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50 years of the pill

The separation of sexuality and reproduction has been a human “project,” or should I call it a “dream,” for thousands of years. Unplanned pregnancies either ended in unwanted (or finally wanted) children or in abortion. Millions of people experienced emotional, physical and relationship tragedies. Throughout the ages, older experienced women, midwives, laymen, priests and chiefs tried to liberate women from the burden of unwanted children; the first physicians, like Soranos, Galen, Avicenna and others, did the same. The recommendations were sometimes simple, (“put wool damped with plants in the vagina as a pessary”) sometimes exotic or eccentric (“jump after intercourse”). As science developed, science in the sense of understanding and influencing nature through experimental research, the grounds were laid to investigate the different parts and steps of the reproductive process as well as ways to influence and control it.

In the 1920s, the physiologist Ludwig Haberlandt paved the way for understanding the role of the ovaries. Scientists already knew that the ovaries produce oocytes; it now appeared that ovulation no longer occurred once a woman became pregnant. The “signals” from the ovaries were studied, their nature elucidated and the molecules involved finally synthesized by biochemists. Adolf Butenandt isolated oestrone in 1929, for which he received the Nobel Prize in 1939. Walter Hohlweg and Hans H. Inhoffen developed ethinyl estradiol and ethisterone, thus providing the basic ingredients for hormonal contraception. Another group of eminent biochemists, including Russell E. Marker, Carl Djerassi and F. B. Bolton, synthesized steroids that would become components of oral contraceptives (OCs).

But science alone does not change the world. It needs people who want to achieve something with what science offers. When these medical possibilities materialized, the political climate in many countries was hostile to birth control, which was considered a criminal act and against God and nature. Two distinguished feminists, Margaret Sanger and Katherine McCormick, had the courage and the strength to fight not only for the right of women to control their fertility but also to convince and support “men of science” like Gregory Pincus, Min-Chue Chang and John Rock to develop the first birth-control pill.

This success story teaches us that a multidisciplinary approach involving not only sound scientific research but also advocacy for women’s reproductive and sexual rights is a basic and mandatory condition for making any progress in the domain of women’s health. Family planning professionals have been and will continue to be involved in political
struggles for the recognition and implementation of these rights. Now that OCs have been available for 50 years, it is worthwhile to look back and try to understand the impact of this milestone in contraceptive history on women’s health and women’s health professionals.

After the big step forward with the introduction of the pill, it became evident that there is no benefit without any risk. The first case of a severe complication was reported in the United Kingdom by a Suffolk family doctor, W. M. Jordan, in a letter to The Lancet medical journal in November 1961. A little later, the Royal College of General Practitioners started its OC study, which was supported by a grant of £38,000, to investigate prospectively over a five-year period the health risks of the pill. More studies followed, and their reports indicated that there was an increased relative risk of deep vein thrombosis and thromboembolism in pill users compared to non-users. However, if expressed as the absolute number of attributable cases, this risk was found to be low and was considered acceptable with respect to the benefit of OCs. Since then, many studies have been conducted to increase our knowledge about risks and benefits of contraceptive methods and this research is still ongoing. With this knowledge, we can make contraception safer by doing away with methods in which risks outweigh the benefits.

Several other developments in contraceptive research and technology followed: lowering of dosage, new steroids, new ways of application, etc. The research based on the use of hormones was complemented by new developments in non-hormonal methods, from the old classical barrier methods like the condom and cap to the new IUDs. New challenges and demands arose. Contraceptive methods should not only be efficient and safe but should also have additional health benefits or even therapeutic actions for specific women’s health problems.

Today, a large array of contraceptive methods is available. It is our duty to provide both information and education for the public and training and quality control for health professionals in order to promote and maintain women’s sexual and reproductive health.

Johannes Bitzer, MD
Professor of Obstetrics and Gynecology,
University Hospital Basel, Switzerland
President of the European Society of Contraception
Executive summary

“Two hundred leading historians have concluded that neither Einstein’s theory of relativity nor the nuclear bomb, nor even the power of computers and the Internet have had a stronger impact on society in the 20th century than the pill.”


Some 50 years after the successful market launch of the first oral contraceptive, this book was written to serve as a factual source of information on modern hormonal contraception. It aims to create a factual foundation for the ongoing public debate about the benefits and risks of modern combined oral contraceptives by presenting sound scientific research. Moving beyond the current discussion, it highlights milestones of the past 50 years, gives an outlook on the role of modern contraceptives in developing and emerging countries and provides insights into future product developments.

Modern combined oral contraceptives are regarded as one of the most reliable methods of contraception.

Contraception for women based on hormones was an entirely novel idea at the beginning of the 20th century. Until then, little information was available about the female menstrual cycle and the role of hormones. Consequently, it took until the beginning of the 1960s for the first oral hormonal contraceptive to be brought to market. And then, due to the prevailing attitudes of that particular time, it was not called contraception for women but introduced as medicine for menstrual disorders. Today, oral contraceptives are a fact of life that is almost taken for granted by many women and their partners worldwide.

Beyond their reliable contraceptive effect, modern combined oral contraceptives provide an ample range of non-contraceptive benefits.

Modern oral contraceptives contain low dosages of synthetic female sex hormones similar to those produced by the female body. Most pill formulas are so-called combined oral contraceptives (COC) with two classes of hormones: estrogen and progestogen. Because of their multiple effects on the female cycle, e.g. the reduction of the body's own hormone production or the suppression of ovulation, COCs are regarded as one of the most reliable options for women to prevent unplanned pregnancies. What is more, their effect is completely reversible and a woman's ability to conceive returns soon after COC cessation. Besides oral contraceptives, a variety of hormonal, chemical, barrier and so-called “natural” methods are also available. Women and men can choose the contraceptive method that is most suitable for their state of health and personal life situation.

In most countries, COCs are classified as medication and only available with a physician’s prescription. Modern COCs are evaluated in clinical trials in regard to their contraceptive efficacy, tolerability and safety. However, continued epidemiological research after market launch is important to assess the entire spectrum of benefits and risks.

Continuous research on modern COCs has shown that they provide a wide range of non-contraceptive benefits, from the alleviation of menstruation-related symptoms to long-term...
benefits such as reduced rates of ovarian cancer. Generally, women tolerate COCs well and serious side effects are rare. Common adverse reactions may include breast tenderness, headache and weight gain. Among the serious side effects, cardiovascular events and especially the risk of venous thromboembolism (VTE) are the most serious. Even so, with all COCs on the market today, the increased risk of VTE is still lower than the VTE risk during pregnancy or post partum. Still, risk factor information is important in deciding whether a COC is a suitable contraceptive choice for an individual woman.

According to a 2009 survey initiated by Bayer Schering Pharma among 24,320 women aged 15 to 49 in 18 countries, some 66 percent of women in Europe have used oral contraceptives. However, between European countries differences in the availability and choice of contraceptive methods are noticeable. The differences apply even more in developing and emerging countries 1. The challenges there range from inadequate sex education to the absence of public health services and a lack of access to modern contraceptive methods. These obstacles are frequently linked to complex social issues like education, public health or economic productivity. Unfortunately, this oftentimes leads to high rates of unplanned pregnancies, unsafe abortions and an unacceptable number of maternal deaths.

Research and documentation by well-known institutions, such as the Guttmacher Institute and the United Nations Populations Fund (UNFPA), show that, among other factors, family planning services that provide basic knowledge about human reproduction, reproductive health and modern contraceptive methods are key to reducing unplanned pregnancy rates 2. This may, in turn, impact women’s roles, the overall wellbeing of society and even result in higher economic output in the long run. The example illustrates possible linkages between modern contraception in general and health, social, cultural and economic issues. Thus, modern contraceptives should be seen in a much larger context in some parts of the world.

Since the 1960s, modern COCs have already led to major improvements for many women. Compared to contraceptive methods in former times, protection against unplanned pregnancies has become safer, more reliable and more convenient. And, as an established modern method of contraception, COCs will continue to do so. Today, researchers have continuously striven to develop lower dosages, new hormone combinations and multiphasic drug formulas. Currently, researchers are focusing on COCs with additional benefits for women. For example, some medications already help against acne or heavy menstrual bleedings. Further ideas being investigated are the development of pills that contain folic acid. A sufficient supply of this essential vitamin is advised before and during the first months of pregnancy to reduce the risk of neural tube birth defects. Taking a COC supplemented with folic acid before conception may support this goal.

As researchers continue their work, it seems certain that new oral contraceptives that yield more benefits for women can be expected in the future.
2 Some basic facts about oral contraceptives

Nowadays, women and men have a variety of modern contraceptive methods at their disposal, above all in industrialized countries. Among them, oral hormonal contraceptives stand out in terms of safety, reliability and ease of use.

2.1 Oral contraceptives today

Since the introduction of the first “birth-control pill” in 1960, half a century ago, it has been an unparalleled success story. Today, about 80 million women worldwide avoid becoming pregnant with the pill. Being able to make a conscious decision on whether and when to have children has decisively strengthened women's role in society. Thanks to modern hormonal contraceptives, couples can now better plan their families and experience sexuality with the security of knowing that pregnancy is prevented. Particularly in western societies, the pill and other modern contraceptives are an integral part of life. Some 71 percent of women in Europe aged 15 to 49 have experience with one or more hormonal contraceptive methods, and 93 percent of these indicate that they had used the pill at some point—meaning that 66 percent have experience with the pill.

What’s more, contraception is no longer a taboo topic. Information about modern contraceptives is freely accessible on the Internet and the different methods available are discussed openly in forums and chat rooms. There has never been such a variety of ways for young people to inform themselves about love, sex and contraception. Nevertheless, as with every generation before, there are knowledge gaps regarding these intimate topics—gaps that are often glossed over when an ill-informed young person wants to look “cool” but in reality has unanswered questions. The consequence is that teenagers are still becoming pregnant unintentionally. In a comparison of industrialized western countries, Germany with 11 pregnancies (per 1,000 women between 15 and 19 years of age) is at the lower end of the table together with the Scandinavian countries (7–11 pregnancies) and the Benelux states (9). Great Britain (20) and Canada (16) are in the middle of this table. The United States, with 53, is at the top. The world ranking is led by Niger (233), followed by Nigeria (103) and India (73).

Despite high levels of awareness and availability, there is thus still a need for information and education about modern contraceptives.
2.2 The female cycle

The female menstrual cycle and the processes in the body associated with it are controlled by hormones. Every hormone dose is precisely regulated by a region in the brain called the hypothalamus and a gland called the pituitary. Each cycle lasts an average of 28 days.

The onset of monthly menstrual bleeding or “the period” marks the beginning of each cycle. This lasts for about three to seven days. Toward the end of bleeding, estrogen (female sex hormones) produced by the ovaries stimulates several ova (eggs) to ripen in the ovaries. Usually only one ovum matures fully.

Estrogen also stimulates the thickening of the uterine lining, so that if it were to be fertilized, an ovum could nest. Now the fimbria of the fallopian tube is activated so that it comes closer to the part of the ovary where the ripening follicle grows and bulges.

On about the 14th day, a protective layer (follicle), that up to now has surrounded the ovum, bursts. The egg is flushed down the fallopian tube into the womb (uterus). For several hours, the egg can now be fertilized. At the same time—at this point under the influence of the female sex hormone progesterone—the lining of the womb is again stimulated. It thickens and prepares for the implantation of a fertilized egg.

If the ovum is not fertilized during this cycle, hormone production stops towards the end of the cycle and hormone levels in the blood are reduced. The thickened layer is shed together with the inner layer of the womb. This happens as part of the monthly bleeding that sets in at this point. Since this marks the beginning of the female cycle, the hormone-controlled cycle now begins again.

2.3 Hormonal effects of the pill

Oral contraceptives (OC) contain synthetic sex hormones. They affect the female cycle in several ways and are similar to the hormones produced by the female body. Most birth-control pills today are low-dose combined oral contraceptives (COC) containing estrogen and progestogen (so-called “combined pills”). The only exception is the so-called mini-pill, which consists of progestogen only (Progestogen belongs to the class of hormones mentioned above called progesterone.). Although the various kinds of combined pills differ in their dosage and composition, their basic modes of action are comparable: The progestogen is the actual contraceptive, while the estrogen component maintains a regular menstrual cycle and supports the contraceptive effect of the progestogen.

The hormonal substances in the combined pill have several effects in the course of the cycle. First of all, hormones make the hypothalamus believe that the body is pregnant, whereupon it reduces its own hormone production. Maturation of the ovum and ovulation are suppressed—and in turn estrogen production in the ovaries is reduced. Furthermore, progestogen ensures that the formation of mucus in the neck of the womb is stimulated, forming a natural barrier to sperm. In turn, the addition of synthetic estrogen supports estrogen-dependent functions such as cycle stability. Thus, the pill’s effects on the female cycle are as follows:

- Hormone production is reduced.
- Maturation of the egg (ovum) and ovulation are suppressed.
- Formation of mucus in the neck of the womb (cervix) is stimulated, forming a “plug” or natural barrier to sperm.
- A regular menstrual cycle is supported.
- The formation of the endometrial lining is suppressed.

These effects on the female cycle are reversible, i.e. a woman’s ability to conceive returns quickly after she stops taking it. Combined oral contraceptives may differ in dosage and composition; their basic mode of action is comparable.

The effects of the pill on the female cycle are reversible. Thus a woman’s ability to conceive returns quickly after she stops taking it.
Nowadays, women and men can generally choose from a variety of modern contraceptives.

2.4 Contraceptive methods—an overview

The list of modern contraceptives is long and includes hormonal and non-hormonal methods—from orally administered drugs to non-hormonal barrier and “natural” methods. They enable women and their partners to choose the contraception that is the most suitable for their state of health and personal life situation.

Oral hormonal contraceptives
Hormonal contraceptives are—if used correctly—regarded as the most reliable method of contraception apart from male or female sterilization. Unlike the barrier methods, they are not used directly before or during sexual intercourse, an aspect that users consider an advantage. The pill is probably the world’s best-known hormonal contraceptive. More than 80 million women worldwide use the pill for contraception. There are several types of pills that differ in terms of their active substance and dose (see chapter 5.4).

Another one is the so-called “morning-after pill,” which can be taken within a strictly limited time frame after unprotected intercourse, or if some other method of contraception has failed (e.g. if a condom bursts), to prevent pregnancy after the event. However, this is not a standard method of contraception and should only be used in exceptional cases.

In most countries, hormonal contraceptives are only available with a physician’s prescription.

Further hormonal contraceptives: injectables, implants and intrauterine devices
Besides oral hormonal contraceptives, there are other contraceptives that are based on hormones with different hormone doses. Examples include patches, hormone-containing vaginal rings, implants, hormone-releasing intrauterine devices (IUD) and long-acting depot injections, such as the one-month and three-month injection.

Non-hormonal mechanical and chemical methods
The so-called “barrier methods” use mechanical or chemical aids to prevent the sperm from entering the womb, thereby preventing fertilization of a mature ovum. Examples of such mechanical aids include condoms, diaphragms (also the vaginal pessary) and cervical caps.

The condom, by the way, is the only contraceptive method that also offers protection against venereal and sexually transmitted diseases, namely HIV infection and AIDS. Diaphragms and cervical caps are inserted into the vagina before intercourse, thus covering the neck of the womb. As an additional precaution, chemical protective agents are frequently used, for example, spermicide suppositories, creams or sponges, which kill the sperm or form foam that is difficult for sperm to penetrate.

Intrauterine device (coil)
Another option is the non-hormonal intrauterine device (IUD), also known as the coil. It usually has a T-shaped structure, is made of plastic, and is often wrapped with a fine copper wire. A gynecologist inserts the coil into the womb, where it can stay for up to five years. The IUD is therefore a longer-term contraceptive that is frequently used by women who have already borne children and/or have completed their family planning for the time being.

Natural methods of contraception
“Natural” contraception methods include the Knaus-Ogino method, which calculates the fertile days of a woman’s cycle, measuring a woman’s temperature on waking, and examination of the cervical mucus (Billings method). The latter two determine the days of ovulation on which the woman can become pregnant by measuring body temperature or examining the consistency of the mucus in the vagina. So-called coitus interruptus also belongs to the natural contraceptive techniques. In this case, sexual intercourse is interrupted shortly before the man ejaculates.

The Pearl Index, which indicates the reliability of contraceptive methods, shows that the “natural” methods are comparatively unreliable and are associated with a high rate of unplanned pregnancies.

Male and female sterilization
Male and female sterilization is the most effective form of contraception. However, since it is generally non-reversible, it is only suited for individuals who definitely do not want to have (more) children.
Putting OC benefits and risks in perspective

No contraception method is both 100 percent effective and totally free of side effects. The choice of family planning method requires a trade-off between the desired level of protection against pregnancy and the couple’s willingness to tolerate the risks and disadvantages associated with a particular method.

3.1 How to assess benefits and risks of oral contraceptives—
The role of clinical and epidemiological research

The prevention of unplanned pregnancies has been part of our cultural history for thousands of years. Contraceptive methods have always been used officially or in secret, depending on the conventions and morals of a particular time. By 2010, a spectrum of modern contraceptives was available, with the combined oral contraceptive being one of the most convenient, safe and reliable options available to women to prevent unplanned pregnancies. Currently more than 80 million women worldwide use COCs as their method of contraception.

COCs are a convenient method, since taking the pill is simple, discreet and does not interfere with sexual activity.

COCs have a method failure rate of about 1 percent or less per year: This means that 1 of 100 women using this method over one year will get pregnant, perfect use assumed. The real life effectiveness of COCs, taking into consideration user errors, use of inappropriate co-medication or illness, is still more than 90 percent, with 3 to 9 of every 100 women using this method for more than one year getting pregnant. Complete return to individual fertility is rapidly achieved after stopping COC use and the length of the reproductive period is not compromised.

Before COCs are brought to market, they are studied in clinical trials that assess contraceptive efficacy as well as the tolerability and safety of the drug. Since clinical trials investigate contraceptive efficacy: unintended pregnancies during the first year

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<td>Spermicide</td>
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<td>18</td>
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<td>Cervix interruptus</td>
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<td>4</td>
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<td>Periodic abstinence (any method)</td>
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use with a limited number of patients, although this number usually reaches several thousand women, well-conducted and continuous epidemiological research plays an important role in assessing benefits and risks of COCs after market introduction. Some side effects shown by COCs may occur too seldom or only late in life so that they cannot be fully investigated in clinical studies. This may be relevant for both undesirable side effects (such as thrombosis) and desirable side effects (such as prevention of ovarian cancer). Continued research provides insights into the overall positive and negative effects of COCs over a life time, for example on cancer risk and death causes.

Over time, researchers learned a lot about how to design studies that will assess the benefits and risks associated with COC use. Careful consideration of potential bias and confounding variables is necessary so that studies provide useful and reliable information to health care providers and users.

In this chapter, we want to: (i) provide an overview of the benefits and risks of COC use, (ii) review epidemiological evidence on the cardiovascular side effects, cancer risks and fertility-related effects of COCs and (iii) share considerations regarding the responsible prescription of oral contraceptives (OC), thus bringing together epidemiological knowledge of benefits and risks with the individual predispositions and preferences of women.

3.2 Overview of the benefits and risks of combined oral contraceptives

Modern COCs provide not only excellent contraception but also a variety of non-contraceptive benefits, ranging from the regulation and reduction of both menstrual bleeding and dysmenorrhea to the treatment of premenstrual syndrome (PMS), menstrual headaches, acne and hirsutism. Long-term benefits include reduced rates of endometrial and ovarian cancer. Serious side effects are rare occurrences among OC users. Modern COCs are well tolerated and adherence to prescribed regimens is generally excellent, thus allowing women to plan their pregnancies. By avoiding unplanned pregnancies, women may also reduce their exposure to serious vascular risks and flares of systemic diseases that can occur during pregnancy.

The side effects of COCs are well documented. For the vast majority of COC users, the benefit-risk profile is favorable when COCs are used as directed.

Common side effects associated with COCs include breast tenderness, nausea, headache, weight gain and acne. Cardiovascular events, rare as they are, likely constitute the most relevant serious side effects of combined hormonal contraceptives. All COCs are associated with an increased risk of venous thromboembolism (VTE). VTE is a known rare event associated with the use of any COC. However, the increased risk of VTE among OC users is lower compared to the VTE risk during pregnancy or post partum. Bayer sponsored two large independently conducted studies (EURAS, Ingenix) in Europe and the United States involving more than 120,000 women that confirmed that the risk of VTE is comparable for all studied low-dose COCs.

Cardiovascular side effects

Venous thromboembolism (VTE)

According to contemporary medical literature, in 1856, Rudolph Virchow suggested that thrombosis was the result of at least one of three underlying etiologic factors: vascular endothelial injury, stasis of blood flow or hypercoagulability of the blood.
VTE encompasses two related conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE).

DVT is a condition in which blood clots (thrombus) form in a deep vein, typically in the large veins in the lower leg, thigh or pelvis. Symptoms of DVT can include: unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg that may be felt only when standing or walking, increased warmth in the affected leg; or red or discolored skin on the leg. Following DVT, a post-thrombotic syndrome may occur with long-term impairment. However, often a DVT is asymptomatic or associated with minimal symptoms.

Part of a thrombus in the deep veins may break away and travel in the circulatory system and may block arteries (so-called thromboembolus). If this affects pulmonary circulation, pulmonary embolism occurs. Symptoms of PE can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing, which may bring up blood; sharp chest pain, which may increase with deep breathing; sense of anxiety; severe light-headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (e.g. shortness of breath or coughing) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections). PE is a potentially life-threatening condition and can cause death. According to a public assessment report about combined oral contraceptives and VTE by the European Agency for the Evaluation of Medicinal Products Committee for Proprietary Medicinal Products in 2001, VTEs are fatal in 1 to 2 percent of cases.6,7

The rate of VTE incidents increases with increasing age.8 The incidence of a first-time VTE increases from less than five cases per 100,000 persons aged less than 15 years to approximately 500 cases per 100,000 persons aged 80 years.9 By comparison, the background incidence among women of reproductive age is 4 to 5 women per 10,000 women-years.10

Clinically manifest VTE is often the result of several predisposing risk factors (i.e. caused by multiple acquired and inherited risk factors and their interaction). The use of estrogen-progestogen combination products, such as COCs, combined contraceptive patches and rings and combined menopausal hormone products, is a well-known risk factor for VTE. The risk of VTE in COC users is known to increase with increased doses of estrogen and is highest during the first year of use. Other risk factors include hip or leg fracture, hip or knee replacement, major general surgery and major trauma, immobilization, pregnancy and the post-partum stage, previous VTE and genetic mutations that affect coagulation (i.e. thrombophilia) as well as increasing age and obesity.8 Approximately 25 to 50 percent of patients with first-time VTE (DVT or PE) do not have a readily identifiable risk factor.9 VTE may occur in both men and women.

**VTE frequency**

Venous thromboembolism is often the result of several predisposing risk factors and caused by multiple acquired and inherited risk factors and their interaction.
COC use and VTE
It has been known since shortly after the introduction of COCs that their use increases the risk of VTE. It was one main reason for efforts to decrease estrogen doses contained in COCs. The risk of VTE associated with modern COCs that contain much lower doses than the first medicines on the market is approximately 2–3 times more than for non-users. However, the absolute VTE risk is still rare (affecting more than 1 in 10,000 but less than 1 in 1,000 women).

Data from EURAS showed that increasing age and body mass index (BMI) had a cumulative effect on the incidence of VTE (which is depicted in the figure above) [14].

In women with no known risk factors for VTE (other than COC use), the risk of VTE was lowest in those aged less than 25 years with a BMI of less than 25 kg/m²; however, the risk increased substantially with increasing age and with increasing weight. The risk must also be seen in the context of the VTE risk associated with pregnancy and delivery. The presence of additional risk factors, such as a personal history or family history of VTE, would add to this risk. Risk factor information is therefore important in deciding whether a COC is a suitable contraceptive choice for an individual woman. For the vast majority of COC users, the benefit-risk profile is favorable when COCs are used as indicated.

EURAS: Impact of age and BMI on VTE incidence in OC users without known risk factors [14]

The risk of venous thromboembolism is highest during the first year of use of a COC but gradually declines with long-term use.

The European Active Surveillance Study on Oral Contraceptives (EURAS-OC) [10] shows that the frequency of VTE in users of COCs that contain a dose of ethinyl estradiol (EE) of less than 50 µg is between 8 and 10 per 10,000 women-years. In comparison, the frequency of VTE is 4.4 per 10,000 women-years in non-pregnant, non-COC users and ranges from 20 to 30 per 10,000 women-years during pregnancy and the post-partum period [10,11].

Progestogen-only contraceptive methods have not been shown to increase the rate of VTE. Transdermal delivery of estradiol in hormone therapy for menopausal women may be associated with a reduced risk of VTE, but available data do not suggest a benefit in terms of VTE risk when non-oral routes (i.e. transdermal and intra-vaginal) are used for delivery of combined hormonal contraception containing the estrogen EE [5]. The risk of VTE is highest during the first year of use of a COC but gradually declines with long-term use and reaches the levels of non-users within a few weeks after cessation of the COC. This increased VTE risk is present after initially starting a COC or restarting it or a different COC (following a four week or longer pill-free interval) [12,13].

Third generation debate
Scientists have long known that VTE risk is linked to the estrogen dose. In the 1990s, an extensive debate ensued about different progestogens having different levels of VTE risk. In the same period, some, but not all, epidemiological studies suggested that COCs that contained “second-generation” progestogens (e.g. levonorgestrel [LNG]) had a lower risk of VTE than so-called “third-generation” COCs (containing e.g. gestodene [GSD] and desogestrel [DSG] as progestogens) [15,16].

Many of these studies were hampered by major methodological shortcomings since they failed to control for relevant variables, including the duration of COC use, baseline risk factors for VTE, and the preferential prescribing of newer products to at-risk women. Although many studies that controlled for duration of use could not find a differential increased risk of VTE with third- versus second-generation COCs, discussions on this topic in Europe concluded with the publication of a Committee for Proprietary Medicinal Products Public Assessment Report in September 2001 that included a revised warning on the risk of VTE with third- versus second-generation COCs [6,8]. Specifically, the report stated that “[on] the basis of a careful scientific evaluation, it has been found that women using a 3rd generation COC with 30 µg of ethinylestradiol have a small increased risk of VTE compared with women using 2nd generation COCs.” This may translate into 1 to 2 additional VTE cases per 10,000 women years of use.
Recent epidemiological studies

EURAS, INGENIX
As part of post-marketing commitments to the European Competent Authorities and the Food & Drug Administration (FDA), Bayer sponsored two large-scale, observational Phase IV studies that were conducted in Europe (EURAS-OC study\textsuperscript{10}) and the United States (Ingenix study\textsuperscript{17}). Both studies independently demonstrated that users of low-dose COCs had a similar risk of VTE, regardless of the progestogen used, including drospirenone (DRSP)\textsuperscript{10,17}. Collectively, EURAS-OC and Ingenix encompass more than 120,000 COC users in Europe and the United States. Both the EURAS-OC and the Ingenix studies were undertaken to compare the risk of VTE associated with the use of ethinyl estradiol 30 µg/drospirenone 3 mg and other COCs.

The EURAS-OC study\textsuperscript{10}, which was conducted between 2000 and 2005, was a multinational, prospective, non-interventional cohort study of new users of DRSP-containing COCs, LNG-containing COCs and COCs containing other progestogens. Overall, 58,674 women from seven European countries were followed for 142,475 women-years of observation. Active surveillance methods were employed in the study; follow-up assessments for each woman were scheduled every 6 months in order to assess the occurrence of rare or unexpected adverse outcomes possibly related to COC exposure.

The Ingenix study\textsuperscript{17} was a large-scale study conducted in the United States; the study assessed VTE events in women who, according to data within a U.S. health insurer database, initiated treatment with Yasmin or other COCs between June 2001 and June 2004. A total of 22,429 women who started Yasmin and 44,858 women who started other COCs were followed for an average of 7.6 months (41,656 women-years). The two cohorts were matched using propensity scores based on variables representing numerous aspects of the subjects’ medical history.

The EURAS-OC and Ingenix studies were sponsored by Bayer. Both studies were specifically designed after extensive discussions with European and U.S. health regulators. The concept, conduct, analyses and reporting of the two studies were performed by two different independent investigation groups, using two different methodologies in two geographically distinct populations. Both studies were sufficiently powered to assess differences in the risk of VTE between COCs containing different progestogens and were designed to achieve balance between the cohorts by controlling for confounding factors (EURAS-OC) or by applying propensity score matching (Ingenix). Because only women starting COC treatment were eligible for inclusion, short-term COC use was compared with short-term COC use. The results of both studies were assessed using a blinded medical adjudication process and were overseen by independent data safety monitoring boards. All case reports were submitted to the relevant health authorities for review. These factors make the results of the studies less likely to be vulnerable to bias and confounding than the results of two other retrospective epidemiological studies published in the British Medical Journal (BMJ) in August 2009.

Beyond the EURAS and Ingenix studies, Bayer is taking efforts to continue studying the safety of its DRSP-containing COCs. So far, recently completed\textsuperscript{18} and ongoing studies have supported the findings of EURAS and Ingenix.

Studies published in the BMJ in August 2009
In August 2009, the BMJ published two retrospective epidemiological studies, one conducted in Denmark and the other conducted in The Netherlands. The studies assessed the risk of VTE for users of different types of hormonal contraceptives\textsuperscript{19,20}. The results of these studies suggested that COCs were associated with a differential risk of VTE based on their progestogen component. More specifically, the results suggested that the risk of VTE was lower in women using levonorgestrel (LNG)-containing COCs relative to women using so-called “third-generation” COCs and women using COCs containing DRSP.

The results of the two studies have been questioned by many experts as well as health authorities responsible for the market authorization of drugs. The results of one of these two studies were not statistically significant. Leading epidemiologists, and Bayer, have identified several methodological issues in these studies that need to be clarified before a final conclusion regarding the level of VTE risk for drospirenone-containing COCs can be drawn. Currently, a reanalysis of one of the studies is being conducted.

In summary, critical analysis of the two studies suggests that the conclusions, in particular those for newer types of progestogens, such as drospirenone, could well have resulted from
methodological flaws and/or misinterpretation of findings.

Summary of VTE
All COCs are associated with an increased risk of venous thromboembolism (VTE). VTE is a known and rare event among women using COCs, but the risk of VTE is lower than the VTE risk during pregnancy/delivery. Bayer sponsored two large independently conducted studies (EURAS, Ingenix) in Europe and the United States involving more than 120,000 women that confirmed that the risk of VTE is comparable for all studied low-dose COCs.

Risk factor information is important in deciding whether a COC is a suitable contraceptive choice for an individual woman. For the vast majority of COC users, the benefit-risk profile is favorable when used as indicated.

Arterial thromboembolism (ATE)
Arterial thromboembolic disease includes myocardial infarction and ischemic stroke. Other types of stroke may include hemorrhagic stroke due to cerebral bleeding, which accounts for approximately 10 percent of stroke cases. ATEs may cause death or disabilities, such as paralysis and heart failure.

Risk factors for ATE include smoking, hypertension, hypercholesterolemia, obesity, valvular heart disease, migraines and type II diabetes. Although ATE is more common in older age groups and is among the most common causes of death in western populations, ATE may occur throughout all periods of life.

In women under the age of 45, the risk of arterial events is very low and reported by various authors to range from 1 to 10 per 100,000 women-years. A European cohort study of COC users (European Active Surveillance study [EURAS]) reported an ATE incidence of approximately 2 ATE/10,000 women-years for OC users and 1.2 ATE/10,000 women-years for past users.

For women of reproductive age, the risk of ATE is higher during pregnancy and in particular during the peripartum period, with eight additional strokes per 100,000 pregnancies. For myocardial infarction during pregnancy the incidence is reported to range between 1 in 16,129 to 1 in 35,700 deliveries, with increasing reporting rates throughout a 10-year study period in one study.

The risk of ATE rises with age and is therefore more common during the menopause. While the incidence of stroke in non-users of menopausal hormonal therapy can be estimated to be in the range of 21–32/10,000 women-years, the Women's Health Initiative Study showed that use of the estrogen-progestogen-combination conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) followed over five years increased stroke risk by 31 to 41 percent and coronary heart disease (CHD) risk by 24 to 29 percent.

COC use and ATE
Shortly after introduction of COCs, cases of ATE in users of COC were reported, often in association with hypertension, smoking and older age. Since an association with the estrogen dose was suspected early on, reports on the estrogen-progestogen-combination conjugated equine estrogens (CEE)/medroxyprogesterone acetate (MPA) followed over five years increased stroke risk by 31 to 41 percent and coronary heart disease (CHD) risk by 24 to 29 percent.

Past studies that included data from women who used COCs containing an estrogen dose of 50 µg or more ethinyl estradiol suggest that the older, higher EE dose medicines increase the risk of arterial events compared to women not using COCs. However, there is no unequivocal evidence that the use of COCs containing 30 to 40 µg of EE increases the risk of arterial problems in young women (<35 years) unless they smoke or have hypertension.

Past oral contraceptive use does not increase or decrease the risk of myocardial infarction. The risk of ATE is lower for new COCs with less than 50 µg ethinyl estradiol and may be lower for preperations with newer types of progestogens such as DSG, GSD und DRSP.

Use of low-dose COCs is thought to increase the risk of myocardial infarction by approximately two times among users even after controlling for cardiovascular risk factors (such as smoking, hypertension, and obesity). Some more recent studies, in which most current users of COC were taking low-dose estrogen and “second-” or “third-generation” progestogens, suggested that these more contemporary COCs were not associated with an increased risk of myocardial infarction.

Based on data from a meta-analysis, the use of COCs is associated with an approximately twofold increase in the risk of stroke. However, the evidence for an increased risk of stroke in users of modern low-dose COCs is not without controversy, as an increased risk of stroke was not found for healthy women.
who do not have specific risk factors and who use low-dose estrogen COCs (<50 µg ethinyl estradiol).

The rarity of arterial thrombotic/thromboembolic events limits the ability to assess potential increase in risk associated with COCs, particularly a differentiated risk for various preparations. Studies conducted before 1990 may be of limited value as many COCs used at that time contained higher estrogen doses (50 µg or more ethinyl estradiol) and are not marketed any longer. Only a few early studies accounted for bias and confounding. Also, medical practices with regard to evaluation of contraindications and ascertainment of adverse events in COC use became more effective over time.

The risk of ATE is increased in COC users who have hypertension or smoke. The risk is much lower in women of all ages who do not have risk factors, such as hypertension and/or tobacco smoking. There is reasonable evidence that ATE occurs often if a woman has a background of pre-existent atherosclerosis. Accordingly, the risk of ATE increases when additional risk factors are present and also with increasing age.

In general, the absolute risk of ATE associated with use of COCs is small and should be balanced against the risk of pregnancy itself, which is also associated with an increased risk of ATE. The benefit-risk balance is considered favorable for the vast majority of users when COCs are used as prescribed under consideration of contraindications and warnings for use.

Summary of ATE
ATE is very rare in young women and the absolute risk remains very low in young users of COCs who do not smoke or have hypertension. Past oral contraceptive use does not increase or decrease the risk of myocardial infarction. The risk of ATE is lower for new preparations with low EE (<50 µg) and may be lower for COCs with newer types of progestogens, such as DSG, GSD and DRSP. Risk factor evaluation is important, since the risk of ATE is more relevant for women who smoke or have hypertension, independent of their age.

Cancer
Breast cancer
Breast cancer is the most common invasive cancer in women, if skin cancers are not considered. The average incidence rate of breast cancer varies greatly according to age. The age-standardized incidence rate of BC in Europe in women aged 15–34 is approximately 10 per 100,000, in women aged 35–44 years approximately 130 per 100,000 and in women aged 55–59 approximately 250 per 100,000, respectively. The annual incidence of breast cancer in women ≥50 years of age as reported by Surveillance, Epidemiology, and End Results (SEER) in the United States was 350 to 400 per 100,000 women, and in women below 50 years of age it was approximately 40 to 50 per 100,000 women.

Factors that are recognized to have an influence on breast cancer incidence include genetic background, reproductive and hormonal factors, lifestyle and environmental factors (such as smoking, alcohol consumption and geographic location), as well as various factors related to socio-economic status and education. Age is the single most important factor. The incidence of breast cancer starts to increase in women over 30 years of age. Experimental data strongly suggest that estrogen plays a role in the development and growth of breast cancer. The role of progestogens is less conclusive. The first full-term pregnancy promotes differentiation of breast tissue, which can be protective against potentially carcinogenic substances, especially if it occurs early in life.

There is a concern that COC use could contribute to breast cancer, which was reinforced by the classification of COCs as carcinogenic agents by IARC (2007). However, analysis of the current knowledge challenges this assertion.

Many observational studies have assessed the risk of breast cancer in relation to COC use. Two meta-analyses and several observational studies have reported on breast cancer risk but mostly failed to show any robust association with the use of COC. A 1996 collaborative reanalysis of 54 studies found an increased risk (relative risk 1.24) of breast cancer with COC use that decreased with discontinued use. Another meta-analysis of 39 studies of premenopausal women conducted after 1980 reported an increased risk of breast cancer (OR 1.19 1.09–1.29) with oral contraceptive use.

Three other studies do not show an association between COC use and breast cancer risk. In 2002, a large population-based, case-control study including 4,575 women with breast cancer compared to 4,682 control women (Women’s CARE study) found no association between COC use and breast cancer.
cancer in women aged 35 to 65 years (current use RR 1.0; 95% CI 0.8–1.3; previous use RR 0.9; 95% CI 0.8–1.0)\(^4\). Similarly, the recently published follow-up data of the Oxford Family Planning Association cohort study of 17,032 women recruited between 1968 and 1974 showed no increased relative risk of breast cancer for OC use (RR 1.0, 95% CI 0.8–1.1)\(^4\).

Three previous large-scale cohort studies described the long-term effects of OC use on mortality: the U.S. Nurses’ Health Study observed 166,755 women during 12 years of follow-up (1976–1988)\(^4\), the RCGP oral contraception study monitored a cohort of nearly 46,000 women over a follow-up of 25 years\(^4\) and the Oxford Family Planning Association study reported follow-up data on 17,032 women from 1968 to 1974 to 2000\(^4\). In all three studies, the risk of death from breast cancer did not differ significantly between women who had used OCs at any time in their life (ever users) and those who had not (never users).

A recent publication from Nurses’ Health II based on 1,344 cases of invasive breast cancer found a small increased risk of invasive breast cancer with current use of COCs that disappeared if the use of one specific preparation was excluded, thereby rendering inconclusive the conclusion of an increased risk of breast cancer for current COC users. No increased risk was found for past use of any type of preparation\(^5\).

The Women’s Lifestyle and Health study observed an increased risk in users of COC after 5 years. This study enrolled 103,027 women between 1991 and 1999, followed up on registries in Norway and Sweden\(^5\). There was a small increase for current, recent and former COC users.

A 2009 case-control study of breast cancer risk in relation to COC use found increased risk among women exposed for one year or more, relative to use for less than one year and never-use combined (multivariable odds ratio (OR) 1.5 (95% CI 1.2–1.8). Since this study compared use of COC for more than one year with use for combined never-use plus less than year use, the data are not comparable to other studies. Possible data distortion by detection and recall bias needs to be considered in this study\(^5\).

In conclusion, studies on breast cancer and COC use suggest either no or small effects of the pill. While the case-control studies conflict, the cohort studies, including long-term observation data, have found no increase in risk. When the relative risk was shown to be increased, this effect disappeared gradually during the course of 10 years after cessation of COC use. Breast cancer is rare in women under 40 years of age. This means that the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence of causation. The observed pattern of increased risk may be due to earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancer diagnosed in ever-users tends to be less clinically advanced than the cancer diagnosed in never-users. In most studies, mortality rates from breast cancer diagnosed in COC users were lower or equivalent to non-users\(^5\).

**Ovarian cancer**

Ovarian cancer is the leading cause of death from gynecological malignancy due to its late presentation and the fact that screening in both high- and low-risk populations has not shown any benefit\(^5, 4\). The etiology of the disease is poorly understood. One theory is based on the cumulative effects of repeated ovulation (e.g. due to repeated repair processes) and exposure to high gonadotropin levels\(^5, 4\). Factors that suppress or prevent ovulation, such as pregnancies, oral contraceptive use and lactation, have consistently been associated with a reduced ovarian cancer risk\(^5\).

There is a substantial amount of evidence in the literature\(^5, 4\) demonstrating a decreased risk of ovarian cancer with the use of COCs. The risk is reduced by about 50 percent for women using COCs for five or more years. The recent Collaborative Group meta-analysis confirmed that the reduction in ovarian cancer risk increases with duration of use, reaching 60 percent after 15 years. The data also show that the decreased risk continues for many years after the COC has been discontinued. This protective effect has also been shown to occur with low-dose formulations\(^5\). Evidence is also mounting that COCs offer a similar level of protection against ovarian cancer for carriers of the BRCA1 and BRCA2 mutations\(^5\). In conclusion, multiple studies and meta-analyses have demonstrated that COC use decreases the risk of ovarian cancer. The longer a COC is used, the greater the reduction in risk observed. The reduction in risk is also seen for two to three decades after COC use is discontinued, but is attenuated with time.
Endometrial cancer

Endometrial carcinoma affects predominantly postmenopausal women. The annual incidence in the postmenopausal cohort is 1 per 1,000 women. Most cases of endometrial cancer appear to be due to prolonged and unremitting mitotic activity of the endometrium, which can occur with unopposed estrogenic stimulation. Oral contraceptives suppress endometrial mitotic activity; this appears to reduce the risk of cancer development. The three major histological types of type I endometrial neoplasia are adenocarcinoma, adenosarcoma, and adenosquamous cell, with the majority being adenocarcinoma. COC use decreases the risk of all three types, which constitute the majority of endometrial cancers. Type II endometrial neoplasia, which affects mostly postmenopausal women, develops unrelated to hormonal influences.

As early as 1982, it was noted that the risk of endometrial cancer for users of COCs was less than half that of non-users. Usage for greater than five years reduces this risk to one-third. Over the past 30 years, numerous epidemiological studies, including case-controlled studies, have provided support for the protective effect of COCs in the prevention of endometrial cancer. A large number of epidemiological studies, including multiple meta-analyses, confirm a 50 percent reduction in the risk of developing endometrial cancer among women who have used COCs compared with women who have never used COCs. Longer duration of use was associated with even greater risk reduction (up to 80 percent) however, even in women with use of less than five years there was significant reduction in risk.

The risk of endometrial adenocarcinoma is reduced by 56 percent after four years of COC use, 67 percent after eight years and 72 percent after 12 years. Protection continues for at least 15 years after discontinuation of pill use and appears to be related to the progestogen component of the pill. The more recent the COC use, the lower the risk of endometrial cancer; however, even after 20 years of discontinuation the protective effect is still above 50 percent. Hannaford et al found in the Royal College of General Practitioners’ Study a RR of 0.5 (95% CI 0.3–0.9) after 20 years.

In conclusion, use of combined hormonal contraception has been shown to decrease the risk of endometrial cancer by at least 50 percent. Longer duration of use appears to be associated with an even greater risk reduction. The protective effect of COCs appears to persist for at least 20 years after discontinuation. Limited data suggest that new COC formulations and lower-dose OCs also provide effective risk reduction.

Cervical cancer

Cervical cancer is caused by human papilloma virus (HPV) infection. Invasive cervical cancer is preceded by pre-cancerous stages, the cervical intraepithelial neoplasias. Women using oral contraceptives are more likely to be exposed to HPV than are those using barrier methods or not having sexual intercourse. Moreover, cervical intraepithelial neoplasia is more likely to regress and HPV infection is more likely to clear in women whose partners use condoms during sexual intercourse than in those whose partners do not. Thus, even if oral contraceptives are not causally associated with cervical cancer, women positive for HPV who use them instead of barrier methods might be more likely to be diagnosed with cervical cancer.

More than 50 case-control, cohort and cross-sectional studies have evaluated the association between COC use and cervical neoplasia that includes dysplasia, carcinoma in situ, and invasive cancer in the last two decades. While some of these studies found no increased risk of invasive or in situ carcinoma with COC use, several studies have found that such use is associated with slightly increased risks: The relative risk estimates have ranged from 1.3 to 2.2 in most well-controlled studies.

In conclusion, the most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behavior including use of barrier contraceptives.

Colorectal cancer

Colorectal cancer (CRC) is the second most common type of tumor affecting women in the world. Established risk factors for colorectal neoplasia are hereditary factors, smoking and high meat and alcohol consumption. In addition, important inverse associations have been observed with vegetable- and fiber-rich diets, nonsteroidal anti-inflammatory drug usage,
hormone replacement therapy and physical activity. It has long been suggested that reproductive and hormonal factors play a role in colorectal carcinogenesis. More than 20 observational studies have investigated this relationship, mainly focusing on reproductive factors (e.g., parity, age at menarche and menopause).

Several studies have provided information on COC use and risk of CRC. Two representative meta-analyses were performed to combine all published data on COC use and CRC to obtain overall and quantitative estimates of the potential association for ever versus never COC use and according to the duration and recentness of use.

In 2009, a systematic review and meta-analysis included a total of 23 independent studies, 14 case-control and nine cohort studies. The relative risk (RR) of CRC for ever versus never COC use was 0.82 (95% CI 0.69–0.97) from 11 case-control studies, 0.81 (95% CI 0.75–0.89) from seven cohort studies, and 0.81 (95% CI 0.72–0.92) from all studies combined. The results were similar for colon and rectal cancer. No significant difference was evident for duration of COC use either for colon or rectal cancer, although there was an indication that the protection is stronger for more recent use on the basis of four of the studies. The results of this meta-analysis confirm the results of a previous meta-analysis, which reported that ever COC users have an approximately 20 percent reduction in CRC risk compared to never COC users.

Based on these data, the observed decrease in risk of CRC is regarded as a potential non-contraceptive benefit of hormonal contraception. Moreover, the data support the assessment by the IARC summarizing data of four cohort and 10 case-control studies that “there is evidence suggesting lack of carcinogenicity in humans for COC in the colorectum”. In addition, the results of a large prospective UK cohort study (RCGP) investigating mortality among contraceptive pill users were published recently. The continued long-term follow-up of this cohort showed significantly lower rates of death from cancer of the large bowel and rectum among ever COC users (adjusted RR 0.62, 95% CI 0.46–0.83).

In conclusion, several studies have suggested an inverse association between current use of COCs and the risk of colorectal cancer. The relative risks for ever-use are around 0.8, and reach statistical significance when studies are combined. However, there is no reduction in risk with increasing duration of use. The mechanism for a protective effect is not understood, but may be related to changes in bile synthesis and secretion, inhibition of the growth of colon cancer cells and tumor suppressor genes.

Overall mortality

Large cohort studies aim at assessing the long-term overall effect of COC use. In a recently published report from the Royal College of General Practitioners’ Oral Contraception Study, mortality in long-term COC users was lower compared to an age-standardized population of never COC users.

This study, based on approximately 820,000 women-years of follow-up gathered over 39 years, reports results that are similar to findings in other large cohort studies. The study concludes that women in the United Kingdom who have ever used the oral contraceptive pill are less likely to die from any cause, including all cancer types and heart disease, compared with never users. These results are important for benefit/risk discussions in the regions where COC use is highest.

COC users compared with never users of COCs had significantly lower rates of death from all cancer types combined, including large bowel/rectum, uterine body ovarian cancer and main gynecological cancer. A higher
rate of violent or accidental deaths among OC users compared to never COC users in past reports from this cohort was confirmed \(^96,97,98\), although other studies did not identify this difference \(^47,49\). The results suggest that a persisting or emerging risk of death over time was not identified in COC users compared to never COC users \(^93\).

It should be noted that the majority of women in studies initiated decades ago used at least one higher dose of estrogen (50 µg ethinyl estradiol (EE)) compared to preparations that are typically prescribed today. The higher estrogen dose could reduce the risk of some cancer (ovarian and endometrial) but also introduce a higher mortality risk for cardiovascular disease. Earlier reports \(^97,98\) based on information from shorter follow-up periods suggested a slightly increased risk of death due to vascular events and smoking. These results led to the development of the lower estrogen dose preparations that are almost universally used today. In the 2010 report from the Royal College of General Practitioners' Oral Contraception Study run over 39 years, a slight increase in mortality during early use could not be excluded \(^93\). In contrast, a recently conducted, large, prospective cohort study \(^10\) of users of modern low estrogen dose COCs (<35 µg EE) that specifically investigated the risk of cardiovascular events found no increase in overall mortality compared to the age-adjusted background rate.

Controlling for confounding factors, such as smoking, obesity, family and personal medical history of disease, is not always feasible in these types of studies. Findings should be interpreted with caution, given the long duration of studies with high loss-to-follow-up rates, mixed data sources and small numbers of subjects included in the subpopulation.

**Fertility-related effects**

**Unintended pregnancies**

COCs are a very reliable type of contraception with a failure rate during typical use of approximately 8 per 100 women over one year and 1 or less per 100 women over one year during perfect use (when taken correctly).

This chart illustrates the risk levels of commonly used family planning methods for both correct (i.e. perfect) and typical use during the first year. Because ceased menstrual cycle during breastfeeding (lactational amenorrhea) is a temporary, natural family planning meth-

As is evident from this chart, both coitus interruptus and periodic abstinence are ineffective by modern standards. Both are superior to the risk of pregnancy when no method of contraception is used (85 percent in the first year). Unintended pregnancies among women practicing natural family planning methods are primarily related to user error. Couples who do not use their method correctly—that is, they have intercourse on days when the method’s guidelines tell them that the woman is fertile—have a much greater chance of unintended pregnancy.

**Ectopic pregnancy**

Ectopic pregnancy is defined as a pregnancy outside of the uterus. Although the majority of ectopic pregnancies occur in the ampullary section of the fallopian tubes, other locations, such as the abdomen, cervix and the ovary, are also possible sites \(^99\). Ectopic pregnancy is an important cause of morbidity and mortality worldwide and continues to account for up to 9 percent of all maternal deaths in developed countries \(^100,101\). Ectopic pregnancy has an incidence of approximately 2 percent in reported pregnancies and has proven to be the most common cause of pregnancy-related deaths in the first trimester \(^102,103\). A prior ectopic pregnancy increases the risk nearly eight times that the next pregnancy will be ectopic \(^104\) and two-thirds of women who have had an ectopic pregnancy will not have a subsequent live birth \(^105\).
The incidence of ectopic pregnancy appears to be stabilizing in many western countries, yet the incidence is still increasing in the United States, where in the context of 6 million recognized pregnancies each year, more than 100,000 ectopic pregnancies are reported annually. The actual number, however, is likely to be much greater because only cases managed surgically are reported. The use of combined oral contraceptives, regardless of the regimen or estrogen dose, decreases the incidence of ectopic pregnancy compared with women not using contraceptive methods or using other methods.

Among women using COCs, the risk of ectopic pregnancy is around 0.005 per 1,000 women-years. In conclusion, all forms of contraception reduce the rate of ectopic pregnancy by preventing conception, with COC users found to have the lowest rate.

**Return to fertility and pregnancy outcomes**

In the early years, COCs were primarily prescribed to women with completed family planning who wanted to prevent additional pregnancies. However, over time COCs were increasingly used to space births and, more importantly, to postpone the birth of a first child. Resumption of ovulation and ability to conceive after cessation of COC use is therefore of utmost importance.

Although the reversible character of contraception with COCs was obvious, the question of return to fertility or time to pregnancy has been controversial for some time. Some studies indicated a delay in achieving pregnancies that was thought to be related to continued suppression of the hypothalamic-pituitary reproductive system but was also more obvious in women who had never given birth and who were above 30 years of age. However, these studies were influenced by older, higher-dosed products. In studies with modern, low-dosed COCs, no delay in conception was found and long-term use was actually associated with greater fertility. The latter effect may be related to the prevention of adverse pregnancy outcomes, such as ectopic pregnancy, and to protection from conditions like pelvic inflammatory disease.

A controlled, prospective, non-interventional cohort study of 59,510 users of COCs in clinical practice in seven European countries assessed pregnancy outcomes of 2,064 participants who stopped COC use after study entry because of a planned pregnancy. In this large dataset of real-life use of COCs, the influence of age, parity, progestogen type, ethinyl estradiol dose, duration of COC use and smoking status on pregnancy rates was assessed. Overall, 21.1 percent (95 percent confidence interval [CI] 19.4–23.0 percent) of the past COC users were pregnant one cycle after COC cessation. This rate increased to 79.4 percent (95 % CI 77.6–81.1%) at one year (13 cycles). Progestogen type, ethinyl estradiol dose, duration of COC use and parity had no major influence on the rate of pregnancy after COC cessation.
Up to the age of 35 years, age had only a minor influence on the rate of pregnancy. Rates of pregnancy were reduced in women older than 35 years and in current smokers.

There is no increase in the incidence of spontaneous abortion in pregnancies conceived after cessation of COCs; it is even slightly lower in former COC users. Also, no adverse effects on pregnancy outcomes are known to occur for former COC users.

In conclusion, previous COC use does not negatively affect initial and one-year rates of pregnancy after COC cessation. The negative effect of aging on fecundity is not amplified by COC use. Pill breaks undertaken to retain the ability to conceive lack a scientific foundation and should be avoided.

Menstruation-related effects

COC use exerts beneficial effects on almost all conditions related to menstruation. The effects are due to both ovulation suppression and reduced prostaglandin release in the uterus. Dysmenorrhea (painful menstruation) and menorrhagia (heavy menstrual bleeding) may considerably reduce quality of life. Besides contraception, reduction of painful and/or heavy periods is one of the greatest immediate benefits for women using COCs.

The oral contraceptive composed of estradiol valerate and dienogest was proven in two clinical studies to achieve rapid, large and sustained reduction of menstrual blood loss volume in women with heavy menstrual bleeding. Moreover, COCs may also have beneficial effects on premenstrual symptoms. A COC containing 3 mg of drospirenone/0.02 mg of EE administered in a 24-day regimen was effective in alleviating the spectrum of symptoms associated with premenstrual dysphoric disorder.

Risk factors (risk variables that directly affect transmission or progression) associated with PID include (1) younger age, (2) multiple sexual partners, (3) prior history of PID, (4) concurrent STI (mostly C. trachomatis and N. gonorrhea) and (5) non-use of barrier contraceptives. Others factors that are deemed possibly associated but remain controversial include low socio-economic status, unmarried status, urban living, race, educational attainment, parity, high frequency of intercourse, coitus during menstruation, smoking and vaginal use of douche.

Consistent use of barrier methods can decrease the risk of STD acquisition and subsequent development of PID.

Most studies that evaluated the role of COC pills in the development of PID have demonstrated a protective role. Proposed mechanisms of protection include thickening of the cervical mucus from the progestogen component of oral contraceptive pills, lessening the amount and duration of menstrual flow, and a decreased “receptivity” of the endometrium to infection under progestogen.
influence. A correlation between regular COC use and less “risky” sexual behavior is also a possible mechanism for protection.

However, two more recent studies by Ness et al. from the United States tend to show no protective effect of COCs studied. They have suggested that one of the reasons could be the greater use of low-dose pills in their studies.

In conclusion, studies have suggested that the pill offers substantial protection against acute PID. Women who use the pill have been shown to have a 50 to 80 percent lower risk of acute PID compared to those using no contraception or a barrier method. The protection only applies to current use and is thought to be due to the cervical mucus thickening effect of the progestogen in the pill. COC use may reduce the risk of PID among women but do not appear to protect against lower genital tract STIs. Therefore, women should be advised that COCs do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

3.3 Responsible prescription practices

No contraception method is both 100 percent effective and totally free of side effects. The choice of family planning method requires a trade-off between the desired level of protection against pregnancy and the couple’s willingness to tolerate the risks and disadvantages associated with a particular method. The level of protection from conception is a function of the method itself and how consistently and correctly it is used. The perceived disadvantages of certain methods can often be overcome or alleviated with appropriate counseling.

Modern COCs offer excellent contraceptive efficacy and good compliance due to their many non-contraceptive benefits. Serious cardiovascular events, such as pulmonary embolism or stroke, rare as they are, likely constitute the most relevant serious side effects of combined hormonal contraceptives since they may have serious consequences for individual women, including fatal outcomes or long-term disability.

Public health is best served when medical management is based on the highest level of scientific evidence and by carefully considering whether any increases in risk outweigh the benefits of treatment. For most women, the very low absolute risks of serious sequelae are outweighed by the well-established benefits of hormonal contraception. Research has shown that individualized risk assessment remains an essential tool to identify women at increased risk for VTE, who might be better advised to use alternative forms of contraception. For most healthy women of reproductive age, the benefits of COCs will outweigh the risks.

Hormonal contraceptives are prescription-only medicines in most countries. Risk factor information is essential in deciding whether COCs are a suitable contraceptive choice for an individual woman. The decision on prescription of hormonal contraceptives should always be based on an individual benefit-risk evaluation and take account of contraindications and precautions for use as indicated on the package insert.

The opportunities of modern contraceptives serve as a good basis for finding an appropriate choice for individual women who want contraception. Patient safety comes first. This principle applies to medicine in general but should of course be of utmost importance when caring for reproductive-aged women.

Bayer remains committed to research and development of innovative contraceptive solutions and improvements in women’s health care.
In developing and emerging countries, the topics of reproduction, sexuality and modern contraception are frequently linked to complex social issues such as education, public health, economic productivity, religion, culture and even, at least indirectly, to global issues like climate change.

4.1 Contraception in industrialized countries: established, accepted and available

Women have had the means to prevent unplanned pregnancies for at least 4,000 years. But the true revolution in contraception—hormonal contraception for women—was only developed in the second half of the 20th century. The birth-control pill had its breakthrough during the late 1960s, when public discussion about sexuality and contraception prepared the ground for its widespread use in industrialized countries. No longer a subject of debate, millions of women started taking the “pill” (low-dose, combined oral contraceptives). Today, their number has increased to about 80 million worldwide. The majority of women taking the pill live in the United States and Europe.

Nowadays, a wide variety of modern contraceptives is generally available in industrialized countries worldwide. These include hormonal methods (e.g. pill, injectables, implants and intrauterine devices), male and female sterilization, condoms and modern vaginal methods. However, there is still unmet need for contraception because it is not affordable for everyone and some women may lack access to it. The unmet need is substantially higher in emerging and developing countries than in industrialized nations.

In industrialized countries, provision of contraception is not a matter of public concern, and any debate that does take place tends to be connected to religious beliefs. Sometimes, a discussion emerges about the safety profile of oral hormonal contraceptives, particularly the question of increased risk of venous thromboembolism (VTE), or deep-vein thrombosis and pulmonary embolism. In general, one can say that modern contraception is widely accepted and used, and represents an essential element of personal choice with regard to private and family life. However, the situation is quite different in other parts of the world.

In comparison, the unmet need for modern contraception is substantially higher in emerging and developing countries than in industrialized nations.
### 4.2 The role of contraception in developing and emerging countries: major challenges

#### Unmet need for contraceptives

Women with unmet need make up 26% of those who want to avoid a pregnancy but account for 82% of unintended pregnancies.

In developing and emerging countries, the topics of reproduction, sexuality and modern contraception are frequently linked to complex social issues such as education, public health, economic productivity, religion, culture and even, at least indirectly, to global issues like climate change. How the link is made and to what extent, depends on the geographic region.

#### Sex education and sexual rights

Even today, a substantial number of women and men in the developing world do not receive impartial sex education or sex education at all. In addition, they do not have access to modern family planning services like counseling, the provision of contraceptives and follow-up guidance. As a consequence, many of these women and men do not use any contraceptive method at all, or they rely on traditional methods, e.g. periodic sexual abstinence and withdrawal. Of the 818 million women across the developing world, 9 percent who wanted to prevent a pregnancy in 2008 used a traditional method while 17 percent used none. That means almost 26 percent of the women in developing countries who did not want to become pregnant did not use a modern contraceptive method.

Of course, regional characteristics need to be taken into account. The unmet need for modern contraceptives tends to be highest in the poorest regions. Almost 60 percent of the women with no access to contraception live in sub-Saharan Africa and South Central and Southeast Asia.

Women face other barriers, too: Besides insufficient education, no access to modern contraceptives and low income, women may be confronted with misperceptions about the effect of contraceptives—e.g. that the pill could lead to infertility—as well as disacceptance by family members.

One of the consequences is a high rate of unplanned pregnancies—about 75 million worldwide in 2008. Even though the numbers have been declining since the mid-1990s, the levels are still very high. According to the Guttmacher Institute, which is well-known in the field of sexual and reproductive health research worldwide, a total of 40 percent of the pregnancies in developing countries in 2008 were unplanned. And in southern Africa, the number was substantially higher: 59 percent of women who got pregnant did not want to. Research showed similar rates in South America, where 63 percent of pregnancies were unplanned, and in South Central and Southeast Asia with 40 percent of unplanned pregnancies.

Family planning services that provide basic knowledge about human reproduction, reproductive health and modern contraception are key measures for reducing rates of unplanned pregnancies, according to the Guttmacher Institute and the United Nations Population Fund (UNFPA). There is also international consensus that individuals and couples should be enabled to decide, on a voluntary and informed basis, whether to use contraceptives or not and which family plan-
ning method best suits them. Furthermore, sex education may encourage women’s awareness of their bodies, provide a basis for a safe and fulfilled sex life, and lay the foundations for planned pregnancies and appropriate child spacing.

Sex education can also influence women’s empowerment. Knowledge about reproduction and safe contraceptive methods can strengthen a woman’s role in a relationship. Also, it has a beneficial impact on society in general, since sex education may help reduce or eliminate discrimination due to gender, sexual preferences or the fact that a person is sexually active. According to the medical journal *The Lancet*, gender equity can in turn be regarded as fundamental for improving maternal and child health.

In international development projects therefore, there have been efforts to focus on adolescent girls. The Center for Global Development, among others, argues that the rights of adolescent girls should be strengthened, e.g. by assuring access to secondary education, health and family planning services as well as through the prevention of child marriage.

**Prenatal care**

Proportion of women attended four or more times during pregnancy by area of residence, 2003/2008 (percentage).

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<tr>
<th>Region</th>
<th>Rural</th>
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<td>Latin America &amp; the Caribbean</td>
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<td>Developing regions</td>
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These measures would improve maternal and child health, ultimately alter the overall well-being of society and result in higher economic output, it says.

In addition, sex education can help achieve the Millennium Development Goals (MDGs), eight major international development goals that the member states of the United Nations and several international organizations have agreed to fulfill by 2015. Among others, gender equality and women’s empowerment are part of the MDGs. These aims are shared by the International Planned Parenthood Federation (IPPF), one of the partners of Bayer Schering Pharma. The IPPF believes that “sexual rights are a part of human rights”.

In conclusion, knowledge about and access to modern contraceptive methods helps reduce unplanned pregnancy rates in developing and emerging countries and may yield benefits for society as well. The IPPF stresses that it can lead to greater equality between women and men, enabling the former to make educated choices (e.g. on the number of children they want) and support overall life planning. In addition, according to the Guttmacher Institute, knowledge about and access to modern contraceptive methods may foster improved national economic productivity and higher income as well as lower public-sector spending on health services in the long term.

Bayer Schering Pharma is committed to the IPPF’s goal of providing modern contraception that is effective and safe based on a voluntary decision and family planning which is accessible to everyone worldwide. That is why Bayer has contributed to family planning programs in more than 130 countries for almost 50 years. Examples of activities that are part of Bayer’s lighthouse project “Family Planning” are the Bayer-initiated World Contraception Day and a cooperation with the German Foundation for World Population (DSW). Bayer is participating in a project organized by the DSW, which runs sexual and reproductive health education programs in developing countries for adolescents aged 10 to 14 years. Sexuality and contraception are taboo topics there. The goal of the project is to educate young people, encourage them to share their knowledge with their peers and create a supportive environment for sex education within their communities.

Access to public health services

In many countries, insufficient sex education and family planning services are symptoms of

* Bayer initiated World Contraception Day as a “day of action”. The goal is to promote awareness of family planning among young people in about 70 countries through educational and fund-raising events, radio talk shows, competitions and events in night clubs and discos. Bayer cooperates with several partners, e.g. the European Society of Contraception and Reproductive Health (ESC), the Pan American Health and Education Foundation (PAHEF) and the United States Agency for International Development (USAID).
poor public health systems. These countries do not have the financial resources or political will for health infrastructure (e.g. they have no or poorly equipped hospitals and insufficiently trained/qualified personnel). As a result, frequent pregnancies—planned or not—pose a major health risk. In sub-Saharan Africa, Arab countries and in South Central and Southeast Asia more than 50 percent of the women do not receive health care during pregnancy or during or after delivery. In 2005, the World Health Organization (WHO) counted 536,000 maternal deaths during pregnancy, delivery or shortly afterwards. Some 99 percent occurred in developing countries.

Abortions imply other major health risks, since in developing countries they are frequently carried out without medical surveillance and under unsafe or illegal conditions. In 2003, there were about 20 million unsafe abortions worldwide, which accounted for nearly 50 percent of all abortions performed. Some 95 percent of those abortions took place in developing countries. An estimated 8.5 million women needed medical treatment because of subsequent health complications and about 3 million did not receive it.

Functioning public health systems that provide family planning services and the WHO’s recommended standards of maternal and newborn care would reduce the number of unplanned pregnancies by about two-thirds, unsafe abortions would decline from 20 million to 5.5 million and maternal deaths could be reduced by 70 percent, according to the Guttmacher Institute. Declining numbers in regions where corresponding standards and family planning services have been put in place in recent years prove their substantial and measurable impact. The spread of diseases that can be transmitted sexually, namely HIV infection and AIDS, poses another serious health threat that is aggravated by the lack of functioning public health systems. Some African countries suffer from immense economic drawbacks because the disease has wiped out or disabled large parts of the working population. Sex education and family planning services can help those at risk to better protect themselves against HIV infections, the virus that causes AIDS.

The availability of family planning services and access to modern contraceptives as part of public health systems depends heavily on investment in this field. The importance given to this topic is sometimes hindered by political or cultural factors as well as financial limitations. While some countries on the verge of over-population are supportive of family planning programs and promote the distribution of modern contraceptives, the situation is different in others. If the local population is in decline, governments are less interested in family planning measures.

Thus, operating public health systems and ensuring access to modern contraceptives for women of reproductive age can improve millions of lives and support the Millennium Development Goals by combating HIV infection/AIDS and promoting maternal health. Women’s health care and in particular reproductive health are one of the major focus areas of reproductive health care.
areas Bayer engages in. Core competencies lie in hormonal contraception, menopause and gynecological diseases. As a global pharmaceutical company, Bayer strives to make drugs available and to contribute to improving health care worldwide. Since 1961, Bayer has distributed more than 2.7 billion cycle packs of oral contraceptives through family planning organizations, such as UNFPA, the United States Agency for International Development (USAID), IPPF, Population Services International (PSI) and Marie Stopes International. In line with local market conditions, Bayer also provides developing countries with oral contraceptives, one- and three-month injectables, implants and intrauterine devices that fulfill international quality standards. The oral contraceptives Microgynon® and Microlut® and the implant Jadelle® are the first contraceptives that have been awarded prequalification status by the WHO. This certification is only awarded to medicines that meet international standards, e.g. in regard to effectiveness, compatibility and quality. In addition, in September 2009 Bayer started a model cooperation project with USAID: Bayer will market oral contraceptives at a reduced price in 11 countries in Africa, e.g. Ethiopia, Tanzania and Uganda. The goal is to give women with low income access to original products. Besides providing up to 110 million monthly cycle packs of oral contraceptives until 2012, the cooperation also involves family planning programs and training of health care professionals.

Nonetheless, it should be taken into account that access to and use of contraception is not only a question of allocation and distribution. It is also connected to education and personal and economic circumstances. If a family is living on the poverty line, other issues than considering contraceptive methods tend to take priority, even though, in the long term, additional children may aggravate the situation. Cultural aspects can also be obstacles to the use of modern contraceptive methods, such as religious beliefs against temporary or reversible contraception (e.g. only sterilization is allowed) or in cases where the number of children determines social standing.

Contraception, demographic effects and climate change

In its current State of World Population report, the UNFPA refers to an expert meeting on climate change and population in 2009, where the following conclusion was drawn: Improved access to sex education and reproductive health and voluntary modern family planning as a part of it is important for individual wellbeing and a way to stabilize the world’s population. According to the UNFPA, “major achievements in family planning have in the past had significant impacts on slowing population growth, and slower population growth in some countries has bought more time to prepare adaptation plans for the coming climate change.”

**Family planning methods and economic costs**

A high rate of unplanned pregnancies and unsafe abortions as well as a lack of adequate health care during pregnancy and delivery endanger the health of thousands of women and children worldwide. Furthermore, disability and premature death among women and their newborns lead to high economic costs, according to the Guttmacher Institute’s estimates. Even though these effects are unmeasured and indirect, they should nevertheless be taken into account. For example, frequent pregnancies at short intervals reduce women’s economic productivity while at the same time threatening their health. In addition, having many children correlates with an increased risk of poverty. Using modern contraceptives for healthy birth spacing and smaller families will improve women’s reproductive and overall health and reduce mortality rates for women and newborns, while increasing productivity.
impacts of climate change. Slowing down the growth of the world’s population, the argument maintains, might balance or even reduce the emission of greenhouse gases. It might also decelerate the exhaustion of natural resources, such as water or land. Additionally, the UNFPA refers to indicators like the size of households, age structure and geographic distribution of the population as important elements that affect the increase of emissions.

The UNFPA believes that better access to family planning services and knowledge about reproductive health would contribute significantly to stabilizing population growth worldwide. The region with the highest birth rates and the utmost projected percentage of population growth, Africa, is also, as has been shown, the region with the highest unmet need for modern contraception and one of the largest numbers of unplanned pregnancies, unsafe abortions and maternal deaths. The fact that acceptance of and access to family planning, more education for girls and women and delayed marriage can lead to a significant slowdown in population growth has been proven in the Middle East and Africa in recent decades.

However, the goal should not be any form of “control” of reproduction but rather the provision of necessary information and resources. Women and men should be enabled to make educated choices, e.g. regarding the number of children they want, and to engage in overall life planning.

4.3 Outlook

The UNFPA’s argument about the correlation between population growth and climate change helps illustrate the multifaceted role and impact of modern contraception. Especially in developing and emerging countries, modern contraception is intertwined with health, social, cultural and economic issues. Thus, the scope of the challenges covers more than solely preventing unplanned pregnancies. Accordingly, modern contraception can play a role in addressing some of today’s pressing problems. Of course, modern contraceptive methods must be provided as part of larger programs that work toward structural changes in society, such as the implementation of family planning services or improved public health systems, and on the basis of long-term international cooperation between governments, international organizations and companies.
The history of oral contraception

Preventing unplanned pregnancy has been an important issue for women and their families all over the world for many hundreds of years. The pill is one of the most important inventions in the field of contraception and is regarded as one of the key pharmaceutical innovations of the last century. What’s more, it fundamentally changed women’s role in relationships—and in society.

5.1 Contraception in former times

For a long time, no truly reliable method of contraception was available that would enable women to decide for themselves whether and when they wanted to become pregnant. The earliest evidence of contraceptives is considered to be the 4,000-year-old Kahun Papyrus from Egypt. It recommends partial obstruction of the vagina with a mixture of natural rubber, honey, soda and rock salt, or with a paste made of crocodile dung and sour milk. The medical manuscripts of the Greeks and Romans recommended tampons soaked in tinctures based on olive oil. In the third and fifth centuries, Jewish rabbis advocated vaginal sponges, a barrier method that became widely used again around 1830. In Byzantium in about AD 600, doctors advised smearing the mouth of the uterus with specific ointments before intercourse. Men were to wash their genitals with vinegar or salt water.

From today’s perspective, these methods seem to be rather strange. Nevertheless, as we now know, a lot of them worked fairly reliably. Acidic plant substances like the lactic acid of the acacia, for example have been shown to have a spermicidal effect, as have rock salt and vinegar.

The first condoms, by contrast, were not particularly effective. A number of sources claim that the first condoms date back to as early as Roman times. What is historically documented, from the Middle Ages on, is the use of sheep intestines, goat bladders and small sacks made of fish skin or linen. They were fastened onto the penis with silk ties and, for cost reasons, were usually used several times. However, they only became safer after Charles Goodyear invented the vulcanization of rubber in 1839. Starting in 1870, rubber condoms were mass-produced. In World War I, they were already part of the standard kit issued to European soldiers. Latex was used as a material for the first time in 1930. About the same time, in the 1920s, Schering (today Bayer Schering Pharma AG) scientists started to study the role of sex hormones, until then an unexplored field of medicine.

The ancient Egyptians used pomegranate seeds for contraception. The fruit contains a natural estrogen and it is possible that the Egyptian mixture, like the modern pill, prevented ovulation.
5.2 The 20th century and the development of oral contraceptives

In 1929, Adolf Butenandt, biochemist and later Nobel laureate, succeeded in isolating estrone, the first female sex hormone. The problem in the 1920s was that most hormones had not yet been chemically identified. It was therefore impossible to produce them in a pure form. The only choice was to use extracts from animal organs, with all the impurities and risks this implied.

The first estrogen to be chemically characterized was estrone in 1929. Other sex hormones were identified in rapid succession. One significant milestone was the development of the first synthetic estrogen, ethinyl estradiol, in 1938 by Schering researchers. Ethinyl estradiol is a very stable molecule and not easily metabolized by the liver. It is therefore possible to use very small amounts to achieve a pronounced estrogenic effect. To this day, ethinyl estradiol is the estrogen component in practically all contraceptive pills.

The basic knowledge of how to inhibit ovulation, and the hormones needed to achieve this, was all available in the 1930s. Someone, probably someone working at Schering, could have invented the pill twenty years before it happened in reality. But history intervened. The Nazis were not in the least interested in birth control. At the same time, many Jewish scientists had to leave Germany because of increasing repression. They took their knowledge to the United States, and this is where the history of the pill really began. But even there, the development of hormonal contraceptives for women only became politically possible in the 1950s with the help of Margaret Sanger, founder of the American Planned Parenthood federation. She convinced biochemist Gregory Pincus of the necessity of a hormonal contraceptive and funded his research together with benefactor Katherine McCormick. In 1956, Pincus and his colleagues successfully conducted the first large trial with 6,000 participants.

In 1961, one year after the first pill was introduced in the United States by the US company Searle, the first European pill, Anovlar® by Schering AG (today Bayer Schering Pharma), reached the German market and after that the whole of Western Europe.

A difficult start: In the first years, the pill is a very controversial topic in Europe. It is only recommended for regulating menstrual disorders and only prescribed to married women.

In 1960, the first “pill” was finally approved in the United States. Contraception based on hormones with a tablet taken orally was an entirely new method. The launch of Anovlar® from Schering AG soon followed in Europe in 1961. At that time, the new hormone-based pill was only prescribed for married women and with their husband’s consent. The prevailing attitude in society was that unmarried women should not have sexual intercourse and therefore did not “need” contraception. Therefore, Anovlar® was introduced as a treatment for painful menstrual periods. The package insert mentioned that during the course of treatment, ovulation would not occur. Thus, contraception was a side effect, not the official purpose of the medication. However, the brand name hinted at the inhibition of ovulation—the main way combined oral contraceptives (COC) function.

It was not until the student movement of 1968 and the major social changes associated with it that a change in attitudes occurred. In the 1970s, the breakdown of taboos, a new freedom to talk about sexuality and women’s self-determination in contraception led to a rapid spread of the pill.

Today, the pill and other hormonal contraceptives are a normal part of life in many regions of the world. About 80 million women worldwide use oral contraceptives (OC). And, 50 years after the introduction of the first pill, scientific research has not ceased. Current product developments aim to increase the choice of options and offer new products with added benefits.
5.4 50 years and beyond—the pill’s evolution

Nowadays, different types of pills are available. The individual preparations differ in terms of composition and dose of the active substances. All OCs contain synthetic sex hormones, normally ethinyl estradiol, and a hormone that belongs to the class of progestogens. Their effect is comparable to the sex hormones produced by the body itself. They function as information carriers, or “messengers”, and their task is to control the female reproductive cycle.

Different hormones, smaller dosages
In the 1960s and 1970s, the first pills contained high hormone doses and often had severe side effects. Thanks to research and development, the hormone content has been gradually reduced since then. Modern combined pills are effective with a smaller hormone dose. For example in 1961, the first OC from Schering, Anovlar®, contained 50 µg of ethinyl estradiol and 4 mg of norethisterone acetate per pill. In contrast, the first pill offered in the United States in 1960 contained 150 µg of a very similar estrogen component. Anovlar® thus started the Schering tradition of minimizing the hormone dose. Today, low-dose preparations contain only 15–30 µg of the estrogen ethinyl estradiol.

The 1960s also saw new variants of the pill offered with new and more potent progestogen components: norgestrel and levonorgestrel. Then, in 1971, Schering introduced a completely different concept of contraception: the mini-pill, also called the progestogen-only pill or POP. It only contained a very low dose of 30 µg of levonorgestrel per pill and no estrogen at all. But in most cases, it must be taken regularly and within a strictly limited timeframe in order to guarantee the contraceptive effect. Since many women experience an unacceptable level of bleeding, this form of contraception has not become generally accepted.

Also in the 1970s, significant dose reductions were achieved with a new class of pills: the “micropills.” Microgynon®, for example, is a COC with only 30 µg of ethinyl estradiol and 150 µg of levonorgestrel per pill. For the very first time, a pill containing less than 50 µg of ethinyl estradiol was available. Since then, the micropill has become standard, and pills with high estrogen doses have more or less disappeared. Microgynon® is still on the market today. It is considered a very effective and well-tolerated preparation, and the World Health Organization (WHO) has included this pill in its list of essential drugs.

In the 1970s, further dose reductions seemed difficult without a negative effect on cycle control. The solution was again found by Schering researchers: reducing the hormone dose per pill in the first days of the pill cycle maintained contraceptive efficacy. Schering’s first triphasic pill, Triquilar®, mimicked the natural hormone fluctuation in the female body during the cycle where, during the first half, the female body does not produce any progesterone. Accordingly, the progestogen dose was reduced in the first days of the pill cycle.

By the 1990s, a further dose reduction was achieved, maintaining the same contraceptive efficacy. Miranova® contains only 40 percent of the ethinyl estradiol and levonorgestrel used in older preparations.

Drospirenone, the next generation of hormones
Another new progestogen that has additional non-contraceptive benefits was developed by Schering scientists and introduced onto the market in 2000: drospirenone. In addition to its sex hormone effect, drospirenone mimics another effect of natural progesterone (but not of the conventional synthetic progestogens)—the so-called anti-mineralocorticoid effect. Progesterone promotes the excretion of sodium and water via the kidneys, counteracting the retention of sodium and water caused by estrogen. Estrogen-induced water retention is the cause of the small but uncomfortable side effects observed by some women when starting the pill: they notice a weight gain of about 1 or 2 kilos, and possibly some breast tenderness or even pain. These effects usually vanish after about two or three months, but many women feel a bit uncomfortable when starting the pill. This water retention, by the way, is the cause of the myth that the pill makes women gain weight.

Drospirenone does not lead to water retention, because the progestogen counteracts the estrogen effect. Pills containing drospirenone include Yasmin®, with 30 µg of ethinyl estradiol, Yasminelle® with 20 µg of the same estrogen, and the latest addition YAZ®, which contains the same hormone dosage as Yasminelle® but in a novel 24+4 intake scheme. Clinical trials have shown that not only YAZ® is an effective contraceptive pill, it also reduces the symptoms of acne and cystic nodules and improves the skin.

Since the 1970s Bayer Schering Pharma (then Schering) has continuously strengthened its leading role in the field of oral hormonal contraception by introducing a stream of innovative products.

In the past decade product developments have aimed to increase the choice of options and offer new contraceptives with added benefits.
The history of oral contraception

of PMDD (Premenstrual Dysphoric Disorder). This additional indication is an approved use of the preparation in many countries world-wide (see chapter 3).

Mimicking the female cycle: novel dosing regimens 24+4 and 26+2

Until today, the most frequently prescribed OCs are monophasic preparations with a 21+7 regimen. They consist of 21 identical tablets with each active tablet containing both an estrogen and a progestogen in a fixed ratio. When taking multiphasic pills, the hormone doses of estrogen and progestogen are varied and the correct sequence of intake is important. Here, the pill is taken every day for 21 days, followed by a seven-day break (or seven days of tablets containing no active ingredient), during which menstrual bleeding takes place. On the 29th day, the woman again starts taking the pill for 21 days, again followed by a break—or seven days of tablets with no active ingredient—and so on.

The 24+4 principle is a new intake regimen. In this case, although the rhythm of the 28-day cycle is retained, these preparations consist of 24 hormone-containing tablets plus four tablets with no active substance, which are distinguished by a different color. Menstrual bleeding occurs during the four days of taking tablets that contain no active ingredient. A multiphasic 26+2 preparation works in a similar way. Here, hormones of varying doses are taken every day for 26 days, while the last two pills again contain no active substance.

Thus, the last decades have seen continuous product innovations in the field of OCs, with new compositions and dosing regimens. But research didn’t stop there.

5.5 A new estrogen and pills with additional benefits: an outlook

In 2009 with Qlaira® Bayer Schering Pharma set another milestone in oral contraception. With an estradiol valerate/dienogest combination in a unique dosing regimen, this preparation is the first in a new class of combined oral contraceptives to deliver estradiol, the estrogen equivalent to the one produced by the female body.

Over the last 50 years, many new progestogens have been introduced as components of the pill. Each has unique properties and some, like dienogest and drospirenone, have additional non-contraceptive benefits. The estrogen component in almost all pills, however, is still ethinyl estradiol, the potent synthetic estrogen first developed at Schering back in 1938.

There have been many attempts to use estradiol, the estrogen produced by the woman’s body, instead, but most of these attempts failed because of poor cycle control. Women will not accept a pill if they have to cope with constant spotting or unscheduled bleeding.

Combining estradiol valerate with dienogest finally succeeded. This estrogen component in the latest pill from Bayer Schering Pharma, called Qlaira®, is immediately metabolized to estradiol, equivalent to the estrogen produced by the woman’s body. Qlaira® revives the idea of a multiphasic dosing regimen first seen in Triquilar® 30 years ago, adapting the hormone content in a unique dosing regimen. This dosing regimen has been designed to deliver hormones at the right levels at the right time during the cycle.

In addition to coming up with new hormonal components, Bayer Schering Pharma’s scientists have a lot of exciting ideas for offering women even more benefits. One example is a more flexible way of taking the pill. Experience has shown that the pill can be taken for extended periods of time, without the need for monthly bleeding. In fact, today many women themselves change their pill intake rhythms, for example when they go on vacation and want to avoid bleeding during that time. The ‘flex’ concept builds on this idea.

Another idea is to include an essential B vitamin, a folate, in the pill. Women planning to have a baby are advised to start taking folic acid at least three months before they plan to become pregnant to reduce the risk of neural tube birth defects. Since many women conceive very shortly after stopping the pill, it makes sense to ensure that they have an adequate supply.

So, even 50 years after the first contraceptive pill, there are exciting new developments yet to come.


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## Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>Clogged arteries</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Blood clotting</td>
</tr>
<tr>
<td>Combined oral contraceptive (COC)</td>
<td>Birth-control pill containing estrogen and progestogen</td>
</tr>
<tr>
<td>Dienogest</td>
<td>Progesterone-like compound</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>Painful menstruation</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>Pregnancy outside of the uterus</td>
</tr>
<tr>
<td>Estradiol valerate</td>
<td>New synthetic estrogen</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>Synthetic estrogen used in most combined oral contraceptives</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>Narrow passageway connecting an ovary to the uterus</td>
</tr>
<tr>
<td>Follicle</td>
<td>Protective covering of an immature egg in the ovary</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>Accumulation of blood within the skull vault</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>Excessive hair growth</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>High levels of cholesterol in the blood</td>
</tr>
<tr>
<td>Hypertension</td>
<td>High blood pressure</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>Region of the brain involved in hormone regulation in the female menstrual cycle</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Decreased blood supply to part of the brain</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>Progesterone-like compound</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>Heavy menstrual bleeding</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Heart attack</td>
</tr>
<tr>
<td>Ovary</td>
<td>Female organ that holds immature eggs</td>
</tr>
<tr>
<td>Ovulation</td>
<td>Release of a mature egg from an ovary</td>
</tr>
<tr>
<td>Ovum (ova)</td>
<td>Egg(s)</td>
</tr>
<tr>
<td>Pearl Index</td>
<td>Indicates effectiveness of birth control methods</td>
</tr>
<tr>
<td>Pelvic inflammatory disease (PID)</td>
<td>Infection of upper genital tract structure</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>Organ in the brain where follicle-stimulating and luteinizing hormones are formed</td>
</tr>
<tr>
<td>Premenstrual Dysphoric Disorder (PMDD)</td>
<td>Disorder that involves premenstrual symptoms severe enough to interfere with work or school or with usual social activities</td>
</tr>
<tr>
<td>Premenstrual syndrome (PMS)</td>
<td>Condition preceding start of menstrual cycle characterized by different degrees of bloating, headache, breast swelling and tenderness, anxiety and emotional distress</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Natural female reproductive hormone facilitating pregnancy</td>
</tr>
<tr>
<td>Progestin/Progestogen</td>
<td>Synthetic female reproductive hormones that belong to a class of progesterone-like compounds</td>
</tr>
<tr>
<td>Thromboembolism (arterial ATE, venous VTE, pulmonal embolism, PE)</td>
<td>Obstruction of a blood vessel; the blood clot is carried by the blood stream from the site of origin to plug another vessel</td>
</tr>
<tr>
<td>Uterus</td>
<td>Womb; organ where fetus develops</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
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<tr>
<td>ACOG</td>
<td>American College of Obstetricians and Gynecologists</td>
</tr>
<tr>
<td>ATE</td>
<td>Arterial thromboembolism</td>
</tr>
<tr>
<td>BC</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BMJ</td>
<td>British Medical Journal</td>
</tr>
<tr>
<td>CEE/MPA</td>
<td>Estrogen-progestogen-combination</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>COC</td>
<td>Combined oral contraceptive</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>DRSP</td>
<td>Drospirenone (progestogen)</td>
</tr>
<tr>
<td>DSG</td>
<td>Desogestrel (progestogen)</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>EE</td>
<td>Ethinyl estradiol</td>
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<tr>
<td>ESHRE</td>
<td>European Society of Human Reproduction and Embryology</td>
</tr>
<tr>
<td>EURAS</td>
<td>European Active Surveillance Study on Oral Contraceptives</td>
</tr>
<tr>
<td>FDA</td>
<td>(United States) Food &amp; Drug Administration</td>
</tr>
<tr>
<td>GSD</td>
<td>Gestoden (progestogen)</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papilloma virus</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<tr>
<td>LNG</td>
<td>Levonorgestrel (progestogen)</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>PID</td>
<td>Pelvic inflammatory disease</td>
</tr>
<tr>
<td>PMDD</td>
<td>Premenstrual Dysphoric Disorder</td>
</tr>
<tr>
<td>PMS</td>
<td>Premenstrual syndrome</td>
</tr>
<tr>
<td>POP</td>
<td>Progestogen-only pill</td>
</tr>
<tr>
<td>RCGP</td>
<td>Royal College of General Practitioners</td>
</tr>
<tr>
<td>STD</td>
<td>Sexually transmitted disease</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
</tbody>
</table>
Important Organizations & Foundations

Asia-Pacific Council on Contraception (APCOC)
www.apcoc.net

Centro Latinoamericano Salud y Mujer A.C. (celsam)
www.celsam.org

German Foundation for World Population (DSW)
www.dsw-online.org

European Society of Contraception and Reproductive Health (ESC)
www.contraception-esc.com

International Federation of Pediatric and Adolescent Gynecology (FIGU)
www.figij.org

International Planned Parenthood Federation (IPPF)
www.ippf.org

Marie Stopes International
www.mariestopes.org.uk

Pan American Health and Education Foundation (PAHEF)
www.pahef.org

Population Council
www.popcouncil.org

The United States Agency for International Development (USAID)
www.usaid.gov
ORAL CONTRACEPTIVES in Perspective