) have been discovered in almost all human cells and recent studies suggest an important role of the vitamin D endocrine system for several extraskeletal diseases (e.g. adverse pregnancy outcomes, reduced fertility and polycystic ovary syndrome (PCOS), as well as cancer).

OC use increases circulating levels of 25-hydroxyvitamin D, and should be considered when interpreting values obtained for clinical evaluation or nutrition research **[233].**

New patents cover the use of vitamin D in combination with traditional oral hormonal contraceptives and genestin **[309].**

Summary:
- Vitamin D is a very promising vitamin with various benefical extraskleletal actions on e.g. adverse pregnancy outcomes, reduced fertility and polycystic ovary syndrome (PCOS), as well as cancer
- Improvement of vitamin D status should be a goal for the general healthcare system as well as for gynecologists.
- No preclinical studies registered at www.clinicaltrials.gov (FDA Homepage for clinical trials)

5.2.5. Genestin Supplemented Oral Contraceptives

Phytoestrogens are a diverse group of plant-derived compounds that structurally or functionally mimic mammalian

estrogens and show potential benefits for human health. Potential beneficial effects of phytoestrogens on breast and prostate cancers, cardiovascular disease, menopausal symptoms and osteoporosis have been examined in various trials **[496].** Isoflavones as i.e. genestin are tested in clinical trials mainly for female postmenopausal hormonal replacement (e.g. vasomotor menopausal symptoms) **[416].**

New patents are covering the use of genestin (20 mg at least; dose range 50–80 mg) and vitamin D (at least 400 IU) in combination with traditional oral hormonal contraceptives **[550].**

Various so-called bioidentical hormones some derived from plant extracts have been chemically modified to be structurally indishinguishable from human endogenous hormones.

The use of bioidentical hormones in postmenopausal women is summarized in a review by **Cirigliano (2007) [97].**

Summary:
- The clinical benefit for a combination of genestin and traditional combined oral contraceptives is not yet evident. Long-term risks of the use of bioidentical hormones from plant extracts have not been evaluated.

- Preclinical studies are not registered at www.clinicaltrials.gov (FDA Homepage for clinical trials).

5.2.6. DHEA-Supplemented Oral Contraceptives

Androgen Restored Contraception (ARC) is a novel concept for oral contraception, invented at Pantarhei Bioscience, a Dutch pharmaceutical company. The concept is based on the fact that the use of combined oral contraceptives (COC's) causes a decrease of androgen levels, especially testosterone (T), due to the inhibition of ovarian androgen production. According to the literature, T levels decrease by up to 50%. However, large prospective studies conducted by Pantarhei have shown that the loss of T is more serious. A phase II endocrinology and safety study performed by J.M. Foidart in Liège, Belgium, in collaboration with Pantarhei Bioscience including 99 pill use starters has shown a significant median decrease by 1.5 to 0.5 nmol/l for total T and by 20 to 2 pmol/l for free T after 3 treatment cycles of COC. This study was reported at the COGI Congress in Berlin in November 2010.

Since the natural human androgen dehydroepiandrosterone (DHEA) is partly metabolized into T after oral administration, restoration of T levels during COC use can be achieved by the concomitant administration of DHEA. The studies by Pantarhei have shown that with a dose of 50 mg DHEA per day T levels can be normalized without exceeding the maximum T levels found in regularly cycling women not using COCs.

In addition to the normalization of T levels, adding DHEA to the contraceptive pill results in significant clinical improvements of mood and sexual function in unselected COC users. The first results of a clinical phase II study using the "triple hormone" oral contraceptive ARC concept and focusing on sexual function and safety were reported in May 2010 at the 11th Congress of the European Society of Contraception in The Hague, The Netherlands. The study including 82 women comprised a crossover design of two treatment periods of five months each and compared use of an oral contraceptive alone to the same oral contraceptive with the addition of 50 mg DHEA per day. The study was performed by R. van Lunsen and E. Laan from the Department of Sexology of the Academic Medical Center in Amsterdam, The Netherlands in close collaboration with the H.C. Bennink and Y. Zimmerman from Pantarhei Bioscience. In these pill users without specific sexual complaints, arousability, genital sensation and lubrication improved significantly in a double-blind study setting. Furthermore a double increase of the frequency of sexual activity and a significant reduction of the frequency of rejection of initiation of sexual activity by the partner were observed.

In the Liège study using validated mood questionnaires, significant mood improvements were observed during 6–12 months DHEA treatment, all in favor of DHEA use.

No effect of DHEA was obtained in two smaller so-called n = 1 studies in women with serious mood or sexual problems.

The addition of DHEA to COCs did not cause any side effects and DHEA had no effect on the incidence of hirsutism in the studies in Amsterdam and Liège lasting 10 and 12 months respectively. The incidence of acne was comparable to the incidence without pill use.

According to the **Bayer Annual Report (2008) [285]**, Bayer HealthCare has performed efficacy and safety studies (phase II) **[267]** of oral dehydroepiandrosterone (100 mg) as a concomitant therapy to oral contraceptives in women complaining of reduced libido. The purpose of the study was to evaluate the effectiveness of the study drug on the libido (sexual desire) of women who are taking oral contraceptives and have experienced libido reductions as a side effect of OCs. The results of these studies are not yet known.

The ARC "triple hormone" concept combining an estrogen (E), a progestin (P) and an androgen (A) in a COC has been patented by Pantarhei Bioscience for oral contraception. In addition, Pantarhei has obtained a sub-license on a broad patent owned by BioSante, USA, protecting the combined use of E, P and A in general.

Summary:
- DHEA is a weak androgen produced by the adrenals which acts a precursor for androgen synthesis.
- DHEA-dosage is very high compared to the dosage used "off-label" and in most countries as an OTC drug for substitution in the postmenopause (10–25 mg/day).
- A preclinical study by Bayer HealthCare **[267]** has been completed, but the dosage of DHEA (100 mg/day) used in this trial was too high and the side effects of DHEA in such high dosage in women of reproductive age are unclear.
- Women with a spontaneous menstrual cycle have significant circulating levels of testosterone, but in women using combined COCs testosterone is suppressed.
- Normalization of testosterone levels during the use of COC by adding 50 mg oral DHEA per day improves both mood and sexual function significantly. As in the case of testosterone substitution in the postmenopause, the effect of testosterone on breast cancer might be the crucial issue.

– The 50 mg dose of DHEA is higher than the 10–25 mg used in HRT studies, but has caused no side effects and has been shown to be safe in the literature.
– Since the clinical effects of restoring testosterone levels by DHEA have been demonstrated in unselected pill users without overt complaints, the ARC pill concept is a first choice pill for all *normal?* women and *but?* not for women with serious psychological or sexual problems during COC use as demonstrated by studies by Bayer HealthCare and Pantarhei. Such women require counseling and not testosterone.

6. Tomorrow will be different

"There will always be a tomorrow
Albeit it will be different from
Anything and everything imaginable."
Egon Diczfaluy (2010)

Conflict of Interest

T. Rabe has held talks for Jenapharm, Bayer-Schering Pharma, HRA, and MSD, receiving payment and in some cases travel expenses. Some advisory board activity.

Alfred O. Mueck has been involved in trials regarding hormonal contraceptives and HRT sponsered by Bayer Schering, Jenapharm, Wyeth, MSD and Novartis. He has received from those companies consultancy fees, lecture fees and financial support to conduct research on sexual steroids. He serves on the board of several societies and journals covering this issue.

H. J. Ahrendt has held talks for Jenapharm, Bayer-Schering Pharma, and MSD, receiving payment and in some cases travel expenses. Some advisory board activity.

P. C. Crosignani held consulting work for Bayer-Schering, IBSA and Merck-Serono.

M. Goeckenjan, R. Sabatini, **P. A. Lohr**, **M. D. Creinin, J. C. Dinger,** and **T. Strowitzki** declared no conflict of interest for this paper.

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