Trends in Andrology and Sexual Medicine
Series Editors: E.A. Jannini, C. Foresta, A. Lenzi, M. Maggi

Maria Cristina Meriggiola
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Female and Male Contraception

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Trends in Andrology and Sexual Medicine

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Female and Male Contraception

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Preface

Effective and acceptable contraceptive methods and safe abortion methods (including post-abortion care) are key to reduce the burden of unplanned pregnancy and its consequences and to reach the 2030 UN Agenda for Sustainable Development Goals no. 3 and no. 5 of sexual and reproductive health and rights (SRHR).

Every year an estimated 99.1 million unintended pregnancies occur, of which more than 50% end in an induced abortion. More than 225 million women of reproductive age who are sexually active and who want to avoid a pregnancy are reported to lack access to effective and acceptable contraceptive methods. Estimates are usually limited to married women or women in union and thus the figures are likely underestimating the true unmet need. Despite an overall increase in contraceptive use globally, the unmet need for contraception remains high and the demand is increasing due to growing populations and a simultaneous increased preference to have smaller families. Furthermore, the only available reversible contraceptive method for men is the condom, centuries year old in concept while no new approaches have entered the market so far. Almost 60 years after the revolution of the Pill, it is time to give men the choice and possibility to share with women the burden of family planning. Ideally shared responsibility means increased responsibility.

Today, many women (and men) are reluctant to use existing methods due to experienced or feared side effects. Research on new contraceptive development should therefore be encouraged. In addition to new methods, increasing knowledge and access and removing barriers to existing methods are crucial.

Provision of family planning services has been recognized as key to SRHR, gender equality, and the development of society. Access to contraception does not only impact the lives and health of women and men themselves, but also those of their children. A special vulnerable group is the 23 million adolescent women with an unmet need for contraception worldwide whose lives and well-being are at risk. Furthermore, post-pregnancy contraception is recognized as an important but frequently neglected issue, including women post-abortion and postpartum. Timing of contraceptive counseling and provision should allow women immediate start of the

most effective method according to her choice and needs. Assuring the fundamental human right of SRH also holds public health benefits for women and men, enhances gender equality, and impacts our environment globally.

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Part I

Overview on Contraception

Birth Control Methods: From Antiquity to the Future

1

Christian Fiala

1.1 The Past: Unimaginable Suffering

For most of human history people have desperately but unsuccessfully tried to limit natural fertility of 12–15 pregnancies in a woman's lifetime to the individually desired number of children.

Nature had planned an average of 12–15 pregnancies over the 35 years of a woman's fertile years, resulting in about ten deliveries and eight surviving children, with each breastfed for 2 years [1]. If still alive, a woman then entered menopause. In other words, the fertile life of women consisted of a succession of pregnancies and lengthy breastfeeding, interrupted by short periods of menstrual cycles. Women only had about 150 ovulations/menstruations over their lifetimes. Today, women experience almost three times as many menstrual periods compared to the past—an average of about 450 [2–5] (Fig. 1.1).

Uncontrolled fertility drove women and their partners into a despair that is hard to imagine today. Marie Stopes called it "slavery" and "torture" in her famous 1918 brochure *Married Love* [6]. The fate of women due to unmanageable fertility was also portrayed in heartbreaking artwork by women of the time, such as by Kaethe Kollwitz from Germany (Fig. 1.2) and in Margaret Sanger's *Birth Control Review* in the USA (Fig. 1.3).

Throughout history, women have desperately tried everything imaginable to change the natural course of fertility and limit their families to the desired number of children. They used a wide variety of means, but most were ineffective, dangerous, or both, such as the withdrawal method, taking herbs, inserting twigs in the vagina, or jumping off roofs [7]. Countless women have died by ingesting poisonous substances or using other unsafe means to prevent pregnancy or end it once it started [8]. In addition ancient methods were quite ineffective, even though

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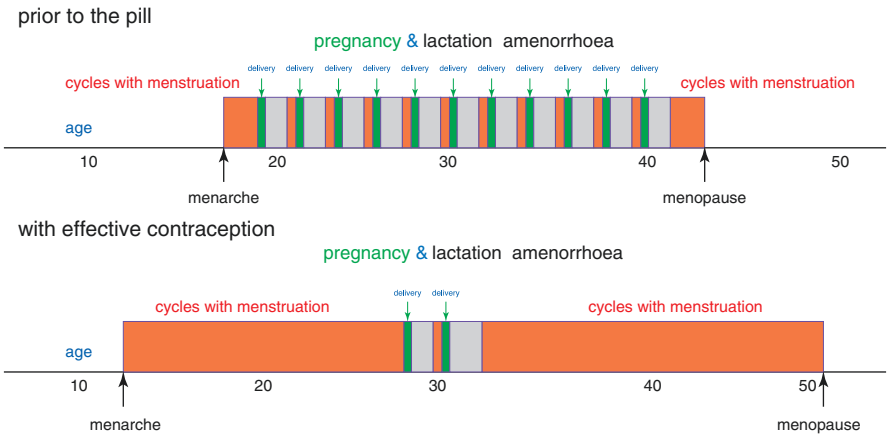

Fig. 1.1 Fertile periods over a woman's lifetime (based on [3, 4])

Fig. 1.2 Charcoal drawing by Kaethe Kollwitz, from "Liebe ohne unerwünschte Kinder" (Love without unwanted children), Vienna, 1913

historical documents indicate that abortion has been practiced occasionally or at least attempted. But there has been a lack or total absence of medical knowledge, pregnancy tests, dedicated instruments, and any way to determine the safe and effective concentration of uterotonic ingredients in plants. In other words, most women throughout history would only realize they are pregnant when they felt "quickening," the first fetal movements around 15 weeks of pregnancy. If they wanted to terminate the pregnancy, they only had highly dangerous and rather ineffective methods available to do what we call today a late abortion. But without any

Fig. 1.3 Illustration from Margaret Sanger's *Birth Control Review*, November 1923

effective contraceptive methods to use after an abortion, it did not make much sense to shorten an unwanted pregnancy, just to get pregnant immediately again. The fact that abortion is forbidden in ancient laws and the Hippocratic Oath therefore rather indicates the fantasy and intention of those in power than real facts.

When contraception was unavailable and abortion was not possible, ineffective, or dangerous, infanticide or abandonment was often the only "solution" for the very frequent unwanted pregnancies. The exposure of newborns was widely practiced in ancient Greece and Rome and throughout the Middle Ages. Even until around 1900, women in Europe would often continue an unwanted pregnancy to term and give away the child to be "cared for." These children were neglected and frequently let to die, which led to the very term of "angel maker," a euphemism attributed in many countries to women who "made an angel" of children by letting it die. This "practice" partially explains the high infant mortality in the past. In the early twentieth century "angel makers" performed more and more (illegal) abortions, which explains that most people today wrongly associate the term with illegal abortion. However the increasing number of abortions performed in the early twentieth century led to a reduced child mortality, although child neglect continued to some extent until the introduction of the pill and legal abortion [9].

> Citation: It would be one of the greatest triumphs of humanity … if the act responsible for procreation could be raised to the level of a voluntary and intentional behaviour in order to separate it from the imperative to satisfy a natural urge. Sigmund Freud, 1898 [10]

Based on real-life past experiences, it is easy to understand Freud's vision of a human triumph as the ability to separate fertility and sexuality. But that dream only became reality a few decades ago.

The discovery of the fertile days by the Austrian Hermann Knaus and the Japanese Kyūsaku Ogino in the 1920s provided the first scientific basis to develop effective contraception [11]. The turning point came with the introduction of the pill and intrauterine devices (IUDs) in the early 1960s. For the first time in human history, women could actually separate their sexuality from their fertility, making it possible for children to be planned and wanted, and for sexuality to express love, happiness, and intimacy as the Swedish activist Elise Ottesen-Jensen worded the human goal [12]. It was a revolution that inevitably led to huge social changes, including the western sexual revolution of 1968.

1.2 The Beginning

A number of dedicated personalities contributed to the development of effective contraception. First the medical and scientific facts had to be developed on which effective methods could later be based on. The Austrian doctor Ludwig Haberlandt has been the first to show that hormonal contraception is possible. In 1921 he demonstrated a temporary hormonal contraception by transplanting ovaries from a pregnant rabbit to a non-pregnant animal [13]. In 1937 Russell Earl Marker discovered the first practical synthesis of progesterone from chemical constituents found in Mexican yams. Carl Djerassi refined the method of synthetic progesterone manufacturing and developed better substances.

In 1951 the biochemist Gregory Pincus received a small grant from the Planned Parenthood Federation of America to begin research into hormonal contraception. Based on his confirmation that progestins induced anovulation, women's right activist Margaret Sanger facilitated a much larger grant in 1952 from her rich friend Katherine McCormick. In total Katherine McCormick granted two million dollars towards the development of the oral contraceptive pill, an enormous amount of money at that time.

In 1953 and 1954 trials were performed with different progestins on infertile patients as contraception was illegal at the time. The physician in charge of the trials was John Rock, a catholic gynecologist who performed the trials at his clinic. Eventually Puerto Rico was therefore chosen for the first clinical trials into the contraceptive effects. Results were mind-blowing. The combination of a progestin and an estrogen gave close to 100% protection from pregnancy. Studies were expanded to Mexico and included thousands of women. One of the main effects of the pill was a reduction in menstrual flow and menstrual pain. In 1957 "the pill" was registered in the USA for these indications. The pill Enovid 10 mg® manufactured by Searle contained 0.15 mg of the synthetic estrogen mestranol and 9.85 mg of a progestin very closely related to the first patented progestin developed by Carl Djerassi. The contraceptive effect was a "side effect." In less than 2 years, close to half a million women were taken the pill, presumably quite often because of the desired "side

effect." In 1957 the pill was approved for contraception in the USA and thereby the first contraceptive pill had been approved.

Around the same time a similar development took place concerning intrauterine contraception. The German gynecologist Ernst Gräfenberg developed the first intrauterine device (IUD) in 1928, which was known as the Gräfenberg ring [14]. But the main challenge in the following decades was to find a material and form that would be highly effective, stay inside the uterus, and not cause too many side effects, especially pain and bleeding. The materials available for early IUDs – silk, silver, gold, or steel – had too many disadvantages for a broader use.

IUD development intensified with the discovery of moldable plastic in the 1960s because it allowed flexible frames. A variety of these new IUDs made it to the market in the 1960s [15, 16], which led the Population Council to organize the first conference on IUDs in 1962 [17].

However, the only mode of action for these inert plastic IUDs was to prevent implantation in the uterine cavity by means of a reaction to a foreign body. This changed with the discovery that a thin copper thread wrapped around the plastic frame increased efficacy by inhibiting sperm from fertilizing an ovum [18]. Since then, all IUDs have consisted of a plastic frame loaded with different active substances, hence the name of the IUD 'Multiload' [19]. Based on this concept, new IUDs were developed with a hormone reservoir that contains a gestagen [20]. These hormonal IUDs are more effective than copper IUDs, have fewer side effects, and are better tolerated.

1.3 Present: The Contraceptive Paradox

Sixty years after the discovery of the pill, an unexpected shift has occurred. Most people have forgotten the brutality of uncontrolled natural fertility. In developed countries, we no longer see families with eight to ten children. Most women have zero to two children and rarely more. Younger generations see this and wrongly assume it is "natural." Twenty percent of women in a recent survey said that zero to three children in a woman's lifetime would be a natural expectation without contraception (Fig. 1.4).

This illusion may be leading many women to avoid artificial/exogenous hormones for contraception and instead search for "natural contraception" without realizing the inherent contradiction of "natural" and "contraception." In fact, letting nature take its course produces an average of 12–15 pregnancies, while contraception subverts nature by imposing one's own will to limit fertility to the desired number of children. It is frequently forgotten today that we must decide whether to control our fertility or let our fertility control our lives.

This distorted perception of natural fertility explains the "pill scare" that occurred in several countries and is documented from the UK and France between 1995 and 2015 [21–24]. Exaggerated and unfounded fears about health risks led to a reduction in effective hormonal contraceptive use, which was not counterbalanced by an increase in effective nonhormonal contraceptive methods [25].

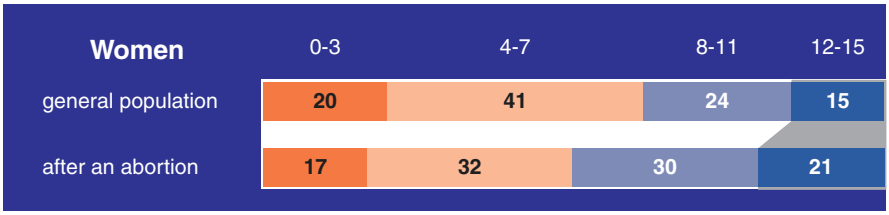

Fig. 1.4 Perception of natural fertility: "How many pregnancies do you think a woman would have in her lifetime if she didn't use effective contraception?". Austrian national contraceptive survey 2019, women n = 881, www.verhuetungsreport.at Survey among abortion patients, Gynmed Clinic Vienna, 2017–2018, n = 300

The "pill scares" led to a reduction in effective contraception, an increase in non-use of contraception, and a subsequent increase in unwanted pregnancies and abortion. This explains the "Contraceptive Paradox" of today: despite an unprecedented number of highly effective contraceptive methods, unplanned pregnancy and abortion rates have stopped decreasing and now remain stable in most Western European countries—but actually increased during media campaigns against the pill.

1.4 The Future

As stated in the Cairo Declaration 25 years ago [26], safe, acceptable, and effective methods for contraception and abortion are fundamental to sexual and reproductive health and rights (SRHR). The leading cause of maternal mortality continues to be lack of access to SRHR [27]. Unrestricted access to effective contraception is also a prerequisite for gender equality and the empowerment of women, especially as long as most methods are to be used by women.

New contraceptive methods are also needed, including improved emergency contraception, new mechanisms of action, and modes of delivery. Additional health benefits of contraceptive methods such as protection against various cancers and a wide range of other benefits should be better recognized.

Until recently, contraceptive development with a few exceptions has focused on the progestogen component of the pill or the dose of ethinylestradiol (EE). New options include exploring other estrogens like E2 and even E4. New delivery systems may not only reduce the risk for complications and side effects but may also offer long-acting reversible and self-controlled methods for women and men, as well as new possibilities for dual protection from unwanted pregnancies and STDs.

Based on mechanisms of action, progesterone receptor modulators (PRMs) might offer notable advantages for many women. PRMs can be used for emergency contraception as well as for regular contraception by various modes of delivery including intrauterine [28]. PRMs have been shown to be effective when used orally as daily pills, once weekly, or monthly and are a well-established method for medical first-trimester abortion as well as throughout pregnancy [29].

The use of PRMs for contraception and their positive health benefits, such as possible protection against breast cancer and prevention of uterine leiomyomas and endometriosis, deserves to be further explored [30]. Progesterone receptor modulators have also been studied for "late emergency contraception" and for menstrual induction [31]. Very early medical abortion (VEMA)—before an intrauterine pregnancy can be visualized by ultrasound—has been shown to be acceptable, safe, and effective [32]. Thus, PRMs provide a model for a woman-centered contraceptive continuum with added health benefits.

1.5 What About Men?

A high number of effective reversible contraceptive methods are available for women, but choices are very limited for men: condoms are only medium-effective (typical Pearl Index 15), and vasectomy is irreversible and thus not an alternative for many men.

As a result, most men depend on their partner's contraceptive use or non-use, which means a lack of control for men. But most men would be willing to use an effective, safe, and reversible method if available, as several studies have shown (with some variation between countries/cultures) [22, 33]. Unfortunately, the biological hurdle is high. It is significantly more difficult to suppress the production of 100 million sperm every day than one ovulation a month. Further, sperm remain viable for up to 3 months in a man's testes, while a woman's ovum can only be fertilized 12–24 h after ovulation. It took humanity thousands of years until 1960 to achieve effective fertility control in women. However, intensive research is underway to develop an effective and reversible method for men as well (International Consortium dedicated to Male Contraception, www.ic-mc.info), so it may just be a matter of time until men have an equal choice of effective contraceptive methods, enabling them to control their own fertility just as women can already do today.

Could an effective and reversible method for men lead to a revolution similar to the introduction of the pill for women? If men can control their fertility, women will find themselves in a new situation: can they trust their partner, or will they prefer to keep fertility control in their own hands? After all, it will always be the woman who gets pregnant. A study has indicated that the majority of women would continue using their own contraception, even if their partner uses an effective method [25].

Nevertheless, improved contraceptive choices for all, including more use of highly effective methods, will bring us a step closer to the vision of Elise Ottesen-Jensen:

> I dream of the day when all children are wanted, when men and women are equal and when sexuality is considered to be the expression of love, happiness and closeness. Elise Ottesen-Jensen, Sweden, 1896–1973.

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Medical Eligibility Criteria

2

Sarah Hardman and Sharon Cameron

2.1 Introduction

The World Health Organization's (WHO) medical eligibility criteria (MEC) were first published in 1996. The WHO MEC document is an internationally agreed set of recommendations that supports safe provision of contraceptive methods to individuals with a range of medical conditions or characteristics (the latter including, e.g., age, body mass index, smoking, breastfeeding). It is used globally to improve the quality of contraceptive care offered. The WHO MEC are kept up-to-date as new evidence emerges, through continuous monitoring and review of published literature. WHO MEC guidance was primarily intended for family planning programme makers in low- and middle-income countries, but the intention was that it should be adapted for a range of settings.

The most recent version of WHO MEC (the fifth edition) was published in 2015 and supersedes previous editions [1]. It contains over 2000 recommendations for use of 25 methods of contraception (hormonal methods, nonhormonal methods, permanent methods, barrier and emergency contraception), in the context of more than 80 medical conditions or medically relevant personal characteristics.

There are also the US MEC [2] and the UK MEC [3], which are adapted from WHO MEC to be relevant to populations in the USA and the UK. They were last fully updated in 2016 and take account of the changes and evidence in the WHO MEC of 2015. US MEC and UKMEC are generally very similar, but each gives guidance for some conditions that the other does not, and UK MEC considers only

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hormonal contraceptive methods, intrauterine contraception and emergency contraception.

2.2 What Are the MEC?

The MEC provide evidence-based guidance for contraceptive providers as to the contraceptive methods that women with a range of medical conditions and characteristics can use safely to prevent unintended pregnancy. Using MEC, a provider can advise a woman as to which contraceptive methods are generally safe for her to use. The MEC do not indicate the *best* or *most effective* method for a woman—such an evaluation must also take into account the woman's preferences and requirements.

Whilst most women can safely use any contraceptive method, there are some conditions that may be associated with a potential increase in risk of adverse health events when certain methods are used. This may be because the method of contraception affects the condition or because the condition or its treatment affects the safety of the contraceptive.

In the MEC tables, the regular contraceptive methods are grouped under the following headings: levonorgestrel intrauterine system, copper-bearing intrauterine device, progestogen-only contraceptive implant, progestogen-only injectable, combined hormonal contraception and progestogen-only pill. Recommendations for 'levonorgestrel intrauterine system' relate to all the currently available 52 mg, 19.5 mg and 13.5 mg devices. Under 'progestogen-only implant' WHO and US MEC include both etonogestrel and levonorgestrel implants, but for the UK MEC, this is only the etonogestrel implant. Under 'progestogen-only injectable', WHO MEC guidance includes both medroxyprogesterone acetate and norethisterone enanthate, but US and UK MEC only medroxyprogesterone acetate (both intramuscular and subcutaneous preparations). For all MEC 'combined hormonal contraception' includes all formulations of combined pill, combined patch and combined vaginal ring; and 'progestogen-only pill' includes both desogestrel and "traditional" progestogen-only pills.

For each of the characteristics or medical conditions, the MEC tables indicate a MEC category 1, 2, 3 or 4 for each contraceptive method. The four categories are defined in Table 2.1.

As well as a MEC category for each condition and contraceptive method, the MEC tables provide summaries and clarifications of the evidence that supports the

Table 2.1 Medical eligibility criteria

MEC category	
1	No restriction to use of the method
2	The method can generally be used safely (benefits usually outweigh risks)
3	Use of the method is not usually recommended unless no other method is available or acceptable (risks usually outweigh benefits)
4	Use of the method represents an unacceptable health risk

MEC category. There are further explanatory comments at the end of each method section in the MEC documents.

Initiation and continuation of a method are sometimes distinguished and classified differently by the MEC. Initiation refers to the starting of a contraceptive method by a woman with an existing medical condition; continuation refers to a woman continuing the method that she was already taking at the time of first onset of a medical condition. Where MEC categories are different for initiation and continuation, this is because use of the method of contraception before the onset of the medical condition could potentially have been a contributing factor to development of the condition. That possibility could influence clinical decisions regarding continued use of the method. For example, the benefits of use of a progestogen-only pill generally outweigh risks (MEC 2) for a woman who has previously had an ischaemic stroke. If, however, she has a stroke while taking the progestogen-only pill, continued use of the method becomes MEC 3 (risks generally outweigh benefits).

It is important to note that whilst efficacy of a method may be affected by the condition or the medication required for the condition, the MEC category reflects the safety of use of the method.

2.3 Development and Updating of the MEC

WHO, US and UK MEC recommendations are developed through rigorous processes of global research and review. This involves input from a wide range of stakeholders and identification of new evidence relating to existing methods of contraception, new methods or new conditions in order to prioritise the research questions to be addressed. Systematic reviews of the literature are conducted, and quality of the identified evidence is assessed using GRADE methodology. A guideline development group of experts in contraception, research methodology and the conditions under consideration is assembled to review the evidence and assign MEC categories. MEC categories for existing methods and conditions can be upgraded and downgraded depending on new evidence. Most trials of contraception exclude women with chronic medical conditions, and so there is often little evidence on which to base safe prescribing. Where evidence is lacking, expert opinion is sought and MEC category is assigned by consensus of the guideline development group. MEC guidance is subjected to wide external peer review before approval.

2.4 Contraceptive Choice

Many factors determine a woman's choice of contraceptive method. Providing she is medically eligible, she should be able to choose the method that is most acceptable to her. For a method of contraception to be effective, it needs to be used correctly and consistently used and this is directly related to its acceptability.

2.5 Effectiveness of Contraception

Contraceptive methods that need to be used consistently and correctly with every act of sex have a wide range of effectiveness. Effectiveness of such methods varies with characteristics such as age and desire to prevent pregnancy. If used perfectly, short-acting contraceptive methods such as combined hormonal contraception and progestogen-only pills can be very effective; with typical use, however, risk of unintended pregnancy is significant. The methods known as long-acting reversible contraception (LARC) are the most effective methods; they are not user-dependent and are thus associated with low failure rate with both typical and perfect use (see table).

2.6 Drug Interactions

Certain medications can affect metabolism of contraceptive hormones; conversely, some contraceptive methods may affect metabolism of certain medications. Such drug interactions can result in decreased effectiveness of a hormonal contraceptive method, with a consequent increased risk of unintended pregnancy. Alternatively, the interaction may adversely affect the efficacy of a medication used to treat a medical condition, with implications for the woman's health and well-being. Online drug interaction checkers can be used to check for drug interactions with hormonal contraception.

It should be noted that the contraceptive effectiveness of the progestogen-only injectable and the levonorgestrel-releasing intrauterine system is not reduced by concurrent use of enzyme-inducing medications.

2.6.1 Conditions that Pose a Significant Risk for Pregnancy

Women who have a medical condition that increases the health risks during pregnancy and women taking drugs that are teratogenic or potentially teratogenic should be advised about the most effective methods of contraception.

2.6.2 Correct Use of MEC: Practical Considerations

MEC are valuable tools to support safe contraceptive prescribing, but in practice there are some common misconceptions that can lead to incorrect use of MEC. A guide to correct use and practical examples are given below.

2.6.3 MEC Relate to Use of CHC *for Contraception*

It is important to remember that MEC categories relate to use of contraceptive methods *for contraception*, but not for other indications. MEC recommendations reflect

the fact that if a particular contraceptive method is not suitable for a woman, there is a range of other effective options that she can use for contraception. In contrast, if a woman is using a contraceptive method for a non-contraceptive indication (e.g., management of symptoms of polycystic ovarian syndrome), there may not be an effective alternative. Balance of risk and benefit may therefore differ from MEC where a contraceptive method is being used for an indication other than contraception.

2.6.4 Different MEC Sometimes Offer Different Guidance

WHOMEC, USMEC and UKMEC categories sometimes differ from one another for the same condition and method of contraception. This is because they relate to different populations with different barriers to accessing contraception.

2.6.5 Women with Multiple MEC Conditions

Confusion can arise when considering the suitability of a contraceptive method for a woman who has multiple MEC conditions. The first point to make here is that MEC scores cannot simply be added. If that were the case, a woman with four medical conditions that are MEC 1 for use of a particular method would appear to have a complete contraindication to that method (MEC 4). In fact, a woman with any number of MEC 1 conditions can use the method without restriction.

Case 1: Multiple MEC 1 Conditions Patient 1 requests a progestogen-only implant. She is 35 years old (MEC 1) and has just had a first trimester abortion (MEC 1). She has controlled hypertension (MEC 1), non-migrainous headache (MEC 1), endometriosis (MEC 1) and a family history of breast cancer (MEC 1). The progestogen-only implant can be used without restriction by a woman with any or all of these (or other) MEC 1 conditions.

If a woman has a MEC 2 condition, however, its relevance must be considered in the context of any other MEC 2 or 3 conditions that she has. MEC 2 indicates that the benefits of use of a method generally outweigh risks, but it also flags up that there is a possible safety concern if a woman has other risk factors. A woman may have several MEC 2 conditions relating to health risks that are completely independent of one another, such that risks are not cumulative. For a woman with several MEC 2 conditions that all relate to the same health risk, however, a clinician may consider that the combined risk outweighs contraceptive benefit (particularly if there are safer effective alternatives).

Cases 2 and 3: The Role of MEC2 Patient 2 requests combined hormonal contraception. She is 41 years old (MEC 2), has a BMI of 31 kg/m^2 (MEC 2) and is epileptic (MEC 1). Her mother had a pulmonary embolism at age 47 (MEC 2).

Individually, each of the three MEC 2 conditions in this case does not contraindicate use of combined hormonal contraception. However, increasing age, obesity, family history of pulmonary embolism and use of combined hormonal contraception are all independent risk factors for venous thromboembolism. A clinician may consider that use of combined hormonal contraception by a woman with three MEC 2 conditions that relate to risk of venous thromboembolism could confer unacceptable risk. Alternative effective contraceptive methods that are not associated with increased risk of venous thromboembolism should be considered.

It is worth mentioning that this woman's epilepsy does not itself contraindicate use of any method of contraception (use of any method is MEC 1 for women with epilepsy). However medications taken for epilepsy could reduce effectiveness of some contraceptive methods; remember that drug interactions must always be considered alongside MEC when assessing suitability of a contraceptive method.

Patient 3 also has three MEC 2 conditions for use of combined hormonal contraception. She is 32 years old and breastfeeding her 4-month-old baby (MEC 2). She has migraine without aura (MEC 2) and cervical intraepithelial neoplasia (MEC 2). In this case, in contrast to patient 2, each of the three MEC 2 conditions relates to a different potential health risk. Combined, they do not cumulatively increase any one health risk and benefits are likely to outweigh risks. Note, however that there *are* alternative effective contraceptive options that are MEC 1 for the conditions that patient 3 has.

A MEC 3 category indicates that the risks associated with use of a method for contraception generally outweigh benefits. Where safer contraceptive alternatives are available, these should generally be used. If, however, safer alternatives are not available, or are not acceptable, use of a method for which the woman is MEC 3 may be considered *so long as* the user is fully aware of potential associated health risks. When making such a prescribing decision, any other MEC 2 or MEC 3 conditions that the woman has which relate to the same health risk must be taken into consideration.

Cases 4 and 5: Prescribing Decisions Around MEC 3 Patient 4 has had breast cancer in the past. This is a condition for which use of all hormonal methods of contraception is MEC 3. Patient 4 has excessively heavy menstrual bleeding that has resulted in anaemia. Patient 4 needs to be aware that hormonal contraception could potentially increase risk of future breast cancer and must weigh this against risk associated with unplanned pregnancy as well as benefit in terms of contraception and management of heavy menstrual bleeding. Clearly, she could also consider alternatives such as sterilisation for contraception in combination with endometrial ablation for bleed management.

Patient 5, who wishes to use combined hormonal contraception, has consistently elevated blood pressure, around 150/95 (MEC 3 for use of combined hormonal contraception). All other contraceptive methods considered by MEC are MEC 1 for use in this situation; thus there is a good choice of alternative contraceptive options that should be offered in preference. This is particularly important if the woman has

other risk factors for cardiovascular disease, even if they themselves are only MEC 2 conditions (such as age over 40 years or non-vascular diabetes).

MEC 4 conditions indicate that use of the method concerned is associated with unacceptable health risk, and alternative contraception should be used. Patient 6 has migraine with aura. MEC indicate that combined hormonal contraception is not a safe option for her (MEC 4) because of risk of ischaemic stroke, but progestogen-only methods would be considered safe options (these are MEC 1 or MEC 2 depending on MEC version).

2.7 The List of MEC Conditions Is Not Exhaustive

Conditions that are not listed in the MEC may still affect safety of use of contraception. The MEC are not exhaustive—partly because they would become unwieldy and partly because there is not evidence to inform safety of use of contraceptive methods by women with many less common medical conditions. Where a woman has a medical condition that is not included in the MEC, clinical judgement is required to assess whether use of a contraceptive method could increase risk of adverse health events. A condition that is not included in the MEC could still potentially make use of a contraceptive method inadvisable.

2.8 MEC Tools and Resources

MEC are one part of a set of resources aimed at improving contraceptive provision and care throughout the world. MEC inform decisions about *who* might use a particular contraceptive, through the provision of information and guidance about the safety and appropriateness of contraceptive methods.

The WHO has also developed a MEC wheel (paper and digital formats) that facilitates rapid determination of WHO MEC categories in the clinic setting. Similarly, the European Consortium for Emergency Contraception has produced a MEC wheel exclusively for determining suitability of emergency contraceptive methods [4]. Smartphone applications (apps) based on the WHO MEC and US MEC can facilitate assessment of a woman's eligibility for contraceptive methods. These are available to download at no cost.

Both the WHO MEC and US MEC have accompanying documents known as '*Selective Practice Recommendations for Contraceptive Use* (SPR)' [5, 6]which provide guidance on *how* to use various contraceptive methods safely and effectively once they have been deemed medically appropriate as per the MEC. Other WHO resources to assist contraceptive providers include the'Global Handbook for Family Planning Providers' [7] and an implementation guide for the WHO MEC and SPR [8] to facilitate the integration of the MEC/SPR guidance into national family planning guidelines This guide aims to help countries take ownership of the guidance provided in the MEC and SPR, to improve the usability of the guidance and to help turn family planning policy into practice.

2.9 Conclusion

The MEC provide evidence-based recommendations for contraceptive providers as to who can use a contraceptive method safely. The MEC do not indicate the best method for a woman nor the most effective method for her—her preferences and requirements will influence her choice of method from amongst those that MEC indicate to be safe. Contraceptive choice is highly important for women. Use of MEC can help expand provision of safe contraception for women around the world.

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Contraceptive Counselling

3

Johannes Bitzer

3.1 What Is Contraceptive Counselling: Theoretical Background for an Integrated Model

The objective of contraceptive counselling is helping the patient to prevent an unwanted pregnancy by enhancing motivation, helping to choose the method which best suits her needs and her medical and psychosocial profile (decision-making), and supporting her during the use of this method.

A central part of counselling is related to the decision-making process regarding methods and ways.

To understand the specificities of this process, several aspects should be taken into account:

1. In medical care, two types of decisions can be distinguished [1, 2]:
   (a) Effective decisions. These are clinical situations in which
      - Large database about benefits and risks
      - The benefit outweighs the risk by far
      - Most of experts and informed patient would take this decision
      - Emergency medicine
   (b) Preference-sensitive decisions. These are clinical situations in which
      - There are not sufficient data available about benefit and risk
      - OR
      - The data are available, but the benefit/risk ratio depends strongly on the patient‘s individual values and priorities

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- Antenatal screening, screening for prostate cancer, management of menopause symptoms, and mammography screening

The choice of a contraceptive method is a preference-sensitive decision.

2. The professional help in the decision-making process is called counselling which is part of medical communication.

Two categories of communication in the health care system can be distinguished [3]:

(a) Relational communication

This is the communication between the health care provider (HCP) and the patient which includes attentive listening, responding to emotions, and assessing the needs of the patient which all contribute to the formation of a positive therapeutic relationship between the HCP and the patient.

Building a trustful relationship

This element is the basis for the success of a joint project of contraception. It accompanies the process from the beginning until the end.

It involves two main components on the side of the HCP, namely, a patient-centered attitude and interpersonal skills. The patient-centered attitude describes the specific emotional and behavioral characteristics of the HCP:

- Respect for the patient
- Interest and openness towards the patient's views and needs
- Acting in the best interest of the patient
- Following ethical standards, like respect for autonomy, non-maleficence, beneficence, and justice
- Being available
- The interpersonal skills involved in building a trustful relationship are, at least:
- Welcoming the patient (client)
- Active listening
- Giving patients (clients) the time and room for telling their concerns
- Summarizing and giving feedback
- Inviting questions
- Responding to emotions
- Providing follow-up during the treatment

(b) Task-oriented communication

This is the communication in which the HCP gives essential information about diagnosis and treatment options and plans to the patient.

Good practice regarding information, education, and empowerment is based on specific skills which have been investigated in the broad field of adult education and other fields of continuous education and includes:

- Understand the language of the client
- Try to find a common language
- Avoid medical and scientific terms
- Use images and visualization
- Use the Elicit, Provide, Elicit model

Elicit pre-existing information and questions
Provide information in small pieces
Elicit the understanding and the meaning given to the information

- Translate statistics into everyday experiences
- Structure the information in chapters and announce important information

Contraceptive counselling deals with needs and personal values in the field of sexuality and fertility and thus should integrate relational communication. At the same time, it is about information patient-centered information giving and should therefore integrate task-oriented communication.

Contraceptive counselling needs an individualized "mixture" of relational and task-oriented communication.

Dehlendorf has summarized the do's and don'ts of communication in contraceptive counselling [3].

3. Regarding the interaction between the HCP and patient, three types of counselling can be distinguished based on the roles of the HCP and the patient [4]:
   (a) Directive counselling
   The counsellor takes the main role. There is the assumption that there is a single best solution for the problem of contraception.
   The counsellor wants the client to use the most effective method with the least health risk based on the assumption that there is a single best method for the client based on scientific evidence. In ethical terms the focus is on non-maleficence and beneficence.
   (b) Autonomy-focused counselling (informed choice)
   Taking into account the intimate and personal context of contraception (sexuality, fertility), the autonomy of the client (patient) is in the center of the counselling process. The counsellor (HCP) provides evidence-based information after assessing medical contraindications to facilitate and is not participating in the selection of the method itself (objective, non-influencing).
   (c) Shared decision-making
   In shared decision-making, the HCP and the patient interact with each other based on the competence in the decision-making process. The HCP has the competence of knowledge and experience about solutions (contraceptive methods), and the patient has the competence of defining individual needs and priorities in relation to the different available solutions (contraceptive methods).
   A description of the process is given by Stiggelbouta [4]:
   - The professional informs the patient that a decision is to be made and that the patient's opinion is important.
   - The professional explains the options and the pros and cons of each relevant option.
   - The professional and patient discuss the patient's preferences; the professional supports the patient in deliberation.
   - The professional and patient discuss patient's decisional role preference, make or defer the decision, and discuss possible follow-up.

Contraceptive counselling should basically be a shared decision-making process which can be adapted to the patient's needs and preferences.

4. Contraception is a preventive behavior with the aim of protecting the woman/couple from unwanted pregnancies.
   The decision about which method to use in order to reach that objective is thus just one step in a process which starts with motivation, leading to the decision to use a chosen method, and correct use over the time period during which the protection is needed (which may last long) with the best possible outcome for the patient.
   This aspect is best reflected in the concept of behavior support interventions aside from the above-described decision support interventions.
   Behavior support interventions describe, justify, and recommend *actions that, over time, lead to predictable outcomes over short-, intermediate-, and long-term time frames and that have relevant and important consequences for those who are considering behavior "change"* [5]. Different elements of motivational interviewing are integrated into this part of the counselling process.
   Contraceptive counselling and care thus include the support of the HCP regarding the motivation and maintenance of the preventive contraceptive behavior [6, 7].
5. Contraception is an important part of sexual and reproductive health and rights. Accessibility to good quality of contraceptive counselling and care is therefore part of general human rights. Good quality is based on ethical standards of care ensuring that the patient is in the center of care, that the autonomy of the patient is respected, that she or he is protected from harm, that her or his sexual and reproductive health is maintained and supported, and that all patients independent of their race, sexual preference, etc. get the same good counselling and care.
   Contraceptive counselling and care must be based on a human rights-based, patient-centered concept of sexual and reproductive health following ethical principles [8].
   Contraceptive counselling has thus different challenges:
   It should be based on the concept of preference-sensitive decision.
   It should integrate relational and task-oriented communication.
   It should use shared decision-making as much as possible.
   It should support motivation and correct use of the contraceptive method chosen.
   It should be practiced under the framework of a patient-centered and human rights-based ethical guidance.
   Based on the summarized principles above and related publications [9–15], we suggest an interactive, structured counselling and care approach which integrates [16]:
   (a) Patient-centered communication based on ethical principles and the model of relationship-oriented and task-oriented communication.
   (b) Transparent shared decision-making process in the context of a human rights-based concept of sexual and reproductive health.
   (c) The provision of support and follow-up to enhance effective, safe, and well-tolerated use of contraceptive methods.

This interactive approach is subdivided in different steps which usually follow each other but which may overlap or be repeated during the process.

3.2 Step 1: Needs Assessment

In the first step, the health care professional should welcome the woman and listen to her, to understand her needs and priorities:

- What is her motivation for contraception? How important is contraception now?
- What are her family planning objectives?
- What are her expectations and her knowledge regarding contraceptive methods?
- What are her main concerns?

Very different scenarios may emerge:

- Avoiding a pregnancy in a new relationship
- Pregnancy would be a catastrophic event
- Spacing pregnancies after birth
- No more children
- Wanting a child after getting a job but not right now
- Concerns about hormones
- No foreign body in my womb
- Have "x" and not well tolerated
- Want regular menstruation
- I forget … I am very stressed

This step serves two purposes:

(a) It is first step in establishing a trustful relationship by being welcoming, open, and interested
(b) The HCP gets an idea about:
    - The motivation for contraception
    - The methods which most probably will not fit into the subjective needs, priorities, and values of the patient

The communication skills needed are:

(a) Relationship oriented:
    - Respect for the patient
    - Interest and openness towards the patient's views and needs
    - Acting in the best interest of the patient
    - Following ethical standards, like respect for autonomy, non-maleficence, beneficence, and justice
    - Being available
(b) Active listening and inviting the patient to talk about her needs and summarizing what has been said.
    "I understand that you need effective contraception for the next years to come … You are afraid of hormones because you have heard a lot of negative things—hormones cause cancer."

The HCP keeps these fears for a moment or he may address beliefs about methods at this point:

"Would you like me to comment from my side about the concerns you were mentioning?"

(c) It may serve as a first step to enhance motivation by complementing the patient for her initiative to protect herself and come to the consultation.

In this first step, the patient has the lead and the HCP's role is mainly listening.

At this stage, the HCP can introduce and show a summary table of methods with a short description of their main characteristics, shown in a hierarchic order with the more effective at top and exclude those which the woman does not want.

This step is the first step **of exclusion or second-line positioning of methods** such as reducing the options to be discussed based on the needs and priorities of the woman.

3.3 Step 2: Medical and Psychosocial Profile

In a second step, the HCP will establish a thorough sexual and reproductive health profile of the client (medical and psychosocial information).

This includes her:

- Age and life phase
- Sexual history including relationship status (single, romantic relationship, married), sexual orientation and preferences, and sexual activity
- Medical history and clinical findings
- Medications
- Socioeconomic life situation and sociocultural background
- Present complaints including mental and sexual health

The medical history, clinical findings, and medications will help the HCP to exclude methods which the patient should not use due to medical relative or absolute contraindications based on scientific evidence.

The medical eligibility criteria of WHO, FSRH [17–20], are helpful tools to give orientation about the risks associated with the use of each method related to the different clinical conditions.

The age and life phase and the socioeconomic life situation as well as the sociocultural background will allow the HCP to evaluate the suitability or non-suitability of methods.

Examples:

- Adolescents with the need for very effective methods with irregular cycles should not use fertility awareness methods.
- Women with behavioral rules regarding sexual activity in relation to menstruation should not use methods with irregular or heavy/prolonged menstrual bleeding.

This is the task-oriented part the HCP is taking thus having the active part in this step.

It is based on her or his **knowledge of evidence-based sexual and reproductive health and the available contraceptive methods.**

The communication skills needed are:

(a) Providing information. This skill includes the following elements:
- Understand the language of the client
- Try to find a common language
- Avoid medical and scientific terms
- Use images and visualization
- Use the Elicit, Provide, Elicit model:
  - Elicit pre-existing information and questions
  - Provide information in small pieces
  - Elicit the understanding and the meaning given to the information
- Translate statistics into everyday experiences
- Structure the information in chapters
- Announce important information.

(b) Taking a sexual history**.**

This includes the appropriate approach which is on one hand pro-active (looking into sexuality-related risks and sexual well-being) but also respectful and noninvasive.

"To be able to best counsel you regarding contraception I would like to ask some questions about your sexual life. Is that ok for you?"

"Are you sexually active?"

"Is your partner male or female?"

"Do you have one partner or several partners?"

"Do you protect yourself against sexually transmitted infections?"

This step will allow the HCP to exclude or put into a second line those methods which are not or less suitable for the woman due to medical or psychosocial contraindications or limitations.

The HCP can again use the table of methods as an aid to visualize the process and mark those methods which are contraindicated or second line for medical and/or psychosocial reasons (**second step of exclusion or second-line methods**).

3.4 Step 3: Individual Benefits

Among the methods which are left, the HCP will look for those which may bring additional benefits to the woman.

At this step, the HCP will go back to step 2 looking into complaints:

The patient may suffer from menstrual disorders, hyperandrogenism, mood disorders, and sexual dysfunction, or she may have specific family risks like ovarian cancer, etc.

For all these conditions, some methods may have a protective or therapeutic effect which would present an additional benefit to the health and the well-being of the woman.

For example:

- Combined hormonal contraceptives (CHCs) are effective against several menstrual disorders (irregular bleeding, heavy menstrual bleeding) and/or alleviate mild to moderate acne.
- CHCs reduce the risk of ovarian and endometrial cancer.
- CHCs in long cycle can reduce premenstrual syndromes. The CHC combined with drospirenone has been shown to be as effective against premenstrual dysphoric disorder as SSRIs.
- The levonorgestrel intrauterine device (LNG IUD) is considered first-line treatment in women with heavy menstrual bleeding without organic pathology.
- The role of the HCP in this step is to give evidence-based information about possible health benefits of methods related to the individual complaints of the patient.

This is the task-oriented communication of the HCP in which the patient contributes his or her knowledge and experience. It is the patient's competence and role to give these possible benefits her individual importance:

"For me it is very important that I get rid of this premenstrual syndrome. It ruins my life."

"For me my skin makes me feel really bad and it keeps me from going out and meeting people because I always think that they look at me."

HCP and patient contribute to this step in a shared way (shared decision-making).

This is a step of inclusion of methods into the decision-making process.

(**step of inclusion**).

3.5 Step 4: Information, Education, and Empowerment Through Shared Decision-Making (SDM)

The HCP and the patient have now after the two steps of inclusion and one step of inclusion different methods to discuss.

These methods have the potential to meet the needs of the patient, are not contraindicated, and may have additional benefits.

Each of the methods has five basic qualities.

Two of them describe positive wanted properties:

- Efficacy
- Benefits

Two of them describe negative unwanted properties:

- Health risks
- Side effect

One property is neutral:

- Way of application

The HCP can use the image of a balance to visualize the trade-off between the wanted and unwanted properties. The HCP has the clinical and the epidemiological (statistical) knowledge regarding these properties. The HCP's role is to present this information to the patient in a way that the patient can understand it. The HCP needs knowledge about evidence-based information (task-oriented communication).

The HCP needs specific communication skills related to benefit/risk counselling.

- Use absolute numbers with a common denominator
- Visualize risks
- Put the numbers into an everyday perspective (everyday risks) using risk scales.
- Describe risks in relation to benefits

The patient is encouraged to give her/his individual interpretation to the benefit/risk balance.

"Is this an acceptable risk for me taking into account the benefit?"

"Is this risk inacceptable for me … although it looks very small?"

The patient is encouraged to ask questions and look for clarification.

The role of the patient is to look into the personal significance and importance of the risk/benefit equation.

In this step the HCP provides evidence-based information in an understandable way (see above). The woman is invited to give her individual importance and weight to the information (benefit-risk balance-shared decision-making).

3.6 Step 5: Supportive Care

Accompany the woman to ensure effective and safe use.

After the decision for a method has been made, the HCP should accompany the woman in a trustful working relationship (main elements see above).

During the follow-up visits, HCPs should:

- Assess the motivation for contraception (changes in the importance)
- Assess the satisfaction, the proper use, and the tolerability of the method
- Ask proactively about the impact on the quality of life, including sexuality and mood
- Encourage questions

This is the step where the behavior-oriented interventions are important (see above). The HCP can assess the importance of contraception in the life context, compliment on the continuous use, increase confidence in use, and serve as a partner in looking for solutions in case of problem.

The contraceptive project is thus a shared experience and task, and it may be necessary to go back to previous steps of the process.

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Contraception and Sexuality

4

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4.1 Introduction

Access to safe and effective contraception is a critical issue for both sexual and social health. Indeed, successful control of fertility leads women to important benefits from personal, economic, and cultural autonomy to the psychological and physical well-being and, consequently, to a better quality of their relationship with their partner [1].

Contraception was expressly designed to enhance and improve sexual activity, freeing it from the concern of an unwanted pregnancy. On the other hand, some essential issues related to contraceptive use, such as sexual acceptability and the impact on sexual experiences, preferences, and practices, have been poorly explored. Few recent studies have suggested that contraception can affect women's sexual function having a wide range of positive and negative effects, exerting their influence on several domains of female sexuality (desire, arousal, orgasm, and enjoyment). However, it is important to stress that satisfaction with sexual activity depends on a multitude of factors that extend beyond sexual function itself. In fact, while social and cultural variables may influence female sexuality in the modality and timing of sexual expression, sexual behavior could be affected by both hormonal changes and the use of hormonal contraception [2]. Some authors have suggested that female sexual interest increases during the periovular phase of the menstrual cycle in women who use reliable non-hormonal contraception [3].

A growing number of reports in the literature have recently focused on sexual aspects of contraception, especially hormonal contraception and its association with libido. However, a holistic approach is needed to understand the complexity of aspects related to women's sexuality and their link with contraception. More

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attention towards these topics could promote both women's sexual well-being and a more widespread contraceptive practice.

In this chapter, we will discuss female sexuality starting from the biological aspects that characterize women in their cyclic physiology, as organic, social, and psychological. In this context, we will focus on the different methods of contraception and their impact on female sexuality, according to the most recent literature reports.

4.2 Findings on Women's Sexuality Across the Menstrual Cycle

For several decades, evolution-minded theories on human sexuality have been almost always based on the assumption that women have lost their estrus, a distinct phase of female sexuality occurring near ovulation, characterized by an enhanced receptivity in terms of sexual motivation [4]. However, recent evidence and theories have suggested that the loss of estrus in humans has not really occurred [5]. Findings on women's sexuality across the menstrual cycle have reported an increase in female sexual desire and activity over the follicular phase, with a mid-cycle peak, followed by a postovulatory decline [3, 6–8].

From an evolutionary point of view, women's sexual motivation during the fertile phase of the menstrual cycle provides a powerful tool to understand the consistency of sexual behaviors with the finalistic purpose of reproduction; thus, women would have evolved rather in another sense, in order to conceal their cyclic fertility or, in our terms, their estrus [9] (Gildersleeve 2014). Other authors have specifically investigated the frequency of sexual activity in both single and partnered women using an effective barrier contraception, observing a clear rise 3–4 days before the LH peak and a second increase before the menstrual period [7]. Changes in sexual activity from the follicular phase to menses seem to reflect the monthly cyclic changes of all ovarian steroids, even if the increase of both the total testosterone and free androgen index during the periovulatory phase is relatively small compared with those observed during other menstrual phases [3]. Interestingly, authors have suggested that estrogens and progesterone have an excitatory and inhibitory effect, respectively, on female sexual desire but did not support a role for testosterone [6]. In a large-scale international study, conducted on 20,000 sexually active couples adopting contraceptives (with the exclusion of hormonal and rhythm methods), it was observed that the frequency of sexual intercourse was lower during menses, but no significant differences were found among other phases of the menstrual cycle [10]. Despite several studies having pointed in the direction of ovarian hormones in the prediction of female sexual desire, evidence about the influence of the menstrual cycle itself on sexual behavior has not been completely clarified. Indeed, cyclic changes in female sexual interest may be masked by the relatively constant sexual desire of the partner or other non-biological dynamics [8]; these factors could explain the difficulties to demonstrate hormonal influences on female sexuality. Moreover, according to some recent findings, there could be different behaviors in

sexual activity between single women and those with a partner [3]. Indeed, women without a stable relationship tend towards an increase in sexual activity during the periovulatory phase, while those with a partner are less likely to report differences across the menstrual cycle. Such correlations could indicate that the model of human sexual behavior is closer to the biological one, especially when it is free from relational influences.

Sexual activity is certainly influenced by the social and cultural context. For example, avoidance of sex during menses is widespread across the world. Current social attitudes often tend toward a high frequency of sexual activity in the evening when people are less inhibited or most frequently on Saturday [3]. Interestingly, some authors argued that menstrual avoidance can lead to a "heaping" of postmenstrual sexual activity without there being any hormonal influence [11, 12], and the combination of menses-associated avoidance, weekend-associated preferences, and associated changes in behaviors (such as sleep and stress) may override hormonal influences making sexual activity independent from ovulation [2].

4.3 Combined Oral Contraceptives (COCs) and Female Sexuality

Over the past half century, a plethora of scientific reports about social and cultural aspects related to the pill has been written [13]. Some authors have argued about the social impact of "the pill" and its role on the so-called sexual revolution supporting that, at least in the first phase, it was misunderstood [14, 15]. The story of the development itself is controversial. It began with the collaboration of two scientists who were conducting experiments on the use of progesterone for two different purposes: John Rock who aimed to use it as a treatment for infertility and Gregory Pincus who wanted to block ovulation. At that time, experimentation for the purpose of contraception was illegal; thus, the pill was approved by the FDA to treat menstrual disorders and it was available only for married women. In 1960, it was approved as a contraceptive, and only in 1972 was it freely available for all women, accompanied by the onset of many ethical and social concerns, as pointed out by a story published in the *U.S. News & World Report* and asking "Can its availability to all women of childbearing age lead to sexual anarchy?"

Despite all the ethical and social controversies and the scientific debate on side effects, the pill has nowadays a well-established role in medical practice [16]. Combined hormonal contraception (CHC) is an affordable and reversible method of birth control, available with a variety of formulations, regimens, and doses of administrations. It is used by over 100 million women worldwide who have gained a remarkable control of their fertility with respect to other methods, such as the male condom [17].

A wide number of studies have examined the effects of COCs, focusing on efficacy and safety in terms of side effects such as nausea, weight gain, and bleeding irregularities; however, few investigated the impact on female sexual function [3, 18].

The vast majority of studies on sexuality in COC users have primarily focused on changes in sexual desire after starting or switching to hormonal contraception [19, 20]. Some authors have suggested that a proportion of women using oral contraceptives report impairment of their sexual interest or response, which may be attributed to the pill [21]. However, findings from studies comparing pill users versus women using non-hormonal methods have shown contrasting results [20].

In a recent systematic review of 36 studies, involving more than 13,000 women, no significant effects on sexual desire with the use of COCs were reported [22]. On the other hand, several studies have shown an association between the use of COCs and changes of sexual function, particularly sexual desire and arousal, frequency of sexual activity, and orgasm achievement but not enjoyment with sexual activity [19, 23, 24]. It is far from clear whether these changes are direct hormonal effects of the oral contraceptive, secondary to pill-induced mood changes, or are primarily psychological reactions towards fertility control or other unrelated factors [25]. The lack of robust evidence highlights the complexity of the female sexual function and focuses on the need for a holistic approach in order to achieve an appropriate understanding.

From a biological standpoint, COCs are known to lower the endogenous levels of free or bioavailable testosterone [21]. This could occur by two mechanisms as follows: oral COCs can increase sex hormone-binding globulin (SHBG) with a consequent decrement in free testosterone (FT); alternatively, they can directly act on the ovary, suppressing androgen production [26, 27]. According to recent studies, CHCs might reduce the blood levels of free testosterone below a critical threshold, potentially leading to, at least in a group of susceptible women, complaints of decreased sexual desire [25, 28]. Evidence supporting or refuting this "desensitization hypothesis" is currently lacking [29]. Differences in terms of anti-androgenic effects and impact on sexuality could be attributed in part to the known effects of estrogen on SHBG synthesis and in part to the androgenic or anti-androgenic activity of the involved progestin [25].

Furthermore, some pathological conditions can have a negative impact on female sexuality, among these the most common are undoubtedly PCOS and endometriosis. COCs have a widely recognized role as effective treatment for these conditions, but their role on sexuality has been poorly assessed. However, they have been associated with an improved sexual function due to the reduction of specific symptoms, such as chronic pelvic pain and deep dyspareunia in women with endometriosis [30] and amelioration of the body image and self-esteem in women with PCOS, due to the reduction of hirsutism and acne [31]. Moreover, extended or continuous regimens of administration have been associated with additional positive changes in a variety of sexual acceptability factors, from sexual function and libido to a reduction in dysmenorrhea, duration of withdrawal bleeds, and breast tenderness [25, 28]. Finally, some studies have focused on the factors that affect women's sexual arousal, finding that fears about unwanted pregnancy had a very negative impact, particularly if the partner did not share these concerns [32]. Women with a clear desire to avoid pregnancy are likely to get benefits in their sexuality by effective methods that make them feel secure about preventing conception. COCs are a highly effective

form of contraception; they help to eliminate anxiety related to the fear of pregnancy, encouraging a more relaxed and enjoyable sexual experience [33].

During the past few decades, due to the increased attention on side effects of hormonal contraceptives, many strategies have been carried out to improve the tolerability of COCs [34]. In order to decrease the impact on metabolism, we have seen a constant reduction of the ethinylestradiol (EE) dosage to 30, 20, and also 15 μg.

Despite a reduction of side effects, a high rate of discontinuation has been reported because of the effects on mood and sexuality. In fact, during the usage of oral contraceptives containing EE 15 μg, women could experience lower sexual desire, arousal, and sexual activity than before starting contraception [35]. Some women could also experience dyspareunia, referring it as related to a decrease in sexual thoughts and fantasies. As previously discussed, the reduction of libido could be explained by the increase in SHBG and the consequent low FT; notably, this effect seems to persist even when the EE dose is reduced [36–39]. On the other hand, the low peripheral dose of EE could be involved in the reduction of vaginal lubrication and, consequently, in experience arousal disorders [35, 40, 41].

In conclusion, the concept of variable sensitivity to sexual steroids should be emphasized and COCs should be tailored to subjective needs. Moreover, another important aspect in contraceptive counseling is related to women's expectations about the effects of COCs on their sexual activity. In the majority of cases women expect an improvement in sexuality with COC use, while a worsening or the lack of changes could lead to discontinuation.

4.4 Vaginal Ring

The contraceptive vaginal ring (CVR) represents a suitable option because of its non-contraceptive benefits in women with indications for CHC who experience sexual dysfunctions with the oral route [42]. It was developed to improve women's compliance and acceptability eliminating the need of a daily intake with the advantage of a route that avoids the first liver passage [43]. Moreover, the vaginal route provides therapeutic hormone levels with low daily doses and a more stable absorption compared with traditional COCs [44].

The etonogestrel (ENG)/EE combined vaginal ring has been shown to be a valid low-dose contraceptive, releasing daily 15 μg of EE and 120 μg of ENG, to ensure an optimal cycle control, with a low incidence of irregular bleeding and withdrawal bleeding. Despite the low dismissing of EE, few reports comparing CVRs with COCs have shown better effects on women's sexuality in the CVR group [45]. The improvement in sexual function in women using CVRs could be related to more stable circulating levels of exogenous hormones. In addition, findings from recent studies have supported the hypothesis that the increased local concentration of EE in the vagina, associated with the CVR, results in the improvement of vaginal wetness and reduction of dyspareunia [46]. Another important effect of the local activity of a CVR is the increase in the number of lactobacilli of the vaginal flora, which can lead to an increased leukorrhea with protective effects against vaginal

colonization by pathogens [47]. Moreover, CVRs could exert a further positive effect on sexual interest and fantasy, as well as on the psyche of the woman and her partner, evidenced by their greater complicity and satisfaction. The presence of a foreign body in the vagina may have a stimulating effect on both partners, more psychical than physical, since only a few couples report feeling it during intercourse [48]. However, studies evaluating CVRs and their effects on sexual function have shown conflicting results. In a randomized study, vaginal ring users had better results related to desire and sexual satisfaction compared with COC users [41]. Sexual desire was also found to be higher in ring users compared with a desogestrel-containing combined COC and a desogestrel-only [49]. A prospective study on women using a vaginal ring in an extended regimen found an improvement in sexual function and a reduction of sexual distress after 60 days of use [50]. On the contrary, in an open-label randomized trial, it was observed that CVR was responsible for a decreased libido more frequently than a COC with 30 μg EE and 3 mg DRSP [51]. Finally, a recent study evaluated sexual function and quality of life (QoL) in healthy women who used a new CVR, manufactured with a new polymer composition and containing EE 3.47 mg and ENG 11.00 mg. Results have shown an improvement in sexuality, the reduction of adverse events, and a better QoL in the new CVR group, compared to the EE 2.7 mg/ENG11.7 mg CVR group [42].

4.5 Progestin-Only Pill (POP)

The most common POPs used in Europe contain low doses of desogestrel. Evidence from clinical trials on POPs has demonstrated no effects on breastfeeding performance and no harmful consequences related to exposure in infants below 6 weeks of age [52]. Evidence from a placebo-controlled, double-blind study compared CHC and POP users has shown that POPs were not associated with adverse events and had no impact on female sexuality. Overall, the available data provides reassurance that progestin-only contraceptives are unlikely to have a major impact on sexual desire [53]. Some studies have supposed a suppressing role for progestins on sexual interest, thoughts, and fantasies, mainly related to the use of triphasic pills, compared with monophasic pills, where the only difference in pill composition was a lower dose of progestin in the triphasic regimen [54]. Another hypothesis is that a particular type of progestin—and not the dose—may be responsible for the effect on sexual function. Studies comparing a levonorgestrel-containing combined contraceptive with a desogestrel-containing one have shown different impacts on SHBG concentrations [55]. Moreover, it has been suggested that desogestrel-containing combined pills may exert positive effects on libido [56]. The question of whether a different dose or the type of progestins could differently affect female sexuality deserves additional research.

4.6 Intrauterine Devices

Thanks to their high contraceptive efficacy and forgettable nature, long-acting reversible contraceptives (LARC) are widely used methods in current family planning programs and policies [57]. To date, LARCs are the best option for women with a history of discontinuation of short-acting reversible (SARC) methods, such as oral, patch, or vaginal combined hormonal contraceptives or non-hormonal contraceptives [58].

In Europe and the USA, a growing interest on intrauterine devices (IUDs) with the advantages of extended use (from 3 to 5 years depending on the device) and a better continuation rate compared to the shorter-acting methods has been observed. IUDs are the most effective form of LARC, demonstrating to be safe and showing a neutral effect on overall women's metabolic and biological function. The levonorgestrel intrauterine system (LNG-IUS) is one of the most used IUDs; in this system LNG is released at the endometrial level, with a very low passage in the blood circulation, resulting in a good balance between effectiveness and metabolic impact [59]. However, sexual acceptability is an important issue that may influence satisfaction and continuation of IUDs. Patients' most commonly cited reasons for discontinuation within the first 12 months include cramps, pain, and bleeding [60], but also the perception that IUDs could negatively affect sexuality—for example, the IUD string can disturb a partner's sexual experience [61]. On the other hand, the absence of systemic hormonal effects makes this IUD neutral on sexual libido compared to other hormonal methods [62].

Several studies have investigated the QoL and sexuality in women using the LNG-IUS, demonstrating an improvement in all the domains of QoL after LNG-IUS placement. Another important reported aspect was the increase in the frequency of sexual activity and the reduction of dysmenorrhea [63]. By contrast, a recent study on healthy women using IUDs as a contraceptive method has reported no change of QoL and sexual life after 12 months [64].

Other studies [63, 65] have confirmed that both frequency of sexual activity and sexual enjoyment are positively related to the satisfaction with a contraceptive method. High levels of satisfaction have been reported in women on LARCs who previously had unintended pregnancies by using an SARC [63], as well as a better QoL [66, 67]. Moreover, some recent studies that have analyzed the effects of LNG-IUS in women affected by sexual dysfunctions have supported a significant improvement of sexual desire, arousal, orgasm, and overall sexual function. According to this finding, LARC methods appear to be a reasonable alternative for women who experience sexual dysfunction with oral hormonal contraceptive use [20].

Finally, IUDs were thought not to be suitable for young women until evidence showed the sexual acceptability and safety of this contraceptive method. Moreover, thanks to its static placement inside the uterus, it has no impact on sex with the advantages of increasing spontaneity and enjoyment during sexual intercourse and reduced sexual inhibition. Despite the high acceptability and tolerability, IUDs could be associated with side effects such as bleeding and cramping. However, the majority of authors agree that IUDs are suitable for every women's choice [65]. In

the circumstances of spontaneous expulsion or uterine cramps, an accurate investigation on the presence of any other symptoms and on sexual acceptability should be performed in order to advise IUD substitution or the use of another LARC.

4.7 Progestin-Only Contraceptive Implant

Progestin-only contraceptive implant (POI) is a subdermal device containing a total of 68 mg of ENG, which is released daily at low doses 25–70 μg on the subdermal tissue of the arm. It is classified as an LARC, having the advantage of being discreet and easy to use [68–70]. The device is usually placed on the internal side of the non-dominant arm and provides an effective contraception for 3 years, ensuring optimal compliance. As we observed for other contraceptive methods, sexual acceptability in subdermal implant users has been poorly investigated. Authors have observed that POIs do not negatively affect libido and sexual function, while an improvement of QoL after 6 months of use has been reported [71]. A recent multicenter clinical trial has shown that POIs have a safe metabolic profile and bleeding pattern that was similar to that observed for IUDs. However, unscheduled bleeding commonly decreased within 6 months of use and it was not perceived as a concern. Relevant advantages on sexual function were also detected: a significant increase in sexual pleasure, personal initiative, orgasm frequency and intensity, and satisfaction, together with a significant decrease in anxiety and discomfort [72]. Another potential advantage of POIs compared to IUDs is the absence of cramps and interference on the partner's sexual pleasure—as the device has a subdermal placement; thus, it could be considered a suitable option in those cases in which the IUD is poorly tolerated.

Finally, it has been shown that androstenedione blood levels in POI users were comparable to those observed in women not using hormonal contraception and more elevated to those detected in women using different CHCs (vaginal ring and three different oral contraceptives). Such a finding encourages the hypothesis that the maintenance of physiological androgen levels, associated with the confidence of contraceptive efficacy, may explain the positive impact on sexual function [73].

4.8 Condom

Sexual satisfaction partly reflects what women think of their contraceptive method when asked about particular dimensions of sexuality. Given male condoms' undeniable presence during sex, it may come to mind more than other methods affecting sexual pleasure. Findings from an exploratory study have suggested that women using male condoms as the main contraceptive method were significantly more likely to report a decrease in sexual pleasure. However, when sexual satisfaction was more broadly investigated, primarily condom users did not show any impairment, and "dual users" (mainly women using condoms and the pill) had the highest sexual satisfaction scores [74]. The link between a contraceptive method and

decreased pleasure is more likely to change contraceptive practices and, potentially, sexual risk. Even if male condoms are not associated with relative sexual dissatisfaction, the sexual attributes that women give to condoms are likely to alter attitudes and practices. If women consider male condoms as an interference for sexual pleasure, they may be less inclined to use them during the full duration of intercourse. In a recent qualitative study, women reported that condoms "cover up" sensation and exacerbate vaginal dryness, which led them to use condoms intermittently or not at all [75].

Another emerging concept is the eroticization of safety. It has been reported that women could not "let go" sexually unless properly protected from unwanted pregnancy and disease. Consequently, in women and men for whom avoiding pregnancy and/or disease is imperative, an effective prophylaxis is an eroticizing precondition, as contraception is considered to take advantage of the educational and professional opportunities afforded to them [75].

4.9 Conclusion

In order to start a contraceptive method, a careful evaluation of contraindications and potential associated risks is necessary. Based on this preliminary assessment and according to the woman's preference, a variety of methods could be recommended, taking into consideration the impact on sexual function [17]. Women may express concerns about the quality of sexual function associated with their method of contraception, particularly in the case of hormonal contraception. Review of a temporal relationship between the onset of female sexual dysfunction and initiation of contraception is warranted, as is an assessment of the biopsychosocial model of other potential contributing factors. Healthcare providers should openly query women about sexuality and sexual satisfaction with their current contraceptive use and should consider alternative options when needed. A multidisciplinary approach is suggested, particularly when multiple contributing or complicating factors are identified, such as sexual pain, relationship discord, multiple comorbid medical conditions, and a history of sexual abuse.

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Contraceptives and Mood

5

Inger Sundström-Poromaa

5.1 Background

The interest in how, and if, hormonal contraceptives influence mood has increased over the past years. This increase is potentially driven by an overall increased prevalence of mood and anxiety disorders in Westernized societies [1, 2], but potentially also because female hormonal contraceptive users are making themselves heard, as mood problems are less stigmatized nowadays than they used to be. Further, contraceptives are most frequently used, and most greatly needed, during a period of life when the first onset of a depressive episode or anxiety disorder may occur [3–5]. Because of the increasing interest and media coverage [6], many women, rightfully so, have questions regarding potential adverse mood effects from hormonal contraceptive use.

The clinical relevance of hormonal contraceptive-induced mood symptoms is also becoming more obvious. Mood symptoms, such as depressive symptoms, irritability, anxiety, and mood swings, are nowadays one of the major reasons for discontinuing hormonal contraceptive use [7]. Moreover, women who discontinue hormonal contraceptives often turn to less effective methods, thus increasing the probability of unintended pregnancies [8–10].

Three systematic reviews have been published over the past years, two dedicated to the mood effects of combined hormonal contraceptives and one to the progestogen-only contraceptives [11–13]. Altogether, these reviews covered the few placebo-controlled randomized trials, observational and cross-sectional studies that had been published up until 2016 and 2017, respectively. Besides pointing to the lack of high-quality evidence, the overall conclusion from these reviews was that the great majority of hormonal contraceptive users, including those using combined methods as well as progesterone-only methods, should not expect to experience negative

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mood [12, 13]. However, a smaller percentage of hormonal contraceptive users are at risk of experiencing a worsening of their mood. The mood effects appear relatively subtle and may be hidden in large observational studies, or even in the randomized controlled trials, as the proportion of women who are unaffected or even experience improved mood outnumber those who experience the negative effects [12]. The exact estimate of women who may experience mood symptoms while on hormonal contraception is essentially unknown, but proportions in the range of 4–10% have been suggested [11].

The lack of high-quality evidence as regards the influence of hormonal contraceptives on mood is still a major problem, and contradictory findings are imminent. Since these two reviews were published, two placebo-controlled randomized trials have been published [14, 15] and, in addition, three large-scale prospective cohort studies on the effect on mood in relation to hormonal contraceptives [16–18]. This review will discuss the high-quality evidence that is at hand, but also discuss the shortcomings and caveats that need to be taken into account when interpreting observational studies in the field.

5.2 Placebo-Controlled Randomized Trials

Randomized, placebo-controlled studies represent the highest level of evidence, and this is also true in the contraceptive field. However, the randomized trials are underpowered to detect more rare outcomes such as mental health problems requiring treatment.

The two recent placebo-controlled studies were investigator-initiated, meaning that they had received no funding from the pharmaceutical industry. The first study was a multicenter, randomized, double-blinded, placebo-controlled study including 202 healthy women. The women were randomized to a combined pill containing 1.5 mg estradiol and 2.5 mg nomegestrol acetate or placebo for three treatment cycles [14]. The main outcome measure was the Daily Record of Severity of Problems (DRSP), which was filled out daily during one baseline cycle and during the final treatment cycle. Secondary outcomes included the Montgomery-Åsberg Depression Rating Scale, filled out at baseline and during the third, and final, treatment cycle. The use of daily ratings on the DRSP opened up for the possibility to investigate mood changes across the treatment cycle, covering the menstrual, premenstrual, and intermenstrual phases. Use of the combined pill was associated with small, but statistically significant, increases in mean anxiety (0.22; 95% CI 0.07–0.37), irritability (0.23; 95% CI 0.07–0.38), and mood swings scores (0.15; 95% CI 0.00–0.31) during the intermenstrual phase but not in the other treatment phases. Further, a significant premenstrual improvement in depression was noted (−0.33; 95% CI 0.62–0.05). While the study was not powered to detect differences in women who had a clinically relevant change in mood, the proportion of women who reported a clinically relevant mood deterioration was 24.1% among those allocated to COC and 17.0% among the placebo users. In addition, the number of women with new-onset subclinical depression during treatment did not differ

between the oral contraceptive group and the placebo group, 9.6% in the combined hormonal contraceptive users and 6.4% in the placebo group [14].

The second placebo-controlled randomized trial included 340 women randomized to a combined pill containing 30 μg ethinylestradiol and 150 μg levonorgestrel [15]. Primary outcomes in this trial were general well-being, assessed by the Psychological General Well-Being Index (PGWBI), and depressed mood, captured by the Beck Depression Inventory (BDI). Treatment with the combined hormonal contraceptive led to significantly reduced general well-being compared with placebo, with the dimensions contributing to the overall result being reduced positive well-being, reduced self-control, and reduced vitality. No difference in depressed mood was noted between the combined pill and placebo, and the proportion of women with moderate to severe depressive symptoms at the end of the trial was similar (7% in both groups) [15].

These relatively modest findings of these two recent placebo-controlled trials are in line with Graham and colleagues who conducted a placebo-controlled, double-blind comparison of a COC (EE 30 μg/0.15 mg levonorgestrel) and a progestogen-only contraceptive pill (levonorgestrel 0.03 mg) [19]. The study included 150 women and was carried out in two contrasting cultures. Besides differences at baseline in mood between the two settings, there were no differences between the placebo and the COC in terms of daily ratings of depression or irritability. However, the COC was associated with more negative mood changes than the POP, but with very small effect sizes [19]. Yet another placebo-controlled trial reported on inner city adolescents ($n = 76$), who were randomized to 20 μg EE/0.10 mg levonorgestrel or placebo for treatment of dysmenorrhea. Depressed mood was a secondary outcome of the trial and was assessed by use of the Center for Epidemiologic Studies Depression Scale (CES-D). The adolescents had relatively high depression scores already at baseline, but throughout the study, depression scores decreased equally in the treatment and placebo groups [20]. No information on frequency of women who deteriorated or improved was given in these two trials.

A number of conclusions can be drawn from these randomized trials, which thus far represent the highest level of evidence on hormonal contraceptive-induced mood changes. First, the overall effect sizes for the mood effects that were noted were small. This finding clearly points to the complexity of studying how hormonal contraception affect women's mood, where some women will report improved mood, the great majority unchanged mood, and a smaller fraction of women clearly being negatively affected by the combined hormonal contraceptive. An example of this distribution is given in Fig. 5.1, derived from one of the placebo-controlled trials.

Secondly, none of these two trials was able to detect a worsening in depressive symptoms or an increase in the proportion of women with clinical relevant depressive symptoms at the end of the trial. In fact, one of the trials reported on improved depressive symptoms during the premenstrual phase of the treatment cycle, in line with evidence suggesting that hormonal contraceptives can be used to treat premenstrual dysphoric disorder [21, 22]. Further, mood worsening and depressive symptoms were also relatively common among the placebo users, emphasizing that women are at increased risk of depressive symptoms, depression, and anxiety

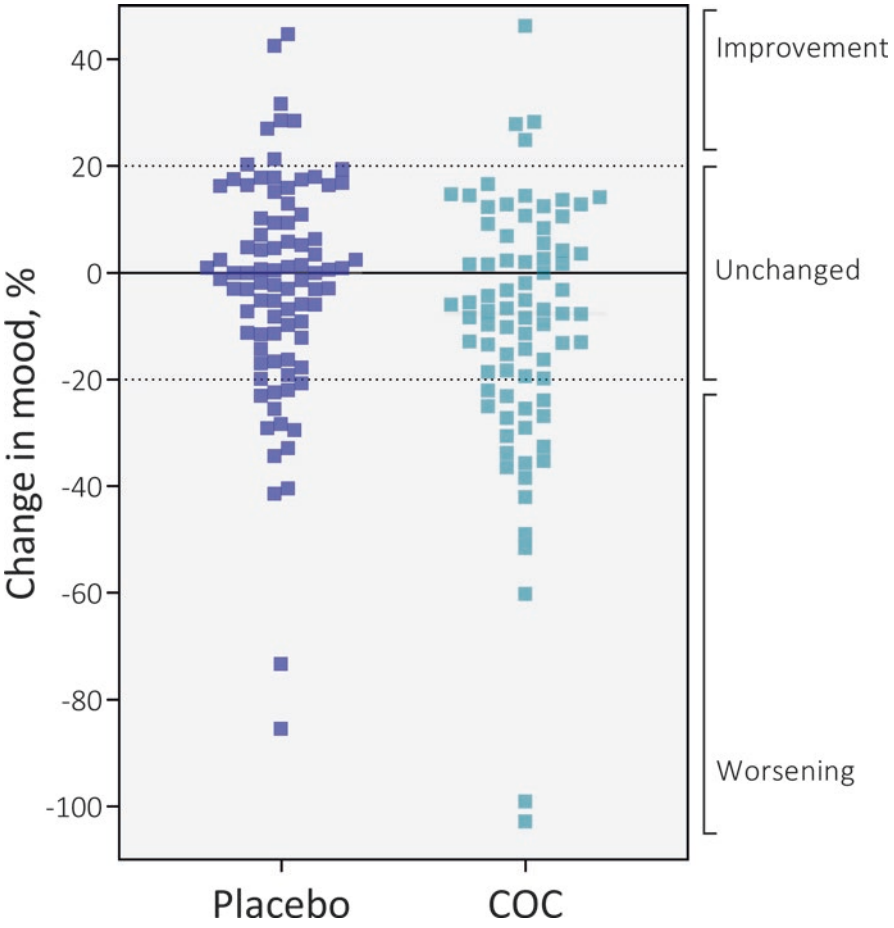

Fig. 5.1 Change from baseline to the final treatment cycle in summed mood scores on the Daily Record of Severity of Problems scale. The summed mood score consisted of anxiety, mood swings, irritability, and decreased interest in usual activities

disorders, just because they are women [23], and especially during this time period in their lives [3–5]. Healthcare providers should be aware that mental health problems are common in women and that they not always (or rarely, see below) are causally related to the use of hormonal contraceptives.

However, at the same time, both studies clearly demonstrated that the combined pill is associated with minor mood changes in symptoms like increased irritability, increased anxiety and mood swings, and lowered general well-being. For some women, these modest changes in mood may be clinically relevant and the final push to a mental health problem in need of psychotropic treatment. Overall, modern contraceptive counselling should include a discussion about the potential risk of minor mood disturbances while on treatment.

5.3 Observational Studies

While none of these studies was able to address anything but subtle changes in affective symptoms, most often outside the clinical range, they cannot be used to estimate relatively rare outcomes of hormonal contraceptive use, like major depressive disorder. For such outcomes, large-scale observational studies are needed. Indeed, in 2016 Skovlund and collaborators published a large-scale prospective cohort study on the risk of developing depression in relation to hormonal contraceptive use [17]. The study was unique in the sense that it was the first longitudinal study in the field. The longitudinal design, in turn, has the advantage of avoiding the healthy user bias. The healthy user bias, or survivor bias, implies that women who develop mood problems while on hormonal contraception are much more inclined to discontinue, leaving a core of healthy, unaffected users. The healthy user bias is a common explanation why most cross-sectional studies report that hormonal contraception is associated with lower risks of depression and other psychiatric problems than non-use [12, 13, 24]. The study by Skovlund and colleagues used depression diagnoses, captured in specialized psychiatric care, and filled prescription for antidepressant drugs as outcomes, ultimately not only capturing major depression but also a range of anxiety disorders for which antidepressant drugs are also used. In essence, the authors found an increased relative risk of antidepressant treatment in oral combined contraceptive users of 1.2 (95% CI 1.22–1.25) and progestogen-only contraceptive users of 1.3 (95% CI 1.27–1.40), compared with non-users, which would translate to an absolute risk of antidepressant use of 0.9/100 hormonal contraceptive users [25]. The risk was most pronounced in adolescents, where the overall risk of filling an antidepressant prescription was 1.8 (95% CI 1.75–1.84) in oral combined users and 2.2 (95% CI 1.99–2.52) in progestogen-only contraceptive users. After the age of 25, the association between hormonal contraceptive use and antidepressant treatment was no longer evident, according to the authors, due to the healthy user bias [17]. The study received massive media coverage but has also met with criticism from the scientific community [6]. While impressive in numbers and design, the study has its own set of important biases, which were not adequately addressed, the most important being confounding by indication. Confounding by indication means that the very reason some women are using hormonal contraception could, in itself, be a risk factor for depressive or anxiety disorders. Besides contraception, many women use hormonal contraceptives for medical reasons, such as dysmenorrhea, endometriosis, polycystic ovary syndrome, acne, premenstrual syndrome, premenstrual dysphoric disorder, or heavy menstrual bleeding. Indeed, each of these conditions has been associated with reduced quality of life, depressed mood, anxiety symptoms, or depressive and anxiety disorders [26–34]. While the study by Skovlund adjusted for PCOS and endometriosis, common complaints in adolescents often include dysmenorrhea and acne. Confounding by indication may also be much more subtle than what is captured with these diagnoses, and there is some evidence in the study by Skovlund and colleagues that such mechanisms may have influenced the results. In comparison with levonorgestrel-containing pills, the risk of antidepressant treatment was higher in users of

cyproterone acetate-containing combined contraceptives, in users of pills containing natural estrogen and in patch or vaginal ring users. Some of these products have been linked to treatment of acne and heavy menstrual bleeding, whereas the vaginal ring and the patch may be prescribed more often to women who have problems with adherence to the daily pill intake. The latter indication is difficult to capture in any register and may mean many things. Indeed, women who use COC for reasons other than contraception are more likely than non-users to report depressive symptoms (OR 1.32, 95% CI 1.07–1.62).

Ultimately, there is no biological reason why the vaginal ring or the patch should confer an increased risk in relation to a levonorgestrel-containing pill, given the relatively similar, or even lower, serum concentrations of the steroid hormones [35, 36]. Further, these findings are at odds with randomized controlled trials comparing the ring or patch with oral contraceptives, showing either positive effects of the transdermal route or no difference between the regimens in depressive symptoms or well-being [37, 38].

Other researchers have also pointed to the absence of dose-response relationships as concerns the progestogen-only preparations, where the low-dose hormonal intrauterine device (IUD) was associated with somewhat higher risks than the systemic oral preparations [13]. Without biologically plausible explanations, the estimates from the observational studies must be questioned.

Similar findings were reported by a Swedish cohort study, investigating the association between hormonal contraceptives and psychotropic drug use (defined as filled prescription of antidepressants, benzodiazepines, atypical benzodiazepines, antihistamine anxiolytics, and melatonin), with a 1-year follow-up. The risk of psychotropic drug use was particularly noticeable in hormonal contraceptive users 12–14 years of age (or for combined oral pills 3.3 (95% CI 2.85–3.81)), followed by women 15–17 years of age (or for combined oral pills 1.52 (95% CI 1.41–1.64)). Already by age 18–20 years were the estimates minor (or combined oral pills 1.08 (95% CI 1.01–1.16)), and after the age of 20, the increased risk disappeared (or combined oral pills 0.94 (95% CI 0.89–1.00)). While the risk reduction in the adult women most likely is due to the healthy survivor bias, it may equally well be argued that most women who receive hormonal contraception in Sweden between the ages of 12 and 14 do so because of medical reasons, such as dysmenorrhea [39]. Further, these medical indications may not be captured in any of the registers (i.e., not being accessible for statistical adjustment), as diagnoses are established by physicians. In Sweden, the grand majority of contraceptive prescribers are midwives, and while they will not formally record any diagnoses, they will most likely respond to the menstrual problems young girls present with. The study by Zettermark and colleagues also found that non-oral hormonal contraceptives, i.e., the ring, the patch, and the implant, generally carried an increased risk in comparison with the oral preparations, regardless whether being combined or progestogen-only non-oral contraceptives. As an explanation to this finding, the authors themselves argued that women in need of methods that require less adherence may represent a more vulnerable group of women, thus suggesting some confounding by indication. Overall, the use of psychotropic medication was low in the population, with 3.7% of hormonal

contraceptives users filling a prescription for any of these drugs during the follow-up, while the corresponding number in the non-users was 2.5%, meaning that the absolute risks are low. These findings are in stark contrast with observational studies in teenagers, reporting no worsening of depressive symptoms or health-related quality of life upon initiation of hormonal contraceptives [40, 41].

Yet another large-scale study of mood effects from hormonal IUD was published recently, although again, the evidence must be regarded with caution. Using the UK general practice electronic medical records, the researchers demonstrated that use of the levonorgestrel IUD, as compared to copper IUDs, was associated with increased reporting of depression (assessed as filled prescription of antidepressants, HR 1.17, 95% CI 1.08–1.26), anxiety (HR 1.18, 95% CI 1.08–1.29), and sleep problems (HR 1.22, 95% CI 1.08–1.38) [18], whereas panic attacks and restlessness were unaffected. These effects were only evident in women with no previous psychiatric history, whereas women with such histories did not report increased mood problems with the hormonal IUD. At the same time, the authors acknowledged substantive differences in the baseline characteristics of the women who choose (or were advised) a hormonal or a copper IUD, making robust conclusions difficult.

Ultimately, the findings from these observational studies point to a small, albeit, increased risk of depression, or other mental problems from hormonal contraceptive use. The absolute risks for hormonal contraceptive-induced mental health problems, where antidepressant treatment is needed, are small and will not affect the great majority of hormonal contraceptive users. Importantly, confounding by indication is likely present in the observational studies, meaning that the estimates may be exaggerated, further reassuring the women in need of hormonal contraception.

5.4 What Women Are at Risk for Negative Effects of Hormonal Contraception?

Given the small, albeit significant, increased risk of hormonal contraceptive-induced mood symptoms, some mentioning of risk factors is warranted. Young age, psychiatric history, genetics, personality traits, interpersonal relationships, and socioeconomic factors are likely to contribute to the adverse mood symptoms experienced by some of the hormonal contraceptive users [16, 42–44], but overall, relatively little high-quality research has been conducted in this area.

The most obvious risk factor is if women claim they have prior experience of hormonal contraceptive-induced mood problems. In a small, randomized placebo-controlled trial, Gingnell and colleagues included 34 women with previous negative mood experience from hormonal contraceptives and randomized them to a levonorgestrel-containing pill or placebo for one treatment cycle [45]. When re-exposed to the combined hormonal contraceptive, the women experienced depressive mood and mood swings. However, only one third of these susceptible women experienced a clear-cut mood worsening during re-exposure. The findings suggest that self-reported contraceptive-induced mental health problems should be taken into account when counselling women. However, these reports do not infer a causal

relationship with the contraceptive, i.e., the mental health problems could have been caused by life stress or other reasons. If interested, women should not be discouraged to try hormonal contraceptives again.

Previous psychiatric history seems to play a role, although findings are not unanimous [12]. Two prospective trials found that depressed mood was associated with hormonal contraceptive-induced moodiness [46, 47], whereas two other prospective studies indicated that women with high levels of depressive symptoms at baseline were those most likely to benefit from the hormonal contraceptive [48, 49]. However, a sub-analysis of a randomized placebo-controlled trial indicated that much of the adverse mood effects noted in the trial were, in fact, driven by women with previous or ongoing mood or anxiety disorders [50].

5.5 Mood Symptoms Are Likely Caused by the Progestogen

It seems reasonable to assume that it is the progestogen of the hormonal contraceptive that causes the mood problems. Several lines of evidence substantiate this assumption. First, one of the randomized placebo-controlled trials indicated that mood worsening was only present in the intermenstrual phase, not in the premenstrual phase [14]. Thus, when the placebo users were exposed to high endogenous levels of progesterone during the luteal phase, no difference to the hormonal contraceptive users could be detected [14]. Secondly, the risk of mental health problems in observational studies was present in the progestogen-only users as well as in the combined hormonal contraceptive users [16, 42]. In addition, a long line of evidence suggests that progesterone has multiple negative effects on emotion processing [51], emotional circuits in the brain, including the amygdala [52], and on mood symptoms in women across the life span [53]. Further, the type of progestogen may play a role for the surfacing of symptoms during combined hormonal contraceptive use. A few direct head-to-head comparisons of mood effects have been conducted, and anti-androgenic progestogens seem to be more advantageous in this respect. Using a single-blind design, Kelly and colleagues compared EE 30 μg/drospirenone with EE 30 μg/levonorgestrel in 280 healthy females during seven treatment cycles. Using the Menstrual Distress Questionnaire (MDQ) as outcome, a greater reduction in negative affect was noted during the menstrual phase among women using the drospirenone-containing pill [54]. Sangthawan and colleagues performed an open-label, but randomized, study comparing EE 30 μg/drospirenone with EE 30 μg/levonorgestrel in 99 women. At completion, negative affect scores in the premenstrual phase were lower in women randomized to the drospirenone-containing pill. The difference in negative affect was mainly driven by changes in anxiety levels, irritability, and depressed mood [55].

Using the same outcome measure, Bruni and colleagues found no difference in overall emotional well-being between EE 30 μg/desogestrel and mono- or triphasic EE 30 μg/gestodene-containing pills among the 1721 women who completed the trial. However, for individual MDQ scores, the EE 30 μg/desogestrel compound was more favorable, for instance, “lack of control” [56]. Winkler and co-workers

compared EE 20 μg/desogestrel and EE 20 μg/levonorgestrel in 788 women. The overall mean Profile of Mood States (POMS) change from baseline was greater in the EE 20 μg/desogestrel than in the EE 20 μg/levonorgestrel group, suggesting a slightly greater improvement in quality of life in the former group [57].

5.6 Final Conclusions

At present there is sufficient evidence to conclude that hormonal contraceptives are associated with small changes in anxiety, irritability, and well-being. However, the proportion of women who develop these mood symptoms are out-numbered by the women who are unaffected or even improved, exemplified by the very small effect sizes noted in the placebo-controlled trials.

While the mean effect sizes are small, for some women the changes in mood may be clinically relevant or even represent the final push to a mental health problem in need of psychotropic treatment. Observational studies have provided some evidence that hormonal contraceptive use may lead to mental health problems in need of treatment. The absolute risk for this outcome is low, in the range of 1/100 hormonal contraceptive users. However, because of residual confounding in the observational studies, these estimates are likely overestimated.

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Part II

Female Contraceptives

Non-hormonal Contraception

6

Juan M. Acuna

NOTE: These red notes are just a place holders screen shots. A ppt slide of actual jpegs are provided with better resolution. This is a publicly available figure from CDC, but for all other figures and pictures, I have permission for inclusion in the chapter. For the CDC, they just require credit (Fig. 6.1).

6.1 Male Condoms

Male condoms act by providing a physical barrier to the spermatozoa, preventing the passage from the ejaculate to the vagina. Male condoms are the quintessential barrier method due to the combined popularity and frequency of use. This method is one of the most common methods of contraception due to the great availability and the increased popularity probably motivated by or associated with the prevention of sexually transmitted infections (STIs) globally. Change of attitudes towards the use of condoms and availability were recently reviewed finding global availability and positive behavioral changes for condom use [1].

The history of condom use is widely known, albeit full of confusing anecdotes, tracing the design into more than 12 centuries before Christ, with debate on whether Egypt was the first place to use them and whether their use was for the pure purpose of contraception [2, 3]. During the renaissance better and more accurate descriptions of condoms can be found, being the description by the anatomist Gabriele Falloppio in the mid-1500s one of the first accurate and uncontested ones available.

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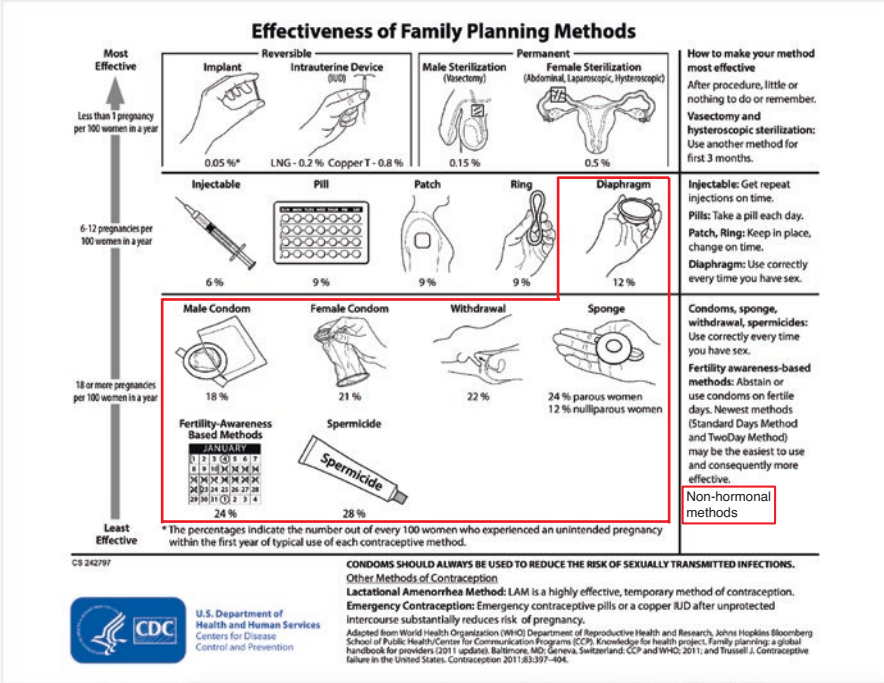

Fig. 6.1 Effectiveness of contraception methods with emphasis (red box) on non-hormonal methods of contraception

Although descriptions of condoms from different biological tissues (such as animal intestines, membranes) are available between then and the 1900s, the first attempt to a more effective male condom came around the mid-1900s when rubber compounds became popular and available throughout. The use of rubber in condoms is the origin to the name "rubbers" for male condoms.

Despite the increased effectiveness provided by the use of rubber, the main battle for its use was lost at the time due to the decreased sensation associated with the thickness of the condoms. Nonetheless, condoms were at the time (early 1900s) highly promoted especially because of the dramatic increase in STIs. Around the 1920s, latex was invented, and it was a game changer in the fabrication of condoms: latex condoms were thinner, more effective, easy to make condoms. Latex continues to be one of the most common, by far, elements to make condoms with emphasis placed on quality testing as mandated by the FDA since the mid-1970s, and thinness, to improve feeling and temperature transmission (improving use satisfaction, one main hurdle for condom use) [4, 5].

In the 1990s, polyurethane and polyisoprene were introduced as synthetic materials to elaborate condoms. Polyisoprene is similar to latex and a bit thicker than polyurethane. These condoms promote their use as an alternative to latex condoms by being less allergenic and producing improved flexibility and heat conduction, thus improving feeling during coitus. They can also be used with any type of

commonly available lubricants as opposed to latex condoms which should be used with water-based or silicone-based lubricants only. On the down side, they are more expensive than latex condoms. A third type of condoms, rare in its use, are the natural membrane (lamb intestine) condoms. The most important difference is that these last ones do not provide adequate protection against STIs [6, 7].

Condoms come in different shapes, sizes, and types. They can be obtained in two sizes, with or without reservoir at the end, and in many colors, textures, and creative designs. The effectiveness of the condom, at the end, relies more on the correct use than in any other characteristic. A common misconception is that condoms with spermicides are more effective than those that are just lubricated. Since the 1980s, evidence has failed to show that with adequate use, such statement is true. Furthermore, there is evidence (discussed later) that spermicides may increase the likelihood of STIs due to irritation of the vagina. Guidelines are available for a comprehensive review for appropriate counseling on the topic especially for young potential users [5, 8] (CDC Condom effectiveness https://www.cdc.gov/condomeffectiveness/index.html. Accessed April 7, 2020) (Fig. 6.2).

Recommendations and Counseling

- Condoms require commitment and are user-dependent methods. Users should be very aware of these facts, and the facts associated with condom use need to be clearly explained to patients, especially if they are young and inexperienced.
- Condoms are quite safe if properly used (up to 98% effective).
- Condoms of major, trusted brands are tested. The user should not try to test the condom by inflating it or stretching it before intercourse.
- Condoms must be placed in the penis when erect and before intercourse.
- The condom should roll down the penis shaft easily. Some inexperienced users may try to roll it inverted (the rolled ring to the inside as opposed to the outside). This happens if the condom reservoir has been pushed in inadvertently and may cause tear of the condom while trying to vehemently unroll it down.
- The condom should be checked once in place to assure a snuggle fit and a complete length coverage of the penis shaft.
- If STIs are a concern, no skin-to-skin or mucosal-to-skin contact of any type (oral, anal, or otherwise) should be allowed before the condom is in place.
- If a lubricant is desired, latex condoms should only be lubricated with water or silicone-based compounds.
- After ejaculation, the base of the condom must be held firmly, especially if time is allowed between ejaculation and withdraw, so that the condom remains in the penis.
- The condom must be checked for integrity after the coitus and removal.
- Thorough cleaning of the penis and a new condom must be done if a second, immediate intercourse is expected to happen.
- Condom use as part of the dual method protection should be discussed and encouraged systematically.
- Condom can/should be recommended for anal and oral sex, if STI prevention is also desirable.

Fig. 6.2 The male and FC2 female condoms

Uses and Benefits

- Pregnancy prevention is the main desired benefit for condom use. Up to 98% prevention is possible if used perfectly. However, with current use, the effectiveness decreases to the mid 80% (13–18% failure rate for couples using the method for a year, with regular sexual activity).
- Prevention of STIs, especially HIV, is a major added benefit of the condoms, being the first preferred method from this perspective, if abstinence is not considered. It is even recommended for STI prevention during oral and anal sex.
- It is one of the most cost-effective methods of contraception, is inexpensive (may times it can be obtained free of any charge in different organizations and settings), and can be obtained by most as over-the-counter product.
- If they are not medicated with spermicides, condoms have very few side effects, very much limited to the potential and relatively uncommon latex allergies. Even in these cases, condoms of synthetic materials may be used.

- Condoms may be used as part of sexual games, foreplay, and other sexual practices to increase couple acceptability. Many condom types (scented, colorful, specially shaped, etc.) are available for these purposes.
- Great and discrete portability.

Concerns

- The main concern for condom use is the lack of motivation or insufficient knowledge, highly associated with method failure for the prevention of pregnancy.
- Decreased sexual sensation is one of the most common complaints especially with thicker latex condoms. Condoms that are thinner or made out of synthetic materials conduct heat better, decreasing the problem.
- Latex allergy (for latex condoms). Consider the recommendation, if the couple/user is motivated of synthetic condoms.
- Because the method is offered over the counter, some potential users may find it difficult or embarrassing to buy them openly.
- Some users (both males and females) may find it difficult to talk to new couples or sex partners about condom use. Empowerment of both men and women is important so, in case of new sex partners they can demand/request their partner the use of condoms.
- Explore erectile dysfunction as a flaccid penis may facilitate condom failure.

6.2 Vaginal Barrier Methods: Female Condoms, Cervical Cap, Diaphragm, and Dental Dam

All the above-mentioned methods of contraception are used by the woman, thus having the importance of being female-initiated methods. As the male condom, they block the sperm passage to upper genital track organs and provide good (female condom) to some (others) protection against STIs [6, 9]. Although the dental dam is not a contraceptive method, it is included in this section to recognize its role in the prevention of STIs during oral sex.

The main difference between the female condom and the cervical cap or diaphragm is that the cervical cap and the diaphragm only cover part of the vagina, while the female condom covers all of it, thus providing better protection against STIs if used properly.

The female condom was designed in the mid-1980s, as an alternative for the male-driven use of the male condom. Several models exist, one of the most popular one being the FC2, especially in the USA, together with its predecessor the FC1. FC2 (Fig. 6.2) is made out of nitrile synthetic latex while FC1 was made out of polyurethane. Other models include the women's condom (polyurethane), VA w.o.w condom (latex), and Cupid condom (latex), available in other countries in the world. All models follow the same principle: an outer ring, larger than the inner ring, designed to cover the outer vaginal and vulvar structures (so all of them become quite evident when used) and an inner ring, smaller in diameter, designed to fit the upper vagina. Those compared in trials perform similarly [10]. This inner ring,

which lies free within the condom, is used, collapsing it, to guide the introduction of the condom into place and to hold it in place in intercourse. Even though it looks "awkward" to most users the first time (seems too big, too complicated, too bulky) the fact that it is under the woman control and that it can be placed in site hours before intercourse has an attractive for the users [11, 12].

Empowering women for the use of the female condom is probably needed. Although the use has increased globally, it is only a small fraction compared to the distribution and use of the male condom.

Recommendations and Counseling

- Female condoms, as with male condoms, require commitment and are user-dependent methods. Special female training and commitment is required.
- Female condoms are also quite safe if properly used (up to 96% effective). However, their effectiveness decreases to about 80% with typical use. Because it is more complicated to use than a male condom, rupture, slippage, and other user-dependent problems (incorrect positioning, torsion, invagination) are more frequent especially in the first-time users and during the first times it is used.
- Condoms must be placed in the vagina before intercourse and placement can be complicated. In fact, it is very often reported by users as such.
- The condom should be held with both hands, after the woman adopts a position for introduction, which should be comfortable for her. Squatting, with one leg up, and lying on their back, with legs flexed, are some of the most common positions. Once in an appropriate position, the inner (smaller) ring is compressed with one hand, while the other hand separates the labia. The ring is introduced as far as it can go. Then, the index finger of either hand is used to further the introduction of the condom (inner ring) into the vaginal canal, making sure that the condom is not twisted and being careful that the nails (if long, sharp, or with jewelry) do not damage the condom.
- Women may introduce the condom up to 8 h before intercourse.
- During intercourse the penis should be guided into the vaginal entrance so it is sure that it enters the condom and not that it goes through the side.
- As with the male condom, if STIs are a concern, no skin-to-skin or mucosal-to-skin contact of any type (oral, anal, or otherwise) should be allowed before the condom is in place.
- Lubricants can be used with most female condoms, with the same precautions of oily-based lubricants for those few that are latex-based (VA w.o.w condom, mostly available in Asia and Africa but also distributed in Europe CE).
- After ejaculation, the outer ring of the condom must be held firmly and twisted three turns to avoid semen spillage.
- The condom must be checked for integrity after the coitus and removal.
- Thorough cleaning must be done, and a new condom must be used if a second, immediate intercourse is expected to happen.
- Female condom use as part of a dual method protection should always be discussed and encouraged systematically.

Uses and Benefits

- As with any other contraceptive, pregnancy prevention is the main desired benefit for female condom use. The level of effectiveness is within that of the male condom, with up to 96% of pregnancy prevention possible for perfect use and 80% for typical use.
- Prevention of STIs is very good.
- No side effects reported.
- The use of the female condom is more complex than the male condom. It is also a bit more expensive, and typically it is not distributed for free as frequently as the male condom is.
- Female condoms may also be used as part of sexual games, foreplay, and other sexual practices to increase couple acceptability. Some couples find it more attractive from this perspective than male condoms.
- Great and discrete portability may be used hours before coitus providing the advantage over the male condom of no foreplay interruption.
- Can be used during menses.
- Because penial guidance is recommended, and because of the inner ring stimulus, the coitus has been reported as more pleasurable by some.
- As it is common with male condoms, those made out of nitrile are best heat conductors (not the latex ones) so the feeling during the coitus is better.
- It is advantageous to use it in case of erectile dysfunction as a potential alternative to male condom.

Concerns

- As with most barrier methods, lack of motivation and insufficient knowledge or experience are highly associated with method failure for the prevention of pregnancy.
- Female condom is a complex method to master. Some women or couples do not get used to it until 5–20 uses. This may be problematic for many and may be a reason for failure, and incorrect placement may be associated with irritation, discomfort, pinching, or failure.
- Latex allergy (for latex condoms).
- Because the design includes a large ring outside of the vagina, some users may find it unattractive.
- Some users may find it difficult to talk to their new couple about the condom, and they may feel embarrassed especially if the male partner does not know or is not aware of the female condom use. Women should be empowered to lead these conversations with their male partners.
- Many couples, especially for polyurethane female condoms (much less for nitrile and even less for latex), report noises during intercourse.
- In some countries, it is only available with prescription.

6.3 Diaphragms, Contoured Diaphragms, and Cervical Caps

All these barrier methods are similar in that they are devices that are placed deep into the vaginal canal, before intercourse, are used together with spermicidal compounds, and are reusable, as opposed to both female and male condoms [5, 13]. Their use is not as common as the male and female condoms. It may partially be because of the complex education required by clinicians to assure proper fitting (sized diaphragms) or adequate placement (all of these methods) through clinical consultation with an expert clinician. These time-consuming practices, in today's hectic and overly time-stretched clinical environments, may be hindering the use of perfectly adequate methods suitable for specific patients after counseling.

Fitted diaphragms are available in 5 mm increments from 60 to 90 mm, with a normal distribution of sizes, the most commonly used size being the 75 mm one. The sized diaphragms are made from different materials (latex, silicone) so attention should be placed to oil-based lubricants for those that are latex-made. They have wide seals, arching springs, coil springs, and flat springs. The most important point about diaphragms today is that they are not widely or easily available and most need to be ordered directly from the manufacturer or require prescription.

The contoured diaphragm has replaced in many instances the use of the fitted diaphragms. Known as the Caya diaphragm (Figs. 6.3 and 6.4), this device does not come in different sizes and fits users that represent most of the previous users of sized 65–85 mm. It has the advantage of suiting a wider range of women without a fitting consultation (thus making it less strenuous for the clinician and busy schedules) but just part of the regular consultation and exam where an adequate insertion technique and positioning are checked. An added advantage over the other similar devices is the addition of a second, inverted (contrasted with the larger cervical dome) smaller dome that is used to facilitate removal by allowing the user's index finger to be lodged there for easier retrieval.

Finally, the cervical cap is a similar device designed to fit snuggly onto the cervix, up in the vaginal canal. It has a distinct separation between the cap and the rim, making it look as a hat. It remains in place by a vacuum action over the cervix, and

Fig. 6.3 The Caya Diaphragm

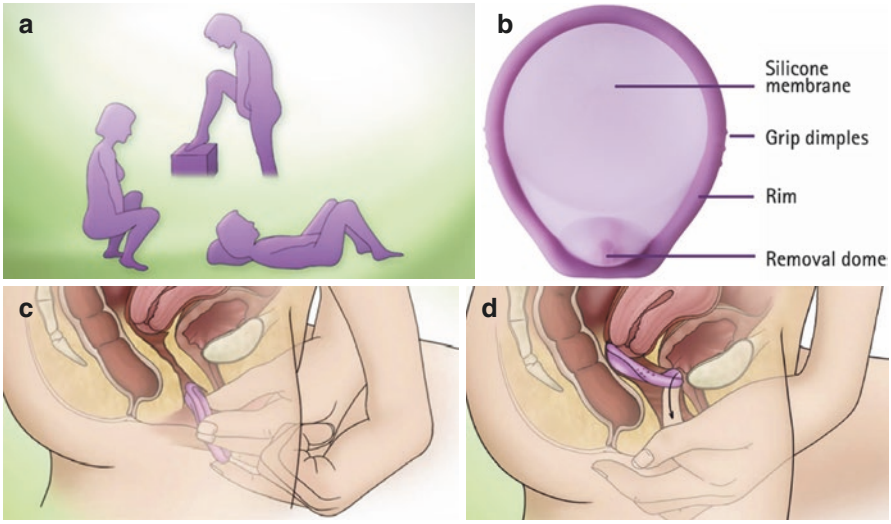

Fig. 6.4 The Caya contour diaphragm. (**a**). Positions usually adopted for easy insertion of the Caya; (**b**) elements of the Caya; (**c**) insertion of the Caya; (**d**) withdrawal of the Caya, using the removal dome

as the diaphragm, both the fitted and Caya diaphragms, require the use of spermicide to achieve an acceptable level of effectiveness. The most common cervical cap available (and the only one available in many countries such as the USA) is the FemCap [14]. This device is made of silicone (suitable for people with latex allergies) and it resembles a miter or mitre (a Catholic ceremonial religious hat), with a dome that fits the cervix and an everted rim with a longer side that snugs against the vaginal walls. The shorter side of the rim is the anterior side. The cap has, on its vaginal side, an arch that facilitates retrieval. Difficult retrieval was one of the most common complaints of users for older types of cervical caps. As with the previous two methods, discomfort during coitus is not uncommonly reported. A relative advantage of the cervical cap over the other two vaginal barrier methods is the possibility to leave it longer in the vagina. However, it is not recommended that the time is longer than 36 h. Finally, cervical caps may be obtained in three sizes for nulliparous, multiparous (no vaginal births), and multiparous (vaginal births). Fitting should be assisted by a competent health practitioner, but it is much easier with the other methods.

Recommendations and Counseling

- Cervical cap, diaphragms, and contoured diaphragms should be recommended together with spermicides. Spermicides should be applied not more than 2 h before coitus.
- All these devices should be left in place after coitus for at least 6 h.
- These methods require ideally a fitting and counseling process that should be done by a competent health practitioner. However, the cap is easier to fit than the other two.

- A prescription is required in many countries and availability is limited. Some methods must be ordered directly from manufacturers.
- All methods share similar levels of effectiveness being the diaphragm slightly better and the cervical cap the least effective (12% and 15% or more, respectively).
- Insertion is done by the user (or her partner, although uncommon) by adopting a comfortable position squatting, with one leg up, or laying down on their back.
- The device should be filled with about two teaspoons of spermicide before insertion.
- Labia are separated with one hand while exploring the position of the cervix with either one or two fingers of the opposite hand.
- The rim of the device is squeezed to facilitate insertion. Both the contoured diaphragm and the Caya cervical cap have a correct direction (anterior and posterior sides) that must be acknowledged.
- The woman then has to introduce the device posteriorly and then anteriorly (in an arch form) to achieve correct cervical placement. Checking that the cervix is completely covered should be done after placement, and be aware of correctly counseling women with a severely retroverted uterus.
- Although insertion is easily done during arousal, the use of lubricants to facilitate the insertion is not recommended (especially with diaphragms) as holding and squeezing the device is more difficult and misplacement is more common.

Uses and Benefits

- Pregnancy prevention is the most desired outcome and some STI prevention is achieved, although not at the level of male or female condoms.
- Used for multiple coitus, placement before sexual acts and prolonged use are clear advantages for many users.
- Women empowerment to define control over their reproductive life, independently, is considered a positive characteristic of these methods.
- Reusable for even long periods of time and easy to clean (boiling is not necessary and may decrease effectiveness of these devices).
- No allergies reported for non-latex devices.

Concerns

- These methods require user training that might be long in many instances, requiring a prolonged period of practice before mastering their use.
- Require clinical examination and possibly a prescription.
- Among the least effective methods for contraception.
- Protection against STIs is not as good as with male or female condoms.
- Some may produce pain or discomfort during coitus.
- May be difficult to remove, especially in unexperienced users.
- Will not work in a substantial number of patients, many times due to anatomical incompatibility (10–20% of potential users).
- Should not be recommended with some other methods (such as IUDs or IUSs).

6.4 Spermicides

Spermicides are substances that kill or inhibit motility of sperm after ejaculation. Several substances are credited with these effects; however, for practical purposes, nonoxynol-9 (N-9) is the only widely available and widely used spermicide in the global market [15]. Other spermicides such as phenylmercury acetate, octoxynol-9, benzalkonium chloride, mephengol, C31G (a mixture of alkyl dimethyl glycine and dimethyl amine oxide is not available commercially), propranolol, and lactic acid compounds (such as Amphora) are or have been used without substantial improvement of effectiveness [16].

The overall effectiveness of spermicides as an isolated form of contraception is among the lowest of all methods (overall effectiveness lower than 80% for most reports for typical use and around 10–12% for perfect use) although some subgroups of women (older but with lesser number of pregnancies) are reported to have better success rates (5% PI). Typically, spermicides are used with other methods or contraception (such as condoms or other vaginal barrier methods or during early use of oral contraceptives or IUDs) and not recommended as the only method to be used. Despite the low effectiveness, spermicides are relatively popular, being used, alone, or on combination with other barrier methods, by around 15% or more of women in the USA that use contraception [17, 18].

The mechanism of action is that of cytotoxicity for the sperm, for most of the above, except for lactic acid derivatives. For these last set of compounds, the ability to maintain a low vaginal pH (at levels less than 5) for a prolonged period of time after ejaculation (semen has a buffering capacity that allows sperm optimal survival) produces a dramatic reduction in sperm mobility with subsequent death. In themselves, these compounds have no cytotoxic activity, thus increasing tolerance and decreasing (at least theoretically) the possibility of vaginal irritation, often associated with an increased risk for HIV and other STI infection.

Among spermicidal use, the sponge is a different device as it is perceived by many users (and might be also true for some inexperienced healthcare providers) to provide some sort of added physical barrier plus the spermicidal effect. However, pregnancy rates are comparable to other spermicides, being still among the lowest in the contraceptive device class. Discontinuation rates and adverse secondary effects, such as allergic reactions, are more common with the sponge than with other barrier methods [19].

Recommendations and Counseling

- Frequently used with other methods due to easiness of use after clinician's explanation.
- Best for women with few partners (ideally one only) and sporadic coitus.
- These compounds should be used between 15 and 25 min (suppositories and films need to melt) before coitus. Reapplication should be done if the time between application and coitus exceeds 30 min.

- The compounds must be placed as deep as possible into the vagina.
- Most products have specific instructions for use. However, although revised, they have been deemed complex and difficult to understand thus requiring clarifications and assurances by an experienced clinician.
- As with the diaphragms and cervical caps, the sponge must be left in place 6 h after coitus minimum.

Uses and Benefits
- Women controlled.
- Inexpensive and available over the counter.
- Relatively easy access and use, high portability, and provide some lubrication.
- Immediate effectiveness.
- Many presentations available (tablets, films, foams, sponge, jelly) suit different user's preferences.
- Some compounds have limited antibacterial and some antiviral activity.
- Better recommended for low parity, older women, with occasional intercourses, who present the best effectiveness (around 5% of pregnancy rates).
- Additional doses must be used if there are multiple intercourses.

Concerns
- The least effective of contraceptive methods.
- Not recommended as single contraceptive method.
- For most women it is difficult to assess the exact placement of the compound in the vagina, some leaving them too close to the introitus if not counseled specifically.
- May produce irritation (or cell wall weakening in the vaginal mucosal cells) associated with an increased risk for contracting HIV especially among those women with multiple intercourses and multiple partners.
- Reported as messy by users (with the possible exception of the sponge).
- If oral sex is a common practice, taste is an issue.
- Because they are messy, a tendency to douche after coitus is possible. Counseling to avoid vaginal douches 6 h after intercourse should be specifically stressed.

6.5 Fertility Awareness Methods (or Fertility Awareness-Based Methods)

Fertility awareness-based methods (FAM, FABM, or also, and controversially, part of the so-called natural contraception methods) [5, 20, 21] for family planning are a series of methods and techniques that rely on the identification, recording, analysis, and interpretation of signs and symptoms associated with ovulation that occur during the menstrual cycle, without the use of medications or devices [22]. These methods are important for specific groups of women that do not or cannot use any other form of contraception and still want to avoid pregnancy while keeping the

possibility to continue having intercourse (as opposed to abstinence). Because of specific counseling and extensive education are needed for these methods, and because much of the topics are related to the biological events of the menstrual cycle as they relate to ovulation, a short explanation of such events will be provided as part of the revision of FABMs.

Failure rates for these methods are high [21, 23], reported to be as high as 27% for typical use to 1% for perfect use. What is noticeable is the wide range of failure rates, wider than probably any other method, evidence of the high user dependence. This gap has nonetheless been reported as much smaller, with much better effectiveness rate for a newer and controversial subset of these methods (discussed further below), the digital FABMs, specifically the "contraceptive or cycle-monitoring apps." [24–27]

Needless to stress that these methods all require a much more detailed than usual counseling and education to the couple (but specifically to the patient) provided by a highly trained clinician, with specific explanation of biological changes, signs, and accurate measurement and interpretation.

The menstruation, menstrual cycle, and associated topics are frequently misconceived by most patients and some health providers. Information is usually incomplete but misinformation about them is very frequent among women, in general, and patients and many healthcare providers in particular. It is this misinformation that is the most damaging to the proper use of natural contraceptive methods, but especially to FABMs. This is the reason behind including a section in this chapter on the most important pointers for counseling, from the biological perspective, about the menses and the menstrual cycle.

The menstrual cycle has three distinct phases: the follicular phase, the ovulation phase, and the luteal phase. The quintessential event in the cycle, at least from our current perspective, is the ovulation. However, the most important predictor for fertile days in a given cycle (except when using clinical, sophisticated diagnostic tests) is the regularity of the previous cycles. For regular cycling women, prediction of fertile days is mostly based on assessing the possible time of ovulation and calculating fertile days based on sperm and ovum survival time. In women with irregular cycles, this estimation fails, for the most part, or will yield a very large amount of days labeled as "fertile" when indeed they could have been infertile. We will detail this aspect when reviewing the methods themselves.

Ovulation occurs, in most cases of regular 28-day cycles, at around day 14–15. From our perspective, contraception, this means that the woman becomes susceptible to fertilization by a sperm. Because the sperm may live up to 5–6 days in the woman's genital track, and because the ovum life span is about 24 h (or 1 day), we consider that any particular woman, in usual conditions is fertile about 6 days per cycle. Although this survival is a probabilistic estimate (most sperm would be dead after 36 h and only 1% will survive more than 5 days), it is very widely accepted to manage these numbers for the estimation of the fertile window [28] (Fig. 6.5).

A second important aspect for counseling is the time of ovulation itself, as it relates to the first day of the menses, which we consider the first day of the menstrual cycle as well. The exact determination of ovulation, without any diagnostic

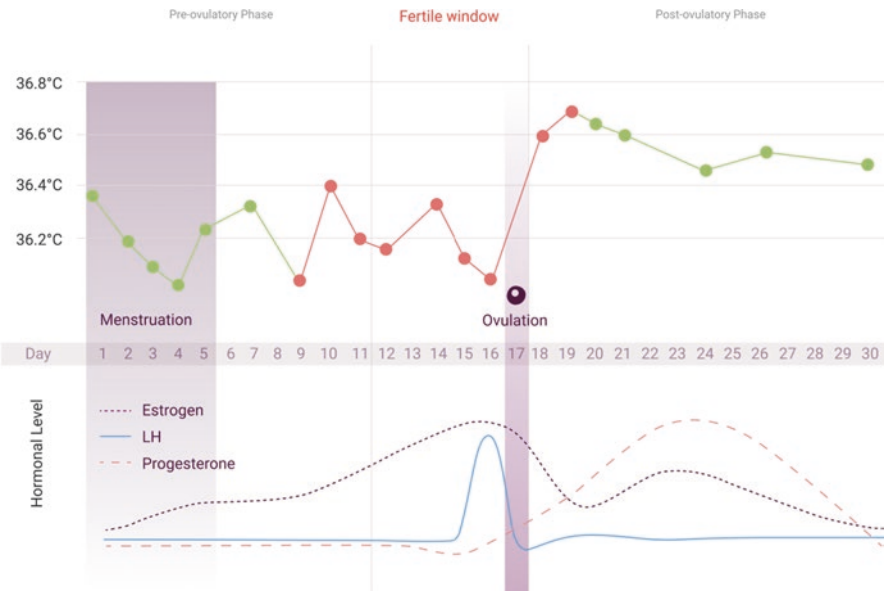

Fig. 6.5 Temperature and hormonal changes during the menstrusal cycle

tests such as ultrasound or hormonal measurement, is difficult. The reason behind this is that the time of the menses (or first day of the cycle) depends on the previous cycle's luteal phase. In other words, just before the ovulation occurs for a particular cycle, the granulosa cells in the ovary change (become vacuolated, yellow, thus the name corpus luteum) to prepare all organs for a potential pregnancy, if the ovum would become fertilized.

The corpus luteum starts, after ovulation occurs, an almost immediate production of both estradiol and progesterone maintained during luteal phase, with a peak in day 21–22. Then, the corpus luteum, in absence of fertilization and implantation, regresses, the hormones decrease, and the new menses come, after estradiol and progesterone reach levels of near zero. This process after ovulation is very constant; thus as long as ovulation happens, the luteal phase does not change very much. However, the follicular phase (the first phase of the cycle) is of a different nature. During this phase, the recruitment of follicles happens, and the selection of the ovulatory follicle among those recruited is complex and dependent on multiple circumstances. Some of these circumstances are even triggered during the previous cycle. Many of these mechanisms of recruitment and selection are still unknown. Nonetheless, as interesting as the follicular phase may be, from the perspective of contraception and fertility the point is the same: ovulation can only be known to have happened after the new menses happen and prediction of ovulation is difficult to do during the follicular phase. For this first part, in summary, and mainly for counseling purposes:

1. Regular cycles preceding any cycle are the best way to predict fertile days during that cycle.
2. Ovulation timing during a cycle is uncertain if estimated during the follicular phase, especially with a history of irregular cycles.
3. The luteal phase is constant and we can estimate the day of the previous cycle's ovulation based on the first day of the menstrual period of the subsequent cycle.
4. The sperm has a life span of up to 5–6 days after deposited into the female vagina.
5. The ovum has 24–36 h of life, once ovulated.
6. The follicular phase is variable and accounts for most of the cycle variability in a given woman.
7. Ovulation is difficult to predict.
8. Any woman has a 6-day fertility window per cycle, but the timing of such window is difficult to do, unless a previous history of regular cycles, best between 26 and 32 days.

At this point in the counseling process, women may be discouraged by uncertainty about ovulation time and the time window where the fertile days will happen after the last menses. The second aspect to be communicated is that during the follicular phase, several hormonal events are paired with signs and symptoms that may be used to predict the best time for the ovulation to occur. During the menstrual cycle, the cervix of the woman changes in consistency, position, and presence of secretions (cervical mucus). Those changes, with the exception of production of secretions that change characteristics near to ovulation, are difficult to evaluate for most women and require very rarely found motivation and detailed education making them very impractical for large clinics and standard clinical practice of contraception. However, some clinics do build group sessions, special interest groups, and targeted clinics for women highly motivated, who are typically very successful with these methods.

Cervical secretions are, by far, the easiest symptom to evaluate albeit still difficult for most women [20, 29]. It requires however an almost perfect vaginal condition so presence of inflammatory processes of the cervix, leukorrhea, or other vaginal or cervical pathologies may impede accurate assessment of cervical secretions. In any case, during approximately the first half of the follicular phase, the cervical mucus is scant (frequently referred to as "dry days") and of a trabecular, molecular microstructure that on macroscopic examination translates into no secretions and a thick mucus. During the second half, after estradiol starts rising, the mucus adopts a linear structure and becomes abundant ("wet days"). It may be detected at the examination, becomes translucid, and elongates (such as egg white) with ease. Maximum clarity and elongation are achieved around ovulation. Because of the effect of estrogen in the cervix, changes in the mucus also include changes in electrolytic (sodium chloride) composition that may cause the phenomenon called "ferning." This test may also be used by some motivated women (it requires a low power microscope) to determine the possibility of ovulation.

The last element usually evaluated by women in the practice of FABM is the basal body temperature (BBT). During the menstrual cycle, due to the thermogenic properties of progesterone influencing changes in the thermal control centers in the central nervous system, the BBT increases by about a half of a degree centigrade (0.6 ± 0.2 °C) after ovulation. This change, although subtle, may be distinctly identified if the correct technique is used. First, a specific thermometer sensitive enough to measure tenths of a degree is needed. Some specific thermometers for this purpose are available; however, nowadays most electronic thermometers should have this capability. Second, the temperature should be measured in true basal conditions: immediately after waking up but before any substantial movement or activity is undertaken. This may be complex to master and routinize; however the importance of such conditions needs to be specifically stressed out to the woman when explaining the methods. Finally, the daily record should be entered into a chart and the overall trend analyzed later. Specific examples of such charts are widely available in the internet for use.

All of these signs and symptoms are used to either predict ovulation (especially in the management of infertile patients) or to predict the fertile days (which, of course, are related but because of the different perspective are not necessarily the same) during a cycle [30]. Due to the need for specific, thorough training and due to the many factors that may influence their accuracy as predictors, their sensitivity (estimation of ovulation and estimation of fertile days) from either perspective has not been very good. The use of all of them combined provides the best assurance that the diagnosis of either ovulation or a fertile day is accurately done. With the recent appearance of digital platforms used by literally millions of women, and the analysis of their published data, we can conclude that the most important factor to be evaluated and that probably accounts for most of the accurate prediction of fertile days is the cycle stability and regularity. Thus, any one of these methods, albeit feasible to use in irregular cycles women, is mostly recommended for those women with cycles between 26 and 32 days of duration whose ovulation is fairly predictable [31].

This next section will describe the most popular and well-known methods. These methods were designed and are described and used to, in essence:

- Identify as accurately as possible the fertile and the non-fertile days and rely on periodic abstinence or another form of contraception.
- Recommend that a particular day is suitable for unprotected coitus according to the labeling of such day as a non-fertile day.
- Recommend the use of a second method of contraception (most commonly a barrier method) if coitus is to happen during a fertile day and no abstinence is possible or desired.

6.5.1 Calendar-Based Methods

These methods rely on the cumulative information that previous cycles provide with respect to fertile days in the current cycle being predicted [5, 32, 33]. In essence, the longer the time of the observations used to calculate the current cycle probabilities,

the better; and the more stable the cycles, the better, being ideal a woman having cycles neither shorter than 26 nor longer than 32 days. There are two common methods: calendar method and the standard days method.

The *calendar method* relies in a relatively simple mathematical analysis. The first step is to identify the shortest and longest cycles reported. Then, subtract 18 days from the shortest and 11 days from the longest cycles, respectively. This information (two numbers) will provide the first and last fertile days of the current cycle. Take the two examples, an ideal woman and a woman with irregular cycles. For the regular women, with cycles of 26 – 32 days for a year, the fertile window would be between day 8 (26 – 18 = 8) and day 21 (32 – 11 = 21). That would be a 13-day window, very long, but manageable for most young couples. For the second case, a non-ideal woman with irregular cycles, if the year-long monitoring of the cycles of a woman provided cycle-lengths between 22 and 40 days, the first day of the fertile window for the current cycle is day 4 (22 – 18) and the last day is day 29 (40 – 11). This is a 25-day-long window almost impossible to manage. These examples point towards the selection of very specific women and the level of uncertainty and problems produced by irregular cycles.

The second method, the *Standard Days* method, selects as a prerequisite very regular women (as before, cycles between 26 and 32 days) and provides, based on the same calculations, a 12-day window of fertile days where no protected intercourse should happen. It uses a string of beads (a wristband named *CycleBeads*) where a red bead marks the first days of the menses, and then the fertile window is a string of white beads. The colored beads after the menses bead and after the fertile, white-bead window mark the "safe" days. A darker, often black bead is placed seven beads after the white series of beads to mark a "short" cycle. If the menses does not start right before the red bead, it marks a "long" cycle. The users are instructed that if the menses happen before the first black bead or has not happen after reaching the red bead, the method is not to be trusted. It is, however, a retrospective assessment. There are different versions of the apparatus, a wearable (similar to a wristband), an analog (a round plate similar to those that are used to carry contraceptive pills), and a digital version (app) of the method using the same principle. Controversies on the effectiveness of the method have recently arisen with the concern of global promotion and widespread use especially in developing countries [34]. The conclusion is that effectiveness may be lower than previously estimated for typical use, supporting further promotion of combined or more effective contraception. Multiple use of contraceptive methods is relatively common among users of any type of non-hormonal contraception (16.5%) at least in the USA [24].

6.5.2 Cervical Secretions Monitoring Methods

These methods rely on the woman's ability to identify the changes in the characteristics of the cervical mucus. These changes were described since the eighteenth century and long have they been, since the middle of the nineteenth century, recognized as linked to fertility. The couple John and Evelyn Billings described it in the mid-1950s and linked it to contraception being recognized throughout the world for

their contribution. Thus, their name identifying the method since those days. The second method, an abridged, simplified version, is called the *two-day method*. These methods are not compatible with the use of hormonal preparations and they modify the cervical mucus characteristics.

The Billings method relies on daily observation of the vaginal secretion on a daily basis to identify the characteristics that are related to the hormonal changes, especially the estradiol production that precedes ovulation. Appearance (thick, cloudy, clear, transparent), feeling (dry, damp, wet), and stretchiness (not present, intermediate, maximum/peak) are the characteristics usually described for the mucus evaluation [20]. Below is the description of the examination and the test to determine them, as described for all methods using cervical mucus characteristics. Women notate these characteristics as well as other notations for the entire cycle. Some model charts are widely available for this purpose in the open web.

The *two-day method* compares the appearance of secretions/cervical mucus over two consecutive days and compares a change from absence to presence. Any day with secretions compared with absence the previous day and consecutive days are considered fertile days [35, 36].

6.5.3 Basal Body Temperature (BBT)

As explained before, the thermogenic nature of progesterone triggers changes in the BBT with an increase of around half a degree °C from the follicular to the luteal phase. This has long been known [37]. These changes, if measured accurately and reliably, may be associated with ovulation. However, the determination of ovulation by BBT measurements has been found to be less than ideal for the prediction of either ovulation or fertile days (due to low sensitivity when compared to more accurate methods), and it is cumbersome and difficult to do for many patients. However, combination of temperature monitoring and computer-based algorithms (AI) has yielded better results lately. Some very motivated patients that can master their BBT measurement and are highly motivated, a gain in accuracy in the prediction of fertile days during their cycles may be achieved. Wearable devices are also helping reduce the error in measurement of BBT [38–41]. One of the main problems of BBT alone as a contraceptive method is that the determination of the fertile days is mostly retrospective [25] (the temperature rises almost concomitantly with ovulation) and comes after the window of fertility provided by the sperm life span is already open. In other words, couples that may have had intercourse 2–5 days before ovulation may not detect changes in BBT until it is too late. This is the main reason behind the utilization of BBT together with other described symptoms of fertility monitoring in combined methods. These combined methods of contraception are the *symptothermal methods* and the *Marquette method* [42–44].

6.5.4 Combined Fertility Indicator Methods

These methods recognize that a single-symptom monitoring (or prediction) of fertile days may not be accurate enough when used independently, so they propose the combination of several of the above symptoms (symptothermal methods) and the measurement of those symptoms and monitoring of urinary hormones (ovulation detection technologies). These methods have one of the highest reported levels of effectiveness for FAMs with the smallest probability of pregnancy reported for perfect use of around 2–4%. It is, however, the typical use where we find more differences between these methods, with reports that fluctuate from close to 30% for symptothermal to 7% for symptoms and urinary hormones monitoring (such as in the Marquette method).

On a final, general note, teaching on these methods (FABM) is not only not part of usual medical curriculums, but most graduate physicians in a small study felt "not comfortable" or "not confident" with their knowledge about them by graduation [45]. This fact makes the common healthcare provider's participation less likely for the appropriate and extensive counseling process needed for the appropriate selection of the right group of motivated patients.

6.5.5 Digital FABMs

As explained in the previous sections, fertility awareness-based methods of contraception (FABM) are based on the correct identification of those days within the menstrual cycle when the woman is fertile and either protecting herself during intercourse by using another method of contraception (such as barrier methods or spermicides, better both) or by abstaining from intercourse completely during fertile days (episodic abstinence) until the non-fertile days window is again reached. Thus, the essence of success in FABM is double: a correct identification of fertile days and successful avoidance of pregnancy during that fertile window. A better calculation of the fertile window will improve the accuracy of the FABM. Digital FABMS (d-FABMs) provide the mechanisms to do so by facilitating data storage, analysis, and interpretation and by providing an interphase with the user that can also provide information, support, and easy access to the method.

With the mass introduction and availability of personal computing in the 1980s and the massive use of smartphones, the ability to connect with patients in a permanent, easier way and more sophisticated formats became readily available. There is conflicting data on the number of health apps available; however with numbers that oscillate between 325,000 and more than 400,000, the accuracy of the estimation is clearly surpassed by the enormity of the number. Also, especially in younger generations, people heavily rely in the connection to smartphones and the trust they have in these apps is undeniable. Contraception and especially FABMs have not escaped such a phenomenon [46]. However, most of these apps, especially those related to contraception, have not been studied carefully. In the case of d-FABMs, the literature is scant and only one app is approved by the FDA and has EC

certificate, both of which need at least some form of scientific support to be approved. Let's now try to understand the difference and implications of d-FABMs when compared with non-digital FABMs.

In a typical cycle, there is a fertile window of about 6 days where unprotected intercourse can lead to a pregnancy (sperm life span of 5 days plus ovum life span of 1 day). This window may "move" in any given cycle as ovulation moves farther from the expected day to the real day when it occurs. The change in the ovulation day determines the change in the length of the cycle.

The movement of the ovulation day may be predicted based on information from cycle length variability for cycles happening before the current cycle of interest and by physical signs and symptoms already described in the sections above. Other more accurate criteria that may help determine ovulation are ultrasound and hormone determination by different methods, which albeit useful and justified for infertility management (where pregnancy is expected to happen relatively soon) are not of practical use for contraception (where its use may span for months or years) except, may be, for some devices/tests (such as Persona and Clearblue Easy monitor) [47] to measure hormones such as LH and estrone-3-glucuronide (EG) in urine [31, 48].

In any form of FABM, the essence of the determination of the fertile window is the calculation of the window based on previous cycle data. However, this could be mathematically cumbersome and challenging for most and requires discipline in collecting data and accurate measurements and recording for relatively long periods of time. For many women it is done incompletely and incorrectly and when done incorrectly is unforgiving in allowing a proper determination of fertile days thus becoming a very important factor in the failure of these methods. Furthermore, counseling for inexperienced health workers on these calculations is also cumbersome, very time-consuming, and complicated. Digital and computer-based fertility trackers and contraceptive apps facilitate data recording and by using AI and more complex algorithms help offset most of the difficulty issues associated with calculations and greatly decrease the burden and complication both for users and healthcare providers [26, 49–53]. They also make the method more "user independent."

Digital fertility trackers have been used for several decades, many for the purpose of assisting women that want to get pregnant. The recommendation then is that, during those fertile days they must have intercourse and to not use contraception. The principle for contraception uses essentially the same principle, identification of the fertile window; however, as opposed to when used for fertility purposes, in contraception the recommendation during the fertile days is to avoid sex (intermittent abstinence) or if intercourse is going to happen, to use a secondary form of contraception. It is evident that most women spend most of their reproductive lifetime avoiding pregnancy than seeking pregnancy. So rapidly, these programs became more useful and popular from the perspective of contraception. We have relatively few computer-based programs and more than 400 app-based fertility trackers.

Based on data from these apps, the use of d-FABMs for contraception is growing especially in women seeking a more effective, natural, non-hormonal method of contraception. Evidence (of low to intermediate scientific rigor and quality) published

until now supports that these apps, probably by facilitating recording of cycles (independently from notes or memory) and by facilitating the traditional calculations but allowing even more complex calculations, are more effective methods of contraception than other barrier or non-digital FABMS for the typical user, at least [27].

The underlying principle is the easier input, storage, and computation of cycle characteristics and (for some) physiological data by the app (or computer program) which then analyzes the data and advises the woman on fertility status. As with traditional FABM, the couple must then either abstain from sex or use barrier contraception on fertile days. However, as opposed to traditional FABM where fertile days determination by hand calculations is difficult, in digital FABMs the algorithms greatly facilitate the math associated with fertile days determination.

D-FABMs may use cycle length measurement only or combinations of cycle length and one or more of the physiological signs or symptoms used in traditional FABM such as basal body temperature (BBT) and other cervical signs and hormonal determinations. In any case, they provide the advantage of achieving more consistent, reliable, and accurate identification of the fertile window through an automated and (sometimes) complex algorithm-based analysis of the data, which includes more calculations than just average cycle length. Prediction of ovulation day IS NOT really the purpose of these apps, especially those used for contraception. The prediction of FERTILE DAYS is. Fertile days window can be individualized to each user by incorporating data from previous cycles into the automated analysis. Variation in the fertile window due to recent use of hormonal contraception or simply due to natural variation can be accounted for when computing the data. Algorithms can be programmed to apply a safe margin when defining the fertile window, to take such and other variations into account. Unfortunately, most of these algorithms are not peer-reviewed and have not been disclosed.

Growth in the use of d-FABMs is probably related to the easy access that women have to download mobile apps directly from the app store and because usually they do not require as much training or education for their use as the traditional non-digital FABMs. Today there are more than 1000 apps [54–57] and many websites available. The purpose behind the use of these apps by women is mixed. In a recent mixed methods study, most users wanted to "monitor the cycle," with other motivations being to conceive and monitor fertility treatments and contraception [57].

Despite the fact that the overall typical effectiveness of FABMs has been reported to be around 15–24%, the reported effectiveness from studies about d-FABMs has been much more optimistic. However, most apps have no peer-reviewed literature supporting them and the ones that have reported effectiveness between 1.2% and 9.8% for typical use and 0.4–6.6% for perfect use. This information is generated from their own convenient samples (registries with variable to unknown design quality) producing an intrinsic limitation to generalizability of their data [25, 27].

Post-marketing surveillance data from the only app approved to this moment both in Europe and in the USA (FDA) for contraception (Natural Cycles (NC) app, Fig. 6.6) suggests that the majority of women currently using digital FABM have a regular lifestyle that allows them to comply with the additional demands of such methods, which often involves measuring basal body temperature each morning

Fig. 6.6 Natural cycles app

before getting out of bed and entering data into the app. Given that the use of digital FABM is predominantly consumer driven, much can be learned about the population who desire this form of contraception from the current user base [58, 59].

In order to achieve the 99% perfect-use effectiveness rate for prevention of pregnancy, FABM requires accurate mapping of the fertile window in each menstrual cycle. With traditional techniques this requires the user to reliably predict ovulation day, so that the five preceding fertile days can be defined. Traditional techniques require extensive training and knowledge of the specific individual's pattern of ovulation in order to be accurate. Learning to detect and predict ovulation based on physiological measures is challenging and prone to a high level of human error. It is therefore unsurprising that the typical use effectiveness of FABM is around 76% [60], but the typical use effectiveness for the digital FABMs is reported to be 90–94%.

With the complexity, accuracy and reliability of d-FABMs calculations, which are computer-based, there is a very good chance that the fertile window is much better estimated that with other FABMs. Furthermore, Bayesian conditional rules and machine-learning artificial intelligence principles may be used to further increase the safety and accuracy of such calculations. As mentioned before, descriptions of such algorithms are not publicly available, so the comments on the characteristics apply to the NC app, whose algorithm is based on strong conceptual principles and has been studied, privately peer-reviewed, and presented for FDA and EC approval purposes [48, 59, 61].

The calculations done while using FABM for contraception are manual; they rely on the calculation of the variability on the cycles and cannot input or include any other data on other variables. At least two essential differences between FABMs and d-FABMs exist and apply to the NC-used algorithm:

1. Machine-learning artificial intelligence principles: The algorithm "learns" from previous data inputted by the patient and determines the conditional probabilities that the next fertile window will occur during a specific set of days in the cycle where it is used. In a study comparing the NC algorithm with two other FABMs

(rhythm and standard days methods), the app reported that by cycle 12, 59% of the days were correctly labeled as non-fertile days correctly with 0.08% of those days wrongly labeled. The app provides immediate estimation of fertile window from cycle 1 (providing a larger number of "fertile days" due to a safety window before and after the fertile days), while the rhythm method requires monitoring of six cycles before it can accurately predict fertile days. After 12 cycles, the number of non-fertile days was 43%, lesser days than with the app.

2. The app's algorithm calculates the random error of the estimations (means and standard deviations) and, based on the level of error, produces a more accurate "safety" margin of days around the fertile window. This is impossible to do in FABMS as it requires explicit computing power.

Further studies in the performance of the use of d-FABMs have provided insight into other aspects of their effectiveness that are important from the perspective of counseling. Women who have used different forms of contraception previously have different performance when using the apps [62]. As seen for the NC app, and shown in Fig. 6.7, women that have used non-hormonal contraception methods perform better when using NC than women that do not.

Furthermore, these differences are probably relevant to the specific method of contraception. Women that use barrier methods (more user dependent) will have higher effectiveness using the app than those that use methods that are more user

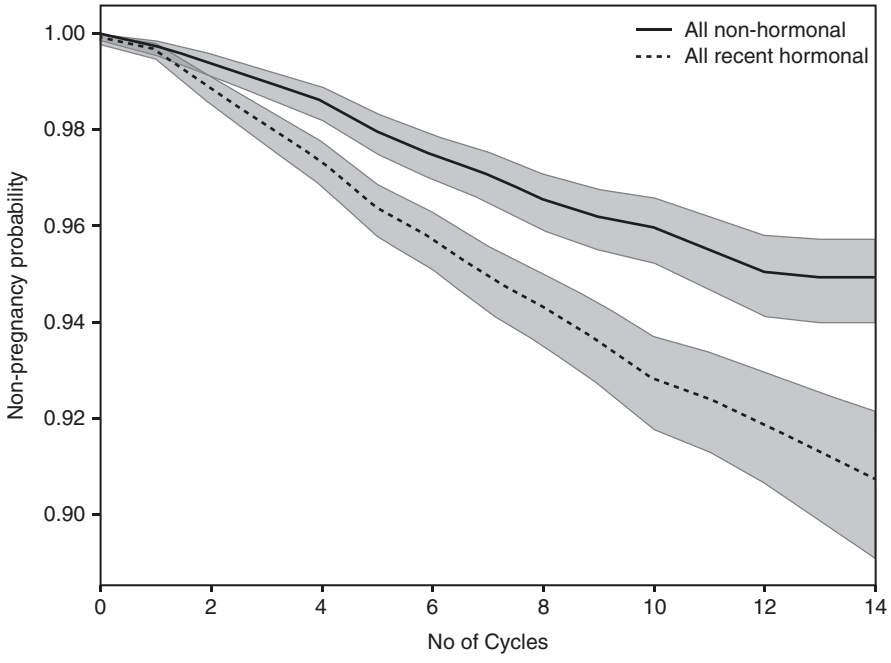

Fig. 6.7 Effectiveness of the use of d-FABM (NC) given previous use of hormonal vs. non-hormonal contraception

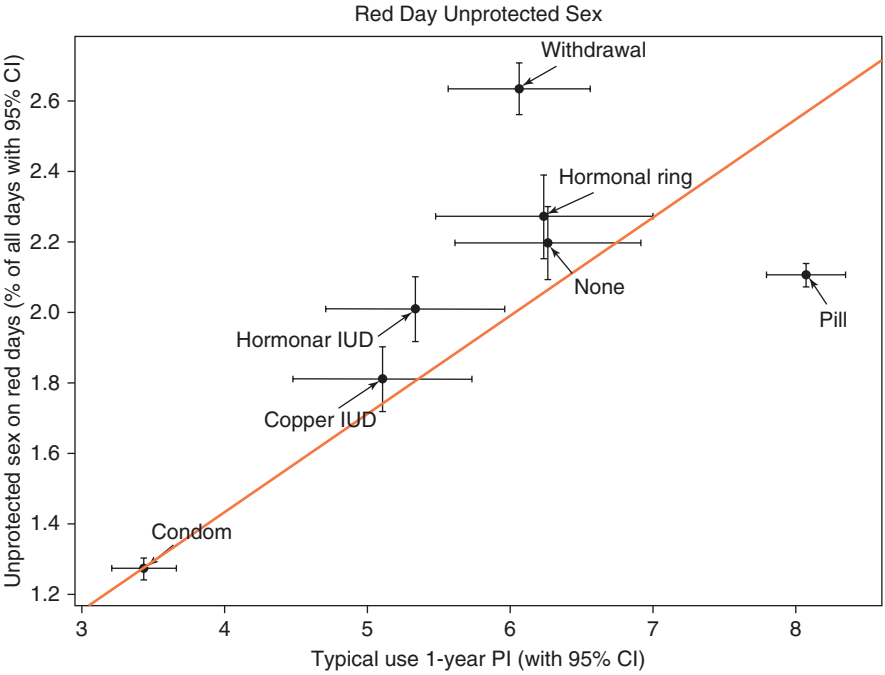

Fig. 6.8 Perl index for natural cycles app by unprotected sex and previous method use

independent, such as IUDs and hormonal. Also, it is easy to think that women that have more experience with the use those secondary methods that are recommended while the fertile days as defined by d-FABMs algorithms, are more likely to succeed in avoiding pregnancy if intercourse would happen during the fertile window. These differences may be seen in Fig. 6.8.

Finally, there are differences inherent to the different apps that are most commonly used for contraception purposes. In Table 6.1, a comparison of those differences is shown as a summary, with information obtained from the app sites and publications available.

6.6 FABMs and d-FABMs

Recommendations and Counseling

- Frequently used due to the level of independency from prescriptions and physicians/healthcare providers' availability.
- Easy download of the apps and available support from the app developers' sites.
- Best for women with fewer partners, steady lives, and knowledge of barrier methods.
- Best if women are less affected by periodic abstinence during fertile periods.

Table 6.1 Summary of characteristics for different fertility monitoring apps

Category	Sub-catergory	Natural Cycles	Dot	Clue	Glow	Eve	Ava	Flo	Apple
App (algorithm) optimized for intended use for									
	Period tracking	☒	☒	☒	☒	☒	☒	☒	☒
	Pregnancy planning	☒	☒	☒	☒	X	☒	☒	X
	Birth control	☒	X	X	X	X	X	X	X
Regulated by Authorities (FDA)									
	Cleared by FDA as medical device for contraception	☒	X	X	X	X	X	X	X
	CE-marked in EU as a medical device for contraception	☒	X	X	X	X	X	X	X
	Effectiveness in contraception based on published clinical studies	☒	☒	X	X	X	X	X	X
Body of Evidence									
Peer-reviewed publications		☒	☒	X	X	X	☒	X	X
	Number of publications	7	1	0	0	0	3	X	X
	Published data on contraceptive effectiveness	☒	☒	X	X	X	X	X	X
Key Features (Core Features)									
Period tracking	Period logging	☒	☒	☒	☒	☒	☒	☒	☒
Fertility tracking									
	BBT (detect ovulation)	☒	X	X	Optional	X	X	Optional	Optional
	LH Tests (detect ovulation)	Supportive	X	X	X	X	X	Optional	Optional
	Cervical Mucus (detect ovulation)	X	X	Optional	Optional	X	X	Optional	Optional
Additional Features									
Get to know your body	Educates user on body and cycle	☒	☒	☒	☒	☒	☒	☒	☒
Follow a pregnancy	Track development of pregnancy	☒	X	X	☒	X	☒	☒	X

- Best in women in the mature years of their reproductive years.
- Few if none data available to support use in young women.
- The gap in effectivity from common to perfect use is less than that of non-digital FABMs.
- Only one app (Natural Cycles) is approved as a contraceptive device in Europe and in the USA (FDA) at the time of writing this chapter.
- The same concept of fertile day determination may provide information for those women and couples that are avoiding pregnancy as well as for those that are seeking pregnancy.
- If used for fertility purposes, it may provide early suspicion of pregnancy, help detect impaired fertility, and orient the couple into further need for medical attention.
- The effectiveness of the FABMs (especially d-FABMs) may be related to the use of previous contraception and the type of previous contraception used. Women with non-hormonal contraceptive methods perform better than women that have used hormonal contraception.

Uses and Benefits

- Women controlled.
- Relatively inexpensive and available over the counter.
- Relatively easy access and use and high portability.
- Immediate effectiveness.

- Does not use hormones.
- If used appropriately, a high level of effectiveness may be achieved.
- Provide very good knowledge and empowerment to women.
- Does not alter women's natural physiology.

Concerns

- Large gap between typical and perfect use indicating a high user-dependent performance.
- Requires the use of other contraceptive method (abstinence, barrier) especially if coitus is desired during fertile days.
- Not recommended for women with irregular cycles.
- Not recommended in postpartum and/or during breastfeeding.
- Not recommended after the use of hormonal methods, in general, but especially after oral contraceptives.
- Not recommended in women that cannot dedicate time to learn the methods.
- Requires a special level of commitment.

6.7 Lactational Amenorrhea

Pregnancy is a change in women condition that requires serious and dramatic physical, psychological, and hormonal adjustments. One of those adjustments, result of the hormonal balance during the postpartum period, is the amenorrhea associated with lactation. During this period of time, the normal functioning of the hypothalamic-hypophyseal-ovarian axis is suppressed by the high levels of prolactin. During this same time, as a result form this blockade, ovulation is suppressed in a vast proportion of women, if lactation is maintained exclusively (skipping lactation episodes by providing formula may increase the chance of ovulation).

During this period of time, set at 6 months from the time of delivery, exclusive breastfeeding is associated with anovulation and pregnancy is prevented as per the Bellagio Consensus [63–65]. After that, ovulation is likely to occur and because ovulation will precede menses, it will be difficult to detect. The best predictors for anovulation are time from delivery (up to 6 months) and breastfeeding. There is not enough evidence to differentiate partial or full breastfeeding. As a personal opinion, given the lack of evidence and the difficult definition of "partial breastfeeding," full breastfeeding should be strongly encouraged when advising women on the level of protection against pregnancy.

Lactational amenorrhea is an alternative for women that want to avoid pregnancy during the first 6 months postpartum. About 98% of women using this form of protection will avoid pregnancy successfully during the 6 months after delivery. However, it has been associated, especially in low- to mid-income countries, with lack of use of more effective methods of contraception after the 6-month period and with lack of use of maternal and child health support services [66]. Also, the success of lactational amenorrhea, especially in developing countries, has been linked to maternal education and social support [67].

In summary, lactational amenorrhea, when associated with maternal education and provision of support health services and other contraceptive methods after 6 months, could be considered a method to avoid pregnancy.

Recommendations and Counseling
- Frequently used especially in challenging environments where immediate postpartum contraception is not available.
- Easy to use.
- Breastfeeding should be exclusive.
- Nearing the 6-month mark is advisable to use other methods of contraception.
- Associated, especially in developing countries, with education and accessibility to other maternal and child services.

Uses and Benefits
- Women controlled.
- Relatively inexpensive and available for all postpartum women.
- Immediate effectiveness.
- Does not use hormones.
- If used appropriately, a high level of effectiveness may be achieved.
- Does not alter women's natural physiology.
- Maintains child-mother bond while providing contraception.
- Overall benefits of lactation.

Concerns
- Does not provide protection against STIs.
- Women need specific instructions on the 6-month time span as it is one of the most important predictors to return of ovulation.
- Careful considerations must be given to women who have problems with breastfeeding.
- May require additional counseling about lubricants if dyspareunia appears (due to hypoestrogenism related to lactation).

Appendix 6.1

Internet-Based Resources as of May 30, 2020.

These are specialty sites that contain information on statistics, epidemiology, resources, and other websites and services on natural contraception as well as other methods for contraception. This list of selected sites does not intend to be a comprehensive list but more a list of trusted institutions for further expansion into more internet-based searches for contraception resources.

1. Contraception page, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Reproductive Health. https://www.cdc.gov/reproductivehealth/contraception/index.htm.

2. National Institutes of Health, **Eunice Kennedy** Shriver National Institute of Child Health and Human Development, Contraception Resources. https://www.nichd.nih.gov/health/topics/contraception/more_information/resources.
3. European Contraception Atlas. https://www.contraceptioninfo.eu/.
4. World Health Organization. https://www.who.int/reproductivehealth/topics/family_planning/en/.
5. Guttmacher Institute. https://www.guttmacher.org/.
6. Medicine Net. https://www.medicinenet.com/natural_methods_of_birth_control/article.htm.
7. New Zealand Family Planning. https://www.familyplanning.org.nz/advice/contraception/contraception-methods.
8. EngenderHealth. https://www.engenderhealth.org/our-work/family-planning/index/.
9. Everyday Health. https://www.everydayhealth.com/birth-control/resource-center/.
10. Family Planning Association—UK. https://www.fpa.org.uk/professionals/resources/leaflet-and-booklet-downloads.
11. Department of Health and Human Services (HHS). https://www.hhs.gov/opa/pregnancy-prevention/birth-control-methods/lam/index.html.
12. National Institute for Health and Care Excellence (NICE). https://www.nice.org.uk/guidance/health-and-social-care-delivery/contraception.

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Short-Acting Hormonal Contraception: The Pills, the Patch, and the Rings

7

Helena Kopp Kallner

7.1 The Beginning

Ludwig Haberlandt (1885–1932) is known as the father of hormonal contraception. In 1921, he carried out experiments on rabbits, and he demonstrated a temporary hormonal contraception in a female by transplanting ovaries from a second, pregnant, animal [1].

Russell Earl Marker (March 12, 1902–March 23, 1995) founded a steroid industry in Mexico. In 1937, he discovered the first practical synthesis of progesterone when he successfully made synthetic progesterone from chemical constituents found in Mexican yams.

Carl Djerassi refined the method of synthetic progesterone manufacturing, and by chemically modifying the substance ethisterone he developed norethindrone which had a higher biological activity. The first progestin to be patented was a very similar substance—norethynodrel.

In 1951, Gregory Pincus (1903–1967) received a small grant from the planned parenthood federation of America to begin research into hormonal contraceptive research. His lab confirmed earlier research that progesterone and progestins induced anovulation.

Women's right activist Margaret Sanger facilitated a much larger grant in 1952 from her rich friend Katherine McCormick. In total Katherine McCormick granted two million dollars towards the development of the oral contraceptive pill—an enormous amount of money at that time.

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In 1953 and 1954 trials were performed with different progestins on infertile patients as contraception was illegal at the time. The physician in charge of the trials was John Rock, a catholic gynecologist who performed the trials at his clinic. Eventually Puerto Rico was therefore chosen for the first clinical trials into the contraceptive effects. Results were mind-blowing. The combination of a progestin and an estrogen gave close to 100% protective effect against pregnancy. Studies were expanded to Mexico and included thousands of women. One of the main effects of the pill was a reduction in menstrual flow and menstrual pain. In 1957, the pill was registered in the USA for these indications. The pill "Enovid 10 mg" manufactured by Searle contained 0.15 mg of the synthetic estrogen mestranol and 9.85 mg of a progestin very closely related to the first patented progestin developed by Carl Djerassi. The contraceptive effect was a "side effect." In less than 2 years, close to half a million women had taken the pill—presumably quite often due to the "side effect." In 1957, the pill was approved for contraception in the USA and thereby the first contraceptive pill had been approved.

7.2 Early Development of the Estrogen Component

In the 1960s, the first reports on serious adverse events in pill users were reported. They included venous thromboembolisms. It became evident in the 1970s that the estrogen was the culprit of these serious side effects. Estrogen doses were rather quickly lowered, and a pill with 30 μg of ethinyl estradiol (EE) was registered as early as in the 1970s. However, pills with 50 μg EE dominated the market until the 1980s and are still available in some countries. Attempts were made with estradiol as the estrogen component as early as the 1970s and research continued onwards with other—WHO performing such studies (1980 WHO two combined oral contraceptives containing the same progestogen, but different estrogens. World Health Organization Task Force on Oral Contraception (gestagen norethisterone acetate)). However, no such preparation reached the market—mostly due to poor bleeding control.

The ethinyl estradiol has evident advantages in oral contraception. It is easily absorbed and has a long half-life (several days compared to hours with estradiol) due to resistance to degradation by 17 β-dehydrogenase. It does not bind to SHBG and therefore circulated freely. In addition, it binds to the estrogen receptors with high affinity. This in turn leads to strong biological effect on target organs such as the uterus for a better bleeding pattern, but also on protein production in the liver. Lowering the dose of EE in pills below 30 μg has been shown to lead to less favorable bleeding patterns with more breakthrough bleeding [2].

The effect of EE on the liver can if fact lead to desired effects in treatment of hirsutism or acne but also to undesired effects such as risk of venous thromboembolism. Thus, the effect of estrogen in a combined hormonal contraceptive preparation depends on type of estrogen foremost and dose of estrogen only secondly. Understanding the difference in biological effect between ethinyl estradiol and estradiol is fundamental when choosing the right combined hormonal contraceptive for every individual woman.

7.3 Progestin Development

Although progestins are essentially artificial or synthetic progesterones, they differ in potency and receptor affinity. Progestins bind not only to the progesterone receptor but may also have an effect on the androgen receptor. The earliest preparations had high doses of progestins in effect causing very low naturally circulating levels of estrogen due to ovarian inhibition. The added estrogen was initially in part there to compensate for these low natural estrogen levels. It became evident that such high doses of progestins were not necessarily needed for anovulation and doses were subsequently lowered. Progestins were patented by the companies when producing contraceptive pills and subsequently used in the different formulations from that same company. The contraceptive effect and ovulation inhibition were the factors that interested the most and that were evaluated in the clinical trials. Side effects were recorded but very similar for all progestins [3].

Attempts at synthesizing the "perfect" progestin are still ongoing. Ideally a progestin should be potent and inhibit ovulation to have a high contraceptive efficacy. Furthermore, it should be selective and have a stabilizing effect on the endometrium to reduce side effect and breakthrough bleeding. Preferably, the progestin should also affect mood less than our naturally occurring progesterone. As combined hormonal contraceptives are taken orally every day, the half-life of progestins and the effect of the half-life on effectiveness in typical use have discerned more interest.

7.4 Combined Hormonal Contraception

7.4.1 Administration-Dependent Differences Between Pill, Patches, and Rings

Short-acting reversible contraception consists of daily pills, a weekly patch, or monthly rings. These naturally have different modes of absorption leading to differences in plasma concentration over the duration of the administration (Fig. 7.1) [4].

Comparisons of patches and rings with COCPs have been evaluated in repeated Cochrane reports. Plasma concentration of EE is higher with the patch. A higher proportion of women using the patch report estrogen-dependent side effects such as breast tenderness [5]. Patch skin reactions and detachment are rare but occur and may lead to early discontinuation [5]. For ring users an increase in vaginal discharge has been established. This may be considered as "less vaginal dryness" or "increased discharge" [5]. Ring users appear to be more satisfied than COCP users [5]. A pill needs to be taken every day. Patches and rings may have the advantage of more stable concentrations of EE and progestins. No difference in contraceptive effectiveness has been shown for the methods [5]. It has been shown that patches and rings lead to more favorable bleeding pattern than a pill containing 30 μg of EE [5]. In the case of the rings, this is established in spite of a lower plasma concentration of EE.

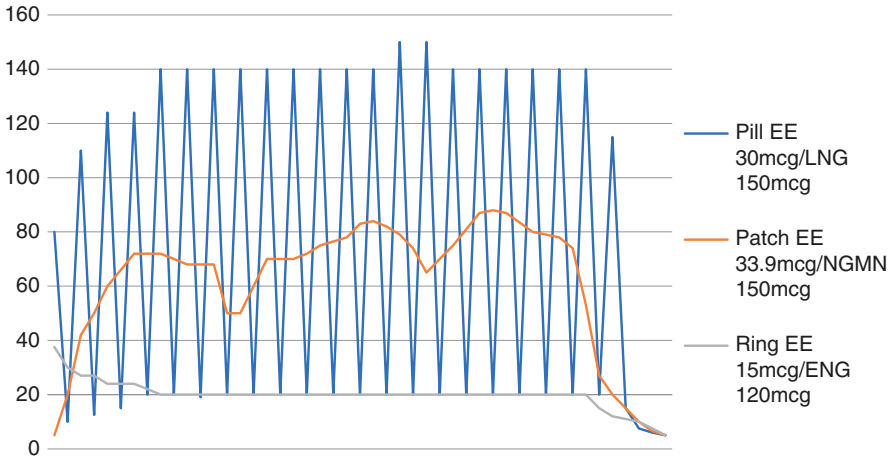

Fig. 7.1 Estrogen concentration depending on mode of administration. Concentration in picograms per milliliter over a treatment cycle of 21 active treatment days. Last measurement on day 24. Levels are rounded off and levels in figure may therefore differ from actual levels. The figure serves to give the reader an idea on differences depending on mode of administration. *EE* ethinyl estradiol, *LNG* levonorgestrel, *NGMN* norelgestromin, *ENG* etonogestrel. (Modified from [4])

7.4.2 Contraceptive Effectiveness

Recently, it has been shown that contraceptive efficacy may not only depend on the ability of the progestin to induce anovulation in a classic 21/7 regimen.

Several factors may affect effectiveness in real life. Such factors may be:

1. User dependent
2. Regimen dependent
3. Dependent on the intrinsic characteristics of the progestin

7.4.2.1 User Dependency

Several studies have shown that younger women have higher failure rates when using oral contraception. This in turn may of course depend on younger women being more fertile. However, recent studies suggest that younger women seem to forget pills more often [6, 7]. Thus, short-acting reversible contraception may not be the best contraceptive method for young women.

7.4.2.2 Different Regimens of Use

The pill was designed to produce a "natural bleeding" once a month. The original regimen entailed taking 21 days with active pills and then having a pill-free break of 7 days. As hormones are withdrawn, this induces a predictable withdrawal bleeding. Thus, the bleeding is completely artificial and is due to the rapid lowering of hormones. Some manufacturers include seven placebo pills instead of recommending a pill-free break.

During the seven pill-free (placebo) days, the follicle suppression ceases and the follicles start to mature, producing endogenous estrogen which makes the endometrium proliferate. This in turn creates a thick enough endometrium to be shed after the 21 days. If pills are forgotten after the pill-free break, the follicles mature even more. For women with a short menstrual cycle, a pill-free break of more than 7 days may be enough for ovulation to happen. An experimental study showed that ovulation occurs in approximately 10% of women if the pill-free break is extended to 10 days [8]. In opposite, with a shorter pill-free break, we ought to achieve less maturing of follicles, less growth of the endometrium, and thus less chance of ovulation and less bleeding. This has now been verified in numerous studies which show that follicles become smaller and that fewer women ovulate if the pill-free (placebo) break is shortened to 4 days [9, 10].

7.4.2.3 Importance of the Progestin Content

As short-acting reversible contraception is dependent on daily, weekly, or monthly administration, the half-life of any progestin in the contraceptive may affect how long it is possible to forget the pill, patch, or ring. It has been shown that the half-life of the progestin may affect the rate of anovulation and thereby contraceptive effectiveness in real life. A progestin with a longer half-life may be more permissive to forgetfulness.

Half-lives of different progestins vary greatly (see Table 7.1).

That regimens with a shorter pill-free break (or a placebo pill intake) and formulations with a progestin with a longer half-life improve contraceptive effectiveness in typical use has been shown in a large prospective study [11].

If shortening the pill-free break increases effectiveness, one might subsequently wonder if abstaining from a break would in fact increase effectiveness further. To this date, no study proving this has been published. Often extended regimens are divided into continuous regimens when no break is made, extended regimens with a planned break—often after 3 months or extended flexible regimens when women can choose to make a break or are told to make a break after a certain number of days with bleeding. A Cochrane review of extended and continuous regimens including 12 randomized trials concluded that there is no difference in compliance between traditional 21/7 regimens and extended or continuous regimens. The studies that reported tolerance found that there was less headache, genital irritation, tiredness, bloating, and menstrual pain in the extended or continuous groups. Although several studies find that spotting and bleeding may be more frequent initially in the extended and continuous regimens, these symptoms often disappear or

Table 7.1 Progestin half-lives in hours in selected commonly available progestins

Dienogest	9.1
Desogestrel	11.2
Levonorgestrel	14.8
Drospirenone	31
Nomegestrol acetate	48

subside with time and that women resulting in a more acceptable bleeding pattern than the 21/7 regimens [12].

7.4.3 Progestin-Only Pills

Progestin-only pills are traditionally taken without a pill-free (placebo) break. The mechanism of action depends on the dose of the progestin.

7.4.4 Low-Dosed Progestin Pills

Classic progestin-only pills are low dosed. The suppression of ovarian function is individual depending on type and dose of the androgen in addition to individual effects. Ovulation has been shown to be inhibited in 40–67% of women [13]. If ovulation is not inhibited, the low-dosed progestin-only pills still affect cervical mucus and thus prevent sperm entry into the uterus. In addition, the tubal transport of the egg is affected and the endometrial lining becomes thin and inhospitable for the fertilized egg [14].

The effect on cervical mucus is short acting. Thus, the pills need to be taken more or less the exact time every day within a margin of 3 h. If this timing is missed, back-up protection is needed. Naturally, the lack of ovulation inhibition and the low tolerance for forgetfulness lower the effectiveness of the low-dosed progestin pills.

Low-dosed progestin pills affect tubal transport—often without affecting ovulation. In addition, implantation in the thin endometrium is affected. This leads to a slightly higher risk of ectopic pregnancy in women taking these pills [15]. In most countries, today medium-dosed progestin-only pills are available, and therefore the market share of the classic low-dose pills has dwindles. However, in the USA no medium-dosed pill has been registered until very recently.

7.4.5 Medium-Dosed Progestin Pills

Medium-dosed progestin-only pills induce ovarian inhibition and thereby follicles do not mature [16, 17]. Recently, a new medium-dosed pill with 4000 mg non-micronized drospirenone has entered the market. Comparative studies have been performed showing comparable ovarian inhibition [18]. Studies show that medium-dosed progestin-only pills maintain ovarian activity with estradiol levels corresponding to early follicular phase [17].

The medium-dosed desogestrel pill is currently registered in a continuous regimen, whereas the drospirenone pill is registered in a 24/4 regimen. A comparative study shows that the number of bleeding days is reduced with the 24/4 regimen during the first 3 months. Thereafter, the total number of bleeding days is similar

(Exeltis, data on file). However, the drospirenone pill in the 24/4 regimen induces a planned bleeding, whereas all bleeding in a continuous regimen may be considered as unplanned.

7.5 Androgenicity and Anti-androgenicity

Androgenicity may affect the added health benefits and the side effect profile of combined hormonal contraception. Whereas the androgenicity and anti-androgenicity of a progestin-only product depends on the dose and the properties of the progestin itself—the androgenicity or anti-androgenicity of a combined hormonal contraceptive product depends on two mechanisms of action.

1. The type of estrogen
2. The dose of this estrogen
3. The androgen receptor action of the progestin

EE has a long half-life and as strong estrogen receptor affinity. EE is resistant to metabolism by 17β-hydroxysteroid dehydrogenase—the enzyme mainly responsible for metabolism of naturally occurring estrogens. Thus, EE circulates many times through the body before it is excreted in feces and through the gall and the urine. In the bloodstream, it is mainly bound to albumin and has very low binding affinity for SHBG. As it circulates through the liver, it affects the production of numerous proteins. EE induces production of among other proteins—the sex hormone binding globulin (SHBG). SHBG acts as a transport protein in human blood for our sex hormones. As the production of SHBG is increased, the amount of free androgens in bloodstream is decreased. Thus, an anti-androgenic effect is created. The higher the dose of EE, the more SHBG is produced and the higher the anti-androgenic effect. On the other hand, estradiol does not affect levels of SHBG as EE. Thus, the anti-androgenic effect of estradiol-based combined hormonal contraception is less.

Progestins may have an effect on the androgen receptor. They may either serve as agonists, be largely neutral, or have anti-androgenic effect by blocking the androgen receptor. Classifying a progestin androgen receptor activity may be done by different methods whereof one is studying the effect on rat prostate. If the androgen shrinks the rat prostate, it is considered anti-androgenic. The androgenicity and anti-androgenicity of common progestins are shown in Fig. 7.2.

When an anti-androgenic progestin is combined with EE, a powerful anti-androgenic effect is created. All currently available combined hormonal contraceptives containing EE are anti-androgenic. This can be shown by analyzing the effect on acne. A Cochrane review shows that although one of the least anti-androgenic EE-containing combined hormonal contraceptive pills (20 μg EE and 100 μg LNG) treats acne more effectively than placebo, the most anti-androgenic pill (35 μg EE and 2000 μg CPA) treats if far more effectively [21].

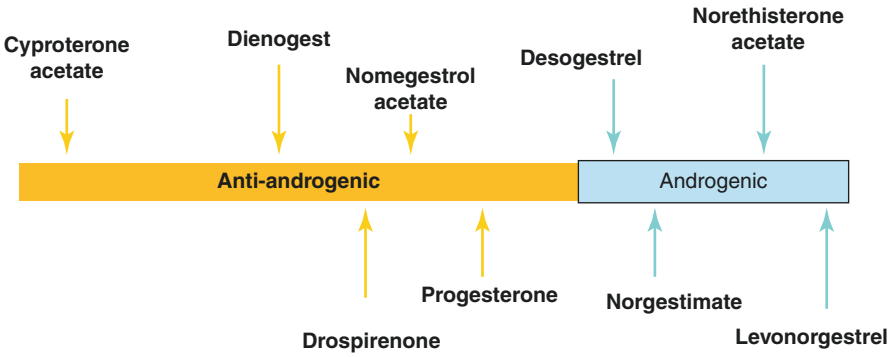

Fig. 7.2 Anti-androgenic and androgenic potency of various progestins. (Modified from [19, 20])

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The Advantages of LARC Methods

8

Luis Bahamondes and M. Valeria Bahamondes

8.1 Introduction

Despite increasing rates of modern contraceptive method use, high rates of unplanned pregnancies (UPs) continue to be reported in many countries. Even higher rates are reported among adolescent girls [1]. UPs occur due to lack of contraceptive use, improper use or method failure.

It is well established that contraceptive effectiveness for typical use and perfect use widely differs. "Typical use effectiveness" refers to real-life use, while "perfect use effectiveness" refers to use during a research study or clinical trial [2]. Many researchers consider the effectiveness during "typical use" to be the most clinically relevant because it takes into account real-life circumstances. The discrepancy between typical and perfect use is eliminated by contraceptive methods that do not require action after placement and whose efficacy is not altered by the user. These are identifiable as "forgettable contraceptives" or long-acting reversible contraceptive (LARC) methods and include various models of levonorgestrel-releasing and copper-bearing intrauterine devices (IUDs), as well as subdermal implants. They were defined as methods requiring attention no more frequently than every 3 years [3].

LARC methods have very low contraceptive failure rates: the cumulative pregnancy rate in the first 3 years of LARC use is 0.9/100 woman-years (W-Ys) [4]. It is important to note that in general, contraceptive effectiveness is influenced by contraceptive efficacy, compliance, continuation, fecundity and timing and frequency of coitus [3]. For LARC methods, many behavioural variables that affect compliance and therefore effectiveness are removed, and pharmacological aspects

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have a greater impact on overall method effectiveness. LARC methods do not require action for years after placement.

In contrast to LARC methods, short-acting reversible contraceptive (SARC) methods have higher rates of UP during the first year of typical use. For LARC methods, the one-year pregnancy rate for typical use is less than 1%. In comparison, the one-year pregnancy rate for typical use is 6% for depot medroxyprogesterone acetate injection and 9% for combined oral contraceptive pills, progestin-only pills, the patch or vaginal ring. For the male condom and diaphragm, the rate approaches 20% [4, 5].

Another important quality of LARC methods is that contraceptive effectiveness is independent of user characteristics such as parity and age. Young women (less than 21 years old) who use the contraceptive pill, patch or ring, on the other hand, have significantly higher contraceptive failure rates than older women [4]. LARC methods are effective and safe for almost all women, including adolescents and nulligravidas. They also have high satisfaction and continuation rates and offer many non-contraceptive benefits [6].

8.2 Intrauterine Devices (IUD)

Intrauterine devices include the various models of the copper-bearing intrauterine device (Cu-IUD) and of the levonorgestrel intrauterine system (LNG IUS).

8.2.1 The Copper Intrauterine Device (Cu-IUD)

The first IUDs, introduced many years ago, were plastic devices. In 1988, the US Food and Drug Administration (US FDA) approved the most highly effective copper-IUD, the TCu380A. This is a T frame device with a 380 mm copper surface distributed across its two arms. In light of the device's safety and effectiveness, IUD use increased and also due to the introduction of the 52 mg LNG IUS worldwide, IUD use increased [7].

The TCu380A IUD is labelled by the US FDA and many other health authorities as being effective for up to 10 years. However, HCPs adopt the policy to maintain the same device for more than 10 years, mainly among women over 35 years old who keep the same device up to menopause [8]. This means that women who received a TCu380A IUD over the age of 25 could potentially keep the same device up to menopause or almost 25 years of continuous use without changing the device.

8.2.1.1 Contraceptive Effectiveness

A review on the use of Cu-IUDs [9] found that in many studies with mostly parous women the TCu380A IUD was more effective than other Cu-IUDs. However, it was not superior to other models in terms of expulsions and in terms of removals due to bleeding and pain. The contraceptive effectiveness rate for the Cu-IUD, mainly the TCu380A, is one of the highest among LARC methods [8, 10]: it ranges from 0.1 to

2.2/100 W-Ys [9]. The World Health Organization (WHO) conducted a study comparing the TCu380A to a frameless Cu-IUD (GyneFix) designed to reduce bleeding complaints and expulsions [11]. Women were followed for up to 8 years and 2027 and 2036 women were randomised to the frameless IUD or the TCu380A IUD, respectively. First-year expulsion rates were 5.3/100 women (95% Confidence Interval [CI] 4.4–6.4) and 2.5/100 women (95% CI 1.9–3.3) for the frameless IUD and the TCu380A IUD, respectively, without significant differences among groups. Additionally, cumulative pregnancy rates were 1.2 (95% CI 0.7–1.9) and 2.5 (95% CI 1.8–3.4) for the frameless Cu-IUD and TCu380A, respectively, through the eighth year of use.

The WHO also conducted a trial to compare the contraceptive effectiveness of the TCu380A IUD to that of the MultiLoad 375 (MLCu375) with 375 mm of copper. They found that the TCu380A had lower contraceptive failure rates at any year of evaluation up to 10 years, with a rate difference (RD) at 10 years of 1.9% (95% CI 0.12–3.59%). Also, the authors observed a trend towards significantly more expulsions with the MLCu375 starting from the fourth year of use [12].

In a large study titled "European Active Surveillance Study for Intrauterine Devices" (EURAS IUD) conducted in Germany, Austria, Finland, the UK, Sweden and Poland, the authors evaluated 61,448 new users of more than 30 different models of Cu-IUD who were enrolled by more than 1,200 HCPs [13]. They reported data on 17,323 users of Cu-IUDs with 17,703 W-Ys of observation. The most commonly used Cu-IUDs were Nova-T (200 or 380; 37%), T-Safe Cu 380 (18%) and MLCu (250 or 375; 14%). Only 12% of the participants were nulligravidas. The reported Pearl Index (PI) was 0.52 (95% CI 0.42–0.64) with a life table estimate of contraceptive failure for the first year of use of 0.63/100 W-Ys. The authors also evaluated contraceptive effectiveness according to copper surface area (<300 mm^2, ≥300 mm^2). They found a PI of 0.56 (95% CI 0.24–1.09) for IUDs with a copper surface area <300mm^2, and of 0.62 (95% CI 0.50–0.78) for those with a surface area >300 mm^2. They also found that the pregnancy rate was higher in young women. The life table pregnancy rate (95% CI) was 1.35 (0.95–1.76) among women aged 18–29, 0.57 (0.37–0.77) among women 30–39 and 0.05 (0.0–0.12) among those 40 or older.

Other authors have reported different pregnancy rates according to different copper surface areas. A Cochrane review which included randomised controlled trials found PIs of 0.5–2.2 and 0.1–1.0 when the copper surface was less or greater than 300 mm^2, respectively [9, 14, 15]. Also, the authors of another large clinical trial found a PI of 0.3–1.3 among users of the TCu380Ag IUD (an IUD with silver in the arms) [16].

Ectopic pregnancy rates among Cu-IUD range from 0.08 to 0.8/100 W-Y [17]. A Hazard Ratio (HR) of ectopic pregnancy versus non-IUD users of 0.20 (95% CI 0.08–0.48) has been described, which did not change after adjustment for age, body mass index (BMI; kg/m^2) and parity (HR 0.26; 95% CI 0.10–0.66) [13]. It should be noted that IUD or any modern contraceptive method use reduces the rates of ectopic pregnancy compared to no contraceptive use.

8.2.1.2 Mechanism of Action

In 1987, the WHO [18] stated that *The IUDs exert their antifertility effects beyond the uterus, and interfere with steps in the reproductive process that take place before the ova reach the uterine cavity*. Alvarez and co-authors [19] were unable to obtain fertilised ova in the fallopian tubes of women with IUDs in situ. They concluded that the mechanism of action of IUDs is unlikely to involve the destruction of existing embryos or any prevention of implantation effect [20–22]. After several studies the scientific community concluded that the main mechanism of action of copper-IUDs is spermicidal action via the development of a local sterile inflammatory process induced by the presence of a foreign body in the uterus [23] leading to prevention of fertilisation.

8.2.1.3 Use of Cu-IUD Among Nulligravidas and Adolescents

When the TCu380A IUD was initially introduced in the USA, the product label included a statement that the … *device is recommended for women with one child* …. However, in 2005, the US FDA approved a new label which does not discourage use by nulligravidas. The WHO has also stated [24] that there are no restrictions to IUD use based on age or parity. Despite these guidelines, IUD use by adolescents and nulligravidas is still being debated [25, 26], and many HCPs are reluctant to use IUDs in these populations [27].

8.2.1.4 Main Reasons for Discontinuation

The main reasons for discontinuation of any IUD are expulsion and complaints of bleeding and/or pain. Regarding device expulsion, there are some reports describing that nulligravida and parous women with one delivery have a trend towards higher rates of expulsion compared to women with more than one delivery. However, the differences were not significant in two studies at 12 months after device placement [28, 29], and when comparing nulligravidas and parous women, the authors did not find differences in expulsion rates [25, 30, 31]. The main reasons for discontinuation among users of any Cu-IUD are an unfavourable bleeding patterns and lower abdominal pain. These account for 14/100 W-Ys up to 10 years of follow-up [8, 16]. However, there is no evidence that users of Cu-IUD have higher rates of anaemia, and removals for bleeding and/or pain may be highly influenced by women's preferences and HCP practices [32].

Historically, concerns were raised about a causal relationship between Cu-IUD use and pelvic inflammatory disease (PID). However, these were based on weak evidence due to numerous confounders and inappropriate comparison groups. It has now been found that there is no association between IUD use and infertility due to tubal occlusion. Rather, the risk of infertility is related to the presence of *Chlamydia trachomatis* antibodies. Also, the incidence of PID is low after 20–30 days of IUD insertion [33, 34].

One of the barriers of IUD use and insertion by HCPs is the fear of uterine perforation. However, a large prospective, non-interventional cohort study [35] examined IUD perforations up to 12–60 months after insertion among new users of the LNG IUS and Cu-IUD. The authors evaluated 61,448 and 39,009 women followed

for 12 and 60 months, respectively. The overall perforation rate was 1.6/1000 insertions (95% CI 0.9–2.5), and for Cu-IUD users it was 1.6/1000 insertions (95% CI 0.9–2.5). The main variable associated with perforation was breastfeeding (RR 4.9, 95% CI 3.0–7.8) and length of time since delivery (RR 3.0, CI 1.5–5.4). Overall, uterine perforation is rare, and the clinical sequelae of perforations are mild.

8.2.1.5 Pregnancy with an IUD In Situ

Although the occurrence of pregnancy with an IUD in situ is uncommon (PI 0.52; 95% CI 0.42–0.64) [13], it is a risk factor for adverse pregnancy outcomes. These include miscarriage (in some cases septic abortion) and preterm labour. When a pregnancy occurs with an IUD in situ, the recommendation is to remove it if the strings are visible at the external cervical os. However, both removing the device and leaving it in place carry some risk for the woman and the pregnancy.

In a systematic review which included nine studies of overall fair quality [36], the authors reported that when a pregnancy occurs with an IUD in situ, there is an increased risk of adverse pregnancy outcomes. The greatest risks are of spontaneous abortion (including septic abortion), preterm delivery and chorioamnionitis and occur when the IUD is not removed [36]. However, even in the cases in which the IUD is removed, there is an increased risk of complications compared to women who became pregnant without an IUD in situ. The instructions are to remove the IUD only if the strings are visible. However, some authors recommended ultrasound-guided removal when the strings are not visible [37]. According to some authors, the rates of spontaneous abortion and preterm birth may not increase after ultrasound-guided IUD removal [38].

8.2.2 The Levonorgestrel Intrauterine System (LNG IUS) "Family"

Currently, there are three different LNG IUS approved in many countries. The first contains 52 mg of LNG and releases 20 μg/day (Mirena®, Bayer Oy, Turku, Finland). It uses a new insertor called EvoInsertor® which has a 4.4 mm diameter tube. The device measures 32 × 32 mm and has brown strings. There are similar devices in some countries, such as Liletta® in the USA, Levosert® in Europe and Avibela® and Eloira® in several countries. These devices are similar to Mirena® but have a tube inserter like the TCu380A IUD except for Liletta® which uses the same insertor system than Mirena®. Smaller LNG IUS also exists which has the same shape as Mirena® but has a device dimension of 28 × 30 mm, with an insertor tube diameter of 3.8 mm (Kyleena®, Bayer Oy, Turku, Finland). Kyleena® contains 19.5 mg of LNG and releases 17.5 μg/day which decreases to 9 μg/day by the end of the first year of use. Another device exists with the same shape as Mirena® but with the dimension of Kyleena® (Skyla® in the USA, Jaydess® in Europe). It contains 13.5 mg of LNG and releases 8 μg/day of LNG. The last two devices contain a silver ring at the top of the vertical arm which facilitates ultrasound visualisation and distinguishes them visually from the 52 mg LNG IUS. The string colour is blue for

Kyleena® and brown for Jaydess®/Skyla® and Mirena. The three differently dosed LNG IUS are comparable in terms of insertion success rates, with more than 90% of devices inserted without problems, even among nulligravidas [25, 34].

8.2.2.1 The 52 mg LNG IUS

The original 52 mg LNG IUS (Mirena®) is the oldest LNG IUS on the market, and it is considered the gold-standard LNG IUS. More than 2000 scientific publications have discussed its contraceptive effectiveness and non-contraceptive benefits. These include its use in the treatment of heavy menstrual bleeding (HMB), for endometrial protection in postmenopausal women using continuous oestrogenic therapy and its use in treating endometrial hyperplasia [6]. The device is identifiable via X-ray as it contains barium sulphate. The initial daily LNG release rate is 20 μg/day; however, this decreases to ~12 μg/day by the end of the 5-year approved life span. Its contraceptive effectiveness is comparable to that of female permanent contraception, with a cumulative contraceptive failure rate up to 5 years ranging from 0.0 to 0.3/100 W-Ys [16, 39–41]. Additionally, extended use up to 7 years after device placement has been described with similar contraceptive effectiveness [41–44], and Liletta was approved by the US FDA up to 6 years of use. Furthermore, in a multinational, prospective, cohort study, the HR for ectopic pregnancy was 0.26 (95% CI 0.10–0.66) when compared to that of Cu-IUD users [45].

In addition to its high contraceptive efficacy, this device has many non-contraceptive benefits [6], and one of these includes the reduction of menstrual blood loss in women suffering from heavy menstrual bleeding (HMB) [46, 47]. Studies have improvements in quality of life comparable to those of women who undergo hysterectomy and better than those who undergo endometrial ablation. There is also evidence on improvements of dysmenorrhoea including among women with endometriosis- and adenomyosis-associated pain [48] and on prevention and/or treatment of endometrial hyperplasia [49].

Mirena® is also approved in many countries for endometrial protection for postmenopausal women on continuous oestrogen therapy, for women on tamoxifen after breast cancer therapy [50, 51] and as a conservative treatment for women with endometrioid cancer stage IA, grade 1 [52].

Similar to the Cu-IUD, there are no restrictions to inserting the LNG IUS among nulligravidas and adolescents [24, 25]. Many HCPs remain hesitant to do so, perhaps because the original trials were conducted only with parous women. Also, the manufacturer at the introduction of the product in many markets does not include in the product insert the recommendation that the device is appropriate for both parous and nulligravida and young women. That said, the expulsion rate is similar between parous and nulligravida women [25] and is also similar across age groups.

The main reason for early discontinuation of the LNG IUS is the unfavourable bleeding pattern, which occurs mainly during the first 6 months after device insertion. Indeed, the number of bleeding and especially of spotting days can initially increase; however, with increasing usage the number of bleeding days decreases and many women develop amenorrhoea with rates of more than 20% at the end of 5 years [53]. Unfortunately, there are no known effective treatments to resolve the

initial irregular bleeding and spotting [54]. Some other reported reasons for discontinuation are acne, lower abdominal pain, breast tenderness, mood changes and dyspareunia. Nevertheless, overall satisfaction with the method is high worldwide and mainly associated with the occurrence of amenorrhoea [55, 56]. Perforation is a rare complication and it was reported in a large multinational study conducted in Europe as 2.1/1000 insertions (95% CI 1.6–2.8) [35].

There are now additional LNG IUS devices to the original 52 mg LNG IUS (Liletta®, Levosert®, Avibela®, Eloira®) that are approved for duration of contraceptive use up to 6 years (only for Liletta®). However, these are not available worldwide. Their contraceptive effectiveness and continuation rates are similar to those of Mirena® [57]; however, they are not approved as a therapy for HMB.

8.2.2.2 The 19.5 mg LNG IUS (Kyleena®)

The smaller, lower dosed LNG IUS introduced in many markets since 2016 is a 19.5 mg LNG IUS (Kyleena®). It is approved for use up to 5 years and only as a contraceptive. It releases 17.5 μg/day of LNG at insertion, which decreases to almost 10 μg/day and 9 μg/day at 1 and 5 years, respectively. All LNG IUS have similar mechanisms of action, which relies primarily on thickening of the cervical mucus and resulting in impaired sperm penetration [58, 59] and prevention of fertilisation. Ovulation is rarely (and dose dependently) suppressed, likely because the levels of LNG in the endometrium are 1000-fold higher than in the serum.

The 19.5 mg LNG IUS has a contraceptive effectiveness comparable to that of Mirena®, which is independent of age, parity and body mass index (BMI, kg/m^2). Additionally, the ectopic pregnancy rate is 0.2/100 W-Ys [60]. Although a reduction of menstrual flow has been described for this device, amenorrhoea rates are lower than those seen with 52 mg LNG IUS [60–62]. Discontinuation reasons and side effect profiles were similar for both devices. However, Kyleena® has lower ovulation suppression rates [61, 62]. Many HCPs recommend Kyleena® to women who prefer to have monthly menses [63].

8.2.2.3 The 13.5 mg LNG-IUS (Jaydess®, Skyla®)

Another LNG IUS introduced in several markets is a small device marketed as Jaydess®/Skyla®. This LNG IUS releases 14 μg/day the first month after insertion, which declines to ~5 μg/day at 3 years. The contraceptive effectiveness up to 3 years is similar to that of the other LNG IUS (PI of 0.33). The expulsion rate is also similar between the different types of LNG IUS (4.6%) [61, 62]. Early discontinuation rates are also similar and include unfavourable bleeding patterns, acne and dysmenorrhoea. Use among adolescents was also associated with high effectiveness and satisfaction rates [64].

In a recent review of the bleeding patterns reported by users of the three differently dosed LNG IUS, amenorrhoea rates were 11%, 5% and 3% up to 6 months after device placement for the 52 mg, 19.5 mg and 13.5 mg LNG IUS, respectively ($p < 0.0001$ for both comparisons). Irregular bleeding rates at 1 year of insertion were 6%, 17% and 23% for the 52 mg, 19.5 mg and 13.5 mg, respectively ($p < 0.0001$ for both comparisons). Frequent and prolonged bleeding rates were similar

over the first 2 years for the three devices. This data is important for HCPs who counsel women about choosing one of the LNG IUS [65].

8.2.2.4 Pregnancy with an LNG IUS In Situ

Due to the low pregnancy rates observed among LNG IUS users, there is limited data about the outcomes of pregnancies occurring with an LNG IUS in situ. In a study conducted in Finland, 40/17,360 users who had a pregnancy with a 52 mg LNG IUS in situ were identified from a questionnaire (58,600 W-Ys). The pregnancies were corroborated with medical records, and 63% were ectopic. Only 10/15 intrauterine pregnancies were continued, and of these eight had spontaneous abortions, and two had uncomplicated term deliveries of healthy infants [66]. In a review including information from the manufacturer and a case series, congenital anomalies were observed in 6% of 34 intrauterine pregnancies [67]. It is not possible to draw any conclusion due to the small number of cases.

8.2.3 Subdermal Contraceptive Implants

Currently, there are two subdermal contraceptive implants marketed worldwide. The one-rod ENG-releasing implant contains 68 mg ENG and releases, on average, 60–70 μg/day at weeks 5–6, 35–45 μg/day at 1 year and 25–30 μg/day at 3 years. It is embedded in an ethylene-vinyl acetate rod and is marketed as Implanon NXT® or Nexplanon® (Merck, Oss, the Netherlands). ENG is the active biological metabolite of desogestrel, which is used in combined and progestin-only contraceptive pills. The main described mechanism of action is ENG binding to receptors in diverse target cells distributed along the hypothalamic-pituitary-gonadal-genital tract axis which in turn interferes with some key processes required for gamete encounter and fertilisation. Additionally, ENG causes anovulation and thickening of the cervical mucus which impairs sperm migration [68].

The other registered implant is a two-rod implant which releases LNG (Jadelle®, Bayer Oy, Turku, Finland) and is marketed for use up to 5 years. Each rod contains 75 mg of LNG and is 43 mm in length and 2.5 mm in diameter. The core rod is a mixture of LNG and an elastic polymer (dimethylsiloxane/methylvinylsiloxane), and the average release rate is 100 μg/day at 1 month, 80 μg/day at 1 year, 30 μg/day at 2 years and 25 μg/day at 5 years after device placement.

Another implant not available worldwide is a two-rod LNG implant approved for use up to 4 years (Sino-implant® or Levoplant®, Pregna, Mumbai, India). For the Sino-implant®/Levoplant® and Jadelle®, the annual pregnancy rates are reported as being between 0.0 and 0.5 per 100 W-Y [69, 70].

The LNG and the ENG implants have very high contraceptive effectiveness. One large clinical trial conducted by the WHO with 1000 women randomised to each implant (Jadelle® and Implanon®) showed a cumulative pregnancy rate of 0.4/100 W-Ys (95% CI 0.1–1.4) up to 3 years, with no significant differences between the two implants [71]. However, due to the low number of pregnancies, no definitive conclusions were made regarding contraceptive failure rates and user

weight. Of the six pregnancies in the study, three occurred among LNG implant users, all of whom weighed ≥70 kg (0.8/100 W-Y, 95% CI 1–5.3). Three other pregnancies occurred among ENG implant users, all of whom weighed less than 70 kg. One of the six pregnancies was ectopic.

One reason for early discontinuation of both LNG and ENG implants is bleeding abnormalities, especially heavy and prolonged bleeding. Data from the WHO study [71] showed that the cumulative removal rate up to 3 years was 16.7/100 W-Y (95% CI 14.4–19.3) for the ENG implant and 12.5/100 W-Y (95% CI 10.5–14.9) for the LNG implant ($p = 0.019$). Limited data indicate that mefenamic acid, mifepristone, ethinyl oestradiol or doxycycline (alone or in combination) can reduce the duration of bleeding. However, these treatments do not maintain adequate bleeding patterns in the long term, and there is not enough evidence to routinely recommend any treatments for abnormal uterine bleeding with contraceptive implants in situ [72]. The other important causes of implant discontinuation were headache, dizziness, acne and lower abdominal pain. Discontinuation rates for these reasons were not significantly different between the two types of implants. In addition, rates of headache and dizziness were not significantly different between implant and Cu-IUD users, although these complaints were frequently reported to be associated with hormonal contraception [71].

Implant insertion and removal are simple outpatient procedures that any HCP can be trained to perform. Common side effects associated with LNG and ENG implant insertions are local irritation, discomfort, paresthesia and bruising. Rarely, there can be nerve or vessel injuries at the insertion site. However, with the manufacturer's new placement instructions of ENG implants (to insert over the triceps area), such injuries have been almost completely eliminated [73]. The pain reported at implant removal was similar among ENG and LNG implant users, and about 80% of the women reported no pain [71].

It is well established that contraceptive implants are an adequate treatment of dysmenorrhoea and pelvic pain and that they reduce the severity of premenstrual symptoms. Recently, the ENG implant was found to have similar results to the 52 mg LNG IUS in terms of cyclic and non-cyclic pain control among women with endometriosis-associated pelvic pain [48, 74].

8.2.3.1 Extended Use of Contraceptive Implants

The ENG implant is only approved for use up to 3 years. However, there is pharmacokinetic data which supports a longer duration of efficacy. It is known that ENG levels greater than 90 pg/mL are enough to inhibit ovulation [75]. One study found that at the end of 3 years of use, the mean serum ENG value was 207.7 pg/mL (range 63.8–802.6 pg/mL); at 4 years of use it ranged from 25 to 470.5 pg/mL; and at 5 years the mean was 153.0 pg/mL [42, 76]. However, serum ENG concentrations can vary widely between participants and even within the same woman [42]. Using the ENG implant beyond the approved 3-year period could increase the cost-effectiveness and even acceptability of this contraceptive method.

Recently, the WHO published a multicentre clinical trial conducted in seven countries in which it compared the clinical performance of the LNG and ENG

implants with a non-randomised group of women using the TCu380A IUD [77]. Although the trial was designed to last 3 years, at the end of that period the participants were invited to continue in the trial for an additional 2 years. The main goal of the study was to obtain information about extended use of the ENG implant up to 5 years. No pregnancies occurred during the 7060 woman-months of observation.

In agreement with these results, in a US-based study, the authors reported that among 223 and 102 ENG-releasing implant users up to the fourth and the fifth year of use, respectively, the pregnancy rate was zero/100 W-Ys [42]. Using the ENG implant beyond the three-year approved life span is beneficial for women and programmes because it saves time and resources and reduces the possibilities of procedural accidents. Unfortunately, extended use has not been officially approved by any regulatory agency to date.

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Venous and Arterial Risks Associated with Combined Hormonal Contraception

9

Jessica A. Reid and Jeffrey T. Jensen

9.1 Introduction

The oral contraceptive pill is used by 9% of women worldwide [1] and is one of the most commonly used birth control methods in the United States, Canada, and Europe. Pills are used by approximately 25% of contraceptive users in the United States [2], 33% of contraceptive users in Canada [3], and the majority of women in Europe—reaching as high as 84% of contraceptive users in Germany [3].

Since combined oral contraceptives (COCs) first became commercially available in the 1960s, we have seen significant changes related to their hormonal formulations and dosing to balance contraceptive efficacy against common side effects and potential risks. Higher dose pills contribute to more side effects, like nausea and breast tenderness, which limit patient tolerability and continuation. Additionally, venous thromboembolism (VTE) was discovered early on as one of the most important risks associated with combined hormonal contraceptive pills [4]. This drove drug development to produce pills with reduced VTE risk and side effects, while maintaining contraceptive efficacy. Compared to the first pill formulations, contemporary oral contraceptive pills contain significantly lower hormone doses.

Today, all combined hormonal pills contain an estrogen component, most commonly ethinyl estradiol, and a synthetic progestogen (progestin), with specific formulations often marketed for their non-contraceptive benefits. Women and their providers now have a large number of combined hormonal contraceptive (CHC) methods to choose from. In addition to pills, transdermal patches and vaginal rings offer alternative routes of administration and dosing schedules—and will be discussed briefly in

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this chapter in relation to their VTE risk. Contraceptive counseling should be guided by evidence about risks and benefits of the method, which are individualized to the patient with consideration of her preferences and comorbidities.

Thrombosis represents the most serious side effects of combined hormonal contraceptives. This side effect occurs in direct relationship to the degree of hepatic stimulation by the estrogen component of combined products. Whether the progestin component modifies the effect of estrogens on thrombosis risk, or acts independent to affect coagulation, remains highly controversial.

9.2 Hormones Used in Contraception

It is important to understand the different types of estrogens and progestogens used in hormonal contraception and the chemistry behind their varying effects in the body [5].

9.2.1 Estrogens

The term estrogen refers to both natural and synthetic hormones which act on the estrogen receptor. Activity and potency vary widely among the family of estrogen hormones.

9.2.1.1 Natural Estrogens

There are four natural estrogens in humans; all contain a 19-carbon steroid backbone and are distinguished by the number of hydroxyl (-OH) groups on the cyclopentanophenanthrene ring as well as their site of primary production. These account for differences in activity in the body and also over a woman's lifetime.

Estrone (E1), the first human estrogen discovered, is the dominant estrogen during menopause. Estrone is produced primary through conversion of adrenal androstenedione by aromatase made by peripheral adipose. Estrone is approximately 12 times less potent than estradiol [6], but can be converted into estradiol by isomerization with 17b-hydroxy-steroid dehydrogenase. In obese women, aromatase in peripheral fat leads to higher levels of estradiol.

Estradiol (E2), the most potent and biologically active natural estrogen, is produced in the ovaries from menarche to menopause. Theca cells in the ovary produce androgens—androstenedione and testosterone—which are then aromatized to estradiol (E2) and estrone (E1) by granulosa cells. E2 undergoes isomerization to the less potent E1, a principle means of metabolism. Ovarian estradiol production is regulated by the hypothalamus-pituitary-ovary axis.

Estriol (E3) is produced by the placenta and is present during pregnancy. It is 80 times less potent than estradiol (E2) [6] and is rapidly metabolized. During pregnancy, the placenta also produces E1 and E2, though in lower quantities.

Estetrol (E4) is produced by the fetal liver and present during fetal life until approximately 1 week after birth. Estetrol is 30–35 times less potent than E2 [7].

It is important to note that E1, E2, and E3 all undergo rapid metabolism when given orally where they are conjugated by the liver, marking the hormone for excretion. These metabolites are inactive. This is known as **first-pass metabolism.** The short half-life of E2 (14–16 h), E1, and E3 limits the utility of these natural estrogens for oral contraception. In contrast, estetrol is minimally metabolized by the liver, resulting in a longer half-life of about 28 h.

9.2.1.2 Synthetic Estrogens

The primary synthetic estrogen used in oral contraceptive pills today is ethinyl estradiol (EE). In the development of the first oral contraceptive—a synthetic progestin-only pill—scientists discovered that norethynodrel synthesis was contaminated with about 1% mestranol, a synthetic estrogen. Mestranol, which is demethylated in the liver, is a pro-drug for ethinyl estradiol. Further studies using purified norethynodrel only found that women experienced breakthrough bleeding (as seen with today's progestin-only pill). Thus, an estrogen was added back in for improved cycle control. EE is used in the majority of oral contraceptive pills today and is also the primary estrogen component in currently available transdermal and transvaginal combined hormonal contraceptives.

Like estradiol, oral ethinyl estradiol undergoes hepatic conjugation and the two actually have similar half-lives. However, ethinyl estradiol is about 100-fold more potent than estradiol [8]. This is due to enhanced estrogen receptor binding and different metabolism. Since EE passes through the liver on first pass without extensive conjugation, the liver effects of EE remain potent on recirculation. While the stimulation effects of estradiol on the liver following oral administration occur primarily as a result of first pass, EE provides potent stimulation regardless of route of administration. Thus, hormonal contraception with transdermal or transvaginal administration of EE is associated with a risk of VTE similar to that observed with oral preparations [9]. While hepatic conjugation of natural estrogens results in decreased potency, conjugates of EE remain highly potent. In contrast, transdermal administration of estradiol in physiologic doses for postmenopausal hormone therapy does not increase the risk of thrombosis [10].

To summarize these points, the enhanced effects of ethinyl estradiol (EE) over estradiol (E2) on induction of hepatic globulins occur due to greater potency, lack of significant first-pass conjugation, and potent induction on recirculation.

9.2.1.3 Other Estrogen Preparations Used in Hormonal Contraception

Estradiol valerate and estradiol cypionate, both esterified forms of estradiol, are rapidly hydrolyzed to estradiol and act as pro-drugs of estradiol. Estradiol valerate is currently marketed in pill form in the United States (Natazia®) and Europe (Qlaira®). Estradiol cypionate is currently combined with medroxyprogesterone acetate as a monthly injectable contraceptive (Cyclofem®, Lunelle®). Pills containing estradiol (Zoely®) have been developed and are available in Europe. Vaginal rings containing estradiol are currently under investigation.

9.2.2 Progestogens

The term progestogen refers to both natural and synthetic hormones which act on the progesterone receptor. It is incorrect to refer to the family of progesterone receptor binding compounds as progesterones.

9.2.2.1 Natural Progestogens

As opposed to the four natural estrogens, progesterone is the only natural progestogen in humans. Progesterone is an early precursor in the steroidal hormone pathway involving androgens, estrogens, glucocorticoids, and mineralocorticoids. The primary source of circulating progesterone is the ovary, predominantly in the luteal phase of the menstrual cycle. Progesterone is produced by the placenta during pregnancy.

9.2.2.2 Synthetic Progestogens

Several synthetic progestogens, or progestins, have been developed for therapeutic use. In some texts, these are classified based on the chronological order of discovery: as first-, second-, third-, and fourth-generation progestins. This classification system provides little information about the biological activity, and thus it is clinically more informative to understand progestins as derivatives of their parent molecule—testosterone, progesterone, or spironolactone.

19-Nortestosterone Compounds (Progestins Derived from Testosterone)

The first progestin synthesized from testosterone was norethindrone. Norethindrone was created in a two-step process, first by the addition of an ethinyl group at the 17-carbon of testosterone, making the androgen ethisterine, followed by removal of the 19-carbon. This modification changes the molecular activity from that of an androgen to that of a progestogen. Thus, all progestogen derivatives of testosterone as the parent compound are called 19-nortestosterones.

The 19-nortestosterone progestins are further subcategorized based on modifications at the 13-carbon position: estranes refer to compounds with a methyl group and gonanes refer to compounds with an ethyl group. Estranes include norethindrone, norethindrone acetate, ethynodiol diacetate, norethynodrel, and lynestrenol, which are all rapidly converted to the parent compound, norethindrone. Gonanes include norgestrel, norgestimate, desogestrel, and gestodene. The ethyl group modification in gonanes makes these compounds somewhat more progestational and less androgenic. Unlike estranes, which are essentially all norethindrone products, individual gonanes do exhibit some differences in activity. Levonorgestrel, the active isomer of norgestrel is commonly used in oral contraceptive pills as well as contraceptive implants, intrauterine devices, and as an oral emergency contraceptive. Etonogestrel (or 3-ketodesogestrel), the active metabolite of desogestrel, is not orally available, but is used in contraceptive vaginal rings and implants.

It is important to note that the androgenic properties are not completely eliminated in these progestins, though androgenic activity is typically considered

minimal with current doses of modern oral contraceptives. In addition, norethindrone can be aromatized to ethinyl estradiol, and some estranes bind weakly to the estrogen receptor, but clinical effects on the estrogen receptor are thought to be minimal in the low doses used in contemporary pills [11]. Finally, while 19-nortestosterones have the potential to exhibit glucocorticoid effects (decrease glucose tolerability or increase insulin resistance), the impact in clinical practice appears to be insignificant.

17-Alpha-Hydroxy-Progesterone Compounds (Progestins Derived from Progesterone)

Chemists developed progestins structurally related to progesterone, by acetylation of the 17-hydroxygroup of 17-alpha-hydroxy-progesterone. These are subclassified as pregnanes or norpregnanes based on whether they contain a methyl group at the 10-carbon position. Pregnanes include medroxyprogesterone acetate (Provera), megestrol acetate, chlormadinone acetate, cyproterone acetate, dydrogesterone, and medrogesterone. Norpregnanes (also called 19-nonprogesterones) include nomegestrol acetate, segesterone acetate, and trimegestone. The norpregnanes have strong progestational activity with no androgenic, estrogenic, or glucocorticoid activity.

Dienogest is a hybrid estrane-pregnane combining the properties of a 19-nortestosterone derivative with a progesterone derivative [12].

17-Alpha-Spironolactone Compounds (Progestins Derived from Spironolactone)

Spironolactone has anti-mineralocorticoid activity and is a potassium-sparing diuretic used to treat hypertension. It also has anti-androgenic and progestogenic activity and has been used for the treatment of androgenic symptoms like acne and hirsutism. Drospirenone is an analogue of spironolactone, which has more progestogenic and less anti-mineralocorticoid activity than spironolactone and is used in modern oral contraceptive pills.

9.2.2.3 Progestin Generations

While the above classification of progestins based on their parent molecule is more valuable scientifically regarding pharmacologic activity, the generation terminology is used frequently in the medical literature. Understanding this classification aids evaluation of the evidence from studies classifying pills this way. The generation classifications of progestins primarily involve testosterone-derived compounds. First-generation progestins are estranes (i.e., norethindrone). Second- and third-generation progestins are gonones, based on when they were introduced. Levonorgestrel (LNG) is a second-generation progestin, used in oral contraceptive pills since the 1980s. Given its long-standing and widespread use, LNG is often used as the reference group in epidemiologic studies regarding oral contraceptive pills. Later progestins with less androgenicity were introduced to reduce androgen-related side effects. Third-generation progestins

include desogestrel, norgestimate, gestodene, and etonogestrel. Fourth-generation progestins include drospinenone and dienogest, introduced most recently, but differ in their androgenicity. Thus, the classification by generation lacks a chemical or biological basis and contributes to the confusion regarding differential effects of formulations.

9.3 Venous and Arterial Thrombosis

Venous thromboembolism (VTE) refers to a spectrum of pathologic conditions where a blood clot (thrombus) forms within the venous system, most commonly within the deep veins of the extremities, known as a deep vein thrombosis (DVT). Approximately two-thirds of VTEs present as DVTs [13]. An embolic event occurs when the thrombus travels through the bloodstream to a distant organ—approximately one-third of VTEs present as pulmonary embolism, where a blood clot travels to the lungs. The most significant mortality associated with venous thromboembolism is pulmonary embolism, which causes sudden death in 20–25% of cases [14]. Other morbidities related to venous thromboembolism include pulmonary hypertension, chronic venous insufficiency, and recurrent thromboembolism.

Arterial thromboembolism (ATE) refers to similar events within the arterial system—most notably myocardial infarction in the heart and ischemic stroke in the brain.

9.3.1 Coagulation and Thrombosis

There are three main categories that influence thrombus formation, described in Virchow's triad. These include hypercoagulability, changes in hemodynamic flow, and response to endothelial injury. Increased tendency to thrombosis can be caused by numerous factors as they interact with the coagulation cascade—including physiologic and exogenous hormones, inherited and acquired thrombophilias, age, smoking, obesity, prolonged immobilization or long-haul travel, surgery, and cancer. VTEs are often the result of several acquired and/or inherited risk factors; however approximately 25–50% of first-time VTE patients present without readily identifiable risk factors [15].

9.3.2 Physiologic Effects of Hormones on the Coagulation Cascade

The risk of VTE in response to combined hormonal contraception is attributable to effects of estrogens on the coagulation cascade, shown in Fig. 9.1. Estrogen stimulates an increase in clot-promoting, or thrombogenic, clotting factors—factor I, II, VII, VIII, and X—as well as a decrease in clot inhibitors—tissue plasminogen activator, antiplasmin, and protein S (Box 9.1).

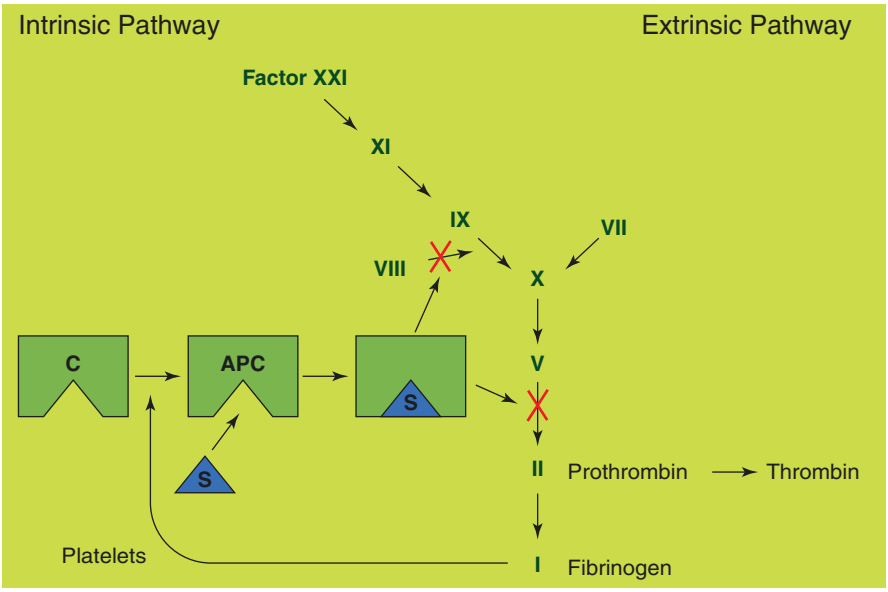

Fig. 9.1 The coagulation cascade. The simplified coagulation cascade. Activated protein C (APC) exerts an anticoagulant effect primarily through inhibition of factor V. Protein S is required for this interaction. C = protein [63]. (From Jensen JT, Burke AE, Barnhart KT, et al. *Effects of switching from oral to transdermal or transvaginal contraception on markers of thrombosis*. Contraception 2008;78(6):456)

Box 9.1 Manipulation of the Coagulation Cascade to Favor Clotting in Response to Estrogen

Favor clotting when increased	Favor clotting when decreased
Coagulation factors	
Factor VII, VIII, IX	Antithrombin III
Fibrinogen	Protein C
	Protein S
Fibrinolytic factors	
Plasminogen activator inhibitor-1	Antiplasmin

Estrogen stimulates an increase in clot-promoting, or thrombogenic, factors, as well as a decrease in clot inhibitors

The effect of estrogen on the coagulation cascade is a physiologic and evolutionarily protective mechanism, to prepare women for the risks of hemorrhage with childbirth. The physiologic effects of estrogens on the liver in the pregnant and nonpregnant state are shown in Fig. 9.2. A prospective cohort study by Sultan et al. demonstrates the increased risk of DVT with pregnancy. Compared to nonpregnant

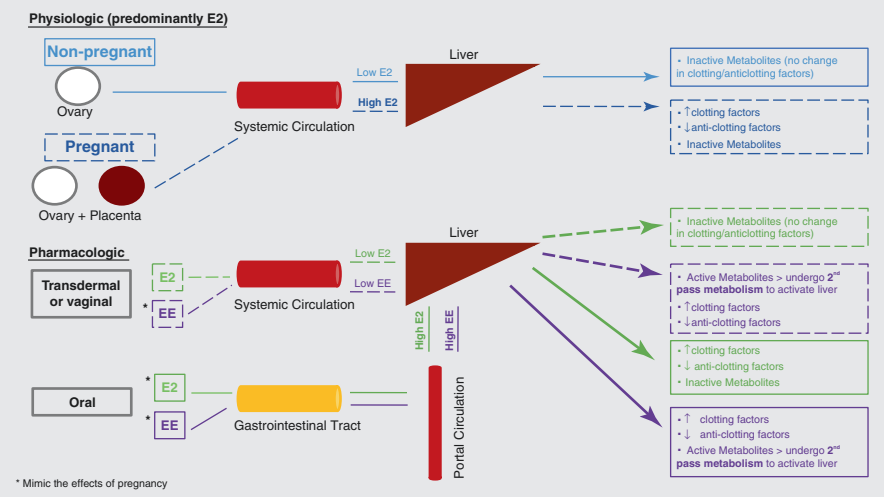

Fig. 9.2 Hormonal effects on the liver and clotting factors. The effects of estradiol (E2) and ethinyl estradiol (EE) on the liver and clotting factors by physiologic and pharmacologic doses, as well as different routes of delivery

women, the incidence risk ratio increases slightly in the first and second trimesters, with a marked increase in the third trimester and early postpartum period. The highest risk is seen within the first 6 weeks postpartum, with a incidence rate ratio 22.1 times that seen in nonpregnant women [16] (Fig. 9.3).

9.3.3 Pharmacologic Effects of Hormones on the Coagulation Cascade

Exogenous estrogens mimic the effects of endogenous estrogens to stimulate hepatic production of clotting factors. The underlying risk of VTE in healthy, nonpregnant women, not using exogenous hormonal birth control, is 5–10 per 10,000 woman-years. This risk increases approximately twofold in women using modern COCs to 10–20 per 10,000 woman-years [17] (Table 9.1).

As early as 1968, the association between oral contraceptives and thromboembolic disease was noted. Vessey and Doll reported that the risk of hospital admission for VTE was approximately nine times higher in women using oral contraceptives compared to those who were not [4]. This finding was confirmed in several other studies [18–22]. Additionally, researchers found this association to be dependent on estrogen dose—higher dose formulations demonstrated increased risk of VTE [23]. Pharmaceutical companies responded. Compared to the first oral contraceptive pill, which contained a daily dose of 150 μg of mestranol, pills today contain 10–35 μg ethinyl estradiol (EE). In fact, all pills today contain less than 50 μg ethinyl estradiol.

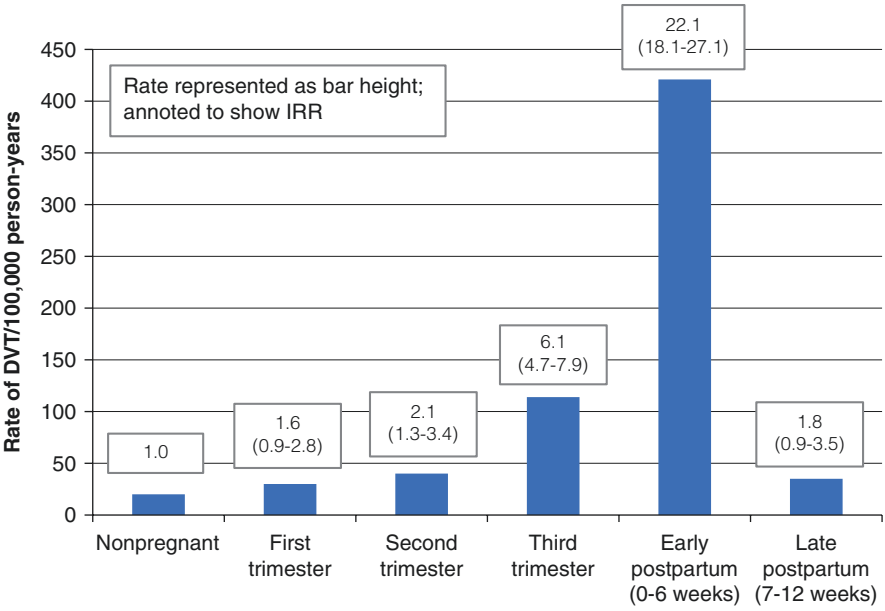

Fig. 9.3 Risk of DVT in pregnancy and postpartum. Rate of VTE per 100,000 person-years during different periods of pregnancy and postpartum compared to time outside pregnancy (nonpregnant = reference). Numerical notations showing Adjusted Incidence Rate Ratio (95% CI) [16]. (Adapted from Sultan, A.A., et al., *Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study.* Br J Haematol, 2012. **156**(3): p. 366–73)

Table 9.1 Relative risk and actual incidence of venous thromboembolism in different patient populations

Population	Relative risk	Incidence (per 10,000 women/year)
Healthy young women (general population)	1	5–10
Pregnant women	12	60–120
Low-dose oral contraceptive users (<50 μg ethinyl estradiol)	2	10–20
High-dose oral contraceptive Users (≥50 μg ethinyl estradiol)	6–10	30–100
Leiden mutation carrier	6–8	30–80
Leiden mutation carrier + oral contraceptive use	10–15	50–100
Leiden mutation homozygous	80	400–800

Taken from Fritz, M., & Speroff, Leon. (2011). *Clinical gynecologic endocrinology and infertility* (eighth ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins [17, 52, 70, 71]

Combined hormonal contraceptive pills have systemic effects, with the primary contraceptive mechanism of action on the hypothalamic-pituitary-ovarian axis to inhibit ovulation. However, pharmacologic doses of hormones also influence other systems in the body—notably the liver and production of hepatic globulins which influence the coagulation cascade.

Estrogens administered orally, both estradiol (E2) and ethinyl estradiol (EE), undergo first-pass hepatic metabolism and mimic the effects of pregnancy: decreased anti-clotting factors, increased clotting factors, increased C-reactive protein, and increased HDL (Fig. 9.2). When given in transdermal or transvaginal preparations, estradiol is diluted systemically, low levels reach the liver, and inactive metabolites are formed. Conversely, despite dilution of EE in systemic circulation when given transdermal or transvaginal, EE produces active metabolites, which stimulate hepatic production of clotting factors when recirculated, known as second-pass metabolism. This explains the increased VTE risk with EE given in transdermal or transvaginal routes [9, 24, 25].

To date, existing studies examining the risk of VTE based on different progestins are limited to observational data. These have given mixed results, discussed in more detail below (see **Controversy Regarding Third- and Fourth-Generation Progestins**). The biologic plausibility of progestin-induced hypercoagulability is challenged by the fact that there are no known progesterone receptors in the liver and that progestin-only methods do not appear to increase risk of thrombosis [26]. If a true biologic difference exists between different progestins, the mechanism is not yet understood, but may be related to a modification of the estrogen response, rather than a direct effect. A modified estrogen effect between the so-called second- and third-generation progestins has been hypothesized to be mediated by the androgenic properties of the progestin. Studies have shown differential effects on hemostatic biomarkers [27, 28] with use of third-generation (desogestrel, gestodene, norgestimate) compared to second-generation (levonorgestrel) progestin-containing pills, but changes were within the normal range and were not associated with increased risk of VTE. Differences in specific surrogate markers, including activated protein C (APC) and sex hormone binding globulin (SHBG), have been identified. Higher APC resistance and higher SHBG levels are measured in response to less-androgenic, newer progestins [28, 29]—leading some to speculate this as a mechanism for differences in estrogenicity and thus VTE risk. However, neither has been prospectively validated and at this time, no surrogate marker for VTE risk has been identified [30].

9.3.4 Pharmacologic Risk of Hormones on Arterial Thromboembolic Events

The risk of arterial thromboembolic events (ATEs) like cerebrovascular stoke and myocardial infarction is much lower than VTE events in young women; however, the sequelae can lead to greater morbidity and mortality. Combined hormonal contraceptives also increase the risk of arterial thromboembolism [31, 32], and certain risk factors modify this risk including age, smoking, hypertension, and migraine headache

with aura [33]. Estrogen-containing methods are contraindicated in these high-risk women [34, 35]. A retrospective cohort of healthy, reproductive-aged women using hormonal contraception found that the absolute risk of ATE events was low, the risk increased by a factor of 0.9–1.7 with oral contraceptives containing a 20 μg dose of ethinyl estradiol and by a factor of 1.3–2.3 with those containing a 30–40 μg dose and with small differences according to the progestin type [31]. Since ATE events are exceptionally rare in healthy young women, the risks with contemporarily dosed COCs do not appear to be significant for most women [33, 36].

9.4 Important Risk Factors for VTE

Overall the risk of VTE with COCs is low and should be balanced against the much higher increased risk of VTE in pregnancy in women desiring contraception. The prescription of combined hormonal contraception should also be considered within the context of patient-specific risk factors. Despite the low overall risk of VTE in both COC and non-COC users, the sequelae can be significant and should be minimized when additional known risk factors are present. A combination of patient factors put certain women at higher risk of VTE both in pregnancy and with exogenous hormones, as summarized in the guidance provided by the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use [34, 35].

In addition to VTE risk during pregnancy/postpartum and with the therapeutic use of estrogen, non-hormonal risk factors for VTE include age, obesity, inherited thrombophilias, personal or family history of VTE, malignancy, surgery, and immobilization or long-haul travel.

VTE increases with age—from incidence estimates of 0.7 per 10,000 women-years in teens aged 15–19 years old to 5.8 per 10,000 women-years in 45–49-year-olds [37]. Obesity also increases VTE risk two- to threefold compared to normal weight women [38, 39]. Inherited thrombophilias contribute significant risk [40] and hormonal contraception magnifies the risk of inherited thrombophilias [18] (Table 9.1). Factor V Leiden mutations are prevalent in 15–20% of patients with VTE [41]. Women using COCs with factor V Leiden mutations have a nearly 30-fold increased risk of DVT compared to nonusers without the mutation [42]. Other important inherited thrombophilias which increase VTE risk include antithrombin deficiency, protein C deficiency, protein S deficiency, and prothrombin mutations [41].

9.5 Controversy Regarding Third- and Fourth-Generation Progestins

In regard to examining VTE risk associated with the progestin component of COCs, studies have contributed conflicting and sometimes biologically confusing data [21, 22, 43–48]. This has led to scientific debate about how the progestin in particular

CHCs modifies VTE risk. The majority of studies finding a differential effect by progestin are database studies, based on retrospective review of medical records and insurance claims or case-control studies. A consistent twofold increase in the risk of VTE with third-generation and fourth-generation progestins compared to levonorgestrel or LNG (a second-generation progestin) has been reported in these studies; however, this effect has not been observed in larger, prospective studies.

Combined hormonal contraceptives containing third-generation progestins were introduced in the 1980s, and by the 1990s epidemiologic studies were published warning of increased VTE risk compared to second-generation pills [21, 22, 43, 45]. A case-control study by the WHO found increased risk with desogestrel (OR 2.4 [1.4–4.9]) and gestodene (OR 3.1 [1.6–5.9]) compared to LNG [21]. A case-control study by the Transnational Research Group also found an increased risk with third-generation pills compared to LNG pills (OR 1.5 [1.1–2.1]) [45]. Additionally, a retrospective study using the UK General Practitioner's Research Database found increased risk with desogestrel and gestodene compared to LNG, with similar risk estimates to the prior studies [22]. In response to these findings, in 1995, the UK Committee on the Safety of Medicine issued a "Dear Doctor" letter and an emergency media announcement, which created the first "pill-scare." Finally, the MediPlus study was published in 1998, analyzed a separate database from the UK, and failed to demonstrate this effect after age was identified as a major confounder [49].

About a decade later, a second "pill-scare" emerged. In 2009, a study using the Danish National Database by Lideegaard and colleagues found increased risk with desogestrel and gestodene, as well as increased risks with drospirenone and cyproterone acetate compared to LNG—with similar risk estimates to the prior studies [46]. The MEGA study, a Dutch case-control study, found even higher risk estimates [48]. Further observational studies in the United States and UK supported these findings, with an approximate twofold increase in risk of VTE in drospirenone-containing pills [50, 51]. Criticisms of these studies included limitations in the collection of baseline characteristics, notably missing data of key confounders. Despite these limitations and an acknowledgment that causality could not be determined, this prompted the US Food and Drug Administration (FDA) to publish a Drug Safety Communication in 2012, warning of potential higher risk with drospirenone. Similar fears in Europe led to Diane® (EE/cyproterone acetate) being pulled from the market in France, despite a near unanimous recommendation for continued approval from the Pharmacovigilance Risk Assessment Committee (PRAC), the French National Agency for the Safety of Medicine and Health Products.

While the epidemiologic data has received significant attention in the popular media, by lawyers, and by regulatory agencies in the United States and Europe, caution should be used in interpreting such studies. There are inherent methodological limitations to these studies including missing data on baseline confounders (age, smoking, BMI, personal/family thrombosis history), unconfirmed VTE diagnosis, misclassification of duration of use, and other sources of information and detection bias [38]. Prospective studies provide better risk estimates by accounting for these limitations, and the data from these studies do not show a differential effect based on progestin.

The European Active Surveillance (EURAS) study, which included over 58,000 new contraceptive pill users and provided over 140,000 woman-years of follow-up, found no difference in risk estimates of VTE between drospirenone and LNG or other oral contraceptives; the adjusted hazard ratio for drospirenone versus levonorgestrel was 1.0 (0.6–1.8) [52]. The International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC) study, followed over 85,000 American and European women and again failed to find a difference in VTE risk based on progestin type—the adjusted hazard ratio for drospirenone versus levonorgestrel was 0.8 (0.4–1.5) [53]. Both of these studies have low loss-to-follow up (2.4% and 3.3%, respectively), account for baseline differences, and reflect real-world prescribing habits. A US study found similar results—the adjusted hazard ratio for drospirenone was 0.9 (0.5–1.6) [54]. Furthermore, the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC) study demonstrated no difference in VTE risk between users of the etonogestrel/ethinyl estradiol vaginal ring and combined oral contraceptive pills [9].

Even with this prospective data, the debate continues among experts. More prospective studies are needed to clarify this debate. Furthermore, the available evidence should be critically evaluated for confounding and bias.

9.6 Critically Evaluating the Evidence

In any scientific investigation, several factors related to study design influence the validity of conclusions reached. No randomized trials have been conducted to evaluate different effects of progestogens on VTE risk. Retrospective database and case-control studies can be informative in examining rare outcomes when RCTs are not feasible; however, they are limited in their collection of confounding variables (to identify differences in baseline characteristics), use of appropriate comparison groups, and ability to draw conclusions of causality. Additional concerns with these epidemiologic studies include problems with clinical care trends over time, exposure measurements (duration of use), and outcome measurements including under-ascertainment of VTE incidence, inability to confirm VTE diagnosis, and diagnostic bias [55, 56]. Moreover, VTE is a rare event and studies are typically not powered to detect differences in these outcomes. Again, prospective studies therefore provide the best data for risk estimates.

Many baseline characteristics are known risk factors for VTE and must be accounted for when comparing groups. Obesity is a known risk factor for VTE [38–40] and must be adjusted for. Given the rise in population obesity in recent decades, cohorts used today are difficult to compare to historical cohorts. Additionally, polycystic ovarian syndrome (PCOS), associated with obesity and hyperandrogenic symptoms, may be an independent risk factor for VTE [57, 58]. Furthermore, these patient characteristics may lead to preferential prescribing of newer, anti-androgenic formulations for non-contraceptive benefits to women with baseline higher VTE risk. Heritable thrombophilia conditions are another important independent risk factor for VTE and can differ between populations studied. Factor

V Leiden mutations are most commonly found in white people, present in up to 5% of the Caucasian population [13, 59]. This population effect must be considered in evaluating large database studies performed in European populations. Significant VTE risk factors also include age, smoking, malignancy, and genetic factors, which are not always accounted for in baseline characteristics of epidemiologic studies.

We have also seen a new-user effect, whereby higher risk of VTE is observed in new users of combined hormonal contraception [52, 60]. Among new users, the risk of VTE is highest in the first several months with the adjusted rate ratio peaking in the first year of use and subsequently decreasing thereafter. This observation is seen for both second- and third-generation pills [60]. This creates an effect referred to as a "cohort of survivors," where healthy patients or those who are inherently at lower risk are selected for over time. New users therefore are untested in regard to their baseline risk, and we would expect those with higher risk for an event to experience that event when they initiate therapy [38, 61]. Studies that compare new users to existing users allow this type of selection bias to occur. In addition to new users being untested for potentially unknown or undiagnosed risk factors, we also observe an increased risk of VTE in women who have used COCs, stop using, and then resume use—even with the same pill [62]. This may be explained by the physiologic changes that occur in response to a changing hormonal environment and an equilibrating period required for any new exposure. Interestingly, we also observe higher risk of VTE in women switching between pills or from the pill to the transdermal patch or vaginal ring [62, 63], which may also represent subtle changes in the hormonal environment and its effect on the coagulation system. Moreover, given the increased risk of VTE with age and the accumulation of other medical comorbidities with time, it can be challenging to compare different episodes of use even in the same woman.

We also must consider how changes in the field of medicine over time have influenced prescribing patterns, particularly in higher risk populations. The range of contraceptive options available during the 1980s and 1990s, the time frame of many of these epidemiologic studies, was more limited than today. More women used pills overall, including higher risk women who today may be counseled to consider other methods. We have observed an evolving understanding of VTE and cardiovascular risk during this time as well. Newer pills were developed containing lower estrogen doses and with later-generation progestins, with decreased androgenicity. These were meant to mitigate androgen-related side effects and to treat hyperandrogenic symptoms in women with conditions like PCOS. This creates a cohort of higher risk women who may have preferentially been prescribed newer pills, and thus, comparisons between pill formulations without accounting for confounders can lead to faulty conclusions.

One example of preferential prescription bias is seen in the study by Farmer and Lawrenson [64], examining the World Health Organization, Transnational, and UK General Practitioner's Database studies, which found an inverse dose-response for estrogen and VTE risk (Table 9.2). Women using 20 μg EE pills (which were newer pill formulations including newer progestins) had higher VTE risk compared to women taking 30 μg EE pills—opposite of the expected estrogen dose-dependent

Table 9.2 Paradoxical decrease in risk with higher E2, an example of prescribing bias [64]

Study	Reference	Case patients	OR	95% CI	Case patients	OR	95% CI
			Desogestrel + 20 µg EE			*Desogestrel + 30 µg EE*	
WHO	Nonusers	8	38.2	4.5–325	27	7.6	3.9–14.7
Transnational	LNG	13	2.8	1.3–6.5	32	1.5	0.9–2.5
BCDSP	LNG	4	2.7	NA	26	1.9	NA
MediPlus UK	LNG	13	2.9	0.9–10.0	19	0.6	0.3–1.5
			Cyproterone + 35 µg EE			*Cyproterone + 50 µg EE*	
WHO	LNG	9	5.1	1.3–20.3	9	1.3	0.5–3.8

OR odds ratio, *CI* confidence interval, *EE* ethinyl estradiol, *LNG* levonorgestrel, *NA* not available in the publication

Inverse dose-response relationships with dose of estrogen with desogestrel and cyproterone from UK and German MediPlus Database Study

Taken from Farmer, R.D. and R.A. Lawrenson, *Oral contraceptives and venous thromboembolic disease: the findings from database studies in the United Kingdom and Germany.* Am J Obstet Gynecol, 1998. **179**(3 Pt 2): p. S78–86

effect. This suggests preferential prescription of newer pills to higher risk women. At the same time, it was discovered that low-androgen progestogens can increase high-density lipoprotein cholesterol (HDL), a cardioprotective factor, which may have led to preferential prescribing in higher risk women with underlying cardiovascular risk or disease. This has been demonstrated in several studies. In a Dutch study, women being treated with cardiovascular medications were more likely to be prescribed third-generation pills compared to second-generation pills [65]. Likewise, the European Active Surveillance (EURAS) study demonstrated that drospirenone pills were more commonly prescribed to obese women and those with preexisting arrhythmias, indicating a higher baseline risk in this group compared to those using levonorgestrel or other progestin-containing pills [52].

Also important is the effect of detection bias regarding VTE diagnosis in older vs. newer studies. Advances in imaging like Doppler ultrasound and computed tomography have improved diagnosis of smaller thrombi, which may or may not be clinically important. Diagnostic bias might also be introduced when women with perceived higher risk are more likely to have tests performed. In a German survey, physicians were more likely to prescribe third-generation pills to higher risk patients and also to refer these women for DVT workup even for nonspecific symptoms [66].

Funding for a study is also a potential form of bias that should be considered, as many contraceptive studies are funded by pharmaceutical companies. However, it should also be noted when these investigations have been mandated by regulatory agencies who review their protocols and are approved independently by review boards.

9.7 Patient-Centered Contraceptive Counseling

What does this mean for our patients? Contraceptive counseling should be guided by evidence about risks and benefits of the method, which are individualized to the patient's preferences and with consideration of her comorbidities. The Medical Eligibility Criteria for Contraceptive Use published by the CDC and the WHO provide useful guidelines regarding safety of birth control methods in women with medical conditions [34, 35]. To date, besides screening for the known risk factors in a woman's history, there are no cost-effective universal screening tests for VTE risk in women initiating combined hormonal contraceptives [67].

In deciding on a birth control method, women consider efficacy, side effects including bleeding pattern, ease of use (which may be lifestyle and patient specific), confidentiality, perceived self-control, and cost. Women consider both positive and negative side effects, and it is important to understand how these considerations influence tolerability and continuation of a method. Side effects are commonly cited as the reason for discontinuation of a method. The many non-contraceptive benefits of birth control will be discussed in the next chapter.

Another important counseling point regarding efficacy relates to cyclic versus extended or continuous dosing and the hormone-free interval. As lower dose pills have been developed, the suppression of the HPO axis is decreased, particularly in the hormone-free interval or with missed doses. As such, lower estrogen dose pills and longer hormone-free intervals are associated with increased follicular development and potential higher risk of ovulation and unintended pregnancy [68, 69]. Pill formulations with shorter hormone-free intervals and the ability for continuous cycling should be offered.

9.8 Conclusions

Patients expect their physician to prioritize their safety and preferences and to provide them with accurate information regarding risks and benefits of therapeutic interventions. In counseling patients regarding birth control, this means not only discussing the efficacy of each method and factors specific to her compliance (given the risks of an unintended pregnancy) but evaluating a patient's baseline risk factors and sharing our knowledge of the body of literature.

We should always evaluate available data with a critical eye for bias and confounders, as well as what is lacking in the evidence. Since DVTs are a rare outcome, randomized clinical trials (the gold standard in examining the relationship) are not feasible. Therefore, we must use the next best data available, while being aware of its limitations.

Despite the heterogeneity in study results regarding the safety of different progestins [13], we must emphasize that the risks of VTE are substantially higher in pregnancy than in women using COCs, both those with and without additional risk factors for VTE, so finding a method which a patient continues is essential in preventing an unintended pregnancy.

Finally, in the development of new hormonal methods of birth control, our focus should be on preparations that reduce the impact of estrogens on the liver. This includes using estradiol (E2) or estradiol valerate (EV2), estetrol (E4), and possibly even estriol (E3) which do not produce the active metabolites seen with EE. We should also take advantage of alternative routes of administration to avoid first-pass metabolism. For example, E2-containing contraceptive vaginal rings are currently being studied. Development of these alternatives will enhance safety for all patients.

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Non-contraceptive Benefits of Hormonal Methods

10

Renato Seracchioli, Simona Del Forno, and Eugenia Degli Esposti

10.1 Introduction

The development of combined hormonal contraceptives is regarded as one of the most groundbreaking achievements in public health of the last century [1]. Initially introduced in the USA in 1960 to prevent unplanned and unintended pregnancies, combined oral contraception (COC) has been used by hundreds of millions of women [2], and it is estimated that nowadays 100–150 million women use them on a daily basis [3]. COC is the second most common method of reversible contraception and has the widest geographic distribution of all modern contraceptive methods [4].

In addition to combined oral contraceptives, which contain both estrogen and progestogen compounds, progestogen-only contraceptives have been developed, and many different formulations are available nowadays, including oral preparations, monthly injections, implants, and intrauterine devices (IUDs) [5].

Since their approval, a growing number of studies have demonstrated that hormonal contraceptives may have several additional health benefits for users (Table 10.1). In the short term, combined oral contraceptive pill reduces many troublesome side effects related to menses, whereas in the long term it reduces the risk of different type of cancers, most notably ovarian and endometrial cancer [6]. In particular, the extensive use of HCs has highlighted its positive effects on many health issues and diseases affecting women, such as [4, 7]:

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Table 10.1 Non-contraceptive benefits of hormonal contraceptives

Established benefits of hormonal contraceptives
• Menses-related – ↑ Menstrual cycle regularity – ↓ Menstrual blood flow – ↓ Iron-deficiency anemia – ↓ Dysmenorrhea – ↓ Premenstrual syndrome • Inhibition of ovulation – ↓ Ectopic pregnancy • Other – ↓ Acute PID – ↓ Endometrial and ovarian cancer
Emerging benefits of hormonal contraceptives
• Positive effects on bone mineral density • Acne, hirsutism, and hyperandrogenism • Colorectal cancer • Endometriosis • PCOS

- Ovarian and menstrual cycle:
  - Reduction of dysmenorrhea
  - Reduction of dysfunctional uterine bleeding
  - Improvement of premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS)
- Endometriosis
- Polycystic ovarian syndrome (PCOS)
- Hirsutism, acne, and hyperandrogenism
- Pelvic inflammatory disease
- Ectopic pregnancy
- Bone mineral density
- Gynecological and non-gynecological cancer incidence

On the other hand, HCs are not devoid of risks and side effects, and the lay press and media influence on this topic has been far-reaching, negatively influencing women's and in some instances general practitioners' ideas of hormonal contraceptives [8]. Common side effects are generally self-limiting and usually decrease with duration of use, whereas serious adverse effects, like venous thromboembolism, are rare among healthy users. Moreover, many false beliefs about hormonal contraception, particularly regarding weight gain, fertility impairment, and oncologic risk, have been proven wrong by several studies [2, 9, 10]. Additionally, no evidence of increased mortality in ever HC users was found by long-term follow-up studies [11, 12]. Also long-acting reversible contraceptives are highly effective in typical use and show a very low risk profile [5].

Patients who are well-informed about the efficacy of HC, its risks and side effects, and the additional non-contraceptive benefits are more likely to choose them, avoiding unplanned pregnancies and all the psychological, economic, and social burdens they carry [7].

10.2 Menstrual and Ovarian Cycle

The non-contraceptive benefits associated with HC, and in particular with COC, are mainly due to its mechanism of action: inhibition of ovulation and local progestin effects on the endometrium and other reproductive trait tissues [13]. One of the most frequent off-label indications for COC is the treatment of menstrual-related disorders. COC has proven itself effective in improving dysmenorrhea, irregular bleeding, and PMS [14].

10.2.1 Dysmenorrhea

Dysmenorrhea is the most common gynecological symptom, affecting up to 50–90% young women [15]. It is defined as severe cramping sensation in the lower abdomen, often accompanied by other disorders such as bloating, headaches, and nausea, all occurring before or during menses [16]. Primary dysmenorrhea refers to menstrual pain without an identifiable associated pathology, whereas secondary dysmenorrhea is caused by an underlying pelvic disorder. Dysmenorrhea has a considerable impact on women's quality of life, work productivity, and healthcare referral, being highly debilitating and accounting for an annual productivity loss of US $2 billion [17–19].

Dysmenorrhea seemly arises from the release of prostaglandins, which results in an augmented myometrial activity and an increased response to vasopressin and leukotrienes [20, 21]. Several studies documented that COC diminishes menstrual prostaglandin release, thus reducing uterine contractility and dysmenorrhea. Indeed, COC seems to be effective in relieving pelvic pain in up to 70–80% of women with primary dysmenorrhea [21–23].

The impact of low-dose hormonal contraception on dysmenorrhea was assessed in a Swedish population in a longitudinal study, demonstrating that prevalence and severity of dysmenorrhea were significantly inferior in COC ever user, both at entry and after 5 years of use, compared to never user ($P < 0.001$ at a 5-year use) [23]. In 1992, Larsson et al. reported that low-dose COC significantly reduced dysmenorrhea: after 6-month treatment, only 4/20 women still complained of menstrual pelvic pain, compared to the 14/20 before the treatment ($P < 0.05$) [24]. More recently, a randomized controlled trial (RCT) compared an OC containing 20 μg ethinyl estradiol (EE) and 150 μg desogestrel, with an additional 20 μg EE in the last 5 days, to placebo for 4 months in 52 young women. Menstrual cramps were significantly reduced ($P < 0.001$) in OC users compared to placebo users [25]. Another RCT showed that dysmenorrhea prevalence decreased from 56% to 39% during 6-month use of oral contraceptives containing low-dose EE [26].

A recent RCT compared pain relief provided by estradiol valerate/dienogest and EE/drospirenone using uterine artery Doppler indices and visual analogue scale scores [27]. According to the authors, VAS score was significantly reduced in both treatment groups after a 3-month treatment ($P = 0.0001$), and the two groups were comparable in terms of mean percentage change of VAS score. Moreover, mean

value of uterine artery resistance index was significantly lower after therapy in both groups.

10.2.2 Heavy Menstrual Bleeding (HMB)

HMB is defined as a menstrual blood loss of >80 mL per cycle that cannot be explained by organic pathology or medical illness and affects approximately 10% of fertile women. Excessive blood loss may lead to iron-deficiency anemia and in some cases necessitate invasive surgical treatments, such as hysterectomy [14]. Early anecdotal evidence strongly supported the role of COC on reducing menstrual blood loss and irregular bleeding. This conclusion was based on studies performed several years ago, showing that high-dose COC reduced menstrual blood loss by up to 50% [28, 29]. Recent studies focused on low-dose COC. Larsson et al. documented a significant reduction in average blood loss in women treated with 30 μg EE/150 μg desogestrel, who passed from an average blood loss of 60.2 ± 3.2 mL to 33.7 ± 4.1 mL after a 6-month treatment ($P < 0.001$). Moreover, the mean duration of menses was significantly reduced during hormonal treatment [24]. Also Fraser et al. reported similar results from their randomized trial involving 45 menorrhagic women, demonstrating a significant reduction in blood loss in women receiving COC [30].

A more recent review by Hoaglin and colleagues compared several treatment classes, including levonorgestrel-releasing intrauterine device and endometrial ablation. Results showed that COCs were effective and comparable with long-term progestin therapy and danazol in reducing menstrual blood loss [31]. Newer estradiol (E2)-based COCs are also showing promising results in treating HMB. Results from some recent studies show that E2-based regimens lead to shorter and lighter withdrawal bleedings than those reported by women using the older and more conventional EE regimens. Moreover, this regimen seems to cause fewer overall bleeding and spotting days during the first 90 days of administration [32]. E2-based regimens were also superior to placebo in randomized, double-blinded controlled trials [33, 34]. To date, no head-to-head trial comparing different COC regimens with regard to their impact on HMB has been published, but evidence from recent well-designed clinical trials suggests that newer and lower-dosed COCs successfully reduce the volume of menstrual blood loss with conventional use.

As for the levonorgestrel intrauterine system (LNG-IUS), the treatment of women with HMB is perhaps its most important non-contraceptive benefit and has been observed since the first clinical trials [7]. LNG-IUS use can reduce uterine bleeding in up to 60% of women, in some cases leading even to amenorrhea, and also improves hemoglobin levels, iron stores, and anemia [35]. Moreover, the efficacy of this device is almost equal or superior to oral medroxyprogesterone acetate (MPA) and endometrial ablation, with an overall risk failure of 13.4% [36, 37]. LNG-IUS can be effectively used to treat HMB due to different causes, including hemostatic disorders, coagulation deficiencies, and anticoagulant drugs [38]. In a randomized controlled trial, Gupta and colleagues evaluated the efficacy of LNG-IUS in the treatment of HMB compared to usual medical treatment (tranexamic

acid, combined oral contraceptives, or progesterone alone) over a 2-year period. Despite observing an improvement in both groups, HMB was significantly lower in the LNG-IUS group and persisted through the period of evaluation [39].

10.2.3 Dysfunctional Uterine Bleeding

Low-dose hormonal contraceptives seem effective in treating dysfunctional uterine bleeding, such as metrorrhagia, menometrorrhagia, oligomenorrhea, and polymenorrhea. A recent randomized, double-blind, placebo-controlled trial demonstrated that more than 80% of women subjected to active treatment with low-dose COC experienced improved bleeding patterns and, more significantly, an improvement from baseline quality of life scores regarding physical functioning [40].

10.2.4 Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

During fertile years, 80–90% of women will experience troublesome symptoms (breast tenderness, bloating, acne, constipation) that negatively impact their quality of life [15], the so-called PMS. Premenstrual syndrome refers to the cyclic recurrence of emotional, physical, and behavioral changes in the luteal phase of the menstrual cycle that remit within 4 days following menses onset [41]. A more severe variant of this syndrome is PMDD, which comprehends serious, mostly psychiatric symptoms that cause major interferences with day-to-day activities and interpersonal relationships. It is estimated that 13–18% of women show evidence of cyclical patterns of distress, treatment-seeking, and life interference. Symptoms of PMDD can be similar to those found in major depressive disorder, panic disorder, and posttraumatic stress disorder [42]. Up to 40% of patients are unresponsive to the standard therapy with selective serotonin reuptake inhibitors [43].

COC has been given to women suffering from PMS or PMDD for over 40 years, but the relief of PMS-related symptoms is apparently associated only with specific COC regimens. Since women with PMS demonstrate an abnormal emotional sensitivity to normal fluctuations of estradiol and progesterone [44], the stabilization of hormonal levels may represent a target for the treatment of this syndrome. Indeed, the suppression of ovarian function, as observed during pregnancy, lactation, hypothalamic amenorrhea, or using GnRH agonists leads to PMS disappearance [45, 46].

Several recent RCTs examined COCs containing EE and a progestin (drospirenone or levonorgestrel) to treat PMS. Typical 21/7 regimens were apparently ineffective compared with placebo [47], whereas two COC trials using 20 μg EE combined with 3 mg drospirenone in a 24/4 regimen have shown significant benefit compared with placebo [48, 49]. In particular, physical and emotional symptoms of PMDD were significantly reduced. On the other hand, Coffee et al. demonstrated a significant improvement in premenstrual symptoms among long-term users of a conventional 21/7 regimen of 30 μg EE and 3 mg drospirenone [50].

Recently Eisenlohr and colleagues reported no significant differences in terms of PMS-related symptoms improvement using either intermittent or continuous combination of 20 μg EE and 3 mg drospirenone. Both treatment regimens seem to lead to a significant decline in premenstrual symptoms. However, similar results were reached also in the placebo group, suggesting that further investigation is needed concerning the role of COC as a treatment for PMS [51].

10.3 Endometriosis and Adenomyosis

Endometriosis is defined as the presence and/or growth of endometrial tissue, both epithelium and stroma, outside the uterine cavity [52]. It affects 10–15% of reproductive-aged women and up to 50% of women with a history of infertility and 80–90% of women complaining of chronic pelvic pain [53]. A minority of patients is asymptomatic, but most are affected by pelvic pain, dysmenorrhea, dyspareunia, dyschezia, and dysuria, greatly reducing their quality of life [54]. Given its estrogen-dependent nature, hormonal contraceptives represent a potential treatment for endometriosis-related symptoms, especially dysmenorrhea, for women wishing to preserve their fertility and needing effective contraception. Progestogen-only methods may be generally preferable since they create a progestin-dominant hormonal environment that reduces nerve fiber density, inhibits angiogenesis, and possibly reduces inflammation in endometriotic lesions [55–57].

There has been debate in literature regarding the potential role of COCs in the development of endometriosis. In fact, it has been postulated that estroprogestins might lead to endometriosis progression, since they cause supraphysiologic levels of estrogens [58]. A large meta-analysis of 18 studies showed that the relative risk of endometriosis onset was 1.19 in ever users of COC, 0.63 in current users, and 1.21 in past users [55]. Furthermore, a cross-sectional study by Chapron et al. found that women who had previously used COC for the management of severe dysmenorrhea were more likely to be diagnosed with endometriosis at a later date [59], a result confirmed also by other authors [60].

On the other hand, according to some studies COC could positively influence endometriotic lesions; in particular, two studies found that size of endometriomas decreased with the use of combined oral contraception [61, 62]. Even so, the administration of conventional COCs in a cyclic regimen could expose women to the risk of experiencing dysmenorrhea and chronic pelvic pain during the hormone-free interval [63]. A recent meta-analysis by Zorbas et al. showed definite benefits of the continuous COC regimen: in particular, two studies by Seracchioli et al. found a positive trend toward favoring the continuous regimen regarding size and growth of endometriomas [64, 65], which was further confirmed by Vercellini et al. [66].

As for the recurrence rate of endometriosis after surgical treatment, a recent systematic review pooled the results of two RCTs, a prospective cohort trial and a prospective clinical trial employing different combinations of estroprogestins either used cyclically or continuously [67]. From the analysis of data, there seems to be a growing body of evidence supporting continuous COC regimes as a more effective

treatment for patients subjected to surgery. These findings appear in line with other studies available in literature, which show that the use of COCs reduces the risk of disease recurrence [64, 66, 68–70].

Regarding symptoms, the European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend to prescribe either progestins (level A) or hormonal contraceptives (level B), to reduce endometriosis-associated pain [71]. However, no clear data exist with regard to the best combination, based on the type of endometriosis and the age of the woman being treated [72].

To date, women have a wide choice of oral estroprogestin combinations, evolving from the predominant use of synthetic EE to estradiol-17β, the natural estrogen produced by the ovaries [73]. Moreover, several new progestogens have been developed, including dienogest, drospirenone, nomegestrol acetate, and desogestrel, to individualize contraception as much as possible.

Several studies suggest that desogestrel [66], gestodene [74], norethisterone [61], drospirenone [62], and levonorgestrel are all effective in reducing dysmenorrhea in the majority of women with endometriosis. In a recent systematic review, Grandi et al. analyzed the results of 17 studies, including more than 700 women [72]. The efficacy on endometriosis-related pain of almost all COCs containing EE combined with different generations of progestins, and of a COC containing E2, was demonstrated. However, a significant improvement in comparison with placebo was obtained only with EE and norethisterone acetate [61] and a flexible regimen employing EE and drospirenone [75]. In addition, the reduction of dysmenorrhea was usually associated with a decrease in chronic pelvic pain and dyspareunia, leading to an improved quality of life. Jensen et al. found similar results in another literature review [76].

Dienogest, a fourth-generation selective progestin, combines the pharmacological effects of 19-nortestosterone, having both an anovulatory and an antiproliferative effect on endometriotic lesions. A recent meta-analysis on the effects of different doses of dienogest (2 mg/day vs. 4 mg/day) showed a significant reduction in terms of severity of endometriosis evaluated by rASRM score for both doses, with no significant differences between them. Moreover, both groups showed a significant and comparable improvement in terms of clinical painful symptoms [77]. Furthermore, a recent retrospective study conducted on 116 women demonstrated the efficacy of dienogest-based hormone therapy in reducing endometrioma's volume, if administered for 1 year, both alone and combined with EE. In particular, all women who received only diegnost had a volume reduction >50%, 82.3% had a volume reduction >75%, and 76.5% had a volume reduction of 100% [78]. These encouraging findings appear in line with another two studies conducted on dienogest alone: the first one demonstrated a maximal endometrioma reduction of about 70% after a 15-month treatment period [79], while the second one showed a less pronounced but significant effect after 12 months, as well as a consistent reduction in terms of chronic pelvic pain, dysmenorrhea, and dyspareunia. Good results, both clinically and ultrasonographically, were also achieved by treatment with norethindrone acetate, but the decrease was significantly lower in the norethindrone group; moreover, women who received norethindrone acetate complained more frequently of uterine bleeding and spotting and weight gain [80].

Various studies have been conducted also on the effects of nomegestrol acetate (NOMAC), combined with EE. This progestin has a long half-life, up to 50 h, and is thus able to cover the 4-day hormone-free interval by its steroidal effects. Very recently, Caruso et al. compared a 6-month treatment with EE/NOMAC with no hormonal treatment, demonstrating that the combination of EE/NOMAC extraordinarily improved painful symptoms, in particular chronic pelvic pain, dysmenorrhea, and dyspareunia [81].

Upon the whole, the interpretation of these findings is complicated, due to many superimposed conditions that contribute to pelvic pain in endometriotic patients, such as PID, and the possibility that different lesions might respond differently to treatment. Despite this evidence, clinicians should bear in mind that almost all of the currently available hormonal drugs are suppressive and do not actually eliminate the disease, so the relapse of symptoms is fairly common at therapy discontinuation [82]. Furthermore, around 30% of women treated with hormonal contraceptives is unresponsive, probably due to an imbalance of estrogen and progesterone receptors, determining an intrinsic progesterone resistance [83].

To date, no definite evidence exists about the exact role of COC as a treatment option for endometriosis, even though results are encouraging [84]. Moreover, insufficient data are available to support the overall superiority of any given COC regimen and the relative benefit in comparison to other approaches [76]. The presence of a low-dose estrogen component may be advantageous in terms of bleeding control, thus maximizing therapy adherence. Preparations containing the lowest possible levels of EE or E2 should be the first-line choice, since the estrogenic content affects the risk of venous and arterial thrombosis and might lead to the progression of endometriosis itself [73].

As for LNG-IUS, many publications show its efficacy in alleviating endometriosis-caused dysmenorrhea, especially in women also presenting with adenomyosis. Results from some RCTs show that both LNG-IUS and GnRH agonists reduce pain scores measured on the visual analogue scale, without significant differences between GnRH users and LNG-IUS users. Also, both treatments improved staging scores and quality of life [85–87]. The mechanism of action of LNG-IUS on pain relief probably involves high intrauterine levels of levonorgestrel, a depletion of estrogen receptors, and a reduction of endometrial cell proliferation [88, 89].

Women with adenomyosis particularly benefit from the insertion of the LNG-IUS, since this device reduces the thickness of the junctional zone and total uterine volume, thus reducing menstrual blood loss and pain. Heavy menstrual bleeding is a key feature of uterine adenomyosis, and its improvement could be imputed to the direct effect of LNG on foci of adenomyosis with decidualization and hypotrophy of the endometrium [90]. The reduction of pelvic pain could be explained by the effect of levonorgestrel on the vascular supply to the pelvis, allowing relief from pelvic congestion. However, the efficacy of LNG-IUS apparently decreases after 2 years of placement, and some reports indicate that the intrauterine device should be replaced before its 5-year life span [91, 92].

10.4 Polycystic Ovarian Syndrome (PCOS), Hirsutism, and Acne

Polycystic ovarian syndrome is a heterogeneous disease involving reproductive and metabolic factors, with a worldwide prevalence of 7–14% [93]. According to the American Society for Reproduction Medicine, PCOS should be diagnosed if two out of three of these features are present: oligo- and/or anovulation, hyperandrogenism (HA), and polycystic ovaries [94]. Excessive androgen biosynthesis is a key pathogenetic mechanism of PCOS, along with insulin resistance and compensatory hyperinsulinism, with a tendency to favoring visceral fat deposition [95–97]. This in turn may lead to dyslipidemia, metabolic syndrome, hypertension, and endometrial cancer, due to the unopposed estrogen exposure caused by anovulation. In addition to lifestyle management, recommended for all patients with this syndrome, combined oral contraceptives, especially those with antiandrogen properties, can be helpful in reducing hirsutism and acne, by reducing testosterone bioavailability [98–100]. In fact, the progestin component of COCs suppresses the secretion of LH and decreases the ovarian androgen production, whereas the estrogenic fraction increases the levels of sexual hormone-binding globulin [101]. Moreover, the use of COC has been proven effective in protecting against endometrial cancer [102].

On the other hand, estrogens can worsen insulin sensitivity and increase the risk of thromboembolic and cardiovascular disease, particularly in women already at risk, such as those with PCOS [103, 104]. Recently, insulin sensitizers like metformin have been proposed as an alternative to COC, despite being ineffective for hirsutism. However, the evidence supporting their being safer than COC is limited [105, 106].

10.4.1 Impact on Acne and Hirsutism

Recent guidelines support the use of hormonal contraceptives as first-line management for concurrent treatment of menstrual abnormalities and clinical manifestations of hyperandrogenism [107, 108]. According to some authors, the use of third-generation hormonal contraceptives (containing gestoden or desogestrel) should be beneficial, as they are less androgenic. Also, the use of antiandrogenic progestins (dienogest, drospirenone, cyproterone acetate) may be recommended, since they directly antagonize the androgen receptor or inhibit the enzyme 5α-reductase activity [109]. A recent systematic review of RCTs comparing COC with different doses of ethinyl estradiol and different types of progestins demonstrated that the greatest improvements in the Ferriman-Gallwey score were obtained with COC containing cyproterone acetate [110]. Indeed after a 3-month treatment with cyproterone acetate, hirsutism subjectively improved in 83% of patients and acne in 40% [111]. Drospirenone was also shown to be effective after a 6-month course, improving acne [112], trunk acne [113], and significantly reducing skin

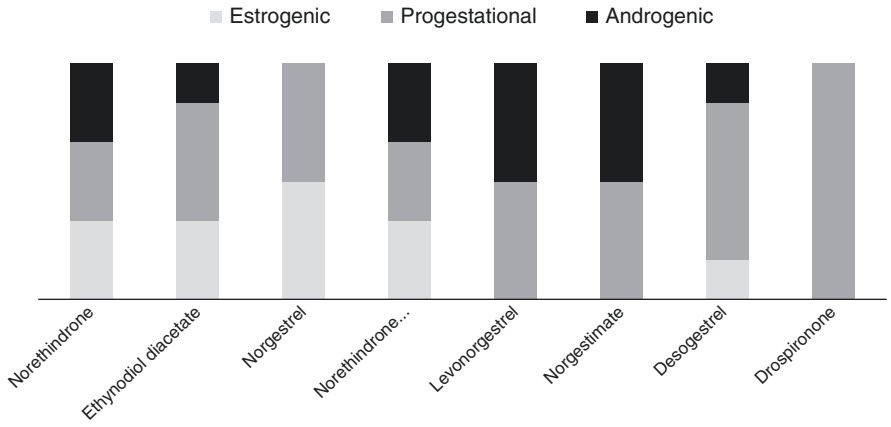

Fig. 10.1 Different hormonal effects (estrogenic, progestational, and androgenic effects) of common progestins

problem treatment costs [114]. Finally, a large meta-analysis of 56 clinical studies, including 2266 patients, reported the efficacy of dienogest on acne [115]. The different hormonal effects (estrogenic, progestational, and androgenic effects) of common progestins are reported in Fig. 10.1.

10.4.2 Impact on Metabolic Parameters and Cardiovascular Risk Factors

It has been postulated that the use of COC in women affected by PCOS may have a greater impact on cardiovascular disease risk, as explained above [116, 117]. On the other hand, some authors suggested that lowering serum androgens with COCs may provide a metabolic benefit, as androgens have been proved to reduce insulin sensitivity and adipocyte function [118]. World Health Organization and Centers for Disease Control and Prevention 2016 guidelines include obesity, hypertension, diabetes, and known dyslipidemia as relative contraindications to COC use (category 2), suggesting that the advantages linked to their use might be greater than their risks.

10.4.3 Impact on Glucose Tolerance

The use of COC in women with diabetes, either insulin or non-insulin-dependent, has limited effect on long-term control of the disease [119]. A recent Cochrane review concluded that COC had no significant effects on glucose metabolism and tolerance in women without diabetes [120]. Another meta-analysis including women with PCOS treated with COC for 3–12 months did not show any significant change in fasting glucose levels, insulin levels, and insulin resistance [121]. However, few studies have evaluated glucose metabolism after randomizing women

with PCOS to different types of COC. One RCT compared the effects of COC containing either drospirenone or desogestrel: women receiving drospirenone had a significant decrease in fasting glucose and insulin levels, whereas those receiving desogestrel showed a relevant increase of both.

Apparently, the use of COC does not seem to significantly influence carbohydrate metabolism; however, most evidence is derived from small studies including women with a normal BMI. Therefore, women with PCOS using COC should be screened for changes in glucose metabolism at regular intervals, especially if they present additional risk factors for diabetes [119].

10.4.4 Impact on Venous and Arterial Thromboembolism

As confirmed by a recent Cochrane review, the use of COC increases the risk of venous thromboembolism (VTE) in the general population (relative risk 3.5, 95% CI 2.9–4.3) [103]. This risk seems to be related to the dose of ethinyl estradiol and the type of progestin, being 50–80% higher with gestodene, desogestrel, cyproterone acetate, and drospirenone than with levonorgestrel. This might be due to the intrinsic ability of each progestin to modulate the effects of estrogen [122]. Evidence about the risk of venous thromboembolism is conflicting, with some studies reporting a lower incidence of VTE in women with PCOS using COC compared to nonusers [123] and others showing a twofold increased risk of VTE in women with POCS taking hormonal contraceptives [124]. However, the absolute risk of venous and arterial thrombosis is low in the young population. Women with PCOS assuming continued low-dose COC should regularly be assessed in order to identify potential associated risk factors.

Despite the little evidence about the optimal estroprogestinic combination, some authors suggest the use of COC with a lower dose of ethinyl estradiol combined with a less androgenic progestin or an antiandrogenic one [119]. It is arguable that the use of COCs in women with PCOS might augment the risk of cardiometabolic complications, compared to the general population. However, the lack of significant evidence on this and the fact that some authors found a reduced incidence of coronary artery disease and ischemic stroke cases in past COC users compared to neverbusers support the idea that benefits derived from COC use might be greater that their risks [125, 126].

10.5 Pelvic Inflammatory Disease (PID)

PID is an infection of the reproductive tract which is due to the ascent of bacteria from the cervix to the endometrium and fallopian tubes. The rate of sexually transmitted disease (STDs) is rapidly increasing, *Chlamydia trachomatis* being the most prevalent infection in Western Europe [15]. The influence of oral contraceptives on the risk of contracting *Chlamydia* is not yet well understood, since earlier studies suggested a decrease in hospitalization for pelvic infections, whereas in other

studies COC use was associated with an increased risk of chlamydial infection and gonorrhea [127]. A recent observational study conducted in the USA concluded that the use of COC did not have a significant impact on the risk of acquiring either chlamydia or gonorrhea, after adjusting for other risk factors [128], a result confirmed also by Ness et al. [129]. Other authors found that the use of COCs was 4.3 higher in women with asymptomatic endometritis [130]. Moreover, oral contraceptive use is associated with cervical ectopia, a recognized risk factor for *Chlamydia* infection [131].

In contrast with the evidence above, some authors suggest that COCs may reduce the risk of PID via progestin-induced thickening of the cervical mucosa and increased mucus viscosity, which in turn may reduce the risk of pathogens ascending the upper genital tract [132]. Also, the lighter menstrual flow quantity could be another possible protective mechanism, since it reduces the possibility for bacterial growth. Women using COC have been shown to have 50–80% lower risk of salpingitis compared with those using no contraception or a barrier method [133–135].

Three case-control studies found a reduced relative risk of hospitalization for PID among women using COCs, compared to women using no contraception or other contraceptive methods [133–135]. It is estimated that the control of PID with COC annually prevents 50,000 cases of PID and 12,500 hospitalizations in the USA [6]. A large, multicenter, case-control study showed that the relative risk of PID in COC users was 0.5 (95% CI 0.4–0.6), and the same degree of protection was also found by Wolner-Hannsen et al. [135]. An even larger reduction in risk of acute salpingitis in women taking combined oral contraceptives was noted by Eschenbach et al. [136]. Moreover, it was found that oral contraceptives are negatively associated with acute PID, even of chlamydial origin. In addition, among women with acute salpingitis, the occurrence of adhesions, tubal occlusion, and tubo-ovarian abscesses is less frequent in COC users compared to non-users [131], accounting for a decreased severity of the disease [134, 137]. Also, the risk of infertility in women with laparoscopically confirmed salpingitis appeared lower in COC users [138].

10.6 Ectopic Pregnancy (EP)

Ectopic pregnancy is one of the leading causes of maternal death during the first trimester of pregnancy, being responsible for up to 10% of pregnancy-related deaths [139]. Its incidence is rising over the decades, and recognized risk factors include age, previous EP, previous pelvic surgery, use of intrauterine devices (IUDs), tubal sterilization, and previous PID [140].

Even though all contraceptives should reduce the rate of ectopic pregnancy, by preventing conception and in some cases ovulation, women using OC have been shown to have one of the lowest rate of all, with an approximate 90% reduction in risk [141]. The risk of EP in COC users is estimated at 0.005 per 1000 women years, a value comparable to that of vasectomy and lower than that of barrier methods, diaphragm, copper IUD, and even tubal sterilization [6].

A meta-analysis conducted by Mol et al. [142] compared ectopic pregnancy rates among women using different types of contraceptives. They concluded that all contraceptives protected against EP, the most probable mechanism involving ovulation inhibition. In line with these findings, a recent multicentric case-control study by Li et al. [143] found that current use of any type of contraceptive, with the exception of levonorgestrel emergency contraception, significantly reduced the risk of EP, with an adjusted OR for COCs of 0.14 (95% CI: 0.07–0.26). On the other hand, in case of contraceptive failure, current use of COCs and emergency contraception determined a fourfold increase of EP risk compared to women using no contraceptive method.

10.7 Bone Mineral Density (BMD)

COC effects on bone health are well documented and include the recognized influence of estrogens (increased calcium absorption and reduced loss, inhibition of osteoclasts) and the less established effects of progestins (decreased urinary calcium excretion, increased bone mass). Evidence in literature is encouraging but not completely conclusive, since the majority of studies have shown a positive effect on BMD associated with COC use, but many others have not found any relevant effect. Moreover, the longer women used COCs, the greater protection they gained [144, 145].

Early studies of pre- and postmenopausal women seem to highlight the bone-sparing effects of COCs. In fact, one of the first studies conducted on this topic found that a past history of COC use provided protection against low BMD (OR 0.4, 95% CI 0.2–0.5) [144]. A Swedish study showed that premenopausal women treated with COCs not only had higher BMD, but this translated also into protection against hip fracture [146], and this effect lasted over decades. The greatest benefit was noted among women having taken COCs after the age 40 and for at least 5 years. Another study involving women aged 20–69 revealed a 3.3% greater mean BMD at the lumbar spine among premenopausal women exposed to COCs ($P = 0.014$) [147], with a significant correlation with exposure duration. It is well established that estrogen replacement improves BMD in hypoestrogenic and postmenopausal women, but these results suggest that the use of COCs might improve bone mass even in patients with normal estrogen levels.

Despite this, many other studies have failed to find a positive association between oral contraceptives and bone mass, even if no detrimental effect on BMD has ever been shown [148].

As for adolescents, Polatti et al. found that while BMD in COCs users did not change significantly over 5 years of follow-up, but in controls receiving no treatment, this measure increased by 7.8% ($P < 0.01$) [149]. On the other hand, two cross-sectional analyses [150, 151] indicated no differences in BMD between low-dose COC users and non-users.

10.8 Prevention of Cancer

Considering the widespread and long-standing use of combined oral contraceptives, concerns have always been expressed about hormonal contraception's carcinogenic potential. Since their introduction, several studies have investigated the impact of COC on different types of cancer. Overall, the evidence seems to suggest that recent and current users of hormonal contraceptives have a reduced risk of endometrial and ovarian cancer, an effect apparently persisting for many years after therapy discontinuation [2, 7]. The most important study evaluating cancer risk in COC users in a large cohort of patients is the Royal College of General Practitioners' Oral Contraception Study, which has been recently updated [2].

10.8.1 Endometrial Hyperplasia

Although off-label in many countries, the use of LNG-IUS in the treatment of endometrial hyperplasia is effective and preserves fertility among young women. A meta-analysis by Gallos and colleagues evaluated the treatment of endometrial hyperplasia with LNG-IUS or oral progestogens and found higher regression rates with the intrauterine device, both for simple (pooled rate = 92% vs. 66%, $p < 0.01$) and atypical hyperplasia (pooled rate = 90% vs. 69%, $p = 0.03$) [152]. These results are similar to previous studies, which showed endometrial regression in 92% and 67% of cases with simple and atypical hyperplasia, respectively [153]. According to some authors, the main variable associated with failure of treatment with an LNG-IUS is a body mass index ≥35, which is also an independent predictor of relapse (hazard ratio = 18.93, 95% CI 3.93–91-15, $p < 0.001$) [154].

10.8.2 Endometrial Cancer

Estrogen normally exerts a stimulating effect on endometrial cell division, whereas progestins block cell proliferation, protecting from estrogen-induced hyperplasia and determining endometrial shedding during withdrawal bleedings [155]. The effects of COC on endometrial cancer risk have been extensively evaluated, and the first systematic review by Grimes and Economy seemed to indicate that COCs have a clearly protective effect against this type of cancer [156]. This tendency was confirmed by the RCGP Oral Contraception Study, which demonstrated that ever users have statistically significant lower rates of uterine body cancer, with an incidence rate ratio (IRR) of 0.72 (99% CI 0.51–1.13 and a RR of 0.58 (95% CI 0.42–0.79). The Cancer and Steroid Hormone (CASH) Study by Maxwell et al. focused on hormonal potencies and was able to conclude that both high-progestin and low-progestin OC users had a significantly reduced risk of endometrial cancer, but among women with BMI > 22 only high-progestin OC had a protective effect (OR 0.31; 95% CI 0.11–0.92) [157].

The protective effect seems to increase with duration of OC use, as found by most studies. Moreover, protection from endometrial cancer risk seems to persist for at least 15–20 years after cessation of use [157–161]. According to most studies, the beneficial effect of COCs is independent of their formulation and of modulating or known risk factors for endometrial cancer, although in high-risk patients OC formulations with higher progestin potency seem to be more beneficial [155].

As for LNG-IUS, its use has been recently associated with a protective effect against endometrial cancer. A recent study by Soini and colleagues demonstrated that women aged 30–49 years who used an LNG-IUS due to HMB had an observed-to-expected ratio for endometrial adenocarcinoma of 0.50 (95% CI 0.35–0.70) after the first use of LNG-IUS and 0.25 (95% CI 0.05–0.73) after the second use [162]. The possible mechanism associated with this protective effect for endometrial cancer could be the downregulation of estrogen receptors, reducing endometrial cellular proliferation and inducing amenorrhea [7].

10.8.3 Ovarian Cancer

Similar to endometrial cancer, a comparable reduction in the risk of epithelial ovarian cancer (EOC) has been observed among users of COCs. The first to demonstrate a significant risk reduction of ovarian cancer in OC users were Winer et al. [163], using source data from 45 studies. The degree of risk reduction is associated with duration of COC use [164]. According to Beral et al. [165], the worldwide use of COC prevents an estimated 30,000 deaths from ovarian cancer annually. These authors conducted the broadest meta-analysis to date, analyzing data from more than 100,000 women. Apparently, the RR of EOC decreased by 20% for each 5 years of COC use, ranging from 0.69 to 0.81, depending on the study design. A recent meta-analysis showed a clinically relevant reduction in ovarian cancer incidence in ever users compared to never users (OR 0.73, 95% CI 0.66–0.81) [166]. This response was also characterized by a significant duration-response relation, since an incidence reduction >50% was observed among women using COCs for 10 or more years. Many other studies confirmed these findings, in particular by the RCGP's Oral Contraception Study, which found an IRR of 0.67 (99% CI 0.46–0.97) in ever users [2, 159, 167, 168].

COCs might interfere with ovarian cancer development through several ways: inhibition of ovulation, reduction of gonadotropin levels, prevention of the invagination of cells from the Mullerian duct, and regulation of oncogenes [155]. A distinct biological mechanism explaining the risk-reducing effects of COCs however has not yet been identified. Recent data suggest that many high-grade serous EOCs do not arise from the ovarian epithelium, but from the distal fallopian tube, whose epithelium is also influenced by ovulatory cycles [169].

Regardless of the mechanism of action, the benefit effect of COCs on ovarian cancer has made this treatment a staple of the management of reproductive-aged women at high risk for developing EOC, especially those with BRCA-1/2 mutations [170]. However, it should be taken into account that the use of COC in BRCA-1/2

mutation carriers increases their risk of developing breast cancer although the risk is small and barely statistically significant [166, 171].

The protective effects seem greater for serous cancers although Beral et al. observed a risk reduction of >20% per 5 years of use for endometrioid cancers and 12% for mucinous cancers. On the other hand, data concerning the protective effect of COC on borderline ovarian tumors are more heterogeneous, since many studies failed to find a significant decrease in RR [172–174]. Notably, the reduction in RR is maintained for several decades after COC discontinuation, but diminishes in postmenopausal women. The protective effect of OC diminishes slowly 10 years after cessation, although a protective effect has been observed after >20 years or even 30 years. Beral et al. found a RR reduction for ovarian cancer by 48%, 38%, and 31% in women who used COC for 5–9 years and ceased <10 years, 10–19 years, or 20–29 years previously, respectively [165].

10.8.4 Colorectal Cancer

Few studies have examined the influence of COC on colorectal cancer (CRC), but literature is consistent in demonstrating a reduced risk of this type of cancer among COC users.

In a meta-analysis of epidemiological studies on CRC, the pooled RR of CRC for ever users was estimated to be 0.82 [175], although no relationship with COC use duration was noted. The pattern of risk was similar for colon and rectal cancer. Similar RR was also observed in studies conducted afterwards [167, 176–178]. Some authors also noted a greater risk reduction for current users (RR 0.38) compared to former users (RR 0.89) [179, 180]. As for recency of use, evidence is scant but seems to indicate that protection is stronger for recent COC users [167, 176].

As for ovarian cancer, the association between COC and CRC risk reduction lacks a definite mechanism of action, with possible hypothesis ranging from a direct effect of hormone on colorectal mucosa to genetic and epigenetic phenomena [181].

10.9 Conclusion

Over the last decades, hormonal methods have demonstrated their efficacy and safety as a valid contraceptive option for women wishing to avoid unwanted pregnancies. Since their introduction, many studies have first observed and then confirmed the presence of many different non-contraceptive health benefits, finding new therapeutic roles for estroprogestins and progestins. However, many women and many practitioners still remain unaware of this and instead focus only on health risks. Continuous education of patients is imperative, in order to involve women in an informed, conscious choice of the most adequate hormonal method, based on their needs, anamnestic characteristics, and preferences.

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Contraception Cancer Risks and Benefits

11

Philip C. Hannaford and Lisa Iversen

11.1 Introduction

Cancer is a major cause of morbidity and death among women, regardless of where they live. In 2018, an estimated 8.6 million women around the world experienced a new diagnosis of cancer, and 4.2 million died from the disease (Figs. 11.1 and 11.2; Table 11.1) [1, 2]. Overall, women have a near 1-in-6 chance of developing cancer before the age of 75; and a 1-in-10 chance of dying from it.

Major differences between populations in age and socioeconomic profile, the prevalence and distribution of key cancer risk factors, and competing risk of death from other causes, results in substantial geographical variations in the pattern of cancer incidence and mortality (Tables 11.2 and 11.3). These patterns also reflect important global differences in the availability of prevention, screening, diagnostic and treatment services for cancer. Breast cancer is the leading cause of cancer incidence among women in most (154 out of 185) countries around the world, with cervical cancer most frequent in nearly all (28) of the rest (Table 11.2). There is greater variation with respect to the leading cause of cancer-related death, partly because of comparatively high rates of case fatality for many cancers in low income countries. Thus, breast cancer is the leading cause of cancer-related mortality in 103 countries, cervical cancer in 42 countries and lung cancer in 28 countries (Table 11.3).

Soon after combined oral contraceptives (COCs) became available in the early 1960s, informed commentators expressed concern about the cancer potential of this novel method of birth control [3]. The critics highlighted research conducted in the 1930s that linked oestrogen to cancerous uterine and breast growths in mice and

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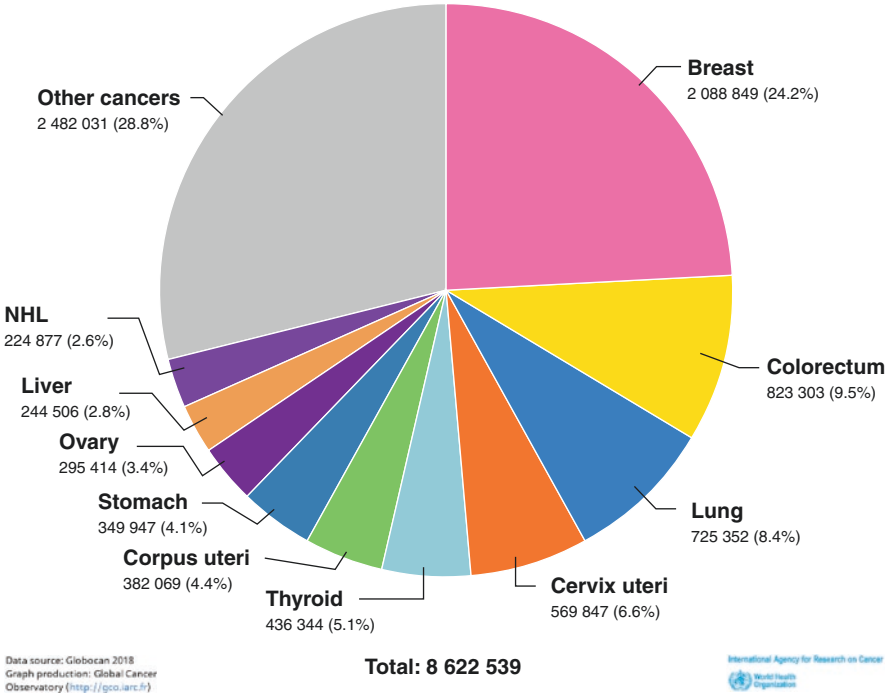

Fig. 11.1 Estimated number of new cases in 2018, worldwide, all cancers, females, all ages

other animals. They also noted that clinical experience gained through the use of hormones to treat infertility or threatened miscarriage during the couple of decades before they were licensed as contraceptives mainly related to use by older women for short durations. This limited usage, the commentators argued, could not adequately inform regulators, clinicians or potential users about the long-term safety of hormones used for contraception by large numbers of healthy young women, for perhaps long durations. Even a small change in cancer risk could have profound public health consequences. Furthermore, the long latent period for cancer development in humans probably meant that a full evaluation of the cancer risks associated with the contraceptive pill would take many years.

Since these concerns were first raised, there have been many hundreds of animal, laboratory and epidemiological studies looking at the possible link between COCs and cancer. Fewer studies have assessed cancer risks among users of other methods of birth control. Investigating the carcinogenic potential of contraceptives has been complex and time-consuming for a number of reasons:

1. It has been unclear whether changes seen in *in vitro* laboratory experiments, or *in vivo* studies of mice, rabbits, beagles, primates or other animals, are relevant to women.

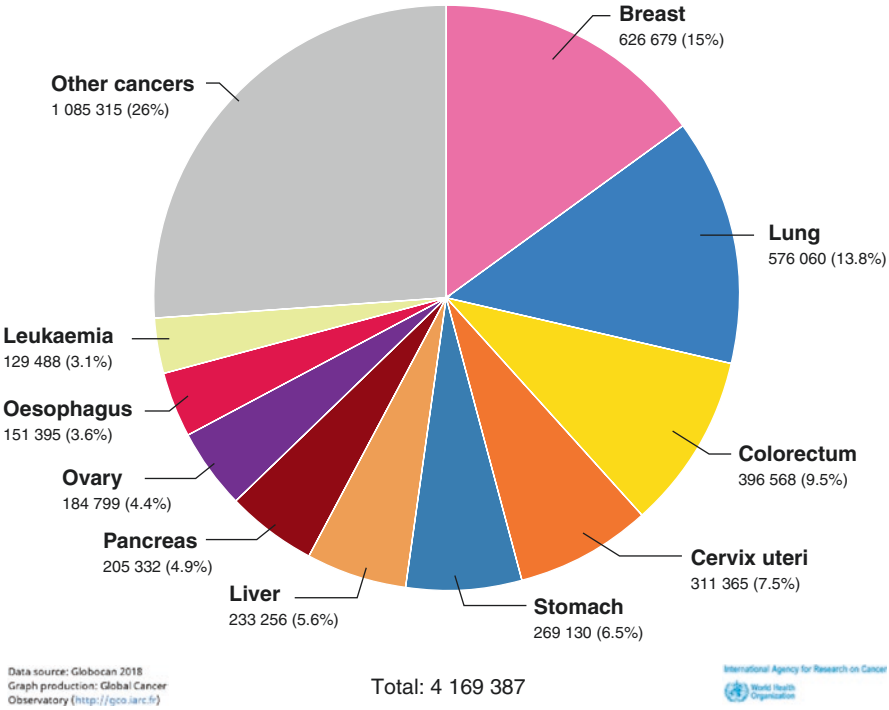

Fig. 11.2 Estimated number of deaths in 2018, worldwide, all cancers, females, all ages

2. Although cancer is common, most events (76.6% of new cases and 85.5% of deaths) occur in women older than 50 years [1], the age by which most women have completed their reproductive life. The comparatively low incidence of most cancers among younger women has necessitated the prolonged follow-up of participants in cohort studies. It has also sometimes made the accurate recall of contraceptive use by participants in case-control studies questionable—especially in investigations recruiting older women who may have used multiple methods many years previously. Some studies, especially those only observing young women during their reproductive years, have had low statistical power to detect an altered cancer risk that might exist—either because not enough women used the contraceptive being studied or an insufficient number of cancers occurred. Another limitation of only studying women of reproductive age is the inability to determine whether important associations continue into, or emerge in, later years.
3. Many women use a variety of contraceptives during their reproductive lives. It has sometimes been unclear whether effects seen in one group of contraceptive users reflects true effects of that method or persisting effects from a previously used method. Complicating matters further, different methods may have opposing

Table 11.1 Estimated number of new cases and deaths from any (including non-melanoma skin) cancer in 2018 in different regions of the world among females

	% Total population	Number new cases (000s)	Age standardised incidence rate per 100,000	Risk of developing cancer before age 75 (%)	Number of deaths (000s)	Age standardised mortality rate per 100,000	Risk of dying from cancer before age 75 (%)
Africa	16.9	609	139.2	14.1	377	90.5	9.6
Latin America & Caribbean	8.4	730	183.7	18.1	327	77.8	8.1
North America	4.6	1104	322.1	30.3	331	80.7	8.6
Europe	9.8	1982	253.3	24.7	858	86.7	9.2
Asia	59.8	4094	151.3	15.3	2246	80.0	8.4
Oceania	0.5	102	335.2	31.3	31	86.9	8.9
All areas	**100.0**	**8623**	**182.6**	**18.3**	**4169**	**83.1**	**8.7**

Source: Globocan 2018 [1]

Table 11.2 Ranking in different parts of the world of top five cases, estimated number of new cases (excluding non-melanoma skin cancer) in females, all ages, in 2018

	1st	2nd	3rd	4th	5th
Africa	Breast	Cervix uteri	Colorectum	Ovary	Non Hodgkin lymphoma
Latin America & Caribbean	Breast	Colorectum	Cervix uteri	Thyroid	Lung
North America	Breast	Lung	Colorectum	Corpus uteri	Thyroid
Europe	Breast	Colorectum	Lung	Corpus uteri	Melanoma
Asia	Breast	Colorectum	Lung	Cervix uteri	Thyroid
Oceania	Breast	Colorectum	Lung	Melanoma	Corpus uteri
All areas	**Breast**	**Colorectum**	**Lung**	**Cervix uteri**	**Thyroid**
Number of countries where this cancer is leading (out of 185)	154	0	1	28	1

Source: Globocan 2018 [1]

effects; for example, condoms protect against cervical cancer whilst combined oral contraceptives appear to increase the risk during current and recent use. Even among users of only one method, formulation changes over time can make the assessment of risk associated with a particular product difficult. For example, the oestrogen content of combined oral contraceptives has been reduced, and new progestogens introduced, since this method of birth control was first marketed. Since

Table 11.3 Ranking in different parts of the world of top five cases, estimated number of deaths (excluding non-melanoma skin cancer) in females, all ages, in 2018

	1st	2nd	3rd	4th	5th
Africa	Cervix uteri	Breast	Liver	Colorectum	Ovary
Latin America & Caribbean	Breast	Lung	Colorectum	Cervix uteri	Stomach
North America	Lung	Breast	Colorectum	Pancreas	Ovary
Europe	Breast	Lung	Colorectum	Pancreas	Ovary
Asia	Lung	Breast	Colorectum	Stomach	Cervix uteri
Oceania	Lung	Breast	Colorectum	Pancreas	Ovary
All areas	**Breast**	**Lung**	**Colorectum**	**Cervix uteri**	**Stomach**
Number of countries where this cancer is leading (out of 185)	103	28	5	42	4

Source: Globocan 2018 [1]

most contraceptive pill users use more than one formulation during their lifetime, there has sometimes been uncertainty about whether an observed cancer association is due to the effects of the preparation used nearest to the cancer diagnosis, persistent effects from previously used products or perhaps both.

4. Cancer risk may be influenced by when a contraceptive is used in a user's reproductive life (e.g. at a young age), by duration of use or by time since last use. Some studies have not been able to examine all of these issues; many have simply compared ever with never users of a contraceptive. In addition, studies have categorised aspects of contraceptive use differently, sometimes hampering comparisons between studies.
5. Confounding (the distortion of the relationship between exposure and outcome because of a third factor related to both exposure and outcome) is a particular consideration when interpreting results from observational epidemiological studies. Many reproductive (e.g. number of children, history of breastfeeding, age at first intercourse and number of sexual partners) and non-reproductive (e.g. smoking, body mass index, socioeconomic status and participation in screening services) characteristics may be potential confounding factors for different cancers in women using different contraceptives. Studies have varied greatly in the level of information collected about possible confounding factors, and the extent to which they have been allowed for in the statistical analyses.

These challenges mean that great care must be taken when interpreting findings from observational cohort or case-control studies of possible cancer risks associated with contraception. It is especially important to remember that statistical association does not necessarily mean causation; bias, chance or confounding may be alternative explanations for the association. This said, observational epidemiological research is the backbone of evidence that guides policy and clinical decision-making in relation to contraception. When considering the evidence, it is important to assess

its totality without placing undue reliance on the findings from just one or two studies, or from a particular subgroup analysis. It is also important to remember that measures of *relative* risk assess the strength of an association (a key consideration when judging causation), whereas *absolute* risk is important when considering the clinical relevance of any association.

11.2 Breast Cancer

Breast cancer accounts for nearly a quarter of all cancers occurring in women around the world; nearly 2.1 million new cases and 630,000 deaths in 2018 [1, 2]. Hereditary (family history of breast or ovarian cancer) and genetic (such as *BRCA1*, *BRCA2* and other breast cancer susceptibility mutations) factors account for less than 10% of cases [2]. A wide range of factors have been linked to increased breast cancer risk: menstrual (early age at menarche, older age at menopause), reproductive (nulliparity, late age at first birth, fewer children), exogenous hormone use (oral contraceptives and menopausal hormone therapy (MHT), anthropometry (greater weight, weight gain during adulthood, body fat distribution) and alcohol intake [4]. Breastfeeding and physical activity appear to be protective.

11.2.1 Combined Oral Contraceptives

Early epidemiological studies investigating whether COCs are associated with an altered risk of breast cancer provided contradictory and confusing evidence. Part of the problem arose from difficulties in comparing studies because investigators categorised aspects of contraceptive use differently, for instance, age at first use or duration of use. Important new insights were gained in 1996 when the Collaborative Group on Hormonal Factors in Breast Cancer published a re-analysis of original data from 54 studies conducted in 25 countries, representing 90% of the then available global data [5]. Each contributing study had at least 100 cases of breast cancer and supplied broadly similar data to the coordinating unit for re-analysis. The re-analysis found that ever users of COCs had a small, but statistically significant, increased risk of being diagnosed with breast cancer compared with never users; summary relative risk (RR) 1.07 (95% confidence interval [CI] 1.03–1.11). The increased risk of breast cancer occurred while women used COCs and for a few years afterwards, before it wore off. Thus, compared with never users, the RR in current users was 1.24 (95% CI 1.15–1.33); former users who stopped 1–4 years previously RR 1.16 (95% CI 1.08–1.23); former users who stopped 5–9 years previously RR 1.07 (95% CI 1.02–1.13); and former users who stopped more than 10 years previously RR 1.01 (95% CI 0.96–1.05). Cancers diagnosed in COC users were more likely to be localised to the breast, even among women who stopped COCs more than 10 years previously; the RR of spread beyond the breast in all ever users compared with never users was 0.88 (95% CI 0.81–0.95). The pattern of risk was essentially the same irrespective of age, country of residence, family history of

breast cancer, ethnic group, reproductive history, duration of use, and dose or type of pill used. A notable exception was risk among women who started COCs before 20 years of age; these women had larger relative risks of breast cancer during current and recent (within 5 years of stopping) use than women beginning at an older age, but similar risks more years after stopping.

These results were generally reassuring, especially for the first generation of COC users exposed for relatively short durations to preparations containing a high (50 μg or more) or medium (30–35 μg) dose of oestrogen accompanied by an older progestogen. Nevertheless, important gaps in our knowledge remained. For example, there was little information about use before age 20 years (only 14% of women in the dataset began using COCs in their teens); most pill use was of short duration (median 3 years); and uncertainty remained about the long-term risk of breast cancer more than 20 years after stopping COC use, especially among women who started use whilst a teenager. It was also unclear whether the observed effects were a 'class' effect seen with all COCs, or limited to particular formulations; or whether temporal changes in pill composition had changed the risk.

Since 1996, there have been more than 40 studies examining different aspects of the association between COC use and breast cancer incidence. Most of them were included in a systematic review and meta-analysis conducted as part of a comprehensive Agency for Healthcare Research and Quality (AHRQ) evidence report, *Oral Contraceptive Use for the Primary Prevention of Ovarian Cancer*, published in 2013 [6, 7]. This report considered papers published between 2000 and 2012, relating to a number of outcomes (breast, colorectal, endometrial and ovarian cancer; venous thromboembolism, stroke and myocardial infarction). Twenty-three studies provided information about ever use of COCs and breast cancer, compared with never use; a modest but borderline statistically significant increased risk was found (summary odds ratio (OR) 1.08, 95% CI 1.00–1.17). Fourteen studies looked at duration of use, with no relationship seen. Eleven studies examined time since last use, observing a diminishing increased risk over time: 0–5 years (OR 1.21, 95% CI 1.04–1.41), 5–10 year (OR 1.17, 95% CI 0.98–1.38), 10–20 years (OR 1.13, 95% CI 0.97–1.31), >20 years (OR 1.02, 0.88–1.18). These results are consistent with the re-analysis of earlier studies [5].

A trend of increasing breast cancer risk with longer duration of use was seen in the Danish Sex Hormone Register Study, a national data-linkage study published in 2017, of 11,517 incident breast cancers occurring during 19.6 million person-years observation of approximately 1.8 million women aged 15–49 years and living in Denmark between 1995 and 2012 [8]. The risk declined after stopping, although perhaps more slowly in women who had previously used COCs for long durations.

A third meta-analysis of 34 studies with information about pre-menopausal breast cancer risk, observed a slightly stronger effect among ever users compared with never users of COCs (OR 1.19, 95% CI 1.10–1.29) [9]. Parity did not appear to affect the risk, but women who used COCs before their first full-term pregnancy had a higher risk (OR 1.44, 95% CI 1.28–1.62) than those who used them afterwards (OR 1.15, 95% CI 1.06–1.26). In addition, the largest risk estimate was seen in women who used COCs for 4 or more years before their first full term pregnancy

(OR 1.52, 95% CI 1.26–1.82). These results are compatible with the slightly stronger risk of breast cancer seen among women who start using COCs at a young age.

The AHRQ report considered papers published from year 2000 to maximise the proportion of women exposed to COC formulations similar to those currently on the market. Indirect assessments of the specific effects of different formulations, for example through the assignment of progestogen or oestrogenic potencies, are controversial [10]. Furthermore, simply grouping COCs by their oestrogen content ignores the biological effects of the accompanying progestogen (and vice versa). Most studies have been unable to look directly at the effects of specific formulations, partly because of insufficient study size or the lack of detailed, corroborated, information about COC use. In addition, as highlighted before, many women use a number of formulations during their reproductive lives, making it difficult to determine whether an altered risk associated with COC use is due to the pill currently/most recently taken, or a lingering effect from a previously used preparation. One recent case-control study in North America examined the association between exclusive use of a particular COC formulation (i.e. the use of that product only and no other COC) and breast cancer risk, among 2282 women with and 2424 women without breast cancer [11]. Thirty-eight different formulations were used, usually by only a few women. None of the ten formulations exclusively used by at least 50 women were associated with a significantly increased risk of breast cancer. Other recent studies looking at breast risk and specific formulations ignored any effects from previously used preparations [8, 12, 13]. Two found statistically significant variations in risk associated with specific formulations, although many comparisons were based on a small number of breast cancer cases and so lacked statistical power [12, 13]. The larger, Danish Sex Hormone Register Study, found most COC formulations examined were associated with an increased risk of breast cancer, with little evidence of important differences between products [8]. Until more data become available, it is best to assume that all of the numerous COCs currently on the market have a similar risk of breast cancer. Likewise, until robust data become available, non-oral forms of combined hormonal contraception (vaginal ring, patch or injectable) should be assumed to have the same breast cancer risk as COCs.

Each of the three longest running cohort studies in the world has now reported on breast cancer incidence or mortality among ever and never COC users, after at least 36 years' follow-up [14–18]. None observed an increased risk of either outcome among ever users, indicating an absence of very long-term breast cancer risk from COCs available in the 1960s, 1970s and early 1980s. Time will tell whether this also applies to today's products.

Most cases of breast cancer (even among those with a family history) occur in women without mutations on the breast cancer susceptibility genes, such as *BRCA1* and *BRCA2*. Although the prevalence of these genes in the general population is low, they convey a greatly enhanced lifetime risk of both breast and ovarian cancer. Thus, compared to the roughly 12.5% lifetime risk among women in the United Kingdom (UK) general population, carriers of *BRCA1* have a 60–90% and *BRCA2* carriers a 45–80% lifetime risk of breast cancer [19]. Five studies published since 2000 were included in a meta-analysis for the AHRQ evidence report, examining

breast cancer risk among *BRCA1/2* mutation carriers [20]. There was a small, statistically non-significant, increased risk of breast cancer among carriers of both *BRCA1* and *BRCA2* mutations who were ever users of OCs, compared with never users (OR 1.12, 95% CI 0.93–1.58). Similar findings were found when carriers were examined separately (*BRCA1* OR 1.19, 95% CI 0.92–1.55; *BRCA2* OR 1.36, 95% CI 0.89–2.10). There was limited data about both duration and time since last use, with no consistent trends seen for either variable. Overall, the results suggest that there is no substantial difference in the relative risk estimates for breast cancer among COC users with each carrier type, which are similar to those seen in the general population.

The pattern of increased breast cancer risk in current and recent users, an inconsistent relationship with duration of use, and loss of effect after stopping COCs, does not fit with the usual model of carcinogenesis. Instead, it may reflect the promotion of tumours which have already started to develop. The tendency for COC users to have more localised tumours within the breast could be due to the earlier detection of disease in ever users versus never users although this preferential detection would have to persist for many years in order to account for the Collaboration Group's observation of more localised cancers in ever users who stopped more than 10 years previously [5]. Alternative explanations include biological effects of COCs on tumour growth and risk of metastasis, or a combination of explanations.

The number of extra cases of breast cancer seen among COC users will depend heavily on the background incidence of breast cancer when they stop using this method of birth control. Many women stop using COCs before their mid-30s, when the background risk of breast cancer is low and so the absolute number of women affected is likely to be small. For example, the Collaborative Group on Hormonal Factors in Breast Cancer estimated that five extra cases of breast cancer will accumulate by the age of 40 for every 10,000 European or North American women who use COCs for 5 years between age 25 and 29 years [5]. The slightly higher RR seen among women who start COCs as a teenager (if real), will result in few, if any, extra cases of breast cancer, provided that such users stop using this method of birth control when the background risk of this cancer is still rare. Conversely, women who use COCs near their menopause have a higher background incidence of breast cancer, and so need to judge carefully whether other benefits outweigh the greater number of extra cases of breast cancer expected from such usage (perhaps 32 extra cases per 10,000 women who use COCs to the age 45) [5]. Current evidence does not suggest that women with *BRCA1/2* mutations or a family history of either breast or ovarian cancer should avoid using COCs for contraception.

11.2.2 Progestogen-Only Contraceptives

Only 0.8% of data in the Collaborative Group on Hormonal Factors in Breast Cancer's re-analysis related to oral progestogen-only products, and 1.5% injectable progestogens, mostly injectable depot medroxyprogesterone acetate (DMPA) [5]. The limited data, however, revealed a broadly similar pattern of breast cancer risk for

progestogen-only products administered by either route to that of COCs (although the associated risk estimates were often statistically non-significant, with wide confidence intervals). Four studies have examined the breast cancer risk among users of injectable progestogen-only contraceptives since 1996 [8, 21–23]. One study of black South African women included 1664 cases with breast cancer and 1492 controls; compared with never users of hormonal contraceptives, the incidence of breast cancer was significantly increased in women who had exclusively used injectable contraceptives within the previous 10 years (OR 1.83, 95% CI 1.31–2.55), but not after 10 years (OR 1.08, 95% CI 0.82–1.43) [18]. The three other studies did not find an increased risk of breast cancer with current or recent [8, 21, 22], or any [21, 22], use of injectables although the number of women using these methods was often small.

Four studies have assessed breast cancer risk among users of progestogen-only pills [8, 23–25]. One North American study found no increased risk among exclusive current or past users of progestogen-only pills [24]. A Norwegian-Swedish study observed an increased risk among current and recent users of COCs and progestogen-only pill, but not exclusive users of progestogen-only products [25]. The third investigation, of black South African women, found a significantly increased risk of breast cancer among those within 10 years of stopping, but not thereafter [23]. The fourth, Danish Sex Hormone Register Study, found an increased risk of breast cancer among current or recent user of progestogen-only pills containing levonorgestrel, but not those with norethisterone or desogestrel [8]. This study was unable to examine the risk among exclusive users of progestogen-only products.

Neither of two studies assessing implantable progestogen-only contraceptives observed an increased risk of breast cancer among users although very few women used this method of birth control [8, 22].

Current or recent users of the levonorgestrel-releasing intrauterine system (LNG-IUS) in the Danish Sex Hormone Register Study had a small but statistically significant increased risk of breast cancer compared with never users of hormonal contraception (RR 1.21, 95% CI 1.11–1.33) [8]. An unknown proportion of the LNG-IUS users will have used COCs beforehand. It is possible, therefore, that at least part of the observed risk could be a hangover effect from previous COC usage, although evidence of a persistent increased risk in women who had used the LNG-IUS for more than 10 years argues against such an explanation. Another study of 93,843 women living in Finland and using the LNG-IUS for the treatment or prevention of menorrhagia observed a higher than expected incidence of breast cancer among LNG-IUS users (standardised incidence ratio [SIR] 1.19, 95% CI 1.13–1.25) [26]. A later paper found that both ductal and lobular breast cancers were increased among users, with the highest risk estimates among women who had purchased the contraceptive at least twice [27]. These results contradict a large post-authorisation safety study conducted for the European Health Authorities, in which 5113 women with breast cancer and younger than 50 years and 20,452 controls were identified in Finland and Germany; neither current nor ever users of the LNG-IUS had an increased risk of breast cancer compared with users of a copper-containing intrauterine device (Cu-IUD) [28]. This study included some participants who were also likely to be involved in a case-control study of breast cancer among Finnish women

aged 20–60 years [29]. An increased risk of breast cancer was seen among exclusive users of the LNG-IUS in post-menopausal (Hazards Ratio [HR] 1.48, 95% CI 1.10–1.99), but not pre-menopausal (HR 0.79, 95% CI 0.54–1.17), women; both compared with never-users of any hormonal contraceptive. Three other studies, conducted in Finland [30], Norway [31] and Israel [32], did not observe an increased risk of breast cancer among users of the LNG-IUS.

Currently there is insufficient evidence to state with confidence whether progestogen-only contraceptives are associated with a different risk of breast cancer to that observed with COCs. It is noteworthy that randomised trials and observational studies in older women indicate that the addition of progestogen to oestrogen for MHT increases the risk of breast cancer above that of oestrogen alone [33, 34]. Until more data becomes available, it is prudent to assume that progestogen-only contraceptives, including the LNG-IUS, have the same breast cancer risk as COCs.

11.2.3 Non-Hormonal Intrauterine Devices

An analysis of over 66,000 women, recruited between 1997 and 2000 for the Shanghai Women's Health Study in China, provided very limited evidence of no change in breast cancer risk among ever users of the IUD (type unknown) [35].

11.2.4 Female Sterilisation

Worldwide female sterilisation is the most commonly used method of modern contraception; used by an estimated 19% of married/in-union women aged 15–19 years in 2015 [36]. Researchers examining possible cancer effects of this method have rarely specified what procedure had been done; for instance, electrocoagulation of the fallopian tubes, tubal ligation, occlusion with spring, titanium clips or silicone rings; partial/total salpingectomy or hysteroscopic tubal occlusion [37].

A meta-analysis published in 2013 of four case-control and four cohort studies found no difference overall in breast cancer incidence among women who had been sterilised, compared with those who had not undergone this procedure (summary OR 0.97, 95% CI 0.84–1.09) [38]. There was inconsistency in the results of case-control studies, with one North American study finding an increased risk of breast cancer, and a smaller Korean study finding a protective effect. There was no evidence of serious heterogeneity among the cohort studies. A study not included in the meta-analysis looked at breast cancer mortality and found a reduced risk of death from breast cancer among sterilised women (adjusted RR 0.82, 95% CI 0.70–0.96) [39]. Another study not included in the meta-analysis compared observed versus age- and calendar-period expected breast cancer incidence rates among women undergoing reproductive surgical procedures in Ontario, Canada; tubal ligation before the age of 45, and after the age of 55, was associated with a reduced risk of breast cancer [40]. Subsequent studies [41, 42] have not observed an altered risk of breast cancer in association with tubal sterilisation, including the Million Women

Study, which observed more than 60,000 cases of breast cancer occurring among almost 1.3 million women who contributed nearly 17 million person-years of follow up [41]. Overall, the evidence does not strongly suggest that women change their breast cancer risk if they choose to undergo tubal sterilisation.

11.3 Cervical Cancer

Although its incidence and mortality has been declining in large parts of the world, cervical cancer remains the leading type of cancer in many Sub-Saharan Africa and South-Eastern Asia countries [1, 2]. Globally, there were an estimated 570,000 new cases and 311,000 deaths from cervical cancer in 2018. A virtually necessary (but not sufficient) cause of cervical cancer is infection with an oncogenic type human papillomavirus (HPV). Important known co-factors include smoking, high number of full-term pregnancies, oral contraception and immunosuppression (particularly arising from human immunodeficiency virus [HIV] infection) [4]. The declines in cervical cancer incidence are thought to be because of improving socioeconomic circumstances, declining levels of persistent high-risk HPV infection and, where available, effective screening. The effective implementation of worldwide HPV vaccination programmes, accompanied by comprehensive screening programmes (especially for unvaccinated women), offers the potential to virtually eradicate this cancer. It has been estimated, for example, that the age-standardised annual incidence of cervical cancer in Australia will be less than 4 per 100,000 by 2028 (range 2021–2035) as a result of the implementation of extensive preventative measures [43].

11.3.1 Combined Oral Contraceptives

The International Collaboration of Epidemiological Studies of Cervical Cancer conducted a re-analysis of individual participant data of 11,170 women with invasive cervical cancer, 5403 women with cervical intraepithelial neoplasia grade 3 (CIN3) and 35,509 controls from 24 (of 35 eligible) studies to examine patterns of COC use and cervical cancer [44]. The reanalysis found an increased risk of invasive cervical cancer among current users, an effect which strengthened with prolonged use (5 or more years of user versus never user: RR 1.90, 95% CI 1.69–2.13). This elevated risk waned after stopping COCs, and had returned to that of never users by 10 years since last use. The pattern of risk estimates was similar among women likely to have had cervical screening and those not screened, and in women positive for high-risk types of HPV. The re-analysis was unable to consider the hormonal content of different COCs, or the effects of specific products. Published data from the mostly small studies not included in the re-analysis suggested similar patterns of relative risks.

Since the International Collaboration of Epidemiological Studies of Cervical Cancer's re-analysis, most studies have not found an association between ever use of COCs and cervical cancer incidence [18, 23, 45, 46], or cervical cancer mortality [14, 17]. An exception was the Oxford-Family Planning Association Contraceptive Study which found a more than three-fold (RR 3.4, 95% CI 1.6–8.9) increased

cervical cancer risk among ever users of COCs [16]. Another was the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study which also found an increased risk with ever use of COCs (HR 1.6, 95% CI 1.1–2.3) [47]. An occupational cohort study of women employed by the Shanghai Textile Industry Bureau found a reduced risk associated with ever COCs use, although the analysis included only one exposed case (RR 0.13, 95% CI 0.02–0.96) [48]. Ever use, however, may mask effects seen during current and recent use. Several of the recent studies reported a higher risk of cervical cancer in women who have used COCs for longer durations [16, 45, 46, 49] and observed a waning of risk with increasing time since last use [16, 18, 23, 45]. The more recent studies, therefore, are generally in line with the International Collaboration's findings [44].

The pattern of risk of cervical cancer among COC users—an increased risk during current use which wanes relatively soon after stopping—is similar to that of breast cancer. Thus, like breast cancer, the extra number of cases of cervical cancer seen among COC users will depend on the background incidence of the disease when the COC is stopped. The International Collaboration of Epidemiological Studies of Cervical Cancer estimated that in more developed countries 5 years use of COCs from age 20 would result in two extra cases of cervical cancer by age 50 per 10,000 users; and 10 years use seven extra cases [44]. In less developed countries, where the incidence of cervical cancer is generally higher (and where preventative services are often absent), the corresponding figures are two and 10 extra cases per 10,000 users.

11.3.2 Progestogen-Only Contraceptives

Only 10 studies in the International Collaboration of Epidemiological Studies of Cervical Cancer's re-analysis assessed progestogen-only products [44]. Risk estimates for progestogen-only pills could not be calculated because only 1% of cervical cancer cases and fewer than 1% of controls had ever used these products. An increased risk of cervical cancer was found for women who had used injectable progestogen-only contraceptives for 5 years or longer, compared with never users (RR 1.22, 95% CI 1.01–1.46), with no clear effect of time since last use. The risk estimates associated with injectable progestogen-only contraceptives use were similar, regardless of whether COCs had also been used.

The Johannesburg Cancer Case Control Study examined injectable progestogen-only contraceptive use and cervical cancer risk in 2182 women with cervical cancer and 1492 controls [23]. This setting was particularly useful as injectable progestogen-only contraceptives are used more often, and for longer periods, in South Africa than elsewhere in the world. The study found that, compared to never users of hormonal contraceptives, women who had only used injectable contraceptives and who were less than 10 years from stopping were more likely to have cervical cancer (OR 1.58, 95% CI 1.16–2.15). When both time since last use and duration of use were examined, the risk of cervical cancer diminished with increasing time since last use and was not related to duration of use. Further adjustment for number of previous Papanicolau (Pap) smears or HIV status did not affect the patterns of cervical cancer risk.

To date, only one nationwide study has examined use of the LNG-IUS and risk of cervical cancer; a cohort of Finnish women aged 30–49 years who were using the LNG-IUS for menorrhagia [26]. There was no evidence of an increased risk of cervical cancer overall (SIR 0.90, 95% CI 0.69–1.15), or cervical adenocarcinoma specifically (SIR 1.18, 95% CI 0.74–1.79). Further studies of progestogen-only contraceptives, particularly of the LNG-IUS, are needed in populations using these products for contraceptive reasons.

11.3.3 Non-Hormonal Intrauterine Devices

The most recent systematic review and meta-analysis to examine the association between use of an IUD and risk of cervical cancer evaluated all studies published to July 2016 [50]. Data from 16 out of 17 studies, relating to 4945 women with incident cervical cancer and 7537 women without, could be harmonised and included in the meta-analysis. Any use of an IUD was associated with a reduced risk of incident cervical cancer (summary OR 0.64, 95% CI 0.53–0.77). Similar results were found when the data were stratified by whether the included studies adjusted for possible confounding by socioeconomic status, smoking history, age at first intercourse, number of lifetime partners, HPV status, number of Pap smears and gravidity. The review could not examine the effects of duration of use. Neither could it look at type of IUD although the time and place of most studies suggested that the IUDs were unlikely to include the LNG-IUS. It is thought unlikely that the observed reduced risk of cervical cancer was due to the detection of cervical abnormalities at the time of IUD fitting, as the use of stains, such as acetowhite, for identifying abnormalities was not routine practice in the included studies [50]. An earlier pooled analysis of 26 epidemiological studies concluded that there was no association between IUD use and cervical HPV [51]. These reviews have led to the hypothesis that IUDs might protect against cervical cancer through the prevention of HPV infection progression to cervical cancer. Importantly, there is no evidence to suggest that IUDs increase the risk of cervical cancer.

11.3.4 Female Sterilisation

Studies into the possible relationship between tubal ligation and cervical cancer were stimulated by the hypothesis that tubal ligation leads to disrupted ovarian function causing hormonal changes, which, in turn, influences the cervical epithelium and cervical cancer risk. A case-control study of 272 women aged 30–77 years with newly-diagnosed squamous cell cervical cancer and 893 community controls living in China did not find an association between tubal ligation and cervical cancer (OR 1.08, 95% CI 0.81–1.44) [52]. Similarly, a hospital-based case-control study conducted in eight countries and involving 2339 women with squamous cervical cancer and 13,506 controls did not find an altered risk of cervical cancer among all women who had had a tubal sterilisation (RR 0.96,

95% CI 0.86–1.07) [53]. However, a reduced risk of cervical cancer was found among women previously screened for cervical cancer, aged 36 or older and within 5 years of their tubal ligation (RR 0.77, 95% CI 0.59–0.99) [53]. This reduced risk within 5 years of tubal ligation was apparent regardless of the frequency of Pap smears or age at first smear. A reduction in cervical cancer risk was not observed in women who had never participated in cervical screening. The authors of the study concluded that any association between altered cervical cancer risk and tubal ligation was due to differences in cervical screening rather than disrupted ovarian function.

A cohort study followed 65,232 Danish women who had tubal sterilisation between 1977 and 1993 for 605,631 person-years; it did not find an overall reduced risk of cervical cancer associated with this contraceptive method (SIR 0.94, 95% CI 0.8–1.1) [54]. In the first year after sterilisation, a higher risk estimate (SIR 1.21, 95% CI 0.7–1.9) was found, together with an increased risk of cervical intraepithelial neoplasia grade 3 (SIR 1.7, 95% CI 1.5–2.0); suggesting a screening effect in connection with tubal sterilisation, i.e. women having the procedure probably also having a Pap smear which led to the detection of cervical abnormalities around the time of sterilisation. In contrast to the findings of these studies, a cross-sectional 'Study to Understand Cervical Cancer Endpoints and Determinants' (SUCCEED) of 2004 women in the United States of America (USA), reported an increased risk of cervical cancer in women with tubal ligation even though women undergoing this procedure were less likely to have had Pap screening during the previous 5 years compared with women using other contraceptive methods [55]. The most recently conducted study, the UK Million Women Study, did not find an association between tubal ligation and cervical cancer (RR 0.98, 95% CI 0.83–1.15) [42]. Taken together with new evidence that tubal ligation does not materially alter hormone levels, the sparse evidence base does not suggest a true biological relationship between tubal sterilisation and cervical cancer.

11.4 Ovarian Cancer

Worldwide, there were 295,414 incident cases of ovarian cancer in 2018, and 184,799 deaths—the second highest number of deaths of all gynaecological malignancies [1, 2]. Many symptoms of ovarian cancer are vague, resulting in many women being diagnosed with advanced staged disease. Thus, survival after diagnosis is poorer than for most other cancers; overall global age-standardised 5-year survival rate is 30–40% [56]. Many risk factors associated with an elevated risk of ovarian cancer are those which influence the lifetime number of, and breaks between, ovulations and levels of sex hormones. Older age, nulliparity, infertility, never having breastfed, history of endometriosis, diabetes, breast, endometrial or colorectal cancer, MHT, family history of ovarian cancer, *BRCA1/BRCA2* gene mutations, Lynch Syndrome and Peutz-Jeghers Syndrome have been associated with an increased risk of ovarian cancer [4]. Conversely, parity, breastfeeding, COCs, tubal ligation and hysterectomy appear to reduce ovarian cancer risk.

11.4.1 Combined Oral Contraceptives

Previous research has shown a reduced risk of ovarian cancer in COC users, a protective effect which increases with duration of use and which persists for many years after stopping [16–18, 57–62]. For example, in a reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls, compared with never users, the RR in users of COCs for less than 1 year was 1.00 (99% CI 0.91–1.10); 1–4 years RR 0.78 (99% CI 0.73–0.83); 5–9 years RR 0.64 (99% CI 0.59–0.69); 10–14 years RR 0.56 (99% CI 0.50–0.62); 15+ years RR 0.42 (99% CI 0.36–0.49) [57]. Results by time since last use were: current and less than 10 years previously RR 0.57 (99% CI 0.50–0.64); 10–19 years previously RR 0.67 (99% CI 0.62–0.73); 20–29 years previously RR 0.76 (99% CI 0.71–0.81); 30+ years RR 0.86 (99% CI 0.76–0.97). The COCs assessed in the re-analysis, and most other studies, usually contained a high or medium dose of oestrogen combined with an older progestogen. Evidence regarding contemporary hormonal contraception, however, is starting to emerge.

A report from the Danish Sex Hormone Register Study included 1249 incident ovarian cancers occurring during 21.4 million person-years observation between 1995 and 2014; compared with never users, current or recent users (RR 0.58, 95% CI 0.49–0.68) and former users (RR 0.77, 95% CI 0.66–0.91) of any hormonal contraception had a reduced risk of ovarian cancer [63]. The protective effect among current users got stronger the longer that women used hormonal contraception, and persisted up to 10 years after stopping. Most of the hormonal contraception usage related to COC use. These results support previous findings [57], and indicate a similar protection resulting from currently available COCs as older products. Furthermore, there was little suggestion of major variations in protective effects according to the progestogen content of the COC, or tumour type.

The pattern of protection during and for many years after stopping COC use has resulted in a profound public health benefit. The Collaborative Group on Epidemiological Studies of Ovarian Cancer estimated that 200,000 cases of ovarian cancer have been prevented by oral contraceptives in high income countries over the past 50 years, and 100,000 deaths [57]. These numbers will increase substantially in the future.

11.4.2 Progestogen-Only Contraceptives

Few studies have examined the possible relationship between injectable DMPA contraceptives and ovarian cancer risk [23, 63–65]. Two case-control studies that investigated exclusive use of injectable DMPA contraceptives found ORs of 0.3 (95% CI 0.1–1.2) [65] and 0.35 (95% CI 0.17–0.71) [23]. A recent analysis of ovarian cancer outcomes in the Danish Sex Hormone Register Study reported an increased risk of ovarian cancer among DMPA users, compared with never users of hormonal contraception [63]. This estimate, however, was based on a small number of ovarian cancers and a very small period of observation, resulting in very

imprecise risk estimates. Other progestogen-only products did not appear to change the risk of ovarian cancer risk in the Danish study, although the evidence was limited because few women in the study were exclusive users of progestogen-only contraceptives.

A data-linkage study in Finland compared the incidence of ovarian cancer among 93,843 women aged 30–49 years and using an LNG-IUS for menorrhagia between 1994 and 2007, with the incidence in the general population; it found a SIR of 0.60 (95% CI 0.45–0.76) [23]. The reduced risk was seen with mucinous, endometrioid and serous ovarian carcinomas [66]. Similarly, the Norwegian Women and Cancer Study found a reduced risk of epithelial ovarian cancer among ever users of the LNG-IUS (RR 0.53, 95% CI 0.32–0.88, compared with never users [31]. These Finnish and Norwegian studies adjusted for several confounders, including ever use of oral contraceptives. However, neither study was able to examine the risk among women who had exclusively used an LNG-IUS. It is possible, therefore, that the observed reduced risk of ovarian cancer among LNG-IUS users was because of persisting protective effects of previous COC use. Overall, there is currently insufficient evidence to conclude whether progestogen-only products, per se, change the risk of ovarian cancer among users.

11.4.3 Non-Hormonal Intrauterine Devices

Few studies, particularly prospective investigations, have examined whether the IUD affects a user's risk of ovarian cancer. IUDs are commonly used in Asian countries; for example, 55.6% of women recruited to the Shanghai Women's Health Study had used an IUD, more than half for at least 20 years [67]. This study of 70,259 women aged 40–79 years accumulated nearly 900,000 person-years of observation and found that, compared to never users of an IUD, users for at least 20 years had a reduced risk of ovarian cancer (HR 0.62, 95% CI 0.40–0.97). Similar patterns of reduced risk among long-term users were found when the analysis was restricted to IUD-users only, i.e. when the comparator group was women with less than 12 years IUD use. After 28 years of prospective follow-up, the North American Nurses' Health Study I found an increased risk of ovarian cancer (RR 1.76, 95% CI 1.08–2.85) among women who reported ever using an IUD [68]. Most of the IUD use in the Shanghai Women's Health Study was between 1975 and 1990, of the stainless steel ring [67]; whereas most of the IUD use in the Nurses' Health Study I occurred during the 1970s and 1980s [68], and was likely to be the plastic Dalkon Shield. Neither of these studies, therefore, provide information about the ovarian cancer risks associated with the now commonly used copper-containing IUDs. The mechanism(s) by which IUDs might influence ovarian cancer risk remains unclear.

11.4.4 Female Sterilisation

Although a number of studies have investigated ovarian cancer risk in relation to tubal ligation, most have been too small to examine method-specific risks [69]. Several meta-analyses have examined the association between tubal ligation and the risk of ovarian cancer [70–73]; all found a protective effect, ranging between a 29% and 34% reduction. The protective effect appears to be the same regardless of age at tubal ligation, persists for at least three decades [72] and is consistent in different populations, including *BRCA* mutation carriers [71] and African American women [74]. In a pooled analysis of 7942 women with invasive ovarian cancer from 13 population-based case-control studies, tubal ligation was associated with a reduced risk of serous (high grade), mucinous, endometrioid and clear cell invasive ovarian cancers [72] However, the size of the risk reductions differed by histological type, with greatest reductions for clear cell and endometrioid, intermediate for mucinous and smallest for high grade serous type—suggesting different mechanisms of action for different types of ovarian cancer.

The mechanism by which tubal ligation might reduce ovarian cancer risk has not yet been established. Suggested theories [75] include the prevention of inflammatory or carcinogenic substances, such as talc, ascending the vagina to the ovaries or tubal ligation stopping the transportation of malignant cells from the endometrium or fallopian tube during retrograde menstruation.

11.4.5 High Risk Groups

Up to 15% of all ovarian cancers can be attributed to *BRCA1* or *BRCA2* mutations. Women who are *BRCA* mutation carriers have a greater risk of ovarian cancer than women who are BRCA-negative; compared to an approximate 2% lifetime risk among women in the UK general population, *BRCA1* carriers have a 40–60% and *BRCA2* carriers a 10–30% lifetime risk of ovarian cancer [19]. The AHRQ report included a meta-analysis of four studies (three case-control and one cohort), which found that ever use of COCs was associated with a reduced ovarian cancer incidence in women who were either *BRCA1* or *BRCA2* carriers; OR 0.58 (95% CI 0.46–0.73) [6]. This protective effect was of similar magnitude to that derived from general population studies. The AHRQ report also tried to consider the influence of COCs in women not known to be *BRCA1* or *BRCA2* gene mutation carriers but who have an increased risk of ovarian cancer because of a family history of breast or ovarian cancer [6]. Few studies have looked at this issue and a meta-analysis could not be conducted due to differences in both the definitions used for family history and against whom the COC users were compared.

A recent meta-analysis identified three case-control studies and one prospective cohort study which examined tubal ligation in relation to ovarian cancer risk in *BRCA* mutation carriers [70]. The summary OR for ovarian cancer after tubal ligation in *BRCA1* carriers in the case-control studies was 0.69 (95% CI 0.53–0.89) and in *BRCA2* carriers 0.73 (95% CI 0.42–1.24) [76]. The prospective study reported an

RR of 0.42 (95% CI 0.22–0.80) in *BRCA1* carriers and RR 0.47 (95% CI 0.18–1.21) in *BRCA2* carriers.

Studies of ovarian cancer in high risk women are sparse, and often small in size. Although there is no evidence to suggest that women at high risk of ovarian cancer should avoid using COCs or tubal ligation for contraception, the evidence-base is insufficient to recommend the use of COCs for the primary prevention ovarian cancer, particularly when other potential benefits and harms are considered [6].

11.5 Endometrial Cancer

Cancer of the corpus uteri (mostly endometrial) is estimated to be the sixth most frequent cancer in women worldwide, with more than 382,000 new cases and 89,929 deaths in 2018 [1, 2]. Factors associated with a raised risk of endometrial cancer include: older age, menstrual (early menarche, late menopause), reproductive (nulliparity), exogenous hormones (unopposed oestrogen), family history of endometrial cancer (and of colorectal cancer in close relatives), personal history of polycystic ovary syndrome, endometrial hyperplasia, obesity, diabetes, any previous cancer, Lynch syndrome and use of tamoxifen [4]. Factors associated with a reduced endometrial cancer risk include: COCs, IUDs, late age at first or last birth, smoking and high parity.

11.5.1 Combined Oral Contraceptives

The Collaborative Group on Epidemiological Studies of Endometrial Cancer examined the association between COC use and risk of endometrial cancer in an individual participant re-analysis of 27,276 women with endometrial cancer and 115,743 controls from 36 studies [77]. The overall relative risk between ever and never users of oral contraceptives was 0.69 (95% CI 0.67–0.72). The protective effect was apparent in current users, an effect that strengthened with longer durations of use; reducing by nearly a quarter (RR 0.76, 95% CI 0.73–0.78) for every 5 years of use. Thus, the risk of endometrial cancer was estimated to halve with 10–15 years usage. The median age at diagnosis of endometrial cancer was 63 years, so most women in the re-analysis had stopped using COCs many years previously—the protective effect remained for more than 30 years after last use. The effects varied by tumour histology with strong risk reductions in ever users of COCs for type I and type II tumours but not for the much rarer uterine sarcoma.

Since the Collaborative Group on Epidemiological Studies of Endometrial Cancer's findings were published, several studies have considered the very remote effects of COCs on endometrial cancer risk [17, 18, 61]. The Nurses' Health Study I accumulated 3.6 million person-years of observation during 36 years of follow-up; ever use of COCs was not associated with uterine or endometrial cancer mortality (HR 0.81, 95% CI 0.63–1.03) [17]. The UK Royal College of General Practitioners' (RCGP) Oral Contraception Study amassed over 1.2 million person-years of

observation after 44 years of follow-up; ever users of COCs had a reduced risk of endometrial cancer (RR 0.66, 95% CI 0.48–0.89) [18]. Assuming that this finding reflects a true relationship, it was estimated that a third of endometrial cancers that would have occurred among ever users of COCs in this study had been prevented by this method of birth control [18]. The third study, the National Institutes of Health—American Association of Retired Persons (NIH-AARP) Diet and Health Study of nearly 200,000 mostly post-menopausal women also found a reduction in incident endometrial cancer (HR 0.78, 95% CI 0.70–0.86) in ever users of COCs [61]. Regardless of age at study recruitment (age 60 or younger, or over 60), longer durations of use were associated with stronger risk reductions.

Two recent papers have provided evidence that currently available COCs are associated with similar endometrial cancer benefits to those seen with older products [78, 79]. The Collaborative Group on Epidemiological Studies of Endometrial Cancer estimated that 400,000 cases of endometrial cancer had been prevented by COC in high income countries over the past 50 years, including 200,000 cases between 2005 and 2014 [77]. These numbers will increase substantially in the future.

11.5.2 Progestogen-Only Contraceptives

Research into the endometrial cancer risks associated with progestogen-only contraceptives (especially progestogen-only pills and injectable DMPA) has been hampered by the small number of women studied who were exclusive users of these products [80].

The LNG-IUS thins the endometrium and so may influence endometrial cancer risk. The Epidemiology of Endometrial Cancer Consortium pooled data from 14 case-control and four cohort studies to investigate the endometrial cancer risk associated with different types of IUD [81]. Hormone-releasing devices were not associated with endometrial cancer risk (adjusted OR 0.97, 95% CI 0.44–2.14), although few women had used these contraceptives. A data-linkage study of 93,843 women in Finland who had used the LNG-IUS for menorrhagia found that LNG-IUS users had a reduced risk of any type of corpus uteri cancer, compared to that expected from national incidence data (SIR 0.59, 95% CI 0.45–0.77), and of endometrial adenocarcinoma (SIR 0.46, 95% CI 0.33–0.64) [26]. Risk reductions were more pronounced in women who had used two or more devices. However, the study was unable to adjust for prior use of COCs, whose protective effects on the endometrium are known to be long lasting. The Norwegian Women and Cancer Study of 104,380 women also reported a reduced risk of endometrial cancer among 9146 ever users of the LNG-IUS (RR 0.22, 95% CI 0.13–0.40), without any evidence of differences when comparing ever and never users of COCs [31]. Further studies are required to ascertain the effects of the LNG-IUS on endometrial cancer risk in women using this product for contraceptive purposes. Until more information becomes available, it is assumed that progestogen-only products confer the same endometrial cancer protection as COCs.

11.5.3 Non-Hormonal Intrauterine Devices

All IUDs, regardless of whether they also contain hormones, elicit a local foreign body inflammatory reaction in the uterus which may have long-term consequences for the endometrium [81]. The Epidemiology of Endometrial Cancer Consortium pooled analysis found a protective association overall with ever use of any type of IUD (pooled OR 0.81, 95% CI 0.74–0.90) [81]. Inert IUDs were associated with a reduced risk of endometrial cancer (pooled OR 0.69, 95% CI 0.58–0.82), but not copper IUDs (pooled OR 0.89, 95% CI 0.66–1.21). Among users of inert IUDs, older age at last use, increasing duration of use and recency of use were associated with a reduced risk of endometrial cancer. There was no evidence of effect modification of the relationship between any type of IUD use and endometrial cancer by ever use of COCs.

11.5.4 Female Sterilisation

It has been suggested that tubal ligation could prevent endometrial cancer by stopping the transport of premalignant or malignant cells from the fallopian tubes to the uterus. A USA case-control study of 437 cases of endometrial cancer and 3200 controls aged 20–54 years did not find a reduced risk of endometrial cancer with tubal ligation after adjustment for parity and age (OR 0.87, 95% CI 0.63–1.20) [82]. Another US case-control study of 405 cases and 297 controls also did not find an association between tubal sterilisation and endometrial cancer after allowing for age, parity and COC use (OR 1.4, 95% CI 0.8–2.4) [83]. Protective effects were also absent in the Women's Health Initiative (WHI) Observational and Dietary Modification Study conducted in the USA (HR 0.97, 95% CI 0.81–1.17) [84] and the Million Women Study conducted in the UK (RR 0.98, 95% CI 0.93–1.03) [42].

A data-linkage study in Denmark followed 65,232 women from the date of their sterilisation for a total of 643,761 person-years, and compared their incidence of endometrial cancer with that expected from national incidence data; the SIR was of borderline significance—0.70 (95% CI 0.5–1.0) [54]. The study, however, could not account for previous OC use and no relationship was found between time since operation and endometrial cancer risk. The NRG Oncology/Gynecologic Oncology Group 210 Trial examined the association between tubal ligation and endometrial carcinoma stage and mortality in 4489 women with well-characterised endometrial carcinoma [85]. Women who had previously had a tubal ligation were less likely to present with stage III (OR 0.63, 95% CI 0.52–0.78), or stage IV (OR 0.14, 95% CI 0.08–0.24), than stage I disease. After allowing for these differences in staging, tubal ligation was not associated with any mortality benefit. The largest study to date has followed a cohort of more than five million women living in Sweden, of which 80,765 had tubal ligation, for more than 123,000,000 person-years [86]. After adjustment for age, parity, calendar time and education, tubal ligation was associated with a reduced risk of endometrial cancer (HR 0.73, 95% CI 0.65–0.83). However, data regarding COC and MHT use were only available for the final 5 years

of study follow-up, so their possible influence on the relationship between tubal ligation and endometrial cancer could not be assessed.

Overall, the evidence does not suggest a strong relationship between tubal ligation and altered endometrial cancer risk.

11.5.5 Women With Lynch Syndrome

An estimated 5% of endometrial cancers are attributed to an inherited genetic predisposition to cancer [87]. Lynch syndrome (or hereditary nonpolyposis colorectal cancer, HNPCC syndrome) is an autosomal-dominant disorder caused by a germline mutation in a mismatch repair gene. Depending on the mismatch repair gene affected, the cumulative risk of endometrial cancer by age 70 in women with Lynch syndrome is estimated to be between 40% and 60% [86]. Despite these large lifetime risks, the influence of hormonal contraceptives on endometrial cancer risk in women with Lynch syndrome has received little attention. To explore the potential of progestogen to prevent endometrial cancer in this high-risk group, a randomised controlled trial examined the short-term effect of DMPA and the COC on the endometrium of 51 women with Lynch syndrome [88]. It found a significant decrease in endometrial epithelial proliferation in women using either hormonal contraceptive. This suggests that women with Lynch syndrome respond normally to short-term progestogens, and suggests an alternative method of reducing endometrial cancer risk (rather than hysterectomy). These findings are supported by those from a retrospective cohort study of 1128 women (mean age 40.6 years, standard deviation 11.3) with Lynch syndrome which investigated hormonal factors and endometrial cancer risk [89]. Compared with never users, ever users of hormonal contraceptives for at least 1 year had a lower risk of endometrial cancer (HR 0.39, 95% CI 0.23–0.64). Further studies of this high-risk group of women are needed.

11.6 Colorectal Cancer

In 2018, there were approximately 820,000 new cases of, and nearly 400,000 deaths from, colorectal cancer in women worldwide; making it the third most common cancer among women (Figs. 11.1 and 11.2) [1, 2]. Familial (family history of colorectal cancer and adenomatous polyps) and genetic (*MLH1, MLH2* and other mutations) factors contribute to only a small proportion of cases. Important factors linked to an increased risk of colorectal cancer include personal characteristics (being tall and having a history of: adenomatous polyps, inflammatory bowel disease, type II diabetes mellitus) and environmental/lifestyle factors (some aspects of diet, such as red and processed meat, physical inactivity, excess body weight, smoking, heavy alcohol intake) [4]. Other aspects of diet, for instance whole grains and fibre, MHT and aspirin intake appear to be protective.

11.6.1 Combined Oral Contraceptives

More than 25 case-control and cohort studies have investigated whether COCs are associated with an altered colorectal cancer incidence. Virtually all investigations have looked at ever use of COCs, mostly in post-menopausal women. Early studies were often limited by low levels of COC use and the small number of cancers included. While several early case-control studies suggested an increased risk of colorectal cancer among ever users of COCs [90, 91], most indicated a reduced risk (although not necessarily with statistical significance). Three meta-analyses have summarised the accumulating evidence [7, 92, 93]; the latest up to mid 2012 [7]. Each reported a statistically significant reduced summary OR between ever and never users of COCs; for colorectal cancers combined [7, 92, 93], and colon and rectal cancer separately [92, 93]. For example, the most recent meta-analysis of 11 studies published between 2000 and 2012 in English, reported a summary OR of 0.86 (95% CI 0.78–0.95) [7]. There was no evidence of a relationship with duration of use in the ten studies examining this aspect of usage. The two earlier meta-analyses also found tentative evidence of a stronger protective effect with more recent use [92, 93]. One case-control study of ever use of hormonal contraception (birth control pills or hormonal implants/injections used for contraception), observed similar size reductions in risk of colorectal cancer among women meeting the screening criteria for Lynch syndrome as those seen in women without a family history of the cancer [94].

Results from cohort studies reporting since 2012 [16–18, 95–99] or not included in the last meta-analysis [15, 100], have not provided consistent evidence of a protective effect among ever users of COCs—for either colorectal cancer incidence or mortality. The studies included the NIH-AARP Study (approximately 200,000 women followed) [95, 100], the Million Women Study (approximately 1.3 million women followed) [97], and the WHI Observational Study (more than 93,000 women followed) [98]. Other papers included prolonged follow-up of the Nurses' Health Study I (up to 30 years) and Nurses' Health Study II (up to 19 years) [17, 96], the Oxford-Family Planning Association Contraceptive Study (up to 42 years) [15, 16], and the RCGP Oral Contraception Study (up to 44 years) [18]. Ever users of COCs did not have a significantly different incidence of colorectal cancer to that of never users in six of the eight studies [16, 96, 97, 99, 100]. Exceptions were the RCGP [18] and WHI [98] studies, which both found a significantly reduced incidence of colorectal cancer among ever users compared with never users. None of the three papers looking at death from colorectal cancer found a protective effect from COC use [15, 17, 95].

It is difficult to reconcile these latest results from the summary estimates produced by the meta-analyses. Each study has allowed for a varying number of potential confounding factors. An important possible confounder is use of MHT; past users of COCs are more likely to use MHT later in life, and MHT has been found to reduce the risk of colorectal cancer in observational studies and clinical trials [101]. While some studies with statistically significant protective effects among COC users have adjusted for MHT use, other have not; and some studies not showing a significant reduction

have also adjusted for MHT (which should result in an apparent reduced risk among COC users if MHT use were confounding the results). Many of the early studies with a low prevalence of COC use are also likely to have a low level of MHT usage, providing further evidence against a strong confounding effect from MHT use. All of the women in the latest publications were post-menopausal, with most ever users of COCs having stopped many years previously. It is likely, therefore, that most of the COC use related to preparations with high- or medium-doses of oestrogen accompanied by older progestogens; similar to those used by many participants in the studies included in the meta-analyses. Nearly all of the studies so far have only assessed ever use of COCs. It could be that COCs (at least with older products) are associated with a protective colorectal cancer effect during current and recent use, which declines over time resulting in no association being observed in ever users who stopped many years previously. Such an explanation, however, does not explain the protective findings seen in the WHI [98] and RCGP [18] studies. Importantly, none of the recent studies have suggested an increased risk of colorectal cancer among ever users. New studies looking at current and recent use of contemporary COCs are needed. Information is also needed about progestogen-only contraceptives.

11.6.2 Non-Hormonal Intrauterine Devices

There is very limited evidence, from a cohort study in China, of no change in risk of either colon or rectal cancer among ever users of the IUD (type unknown) [35].

11.6.3 Female Sterilisation

The Million Women Study accrued 18,197 cases of colorectal cancer during nearly 17 million person-years of follow-up; no association was seen in women who had ever undergone tubal ligation, compared with those not having this procedure (RR 0.99, 95% CI 0.96–1.03) [42]. These results are supported by limited evidence from a study of women in China [35]. A Canadian study of 730,000 women who underwent a number of gynaecological surgical procedures, observed a lower colorectal cancer incidence among those who had undergone bilateral tubal sterilisation, compared with that expected from population incident data (RR 0.81, 95% CI 0.70–0.93) [102]. Collectively, the evidence does not suggest a substantial change in colorectal risk as a consequence of tubal ligation.

11.7 Anal Cancer

Most studies looking at the risk of colorectal cancer have probably also included a small proportion of anal cancer cases. The Million Women Study examined reproductive risk factors among 517 cases of anal cancer; compared with never use, ever use of COCs was associated with an increased risk of anal cancer (RR 1.51, 95% CI

1.24–1.83), with a stronger effect seen in women who had used COCs for more than 4 years (RR 1.68, 95% CI 1.37–2.07) and no evidence of important differences between squamous carcinoma and adenocarcinoma [103]. No such association was observed in an earlier case-control study conducted in Denmark and Sweden [104]. The Million Women Study also observed a higher risk of anal cancer among women who had undergone tubal ligation; RR 1.39, 95% CI 1.13–1.70 [103]. The biological mechanisms by which these findings might occur is unclear.

11.8 Liver Cancer

Liver cancer (predominantly hepatocellular cancer) is the ninth commonest cause of new cancer in women worldwide; nearly 250,000 cases in 2018 (Fig. 11.1) [1, 2]. Very poor survival rates mean that liver cancer is the sixth most common cause of cancer death in women; an estimated 233,000 deaths in 2018 (Fig. 11.2). The main risk factors for hepatocellular carcinoma are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin-contaminated foodstuffs, heavy alcohol intake, obesity, smoking and type II diabetes [4]. The relative importance of each risk factor varies around the world. The widespread adoption of HBV vaccination into national immunisation programmes is greatly reducing the incidence of HBV-associated hepatocellular cancer.

11.8.1 Combined Oral Contraceptives

A meta-analysis published in 2007, of 12 case-control studies, found a modest, statistically non-significant, increased risk of hepatocellular carcinoma among ever users of COCs, compared with never users (age- and sex-adjusted summary OR 1.57, 95% CI 0.96–2.54) [105]. Most of the studies were small, conducted in areas with a low prevalence of HBV (USA, UK and other European countries), and adjusted for a varying number of potential confounders, such as alcohol intake, hepatic infections, diabetes and obesity. Most studies were conducted at a time when COCs continued to have a high or medium dose of oestrogen, combined with an older progestogen. Study differences in how prolonged use was categorised prevented meta-analysis by duration of use. Nevertheless, longer durations of COCs use were associated with higher ORs (between 2.0 and 20.1) than shorter use (OR range 0.3–2.6). Two studies conducted in countries where HBV is endemic, found no association between COC use and hepatocellular cancer, irrespective of duration or recency of use. This suggests that COCs do not enhance an already higher background risk of hepatocellular cancer in women living in these areas.

Neither the Oxford Family Planning Association Contraceptive Study nor the RCGP Oral Contraceptive Study found an increased risk of incident liver or gallbladder cancer combined among ever users of COCs, compared with never users (RR 1.4, 95% CI 0.4–4.2 [16] and 0.87, 95% CI 0.45–1.69 [18], respectively). Ever use of COCs was also not associated with death from liver or gallbladder cancer

combined in the RCGP Oral Contraception study (RR 0.65, 95% CI 0.30–1.39) [14]; or Nurses' Health Study 1 (RR 0.98, 95% CI 0.74–1.30) [17]. All of these risk estimates were based on data from prolonged follow-up, with no sign of a risk emerging many years after stopping COCs.

Although sparse, evidence suggests a possible link between prolonged use of COCs and hepatocellular carcinoma in populations where the prevalence of HBV infection is low; the risk is presumed to be masked in HBC endemic populations because of the high risk of hepatocellular carcinoma from HBV infection itself. In most low HBV prevalent countries, however, the incidence of hepatocellular carcinoma is low, so the number of extra cases of hepatocellular cancer among COCs users in these areas will be very small—especially since there is no evidence of a persisting effect after COCs are stopped.

11.8.2 Female Sterilisation

Tubal sterilisation was not associated with liver cancer in the Million Women Study analysis which included 1267 cases of liver cancer; RR between women who had this operation and those who had not 0.98 (95% CI 0.85–1.13) [42].

11.9 Other Cancers

11.9.1 Combined Oral Contraceptives

In 2008, a Working Group of the International Agency for Research on Cancer evaluated and summarised available evidence about the possible carcinogenic risks associated with COCs [106]. It concluded that the use of COCs is unlikely to alter the risk of cancer of the thyroid, lung, stomach, urinary tract, gallbladder, pancreas, or the risk of lymphoma, cutaneous melanoma and tumours of the central nervous system. Publications since this evaluation have not provided consistent, strong evidence to contradict the Working Group's conclusions.

11.10 Net Cancer Effects

Contraceptives have diverse cancer effects in different organs. As well as wanting to know whether a particular contraceptive changes the risk of cancer at a specific site, many women, their health care providers and other advisors want to know whether its use affects the lifetime risk of any cancer. In other words, they want to know the overall balance of lifetime cancer risks and benefits. Cohort studies with prolonged follow-up into older age (when most cancers occur) provide the best, direct information about net cancer effects of contraceptives.

11.10.1 Combined Oral Contraceptives

The RCGP Oral Contraception Study accrued over 1.2 million person-years of observation during 44 years of follow-up, and found no difference in the incidence of any cancer among ever and never users of COCs (RR 0.96, 95% CI 0.90–1.03) [18]. This contrasts with a modest reduction in the incidence of any cancer among ever users of COCs, compared with never users, seen in the NIH-AARP Diet and Health Study after 26 years of follow-up (RR 0.97, 95% CI 0.95–0.99) [61].

An earlier report from the RCGP Oral Contraception Study, of mortality after 39 years of follow-up, observed a reduced risk of death from any cancer in ever users compared with never users of COCs (RR 0.85, 95% CI 0.78–0.93) [14]. No such benefit was found in the Oxford Family Planning Association Contraceptive Study during over 600,000 person-years of observation accumulated during 41 years of follow-up (RR 0.9, 95% CI 0.8–1.0) [15]. Neither was an all-cancer mortality benefit seen in the Nurses' Health Study I during 3.6 million person-years of observation amassed over 36 years of follow up (RR 1.01, 95% CI 0.7–1.06) [17].

All of these cohort studies with prolonged follow-up have assessed women living in the UK or the USA. Their results, therefore, may not reflect the experience of COC users in other parts of the world. It is reassuring, however, that in two areas of the world with both high rates of COC usage and high incidence of cancer, there is no indication of an increased lifetime risk of any cancer among ever users of this method of contraception.

11.10.2 Other Reversible Contraceptives

A study of over 250,000 Chinese textile workers followed for up to 11 years found no association between monthly combined injectable contraceptives and the incidence of any of 12 common cancers (RR 0.91, 95% CI 0.81–1.03), although the power of the study to detect an increase was low because few women used this contraceptive [107]. This study also assessed the combined cancer risk among oral contracptive users (RR 0.94, 95% CI 0.88–1.01) although there was also limited use of this contraceptive. A smaller study of 67,000 inhabitants of Shanghai, followed for a median of 7.5 years, found no changed overall risk of 11 common cancers among ever users of any contraceptive-which included COCs, injections, IUD and tubal sterilisation (HR 1.02, 95% CI 0.92–1.12) [35].

11.10.3 Female Sterilisation

The RCGP study observed, after an average of 28 years of follow-up, a similar risk of any incident cancer among women who had a tubal sterilisation as that of those who did not have this operation (HR 0.92, 95% CI 0.78–1.08) [108]. Tubal sterilisation was not associated with an altered risk of any of 26 cancers during 17.6 million person-years of observation accumulated by the Million Women Study (RR 1.00, 0.98–1.01) [42].

11.11 Male Sterilisation

In 2015, an estimated 28 million married or in-union couples relied on male sterilisation (vasectomy) for contraception [35].

11.11.1 Prostate Cancer

Prostate cancer is the second most common cancer in men, accounting for 1,280,000 new cases and 359,000 deaths in 2018 [1, 2]. Since the early 1990s, numerous studies have investigated whether vasectomy is linked with prostate cancer. These studies have been summarised in a number of systematic reviews and meta-analyses, with some finding a small effect [109–111] and others no effect [112–114]. The most recent meta-analysis included all epidemiological studies to March 2017; 16 cohort studies (including 2.56 million participants followed for between 1.8 and 24 years) and 33 case-control studies (with 44,536 participants) [111]. There was a weak association between vasectomy and prostate cancer in seven cohort studies with a low risk of bias (summary RR 1.05, 95% CI 1.02–1.09) and no significant association in the six case-control studies at low risk of bias (summary OR 1.06, 95% CI 0.88–1.29). Similar non-significant relationships were seen between vasectomy and high-grade, advanced-stage, or fatal prostate cancer. When studies with high or moderate risk of bias were included, the summary risk estimates moved away from the null. These results suggest that bias is a likely explanation for any associations seen in individual observational studies. Detection bias has been a particular concern. Most cases of prostate cancer are not clinically significant and many will go undiagnosed unless detected through screening. Different levels of assessment among men undergoing and not undergoing sterilisation (e.g. through pre-vasectomy screening or post-operation monitoring of vasectomised men) could result in spurious associations emerging between vasectomy and prostate cancer. Even if real, the strength of association is so modest that the public health consequences will be small, perhaps a 0.6% absolute increase in lifetime risk of prostate cancer [111]. This level of risk should not stop clinicians from offering vasectomy to couples wishing to have permanent contraception.

11.11.2 Testicular Cancer

Testicular cancer is uncommon, accounting for roughly 1% of all cancers in men. A systematic review and meta-analysis of eight studies published between 1980 and 2017 found two studies reporting a positive association between vasectomy and testicular cancer, and six showing no effect; summary OR 1.10, 95% CI 0.93–1.30) [115]. Five studies were conducted in the USA and three in England. Most were not recent studies. This relatively sparse evidence-base does not suggest an important association between vasectomy and subsequent testicular cancer.

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Emergency Contraception

12

Hang Wun Raymond Li

12.1 Introduction

Although effective contraceptive methods are widely available nowadays, contraceptive failures are still not completely avoidable. Each of the current contraceptive methods may have an intrinsic failure rate as well as limitations to various degrees in relation to its method of use and user dependence. In cases of omission or failure of one's regular contraceptive method due to various reasons, such as unplanned unprotected sex, missed dose of hormonal contraception, condom accidents or dislodged intrauterine contraceptive device (IUCD), or in the case of sexual assault or coerced sex, emergency contraception (EC) would serve as an important contraceptive back-up to prevent an unintended pregnancy.

Currently available methods for EC include the copper IUCD and oral hormonal methods. Established options of the latter include the Yuzpe regimen, levonorgestrel (LNG), ulipristal acetate (UPA) and mifepristone [1, 2] (Table 12.1).

12.2 Historical Methods of EC

In history, various physical manoeuvres, such as jumping and sneezing, as well as "chemical" manoeuvres by douching the vagina with substances like lemon juice, coke drinks and disinfectants, have been described for the purpose of EC after unprotected sexual intercourse (UPSI) [3]. In the 1920s, the concept of "hormonal EC" emerged when post-coital oestrogen administration was shown to prevent pregnancy in animal studies, but the human application of hormones for EC only started in the early 1960s, when high doses of oestrogens, such as ethinyl-estradiol 5 mg,

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Table 12.1 Current options of emergency contraception

Regimen	Licensed use (coitus-treatment interval) (h)	Availability	Target(s) of action
Yuzpe regimen (ethinyl-estradiol 100 μg + levonorgestrel 0.5 mg)	72	Most countries	Ovulation ? Cervical mucus
Levonorgestrel 1.5 mg single dose	72	Most countries	Ovulation ? Tubal function
Mifepristone 25 mg single dose	120	Few countries	Ovulation ? Tubal function Implantation
Ulipristal acetate 30 mg single dose	120	Many countries	Ovulation ? Tubal function ? Sperm function
Copper intrauterine contraceptive device	120	Most countries	Gamete function Tubal function Implantation

? Denotes inconsistent evidence or doubtful significance in the emergency contraception context

conjugated oestrogens 30 mg or diethylstilbestrol 25–50 mg taken daily for 5 days were employed for this purpose. Despite their very good effectiveness, with failure rates of 0.6–1.6% only, these methods were phased out because of their side effects, mainly nausea and vomiting related to the high oestrogen dosage, as well as the teratogenicity of diethylstilbestrol [4].

12.3 Oral Hormonal Methods

12.3.1 Yuzpe Regimen

This was first introduced in 1974 by Dr. Albert Yuzpe, a Canadian gynaecologist. It consisted of two doses of ethinyl-estradiol 100 μg combined with dl-norgestrel 1 mg (or levonorgestrel 0.5 mg) taken 12 h apart, with the first dose commenced within 72 h of UPSI [5]. It has been a mainstay method of EC till recently. An equivalent dose can be easily made up by several tablets of ordinary combined oral contraceptive pills, although such use is off-label. Due to the high oestrogen content, nausea (54%) and vomiting (16%) are the main side effects, which may affect the absorption and hence efficacy of the drug [6]. The overall failure rate of the Yuzpe regimen is 3.2% if administered within 72 h of UPSI, and it increases with the coitus-treatment interval [7, 8].

The Yuzpe regimen acts mainly by inhibiting or postponing ovulation [9, 10]; the high progestogen dose may also thicken the cervical mucus, hence impairing sperm penetration, although it is not very relevant in the context of EC which is usually

administered some time after UPSI [11]. Its effect on sperm or tubal function has not been reported.

12.3.2 LNG

LNG, the levo-rotatory form of norgestrel, is a synthetic progestogen derived from 19-nortestosterone. LNG as an oral EC was first compared with the Yuzpe regimen in a randomised controlled trial in Hong Kong published in 1993 [12]. The regimen used in this first trial consisted of LNG 0.75 mg given orally within 48 h of UPSI and repeated 12 h later. The incidence of side effects, in particular nausea and vomiting, was significantly lower with the LNG regimen than the Yuzpe regimen [12]. A subsequent multinational study with larger sample size by the World Health Organization (WHO) confirmed that the same LNG regimen, commenced within 72 h of UPSI, had significantly lower failure rate compared with the Yuzpe regimen (1.1% vs. 3.6%) [7]. The Cochrane systematic review showed that the LNG regimen had significantly lower failure rate than the Yuzpe regimen (relative risk 0.57, 95% CI 0.39–0.84, 6 studies) [2]. It was subsequently shown that a single oral dose of LNG 1.5 mg taken within 72 h of UPSI had similar failure rate as the original split-dose regimen (relative risk 0.84, 95% CI 0.53–1.33) [2], and it is currently the recommended regimen due to its better user-friendliness than the split regimen [13]. The LNG-EC is licensed for use within 72 h of UPSI, after which the failure rate will be significantly higher (relative risk 0.51, 95% CI 0.31–0.84) [2, 8] although it may still be moderately effective up to 96 h after UPSI [1, 13]. LNG-EC mainly acts by blocking the LH surge and hence inhibiting or postponing ovulation.

It was shown that LNG was no longer effective in inhibiting ovulation when administered after the onset of LH surge [14–16]. Furthermore, other in vitro studies suggested that LNG at concentrations relevant for EC did not significantly interfere with post-ovulatory events such as sperm function, fertilisation and endometrial attachment [17–21]. Although one study suggested some inhibitory effect of LNG on muscular contractility of the Fallopian tube [22], another study suggested that ciliary beating and muscular contractility of the Fallopian tube was inhibited by LNG only at supra-pharmacological concentrations [23]. Given the minimal post-ovulatory action of LNG as suggested by these studies, this may explain the clinical finding that LNG is only effective as EC when it is administered before but not after ovulation has occurred [24, 25].

12.3.3 Mifepristone

Mifepristone is a progesterone receptor modulator, which acts as a competitive progesterone receptor antagonist in the presence of progesterone. The first randomised trials on its use for EC at a dose of 600 mg within 72 h of UPSI were published in 1992 by two groups in the United Kingdom [26, 27]. Subsequently, a study by the

WHO showed that mifepristone was equally effective as an EC at lower doses of 50 mg or even 10 mg [28, 29]. The Cochrane systematic review suggested that a mid-dose of mifepristone at 25–50 mg administered within 120 h of UPSI was the most effective method of oral EC, with significantly lower failure rate and incidence of side effects than both the Yuzpe and LNG regimens [2] although more users might have delay of the subsequent menses due to postponement of ovulation which may sometimes cause concern [2, 27]. The main limitation is that mifepristone is only licensed at the EC dose in a very limited number of countries such as Armenia, China, Moldova, Russia, Ukraine and Vietnam.

The higher efficacy of mifepristone than LNG may be attributed to its wider scope of action including post-ovulatory mechanisms. Although it mainly acts by delaying follicular development and rupture, some in vitro studies suggested that mifepristone at EC dose may inhibit endometrial receptivity as well as ciliary beating and muscular contractility of the Fallopian tube [19, 20, 22, 23, 28, 29], while some others suggested that it probably has no effect on fertilisation [30, 31]. With regard to human sperm function, an early study suggested that mifepristone did not abolish the effect of progesterone on acrosome reaction and sperm hyperactivation [30], but a more recent study revealed that mifepristone could inhibit progesterone-induced acrosome reaction, sperm hyperactivation and intracellular calcium [32]; however, the clinical significance in the EC context is not certain.

12.3.4 UPA

UPA is another selective progesterone receptor modulator with partial agonistic and antagonistic effects on the progesterone receptor. It was first studied as an EC in the last decade. The first two randomised trials comparing UPA- to LNG-EC were reported in 2006 and 2010, respectively [33, 34]; the latter showed that UPA 30 mg taken within 72 h of UPSI had lower failure rate than LNG-EC (1.4% vs. 2.2%) by meta-analysing the data from the two studies, and that UPA-EC taken between 72 and 120 h after UPSI was equally effective [34]. This, together with subsequent clinical studies, suggested that the effect of UPA-EC is maintained up to 120 h following UPSI [34–36], and this is now the recommended time frame according to the product licence and clinical guidelines [1, 13].

UPA-EC mainly acts by inhibiting or postponing ovulation, and such effect remains even when it is taken after the onset but before the peak of the LH surge [37, 38]. These results implied a wider window of action of UPA-EC compared to LNG-EC in the periovulatory phase, the time of highest conception probability, thus explaining its higher efficacy compared to LNG-EC. It has been shown by in vitro studies that UPA at pharmacological concentration may suppress certain aspects of human sperm function (progesterone-induced acrosome reaction, hyperactivation and intracellular calcium) [32] as well as tubal function (ciliary beating and muscular contraction) [23]. On the other hand, another study suggested that UPA did not interfere with cumulus mass penetration by sperm [39]. The clinical relevance of these findings is uncertain, as sperm may reach the fallopian tube in 5–10 min after intercourse [40] which is too short to be a target of EC, and the effect of UPA on tubal function would only be

clinically important if it is administered at the relevant narrow window. Predisposition to tubal ectopic pregnancy is a theoretical concern should there be inhibitory effect on tubal transport, and yet a post-marketing pharmacovigilance report did not suggest any increased risk of tubal ectopic pregnancy following use of UPA-EC [41]. Although there has been suggestion that UPA might induce certain immunohistochemical and molecular changes in human endometrial tissue [37, 42–44], whether these translate into significant interference with implantation and pregnancy establishment is not proven. Two studies with in vitro endometrial attachment models, using either endometrial cell lines or endometrial biopsies from healthy women taken in the luteal phase, revealed that UPA at a dosage relevant for EC did not affect embryo viability nor embryo attachment [45, 46]. Furthermore, in a prospective clinical study on 700 women, UPA-EC had significantly higher efficacy in subjects taking it before ovulation (77.6%) compared to those taking it after ovulation has occurred (36.4%, $p < 0.0001$) [47], supporting that the mechanism of action was mainly pre-ovulatory.

12.4 THE Copper-IUCD

The first report on the use of the copper-IUCD for EC was published in 1976 [48]. It is currently the most effective method of EC when administered within 120 h of UPSI [2, 13], with a failure rate of 0.09% [49], and should be a first choice wherever acceptable and applicable. Its use can be extended beyond 5 days after UPSI provided that it is still within 5 days after ovulation if the latter can be reasonably estimated [13]. Apart from serving as an EC, the copper-IUCD can also be retained as an ongoing contraception, which is another benefit.

The copper-IUCD releases copper ion into the intrauterine and intra-tubal environment, which may interfere with sperm and oocyte function, fertilisation and tubal transport [28, 29, 50–53], as well as inducing a local inflammatory reaction in the endometrium, rendering it unfavourable for implantation [28, 29, 53].

The levonorgestrel intrauterine system has been shown in a recent randomised trial to be non-inferior to the copper-IUCD as EC in terms of failure rates and adverse events [54], and is expected to be introduced for this application. The mechanism of it as EC would worth further investigations.

12.5 Factors Affecting Efficacy of Hormonal EC

12.5.1 Effect of Obesity

Data from meta-analyses showed that women with body mass index (BMI) ≥30 kg/m^2 had higher failure rate after EC compared to those with normal BMI, and the excess in risk was more pronounced for LNG-EC (odds ratio 4.41; 95% CI 2.05–9.44) compared to UPA-EC (odds ratio 2.62; 95% CI 0.89–7.00) [36, 55] although these trials were not primarily designed to explore the effect of BMI on EC efficacy. A more recent pooled analysis on nearly 7000 women conducted by the WHO also reiterated that LNG-EC had higher failure rate among obese women

compared to women with normal weight [56]. In a pharmacokinetic study, longer time was taken to achieve steady-state levels in LNG-EC users who were obese than those with normal BMI, an effect which was corrected by doubling the dose (i.e., 3 mg) [57]. On the other hand, another pharmacokinetic study demonstrated that the serum drug concentration of LNG but not UPA was reduced in obese women [58]. The effectiveness of the copper-IUCD is not known to be affected by BMI; hence, it should be the preferred choice among obese women who need EC. The current guideline in the United Kingdom recommends women weighing >70 kg or with BMI > 26 kg/m^2 be offered UPA-EC, or alternatively a 3 mg dose of LNG-EC, if the copper-IUCD is not preferred. It is not known which option is more effective in those weighing >85 kg or with BMI >30 kg/m^2 [13].

12.5.2 Further Acts of UPSI in the Same Cycle

It has been reported that women using oral EC have a three- to four-fold increased failure rate if they had further acts of UPSI in the same cycle, and among those who had UPSI within the most fertile window [36, 55]. Repeat use of the same agent (to avoid potential interaction between a progestogen and anti-progestogen) is recommended for those who have further acts of UPSI beyond 24 h from the last use of LNG-EC or UPA-EC [13]. Repeated use of oral EC as the sole form of regular pericoital contraception has relatively high cumulative pregnancy rate of 11 per 100 women-years and may also result in irregular bleeding [59], and is hence generally discouraged.

12.6 Side Effects and Safety

The oral hormonal ECs are considered very safe in general. They are not considered to be contraindicated in any medical condition, including those where the use of hormones is a concern, as the health risk associated with a one-off course of hormonal EC is likely negligible. Table 12.2 shows the medical eligibility to the use of EC in selected common clinical conditions. Minor side effects, such as nausea, vomiting, headache and dizziness, may be encountered with the use of hormonal EC, but much less commonly with LNG-EC and UPA-EC compared with the Yuzpe regimen. A repeat dose is recommended by the product inserts if vomiting occurs 2 and 3 h after intake of LNG-EC and UPA-EC, respectively. The side effects and contraindications for use of copper-IUCD as an EC should be in line with its regular use. The copper-IUCD can still be used for EC in women with perceived risk of sexually transmitted infections, such as victims of sexual assault, and antibiotic cover can be offered in such circumstances [13].

Both hormonal and intrauterine methods for EC do not act as an abortifacient. Theoretically, any post-fertilisation mechanisms of an EC, even if existing, act before establishment of pregnancy, which is defined as the time of implantation. Nonetheless, some individuals may have personal objections to EC methods which

Table 12.2 Medical eligibility to the use of emergency contraception

Condition	Levonorgestrel	Ulipristal acetate	Copper intrauterine device
Time since last unprotected intercourse	1	1	1
– 24–72 h	2	1	1
– 72–96 h	2	1	1
– 96–120 h	3[a]	3[a]	2[b]
– >120 h			
Post-sexual assault	1	1	
Previous use of levonorgestrel in this cycle (>24 and <120 hours ago)	1	3	1
Previous use of ulipristal in this cycle (>24 and <120 hours ago)	3	1	1
Young age (up to 18 years)	1	1	1
Nulliparity	1	1	1
Obesity (body mass index >=30 kg/m^2)	2	2	1
Breastfeeding	1	2[c]	1
Past ectopic pregnancy	1	1	1
History of ischaemic heart disease, cerebrovascular attacks or other thromboembolic conditions	1	1	1
Severe asthma on oral steroids	1	3	1
Severe liver disease	1	1	1
Migraine	1	1	1
Active cervicitis or pelvic inflammatory disease	1	1	3
Strong CYP3A4 inducers	2	2	1

Adapted from the Emergency Contraception Wheel published by the European Consortium for Emergency Contraception (http://www.ec-ec.org/ecmethod/)

1. May be used
2. Can generally be used but more effective method is recommended if available and/or additional remarks should be considered
3. Not recommended and/or further assessment by a clinician is required

[a]Not causing harm but not effective

[b]Can be inserted beyond 5 days of unprotected intercourse if still within 5 days of ovulation, if the latter can be estimated

[c]Breastfeeding not recommended for 1 week after use of ulipristal

may interfere with fertilisation or implantation; their informed choice should be respected, and they can be offered LNG-EC or UPA-EC. In cases of EC failure, the reported risk of miscarriage or ectopic pregnancy is not higher than that in the general population [41, 60].

Although the use of hormonal ECs is generally considered to be contraindicated in case of a known pregnancy as it is not going to work, the inadvertent use of EC in pregnancy which is known subsequently should not be a reason per se to advise pregnancy termination. The current evidence has not indicated any teratogenic effect of the Yuzpe regimen, LNG-EC or mifepristone [61–64]. There is very limited data on UPA-EC in this regard, although a post-marketing pharmacovigilance

report revealed no case of birth defect among 20 live births following UPA exposure [41].

EC is not required within the first 3 weeks postpartum [13]. A systematic review did not identify any adverse effects on breastfeeding and infant development in lactating women using progestogen-only contraception [65]. Current guidelines recommend that lactating women taking LNG-EC can continue breastfeeding [13, 66]. There is no safety data available on the use of UPA in lactating women, and the current guidelines endorsed the suggestion by the product insert to discard breast milk for 7 days after use of UPA-EC [13, 66].

12.7 Care After EC

After receiving EC, the women should be advised to observe for return of menstruation; if it does not happen by 1 week after the expected date, pregnancy test should be performed. It may be noted that LNG-EC may tend to result in delay, while UPA-EC may tend to result in advancement of the subsequent menstruation [2]. In case there is an unintended pregnancy, proper counselling should be arranged. If a copper-IUCD has been inserted for EC, the follow-up care can be in line with that for regular IUCD users if the woman wants to keep it for ongoing contraception; otherwise, it can be removed after the subsequent menstruation. Following the use of hormonal EC, proper counselling on a reliable ongoing contraceptive method should be offered. Barrier contraception or sexual abstinence should be advised till the return of menstruation. After intake of LNG-EC, women who had not been using a hormonal contraception may quick-start on it [13]. As use of UPA-EC may potentially reduce the efficacy of a progestogen-containing contraceptive shortly after, a hormonal contraception should be started at least 5 days after UPA intake [13].

12.8 Improving Access to EC

While the insertion of copper-IUCD is dependent on the healthcare provider, it is suggested that hormonal EC can be provided outside the confine of a healthcare institution, such as over-the-counter or in advance, which may facilitate its timely access when needed. This is particularly true as the effectiveness of oral EC generally hinges on the time it is administered after UPSI, and that the access to EC can also be hindered by the geographic and time inconvenience as well as embarrassment in obtaining a prescription.

LNG-EC is available over-the-counter in some but not all countries. Reservations are common among both users and healthcare providers in making oral EC available over-the-counter [67–71], mainly because of the myths that deregulated supply of EC might discourage the use of regular contraception or encourage casual and irresponsible sexual behaviours, hence predisposing to sexually transmitted infection; these myths have actually been clearly disproved by various studies [72–75].

With regard to advanced provision, in contrast to the common belief, it would not discourage the use of regular contraception nor increase the occurrence of UPSI or sexually transmitted infections [76, 77]. However, advanced provision of EC has neither been shown to reduce the incidence of unintended pregnancies or induced abortions compared to standard provision [77, 78], probably because many women are under-estimating their risk of accidental pregnancy and under-utilising the EC even if an advanced supply is provided [79].

It is worth noting that studies on over-the-counter or advanced provision of oral EC have mainly been confined to LNG-EC. For anti-progestogens, although the current evidence does not support an abortifacient effect at the EC dose, there is still concern about misuse for self-induced abortion by an excessive dose, and there have been insufficient safety data to support provision of anti-progestogens over-the-counter or in advance.

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Part III

Management of Female Contraception Throughout Women's Lifetime

Critical Issues in Adolescent Contraception

13

Vincenzina Bruni and Metella Dei

13.1 Introduction

Protection at sexual debut is a well-known marker of lifelong sexual health and the target of many educational projects for adolescents and of contraceptive counselling. A very young age at the approach of sexuality is often linked to unprotected sex worldwide. The proposal of Palmer [1] and coworkers to focus more on "competence" at first intercourse than on timing is probably more appropriate because it underlines the importance of contextual factors in defining the quality and safety of a sexual relationship. A competent sexual debut means that the choice is consensual, with autonomy in decision and perceived as in the right moment for both the partners, in addition to using contraceptive protection. To promote a responsible choice in approaching sexuality is the challenge for all health care personnel dealing with adolescents, during specific consultations, as well as on other occasions of meeting them (vaccinations, follow-up visits). In many countries, we still need laws and policies to counteract cultural and economic barriers preventing consistent use of contraception by young people.

Contraceptive counselling with young people should take into account both biological and contextual factors in order to develop a shared decision-making approach to help a choice responding to patient characteristics and to promote contraceptive continuation and adherence. From a practical point of view, the medical history and the socio-psychological items are generally collected together, but in our text we will synthetize first the contextual variables known to influence sexual health behaviors and the biological aspects to follow.

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13.2 Contextual Factors Significant for Contraceptive Protection

Information: the availability of health information related to sex education programs at school, to the ability of finding reliable specific websites, and to the possibility of having help and reference in relatives or educators are, of course, preconditions for a contraceptive choice. Very young girls, migrants, and people with intellectual disabilities have fewer opportunities to reach information sources. However, we know well that in all adolescents the gap between knowledge and effective protective behaviors is anyway often deep. Educational interventions and health care consultations must focus on specific difficulties and motivations to disregard what they know about prevention of unwanted pregnancy and of sexually transmitted infections.

Family relationships: In every culture, parents transmit the models of femininity and masculinity, of their relationships and the attention to self-care. The involvement in the daughter's life and a flexible monitoring together with an open communication about sexual and reproductive health, especially by the mother, are associated in every country with delayed sex and higher contraceptive use [2].

Attitude to risk-taking: various surveys on young people [3–5] demonstrated the correlation between risk behaviors and unprotected sex, precocious sexual debut and elevated sexual partner turnover. Therefore, we have to find the words to investigate on alcohol and substance abuse, on the use of the so-called new psychoactive drugs, mixtures of herbs, dusts, crystals, or tablets partially reproducing the effects of cannabis, ecstasy, or other substances. The attitude to risk in young people is mainly related to the need to be similar or considered by peers, sometimes is a component of pleasure or a hidden way to seek help. Longitudinal studies demonstrated that adolescents living in a conflicting or inattentive family milieu, in financial hardship, or with a history of adverse childhood events are more vulnerable to risky behaviors. Most risk-behaviors tend to be associated with depression and correlate with the severity of depressive symptomatology [6]. Poor personal or professional projects, more than school results, can be an indirect measure of self-esteem and of a positive attitude toward life.

A *negative body image*, related to overweight [7], dermatological diseases, chronic diseases interfering with everyday life, are also linked to low self-esteem, depressive thoughts and can potentially lead to disordered eating and sexual risk behaviors. A strict correlation between having positive feelings about one's body and oneself and sexual assertiveness, that include the ability to negotiate condom or contraception, has been demonstrated [8].

Problematic internet use is recently considered a risk factor also for sexual behavior [9]. The web is worldwide the place for shopping, meetings, cyberbullying, gambling, but also where it is possible to meet virtual or real sexual partners. Social networks consent a very high number of contacts, reducing a genuine interpersonal communication and spread the idea that everything is public and representable, rarefying the space of privacy and intimacy. Sexting, i.e., the sending of sexually explicit digital images or videos by cell phone, usually in order to seek

attention, is related to higher exposure to sexual violence or coercion [10]. It is, therefore, important to rule out a pervasive use of media devices. Considering that about 70% of teenagers use the smartphone during the night, questions about sleep quality are good markers of internet dependence [11].

The characteristics of the couple and the partner: gender norms and attitudes, as Global Early Adolescent Study demonstrated [12], are shaped in early adolescence and impact on first intimate relationships. Currently, peer narratives and experiences and social networks influence generally reinforce traditional gender roles. Partners acting stereotyped masculine role tend to communicate less about sex, to boycott contraception, to act unrealistic pregnancy promoting behaviors and sometimes to impose intercourses [13]. So exploring pregnancy intention and opinions about contraception of the male partner may help to identify girls at risk of unwanted pregnancy, sexually transmitted infections, and intimate partner violence. Sexual coercion, that is quite frequent in adolescent relationships, impact also on future sexual functioning and health protecting behaviors.

In our personal framework of interview for evaluating adolescent contraceptive needs, we have to include the preceding items if we want to identify elements affecting both starting and continuing contraception, as well as biological factors affecting the choice of the method.

13.3 Critical Biological Issues in Adolescents

The immaturity of cervico-vaginal epithelium and the exposure to Sexually Transmitted Infection (STI) risk.

Reports from various European and non-European countries put in evidence that prevalence of Chlamydia, as well as Gonorrhea infections in young people is still increasing. This increase is probably in part the result of more diagnostic efforts and of the use of more sensitive diagnostic tests, but also of a wide diffusion facilitated by the high rate of asymptomatic infections.

Biological factors related to the immaturity of the cervical-vaginal epithelium should also be taken into account. The extension of columnar epithelium, that is by nature more immune tolerant, is prevalent in adolescent girls compared to squamous esocervical and vaginal epithelium, more efficient in response to pathogens, especially Chlamydia and Gonorrhea [14]. The junction between squamous and mucous-secreting epithelia (cervical transformation zone) is particularly dynamic in post-menarchal years. An estrogen-dependent metaplastic process occurs with progressive replacement of columnar epithelium by squamous foci, driven by specific reserve junctional cells. The proliferation and differentiation of these reserve cells increase the susceptibility to HPV infection through a deficient expression of innate molecules inhibiting the intracellular steps of virus processing [15]. Few components of cell-mediate immune response (T lymphocytes, and antigen-presenting cells) are also prevalent in the transformation zone and surrounding tissues; therefore, this is also the primary infection site of HIV virus [16].

The production of antimicrobial substances and the acquired immune response are less efficient in adolescents than in adult subjects: IgG and IgA secreting plasma cells are reduced. Bacterial species associated with vaginal microbiota of adolescents resemble those of adults; including lactobacillus crispatus, L. iners, L. gasser, L. Jensenii, and Gardnerella vaginalis, but vaginal pH often remains above what is considered typical in healthy women [17].

Younger sexually inactive girls are at increased risk of infections upon sexual debut [18]. Disruption of the epithelial barrier that may occur in response to seminal plasma cytokines or to micro traumas related to nonconsensual sex is another risk factor. The not rare comorbidity between different infections, increasing inflammatory state, or activating Langherans cells, enhances the risk of extension and complication of the symptomatology. Smoking is an additional risk factor, because nicotine, and its metabolite cotinine, concentrate in cervical mucus more than in blood promoting cell proliferations and suppression of specific cytokines [19]. Cannabis and other psychoactive drugs also reveal immunosuppressive activity.

Finally, the perception of sexuality as a field of curiosity and experimentation promote in adolescents the trend to multiple sexual partners, sequentially or concurrently, often with inconsistent protection.

An evaluation of the risk of STI is part of the contraceptive counseling at any age, but particularly with adolescents. The known risk factors are an early sexual debut, more than three sexual partners in the last year, using dating apps, previous sexually transmitted infection, condom misuse, selling sex, together with poor information on the topic. Probably these appear as hard questions to ask, but if well motivated, are generally accepted by young people. Sometimes the starting of a hormonal contraception after a period of condom use is the circumstance of acquisition from the partner of a silent infection and breakthrough bleeding is the sign of endometrial involvement. The best strategy should be to foster condom use, especially at the beginning of a relationship, before eventual test for STIs, even in association, for subjects using either SARC or LARC. Encouraging condom use means also promoting positive peer norms regarding mechanical protection and improving communications about its correct use.

Evidence on the association between specific contraceptive method and risk of STI is lacking, with few perspective studies. We know that the use of combined hormonal contraceptives generally increases the presence of a healthy vaginal microbiome with H_2O_2 producing Lactobacilli species and decreases the vaginosis-associated bacterial taxa [20]. The impact of intrauterine contraception is less clear: probably a short-term decrease in lactobacilli colonization is present with a trend to a restoration during time [21]. A highlighting of a possible facilitating effect on endocervical persistence of Chlamydia through a mechanism distinct from vaginal microbial alterations has been reported [22]. In a case-control prospective study, Cu IUD users have higher HPV clearance rates in comparison with non-users [23]. Recent evidence supports an increased risk of Herpes virus two infections among DMPA users [24].

Contrary to diffuse belief, there are no clinical or epidemiological data pointing out that the risk of acquisition or of pelvic complications of sexual infections using

intrauterine contraception or systemic hormonal contraception [25, 26]. So in young people, increasing the awareness of the diffusion of sexual pathogens and facilitating diagnostic testing and condom use are the cornerstones of prevention, independently of contraceptive choice.

13.3.1 Immaturity of Hypothalamic Pituitary Ovarian Axis

During the first postmenarchal years, menstrual disorders are frequent; but a large proportion of healthy adolescent girls with irregular menstrual cycles are still ovulating despite infrequent menses [27]. Young girls with anovulatory cycles or ovulatory cycles with a short luteal phase do not display differences in length from normal ovulatory cycles. Adolescents with ovulatory cycles demonstrate a mature feedback to estradiol, but continue to have lower gonadotropin levels, diminished ovarian responsiveness, and decreased corpus luteum sex steroid synthesis compared with adults, indicating that reproductive axis maturity still requires a complete development of all components of the hypothalamic–pituitary–ovarian axis [28]. A recent study demonstrates the possibility of induction of LH surge using transdermal estradiol (200 ore 300 μg according to body surface for 7 days) even in premenarchal girls [29], indicating an early maturation of hypothalamic sensitivity to ovarian hormones.

Few longitudinal studies pointed out the possibility of a dys-synchrony between central and peripheral maturation: the neuroendocrine mechanisms of GnRH regulation are rapidly established, while the ovarian follicular structures may be still immature [30, 31]. The interaction between oocyte, granulosa, and theca cells may evolve through an increase in thecal androgen production probably related to impaired aromatase activity, with consequent reduced progression of antral follicles and oligomenorrhea. AMH, secreted from granulosa cells, seems to play a critical role, inhibiting FSH action on follicle growth. The ovarian functional pattern of postmenarchal oligomenorrhea generally evolves during time in normal ovulatory cycles, even if a persistence of increased androgen production and menstrual irregularity has been described in the 12% of subjects [32].

Weight modifications are important determinants of menstrual function in this period of life. Low BMI, generally related to reduced energy availability for eating disorders or excess of physical acitivity, has more impact on hypothalamic centers. Weight increase, especially in subjects with genetic or epigenetic predisposition to polycystic ovary syndrome, accentuates ovarian androgen productions and slows down follicular maturation.

Data on adult women demonstrated that there is no impact of hormonal contraception on long-term fecundity [33, 34]. A possible impact of the use of contraceptives inhibiting ovulation on hypothalamic-pituitary axis maturation in very young people is sometimes proposed as a matter of concern. A longitudinal study performed in the past did not find any modifications of hypothalamic-pituitary function before and after the use of combined hormonal contraceptives, in agreement with what we know now about the precocious maturity of neuroendocrine centers [35].

Table 13.1 Risk factors for eating disorders

Family particular attention on food, weight, dieting
Nutritional disturbances during infancy
Previous overweight
Dissatisfaction with body image
Exposure to social networks' sites related to weight and nutrition
Physical activities requiring low weight and body silhouette (dancing, artistic gymnastics, skating…)
Chronic diseases requiring nutritional care
High selection of nutrients
Skipping meals
Cold intolerance
Perfectionism
Fear to disregard the expectations
Mourning, losses and depressive states

Anyway, before prescribing hormonal contraception to girls with menstrual disorders, it is advisable to understand, with a careful medical history (Table 13.1), the causes of the dysfunction and to identify eating disorders, even if atypical. If we suspect an energy deficiency related to restrictive eating behavior, strenuous physical activity, pathologies causing malabsorption or other chronic diseases that affect menstrual function together with bone structure [36], it is mandatory to elaborate a therapeutic project and share its objectives with the girl, at the same time of contraceptive options.

Postmenarchal oligomenorrhea may also reveal girls at risk of developing a Polycystic Ovary Syndrome (PCOS) phenotype: exposure to androgens in the intrauterine life [37], as daughters of PCOS mothers, low birth weight, and precocious catch-up growth, subject with premature adrenarche [38], visceral adiposity or elevated insulin levels. In presence of clinical signs or of biochemical evidences of androgen excess, a diagnosis of PCOS is sometimes already possible. In all these subjects, the use of hormonal contraception reduces ovarian androgen production [39], even if a minimal follicular development is still present during treatment, with minimal impact on metabolism. If they are motivated to follow indications about their lifestyle (physical activity, a nutrition program), ovarian functionality will improve under treatment.

So contraceptive consultation becomes also an opportunity to evaluate adolescent menstrual disorders.

13.3.2 Attainment of Peak Bone Mass

Peak bone mass is the amount of bone acquired when accrual ceases or plateaus after completion of growth. The greatest gain in bone mass in girls occurs approximately 6 months after the pubertal growth spurt, but the increase in bone mineral content continues in the years following the menarche. Timing and determinants of bone acquisition in late adolescence are not completely understood. The exact age

when bone mass reaches its peak in various skeletal sites is not clearly defined, but probably for femoral neck, total hip, and spine by 20 years [40] and beyond 30 years for the skull.

Cortical and trabecular components of the bone differ in their responsiveness to disease effects, medications, muscle-loading, and mechanical loading related to physical activity, and hormonal changes. Up to 80% of bone mineral density is genetically determined, while lifestyle (Table 13.2) influences 20–30% of adult peak bone mass [41]. Bone growth, repair, and adaptation to mechanical stimuli are regulated by the structure and the cells of the periosteal membrane. Steroid hormones (androgens and estrogens) have physiologically important effects on periosteal function in adolescence. Estrogens have a biphasic action, with low levels stimulating the periosteal expansion through the increase in the sensitivity for mechanical stimuli and for the effect of IGF-1. On the other hand, high estrogen levels inhibit periosteal bone formation.

At least 14 longitudinal studies investigated the effect of precocious assumption of hormonal contraceptives on bone accrual with different results, but most of them suggested that in young girls the increase of Bone Mineral Density (BMD) could be lower in CHC users than in non-users. WHO Medical Eligibility Criteria (WHO MEC) for Contraceptive Use published in 2015, focusing specifically on the fracture risk, stated that evidence on fracture risk is inconsistent, even if hormonal contraceptives may decrease bone mineral density in adolescents. Considering progestin only contraception, WHO MEC put in evidence that an effect on BMD is also documented for DMPA users and it is unclear whether adolescents can reach peak bone mass after discontinuation. A recent meta-analysis [42] on eight selected studies showed a weighted mean BMD difference at lumbar spine in 1535 adolescents

Table 13.2 Risk factors for low peak bone mass

Genetics
Low birth weight
Late puberty
Calcium intake (especially prepubertal)
Sun exposure and vitamin D status
Physical activity
Being underweight. Eating disorder.
Body composition (lean mass > fat mass)
Malabsorption, undiagnosed coeliac disease
Lactose intolerance
Chronic inflammatory disease
Obesity
Diabetes
Exposure to per- and polyfluoroalkyl substances (PFASs)
Smoking
Carbonated beverages and cola consumption
Corticosteroids use (also inhaled)
Antiepileptic drugs
Immunosuppressive treatment

of -0.02 g/cm^2 after 12 months ($P = 0.04$). The 24-month LS meta-analysis with five paired comparisons in 885 adolescents showed a highly significant weighted mean BMD difference of -0.02 g/cm^2 in CHC-exposed adolescents ($P = 0.0006$).

The discussion about these results is also related to the methodology of evaluation: dual-energy X-ray absorptiometry (DXA) evaluates bone density as a ratio between bone mineral content and bone area measurements. Areal BMD is not a volumetric density, it is influenced by vertebral sizes and displays a trend to a continuous increase during growth. Furthermore, bone mineralization is only one determinant of bone health and fragility and does not always reflect the risk of fracture [43].

Even if an impact of precocious hormonal contraception on bone is probable, as a recent document of The Faculty of Sexual and Reproductive Healthcare (FSRH) reminds [44], data present in the literature do not give us information about a "safe" gynecological age for starting contraceptives or about reversibility of their effect. Moreover, we miss clear evidences about the differences between various ethinyl-estradiol dosages, between ethinyl-estradiol and natural estrogens, and between different progestins. Therefore, we currently do not know if specific associations can be considered "neutral" for adolescent bone mass accrual. For this reason, it is important, in the clinical history, to focus on other factors affecting bone mineralization, such as disordered eating, in order to increase the awareness on the central role of adolescent age in building bone for life.

13.3.3 Mood and Hormonal Contraception

Mood changes in women under treatment with hormonal contraceptives have become an important issue in recent years, and it concerns both CHC and progestin-only methods. The relationship between mood and hormonal contraception treatments is complex. We know that sex steroids and the metabolism of progesterone and progestins in neuroactive steroids can have important neuroendocrine effects. Hormonal contraceptives can interfere in various ways, depending on the combined or progestin-only substances, the characteristics of the progestin, dosage and method of administration (oral, injection, subdermal implant, intrauterine system). Different intrauterine systems release different concentrations of LNG, affecting levels in the endometrium and myometrium and in plasma in the diverse body systems (Table 13.3). The data available for combined hormonal contraception regarding combinations containing ethinylestradiol and various progestins, and the dosages of the two components are not always reported. In addition, the formulation of the combination (monophasic or multiphasic), the regimen of administration (21 + 7, 24 + 4, or extended regimen), and the method (vaginal, cutaneous) all condition the pharmacokinetics, influencing substance concentrations in blood and, probably, mood.

Studies on mood effect show that hormonal contraception may induce interaction of sex steroids with the serotoninergic and noradrenergic pathways (Fig. 13.1). The modifications in allopregnanolone in the central nervous and circulatory

Table 13.3 Pharmacological characteristics and clinical indications of LNG intrauterine systems

LNG IUS 20	LNG IUS 12	LNG IUS 8
LNG total content 52.5 mg	LNG total content : 19.5 mg	LNG total content : 13.5 mg
LNG release : 20 μg	LNG release : 13 μg	LNG release : 8 μg
	17.5 μg/day after 24 days, 9.8 μg/day after 1 year 7.4 μg/day after 5 year	(average approx.8 μg/24h over the first year)
0.1-0.4 ng/mL serum levels		
470-1500 ng/g in endometrium (1)		
1.8-2.4 ng/g in myometrial tissue (2)		
Duration of use 5 years	Duration of use 5 years	Duration of use 3 years
Indicated for Contraception Treatment of idiopathic menorrhagia Treatment of dysmenorrhea Endometrial protection during ERT	Indicated for Contraception	

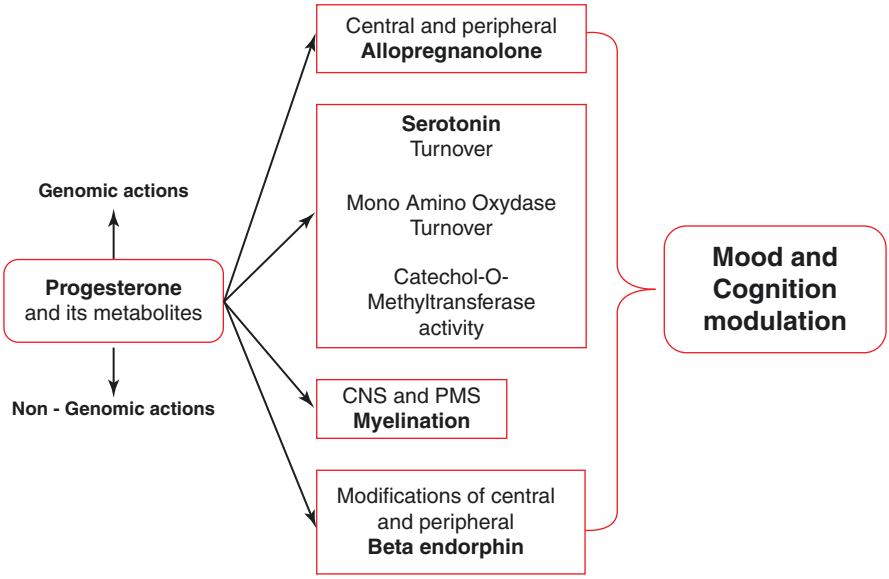

Fig. 13.1 from Pluchino et al. 2006 [86]

systems, induced by hormonal treatments, are related to changes in GABA activity. It is still unclear whether the neuroendocrine effects of progestins are direct or mediated by their metabolism in allopregnanolone [45]. Hormonal contraception affects allopregnanolone brain concentration in an animal model (rats) and the effect of synthetic progestins differs from that of micronized progesterone [46]. One randomized, controlled, double-blind placebo trial that evaluated changes in brain reactivity in regions previously associated with emotion processing showed that OC users had lower emotion induced reactivity in the left insula, left middle frontal gyrus, and bilateral frontal gyri than placebo users [47]. Another study on synthetic estrogen and progestins in oral contraceptive pills reported bilateral decrease of cortical thickness in the lateral orbitofrontal cortex and the posterior cingulate cortex during oral contraceptive use. The functional significance of this cortical thinning remains to be investigated [48]. We note a very recent report on the relationship between hormonal contraceptives and mood that focuses on relevant underlying mechanisms, such as emotion recognition and reactivity, reward processing, and stress response [49]. These are topics that must be given due consideration also in the case of adolescent contraceptive choice.

The hypothalamic-pituitary-adrenal axis may also be involved in the effects of female hormones on mood and depression, moderated by mineralocorticoid receptors and glucocorticoid receptors [50]. Another mechanism has also been correlated with depression risk in women using progestin only contraception: in one pilot study investigators found reduced beta-arrestin 1 (β-AR 1) protein levels in peripheral blood mononuclear leukocytes (PBMC). Previous studies [51] demonstrated apparent correlations between β-AR 1 and depressive symptoms in reproductive women. The study involved 29 young women, 12 of whom were using progestin only contraception (4—LNG IUS 20; 1—LNG IUS 12; 4—Nexplanon subdermal implant; 1—DMPA; 2—mini-pill). The authors concluded that since β-AR 1 has been shown to facilitate estrogen-mediated neuroprotection, the estrogen in COC may attenuate the effect of progestin on β-AR 1 levels. We need to discover the specific significance of these two findings, increased cortisol and reduced β-AR 1, in adolescents [52].

The main discussion is centered around LNG IUS 20 in relation to recent studies on the possible causes of mood changes. One study on a wide age range of women, 18–45 years old, suggests that panic attacks, anxiety, mood changes, sleep disturbances, and restlessness may be related to elevated cortisol levels during treatment [53]. The authors found an exaggerated salivary cortisol response to the Trier Social Stress Test -TSST (24.95 ± 13.45 nmol/L, 95% CI 17.49–32.40), compared to EE30/LNG (3.27 ± 2.83 nmol/L, 95% CI 1.71–4.84) and natural cycling women (10.85 ± 11.03 nmol/L, 95% CI 6.30–15.40) ($P < 0.0001$). The conclusion is that LNG-IUD contraception induces a centrally-mediated sensitization of both autonomic and hypothalamic-pituitary-adrenal (HPA) axis responsivity. The European Society of Contraception (ESC) expert statement considers it “unlikely that slightly higher cortisol levels in LNG IUS users, as found in this one study, are associated with evidence of an increased risk of an adverse event” and calls for further studies, larger and clinically appropriate [54].

Another important point to consider is the effect of hormonal contraceptives on mood in specific gynecologic and psychiatric populations, such as those with polycystic ovarian syndrome and premenstrual dysphoric disorder who may need treatment, during the postpartum period or even in early adolescence [55]. In any case, we emphasize the importance of family history as a risk factor. It is necessary to evaluate mood and risk factors for depression and its very first symptoms in girls who have early menarche [56]. Below, we present the most relevant findings regarding adverse effects of contraceptives on mood with particular reference to adolescence.

Progestin only contraception. One systematic review [57] of 26 studies (5 randomized controlled trials, 11 cohort studies and 10 cross-sectional studies) on the relationship between progestin hormonal contraception and depression concluded that despite perceptions in the community of increased depression following the initiation of progestin contraceptives, the preponderance of evidence does not support an association based on validated measures. The substances evaluated were injectable medroxyprogesterone acetate (DMPA), subdermal progestin, levonorgestrel intrauterine device, and progestin only contraceptive pills. The association between contraception and depression in adolescents was evaluated in trials using DMPA.

DMPA. Three previous studies [58–60] had also concluded that depression symptoms were no more likely in adolescents taking DMPA than other hormonal contraceptives. A fourth study [61] found little evidence of increasing depression in young girls with long-term use of DMPA and no evidence of a short-term effect of dose (within the contraceptive range) on mood. Then, 13 years later, a study published in 2008 found no negative mood changes with either DMPA or oral contraceptive pill in 805 patients divided into two age groups, 16–24 years and 25–55 years. DMPA was considered to be protective against mood swings (OR 0.7) and the contraceptive pill against nervousness (OR 0.5) as well as mood swings (OR 0.7) [62]. Another study published the same year [63] involving 328 girls, 14–17 years old (mean age 16.7 years), had different findings. The participants were followed longitudinally for up to 41 months at primary care clinics to evaluate the effects of hormonal contraceptives on mood and sexual interest. The girls kept daily diaries where they recorded positive mood, negative mood, and sexual interest. A total of 938 diary periods were analyzed: participants reported significantly higher mean weekly negative mood in the periods of DMPA use than in periods of non-use. A recent study related to use of hormonal contraception by 800,000 Swedish women [64] states that hormonal contraception increases the risk of psychotropic drug use in adolescent girls but not in adults; the OR for DMPA is 2.37; 95% (CI: 1.46–3.84).

Etonogestrel implants. In a large multicenter study [65], designed to assess the safety and efficacy of the etonogestrel (ENG) implant in 474 American women (18–48 years) who used the implant for up to 2 years (6186 cycles of exposure), common adverse experiences that led to discontinuation, besides bleeding irregularities, were emotional lability (6.1%), weight increase (3.3%), depression (2.4%), and acne (1.5%). Another American study [66] involving 160 adolescents and young women (12–24 years) with ENG subdermal implant or levonorgestrel IUS,

found that the reasons for discontinuation of the contraceptive treatment included bleeding problems (59%), weight gain (22%), pelvic pain/cramps (15%), desire for pregnancy (15%), and mood changes (11%).

LNG intrauterine systems. The LNG IUS 20 [67, 68] system in adolescents is used for contraception with certain therapeutic indications, such as idiopathic heavy menstrual bleeding, other causes of heavy bleeding (adenomyosis), pain treatment from endometriosis or adenomyosis, and endometrial hyperplasia. The device is prescribed also for adolescents and young women with hemostasis defects and bleeding disorders [69–71]. In general, studies on mood changes during contraceptive treatment with LNG IUS 20 have involved prevalently adult populations or a wide range of ages, and the results are contradictory [72–74]. A systematic review [75] regarding hormonal contraception in women (15–45 years old) clinically diagnosed with depressive or bipolar disorders evidenced no significant differences between four treatment groups in the number of hospitalizations for bipolar disorder (Cu-IUD 3.6%; LNG-IUS 5.3%; sterilization 5.7%; and DMPA 6.0%) or depression (LNG-IUS 0.7%, Cu-IUD 0.9%; DMPA 2.2%; and sterilization 3.2%). In particular, no significant associations between hormonal contraception and increased risk of depressive symptoms were found in two of the studies: one regarding 9688 young women (18–23 years old) in Australia [76], the other 103 adolescents under 18 years old in the USA [77]. To the contrary, recent studies on Swedish adolescents show that LNG IUS had the strongest association with use of psychotropic drugs (adjusted OR 2.90; 95% CI: 2.22–3.79) [64]. Furthemore, the above-mentioned study done in the USA [66] reported mood changes in 11% of 160 young women (12–24 years old) using LNG IUS 20 or subdermal implant the majority of treatment discontinuations was due to other factors.

Concerning possible mood change risk, one group of investigators has proposed precise pre-insertion counseling regarding potential effects on mood, as part of good informed choice, with additional counseling 6–12 weeks and 12 months after insertion [78]. To date, there have been no reports of a causal relationship of adverse effects regarding mood in LNG 12 and LNG 8 users [79]. We do note that both these devices release low concentrations of LNG (Table 13.4) and that more of the users ovulate compared to LNG IUS 20 users.

Progestin-only pill. The recent findings on adolescents 15–19 years of age include a report of increased depressive symptoms with RR 2.2 (95% CI, 1.99–2.52) with first use of an antidepressant in subjects taking progestin-only pills, compared to RR 1.4 (95% CI, 1.31–1.42) for LNG IUS and RR 1.8 (95% CI, 1.75–1.84) for combined hormonal contraception. The absolute increase in depression diagnoses for girls was 3 per 1000 for depression diagnosis and 8 per 1000 for first use of antidepressants, compared to boys who had an increase of 1.1 and 3 per 1000, respectively [80]. In another study, the same authors found that use of hormonal contraception was positively associated with subsequent suicide or suicide attempts, with an estimated risk for attempted suicide of 2.29 (95% CI = 1.77–2.95) for oral progestin-only products and 1.91 (95% CI = 1.79–2.03) for combined oral contraceptive preparations [81].

Table 13.4 Daily hormone release over time with available LNG intrauterine systems

	LNG IUS 20 (52.5 mg)	LNG IUS 12 (19.5 m)	LNG IUS 8 (13.5 mg)
Nilsson C.G. et al., 1980 Contraception;41:353–62	260 ± 68 pg/mL within 3 months		
	166 ± 32 pg/mL within 18 months		
	101 ± 37 pg/mL within 24 months		
	74 ± 15 pg/mL within 60 months		
Lockhat F.B. et al., 2005 Fertil. Steril. 83:398–404	425.9 ± 100.2 pg/mL within 1 month		
	348 ± 51.8 pg/mL within 3 months		
	331 ± 53 pg/mL within 6 months		
Apter D. et al., 2014 Fertil. Steril. Jun; 101(6) 1656–62	342 ng/L (CV 43.1%) after 11 days	214.0 ng/L (CV 60.8%) after 11 days	148.0 ng/L (CV 43.4%) after 11 days
	218 ng/L (CV 35.2%) over the 3-year period	114 ng/L (CV 52.9%) over the 3-year period	74.3 ng/L (CV 35.8%) over the 3 year period
	165 ng/L (CV 40%) decline over time	95.1 ng/L (CV 60.9%) decline over time	68.3 n/L (CV 34.1%) decline over time

Combined hormonal contraception (CHC). A 2002 review of the literature found that CHC users presented more stable affectivity than non-users throughout the entire menstrual cycle [82]. Subjects taking combined hormonal contraceptives who have negative mood changes generally report a history of depression, psychiatric problems, dysmenorrhea with premenstrual syndrome, family history of mood disturbances related to hormonal contraceptive treatment, or particular life events (post-partum, age). A Swedish double-blind, placebo-controlled randomized trial on a combined oral contraceptive containing levonorgestrel (EE 30/LNG 150 μg) evidenced higher scores of depressed mood, mood swings, and fatigue in the CHC than placebo users. All the 34 women (18–45 years old) randomized for the trial, had had previous episodes of mood problems during CHC use [47]. Another Swedish study was done using telephone screening of 347 young women, 18–35 years old. The investigators evidenced a statistically significant reduction in general well-being in the women who took CHC (first-choice: EE30/LNG 150 μg) compared to those on placebo; the findings were based on the first 3 months of treatment. There was no information regarding any statistically significant effects on depression [83]. Recent data, again in Sweden, on the use of psychotropic drugs show an association with CHC treatment (adjusted OR 1.34, 95% CI 1.30–1.37). Age-stratified analysis evidenced that this association was strongest in adolescent girls (adjusted OR 3.46, 95% CI 3.04–4.94 for age 12–14 years), and non-existent in adult women. The 12–14 year olds were found to present the strongest

relationship between psychotropic drugs and CHCs, specifically non-oral methods (skin patch or intravaginal ring) with OR 4.47 (95% CI: 2.08–8.78). This was a pharmaco-epidemiological study with a total population of 815,662 women aged 12–30 years who had no history of psychiatric disease [64]. A prospective cohort study (Tracking Adolescents' Individual Lives Survey TRAILS) of a total 1010 girls analyzed at the first assessment of oral contraceptive use (mean age 16.3) done in the Netherlands showed no association between CHC and depressive symptoms for the total of all age groups. However, the 16-year-old girls were found to have higher scores for depressive symptoms with oral contraceptives than older age groups [84]. To the contrary, data specifically related to 4765 adolescents (13–16 years old) in the USA who took CHC did not evidence any increase in depressive disorders. The type of oral contraceptive was not specified [85].

The European Society for Contraception [54] recommends the following steps for balanced and individualized counseling:

- "Take a thorough medical history, considering especially any conditions that could cause a complication with use of a contraceptive method.
- Identify women predisposed to depressed mood by taking a past and current psychiatric history; ask specifically about ever-use of antidepressants. Include a family history to identify women at increased cardiovascular risk.
- Take time to cover in a personal history the woman's life situation, partnership, and sexual life.
- After starting a new method, offer a follow-up visit to discuss options in situations of severe or troublesome adverse events. Adverse events should include affective symptoms and sexual function."

This is particularly true dealing with very young subjects, because issues such as changing body, parents and academic expectations, peer pressure can induce significant distress and sometimes overwhelming emotional and mood disorders.

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Contraception After an Induced Abortion and Childbirth

14

Oskari Heikinheimo and Satu Suhonen

14.1 Return of Ovulation and Resumption of Sexual Activity

14.1.1 After an Induced Abortion

After either medical or surgical abortion, and expulsion of the placenta, the circulating levels of both estradiol and progesterone decline within few days [1, 2]. The disappearance of hCG follows a slightly different pattern and occurs in several phases. The initial half-life of hCG is rapid, less than 20 h following both surgical and medical abortion. However, the total elimination of hCG may take up to 35 days after termination of first trimester pregnancy [2].

Nevertheless, the recovery of ovarian function is fast. First ovulation takes place on the average at 16 days after first trimester surgical, and 21 days after administration of mifepristone in medical abortion [2, 3]. However, it may occur as early as 8 days after early medical abortion [3]. The first post-abortion menstrual cycle is ovulatory in approx. 80–90% of women undergoing a first trimester abortion. Thus, effective contraception without delay is needed after an induced abortion regardless of the method of abortion.

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14.1.2 After Delivery

In non-lactating women, ovulation rarely occurs until 6 weeks from delivery [4], but earlier ovulation cannot be excluded. It is recommended that these women should start use of contraception 3 weeks after childbirth [5, 6].

In contrast, exclusively breastfeeding women ovulate seldom (20%) during the first 6 months after childbirth [7]. There is, however, great individual variation how strongly lactation inhibits recovery of ovarian function. Therefore, lactation itself cannot be regarded as a reliable method for preventing pregnancy.

14.2 Contraception After an Induced Abortion

14.2.1 Surgical Abortion

For several decades, surgical abortion has been, and continues to be, the standard of care in several countries. Initiation of contraception after surgical abortion is rather straightforward. In the absence of contraindications, all systemic hormonal methods (incl. oral contraceptive pills, and contraceptive implants, injections and patch) may be started immediately after surgical abortion [6].

Also, intrauterine contraception (IUD) can be safely initiated at the time of uncomplicated surgical abortion [6]. While immediate IUD insertion is associated with somewhat increased risk of expulsion, the number of women using IUD during follow-up is higher among women receiving the device at the time of abortion [8]. Moreover, post-abortal use of IUD has been proven effective in reducing the need of subsequent abortion. In several cohort studies, the use of intrauterine contraception has been associated with 60–70% reduction in the need of subsequent abortion compared to non-IUD contraception [9, 10]. Thus, insertion of IUD at the time of surgical abortion has become a standard of care and should be liberally provided.

14.2.2 Changing Landscape of Abortion Care

Medical abortion by means of the antiprogestin mifepristone, followed by administration of synthetic PGE1-analogue misoprostol 1–3 days later, is being increasingly used in several countries. In the Nordic countries and in Scotland, more than 80% of all induced abortions are currently medical abortions [11]. As misoprostol can be self-administered at home, most women undergoing early first trimester abortion visit the gynecological unit responsible for abortion care only once. As in the case of surgical abortion, all hormonal methods with systemic action can be started at the time of medical abortion (Table 14.1).

However, increasing use of medical abortion, and recognition of the high efficacy of LARC methods and recommendations for their liberal use in women of all ages pose a challenge to the post-medial abortion contraceptive service-delivery system.

Table 14.1 When to start contraception after medical abortion?—Strategies modified according to different service provision

	Day of		
	Mifepristone administration	Misoprostol administration	1–(2) Weeks after
CHC/POP		+	
Implant	+	+	(+)
DMPA	(+)	+	(+)
IUD/IUS		+	+

14.2.3 Medical Abortion and Contraceptive Implants

Contraceptive implants are among the most effective contraceptive methods. The high efficacy of implant contraception has also been shown in post-abortal use [12, 13].

The optimal timing on implant insertion at the time of medical abortion has been studied in two randomized trials. Recent North European and American studies assessed implant insertion at the time of mifepristone ingestion *vs.* insertion later, following completion of medical abortion [12–14]. In both studies, the efficacy of medical abortion was not affected by the immediate insertion of the implant. However, the uptake of implant contraception and its use during the follow-up period was significantly higher when provided at the time of mifepristone ingestion. Thus, providing contraceptive implants at the clinic initiating medical abortion is a very logical and cost-effective means of providing effective long-term post-abortal contraception after medical abortion.

14.2.4 Medical Abortion and Intrauterine Contraception

According to current global guidelines, intrauterine contraception after medical abortion may be started as soon as the pregnancy has ended [5, 6]. In most clinical settings, this would imply insertion at post-abortal follow-up visit or at the time of next menstruation. However, the need of post-abortal follow-up visits is questionable, and not routinely recommended in international guidelines on abortion care [6]. Also, the compliance with such routine visits is often not good.

We recently performed an RCT comparing early *vs.* late provision of LNG-IUS following medical abortion. The LNG-IUS was provided within 3 days (i.e., next working day) after early first trimester medical abortion, or on the day of late first trimester (i.e., weeks 9^{+0} – 12^{+0}) or second trimester (12^{+1} – 20^{+0}) medical abortion, and compared with that of the routine IUD provision between 2 and 4 weeks [15, 16]. The uptake of the LNG-IUS was significantly higher if provided rapidly. However, the rate of partial IUS expulsions was higher among women randomized to early LNG-IUS provision. Nevertheless, the use of IUS at 1-year follow-up was higher among women receiving the device immediately. Moreover, the incidence of

Table 14.2 Fast-track/immediate vs. delayed insertion of the LNG-IUS after medical abortion [17]

	Fast track (%)	Delayed	RR (95%CI)	*P*-value
Insertion successful	95.5	84.7	1.13 (1.04–1.22)	0.004
Expulsion (total or partial) by 3 mo	20.7	4.0	5.22 (1.88–14.55)	
Verified IUS use at 3 mo	72.2	57.3	1.26 (1.05–1.51)	0.014
Verified IUS use at 1 y	62.4	39.7	1.57 (1.23–2.02)	<0.001
New pregnancy by 1 y	4.5	12.2	0.37 (0.15–0.91)	0.027

various post-abortal complications was similar between the groups randomized to early vs. late IUS provision. Also, the bleeding patterns did not differ between the groups of early and late LNG-IUS provision (Table 14.2, Fig. 14.1). These results are in line with previous studies assessing the use of early (within 1 week) IUD provision after medical abortion [18], and encourage early provision of IUD also after medical abortion.

Thus, intrauterine contraception may be initiated rapidly after medical abortion. Provision within 1 week after medical abortion is safe and no interval contraception would be needed. The challenges in early IUD provision lie in organizing the service-delivery system as well as in ensuring the compliance to attend the early IUD insertion visit. Structure of the health care system is likely to have a major effect on how successful this is.

14.2.5 Injectable Progestin After Medical Abortion

Injectable contraception, especially that of depot medroxyprogesterone acetate (DMPA), is widely used globally, and considered by some authors an LARC. Immediate injection of DMPA, administered at the time of mifepristone ingestion was compared to later administration in randomized trial performed in the USA and in Mexico [14]. Surprisingly, the rate of ongoing pregnancy was significantly higher following immediate injection (3.6% vs. 0.9%) [14]. However, no such difference in the rate of ongoing pregnancy was seen in follow-up cohort study in which DMPA was administered 1–2 days later, i.e., at the time of misoprostol administration [19]. Theoretically, the reduced efficacy of simultaneously administered mifepristone and DMPA might be related to pharmacological interaction of MPA competing with mifepristone for binding to the uterine progesterone receptors. Nevertheless, the possible reduced efficacy of medical abortion must be considered if DMPA is to be administered at the same time with mifepristone.

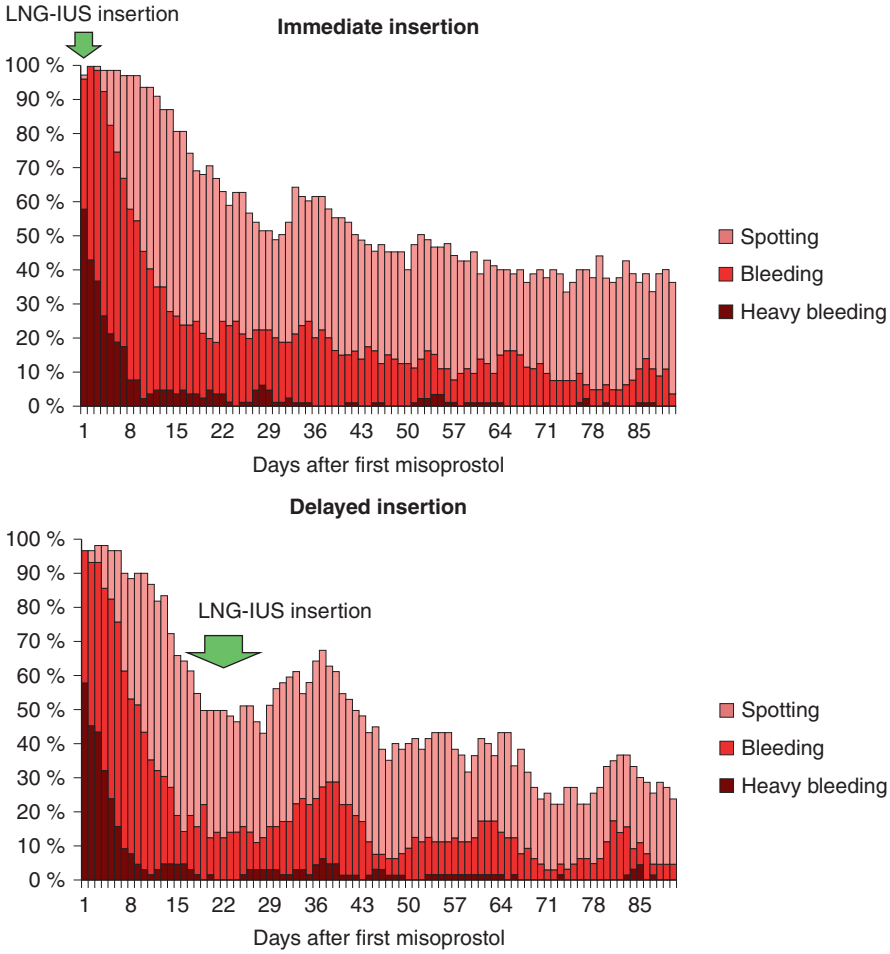

Fig. 14.1 Bleeding profiles after fast-track (≤3 days) or delayed (2–4 weeks) LNG-IUS insertion following early first trimester medical abortion. Heavy bleeding was described as the need of large sanitary towels during the day, or overflow at night; bleeding as the need of normal sanitary towels or tampons; and spotting as the need of panty liners or small tampons, or no need of sanitary protection (modified from [15, 16])

14.3 Contraception After Childbirth

14.3.1 Can Breastfeeding Be Used as Contraception?

WHO and UNICEF recommend exclusive breastfeeding for 6 months after delivery, especially to ensure the health and growth of the newborn. However, this goal is seldom achieved. Globally, less than 40% of children under the age of 6 months are exclusively breastfed [20].

As described previously, breastfeeding suppresses ovulation, but for an individual length of time due to individual responses in secretion of GnRH and prolactin to lactation. Lactational Amenorrhea Method (LAM) as a contraceptive method after childbirth was defined in 1988 [21]. If the infant is less than 6 months old, the mother is amenorrheic and the infant is exclusively breastfed, LAM gives a 98% protection from pregnancy. However, all these three criteria must be met. As regards the last of them, this criterion is quite strict; only vitamins, infrequent intake of water or juice are allowed, the breastfeeding must be regular; during daytime, feedings should not be more than 4 h apart, and during night-time, 6 h apart. Thus, in real life with a newborn, the last criterion is not easily met as rest and sleep are valued and important for the mother, too. Therefore, return of fertility, need of contraception and alternatives in it, must be discussed, information given and an efficient method started early enough. This does not exclude or underestimate the importance and value of breastfeeding.

14.3.2 Interpregnancy Interval

Recovery, both physical and psychological, after an abortion, spontaneous or induced, needs and takes its time. Counseling must be available and offered, especially for those with history of psychosocial contacts and needs. Also counseling as regards the eventual risks of future pregnancies and/or the need of contraception must be covered. Similarly, after the childbirth, it takes time and energy both physically, psychologically and socially of the mother and her nearest to adapt to the new and different way and rhythm of the everyday life.

An interval between pregnancies is generally recommended (IPI, interpregnancy interval). Pregnancies with short intervals carry risk for preterm delivery, small birth weight, neonatal deaths and also maternal anemia [22, 23]. Generally, the recommended IPI time has been 1 year, i.e., the time between the delivery and time to next conception. However, WHO recommends an even longer IPI, up to 2 years [24].

Thus, the contraceptive wishes, needs, and alternatives must be discussed and offered timely after every pregnancy. However, also contraceptive methods differ and the outcome of the recent pregnancy, delivery, and postpartum period must be kept in mind while choosing the method. Table 14.3 summarizes the usable methods in relation to breastfeeding and time from delivery [5, 6].

Table 14.3 Safe windows (MEC1-2) to start contraception after childbirth in relation to time from delivery and lactation when general contraindications have been excluded [5]

Lactation	Method/time from delivery		
	CHC	PO (pill, implant, injection*)	IUD
Breastfeeding	6 weeks–6 months MEC2 >6 months MEC1	Immediately *0–6 weeks MEC2 *>6 weeks MEC1	0–48 H MEC1 ≥4 weeks MEC1
Non-breastfeeding	3–6 weeks MEC2 >6 weeks MEC1	Immediately MEC1	0–48 H MEC1 ≥4 weeksMEC1

14.3.3 Short- and Long-Acting Alternatives in Contraception After Childbirth (SARCs and LARCS)

Although an interval between pregnancies is recommended, families have different wishes. The constantly advancing age of the mother at first delivery, especially in developed countries, sets limits to the time when a new successful pregnancy is likely and reasonable. The growth, health, and favorable prognosis of both the fetus and the mother are to be evaluated. In Finland, the age at first delivery was 29.3 years in 2018, being 26.6 years in 1990. During the same time period, the percentage of mothers over 35 years of age at the time of delivery increased from 13.3% to 23.7% [25]. The increasing risks in a new pregnancy and also the method of contraception with advancing age of the mother must be kept in mind.

In most developed countries, a check-up after childbirth is routine. At least then is the time to discuss, plan, and schedule the start of contraception.

14.3.3.1 SARC

As the name tells, the efficacy of these contraceptive methods per intake does not last long. If pills are chosen, daily remembering is essential, if patch, it is weekly, and in case of contraceptive ring, at least once a month. Does this fit in in the everyday life with an infant is worth discussing with the woman considering SARC methods.

14.3.3.2 Combined Hormonal Contraception (Pill, Patch, Ring)

Contraceptives with estrogen-progestin combination (combined hormonal contraception, CHC) carry a risk for deep venous thrombosis and the risk is highest during the first months of use. After childbirth, there is an endogenous tendency for hypercoagulation and thus, risk for deep venous thrombosis (DVT) [26]. Therefore, during the first 6 weeks after delivery, other contraceptive methods should be preferred. Naturally, general contraindications for combined hormonal contraception must be taken into account (see section CHC), as well as general health, including especially present BMI and blood pressure. There is no data supporting that CHC use, started after 6 weeks following childbirth, has a negative effect on breastfeeding or infant weight gain [27, 28].

14.3.3.3 Progestin-Only Pills (POP)

Progestin-only contraception does not interfere with breastfeeding, does not carry risks either for the infant or the mother. If POP is chosen, they can be started immediately after delivery. If a follow-up for the infant and mother are included in the health care system, during these visits also, contraception, the acceptability and the suitability of the pills must be discussed. Daily remembering is required, and in an everyday life with a newborn, this limits both adherence and acceptability and thus, also the efficacy of the chosen method. Especially when breastfeeding is gradually reduced and ovarian function restored, irregular bleeding and spotting typical to progestin only contraception may occur. Non-breastfeeding mothers can experience this earlier. Counseling concerning the characteristics of the chosen method, especially as regards bleeding, is essential also in postpartum contraception.

14.3.3.4 Injectable Progestin Contraception

Although there has been some concern that progestin-only injections might carry a slight risk for DVT in the first few postpartum weeks or have an unfavorable effect on lactation and infant growth, there is no reliable data supporting this. Thus, the first injection can be given already at the delivery unit, if progestin injections are the chosen method.

14.3.3.5 LARC

The contraceptive efficacy of long-acting reversible contraception is well-established, and the easiness of the method and trust in it are highly appreciated by the users. However, it is also important in counseling women after childbirth choosing LARC, especially if a new pregnancy is planned in the future, that resumption of fertility is rapid after removal of an LARC method.

14.3.3.6 Progestin Implants

If a longer-term contraception is planned, progestin implant is a valuable option without the need of daily remembering. The implant(s) can be inserted at the delivery unit or later at maternity care or family planning services. Prior to a later insertion is in question, it should be checked that LAM criteria are fulfilled, or POPs have been used as a bridging method or some other contraceptive method and the risk of pregnancy is ruled out. Similarly to POPs, information about the typical effects of the method on patterns of bleeding is important. Depending on the type of implant chosen, either one releasing etonogestrel or levonorgestrel, the recommended time of use can be up to 5 years.

14.3.3.7 Intrauterine Contraception

Intrauterine devices (IUDs) have traditionally been regarded as a method recommended especially to parous women. As stated above, nulliparous and also nulligravid women are at present satisfied users of this method and LARC with IUDs recommended for them, too.

IUDs either copper-IUDs (Cu-IUD) or LNG-IUS offer contraceptive efficacy from 3 up to 10 years depending on the type of IUD. Especially, if the couple considers that the recommended IPI (1–2 years) suits their family plans or no further pregnancies are wished at all, intrauterine contraception is a valuable option to be discussed.

The typical effects on menstrual bleeding and pain and eventual hormonal side effects, if LNG-IUS is chosen, must be covered in the counseling and especially when considering whether to choose copper- or LNG-IUS.

14.3.4 Time of Insertion

Early, easy and user-friendly initiation of an efficient contraceptive method after childbirth is important, increases continuation rates as described earlier in this section and reduces the risk of an unplanned pregnancy.

An IUD can be inserted as soon as the placenta is delivered and up to 48 h postpartum. If a cesarean section is performed, the IUD can be fitted in after removal of the placenta. Heavy bleeding, signs of infection or uterine malformations are contraindications for post-placental insertion. The risk of expulsion in post-placental insertions is higher [29] than during later insertions (≥4 weeks), but continuation rates are higher. Especially, if a prompt start of a long-term, effective contraception is important and attendance to a later insertion unlikely due to social or logistic reasons, post-placental insertion is worth considering. In post-placental insertions, a later check-up is recommended to verify that the IUD is *in situ*. If needed, a new IUD can be inserted.

The high efficacy of postpartum IUD provision was highlighted in a recently published FIGO sponsored large multicenter trial performed health care settings from low- and middle-income countries. Following systematic training of the health care providers (both medical doctors and nurses), the insertions were highly successful and the rates of IUD expulsion low (<4%) following insertion after both vaginal and cesarean delivery [30]. Also, the rate of complications, such as pelvic inflammatory disease, was low (0.1%).

In the time window from 48 h till 4 weeks, postpartum as regards IUD insertion, the risk of IUD expulsion is higher and outweighs the benefits, and is thus not recommended [5, 6, 29].

After 4 weeks postpartum, the IUD insertion is again a valuable option to be considered in contraception. Especially if a longer time from delivery has elapsed, the appropriate use of preceding contraception whether LAM, condom, or pills, and possibility of a new pregnancy are important to evaluate before the insertion.

However, every IUD insertion carries a risk of uterine perforation, although small, 0.4–1.4/1000 insertions [31, 32]. Most of the perforations have been diagnosed in women with a recent delivery (<6 months) and/or breastfeeding [32, 33]. Lactation increased the risk of perforation to 4.5/1000 insertions [33]. Also, the inexperience of the health care provider correlates with the risk of perforation [31]. Experience in the insertion procedure and knowledge of uterine involution during puerperium is important as the uterus is smaller, and myometrium is thinner and softer.

If an LNG-IUS is inserted, it is important to inform that irregular spotting might occur during the first few months similarly to insertions during normal ovarian function and is due to the mechanism of action of the IUS on the endometrium and does not necessarily mean resumption of menstruation.

Table 14.4 summarizes the risks and benefits of the different post-abortion and postpartum IUD insertion times.

14.3.5 Emergency Contraception

14.3.5.1 Oral Options

Ovulation is unlikely in breastfeeding women during the first 3 weeks after childbirth. After this, emergency contraception (EC) is recommended in case of

Table 14.4 Immediate/early initiation of LARC in post-abortal and post-partum contraception—a win-win strategy

	Immediate/early	Delayed
Patient satisfaction	Optimal	Decreased
Uptake of the method	High	Lower
Compliance during follow-up	Optimal	Decreased
Need of additional visits	Not needed	Needed
Risk of unplanned pregnancy	Low	Higher in some studies
Cost efficacy	Optimal	Decreased

unprotected sex. In exclusively breastfeeding women fulfilling LAM criteria, especially if the time since delivery is close to 6 months, EC must also be kept in mind and used if needed. If breastfeeding is partial, EC is important already earlier. Both levonorgestrel or ulipristal acetate can be safely used in the postpartum period. If a breastfeeding mother chooses to use ulipristal acetate, she must be informed not to breastfeed during the first week after taking EC. However, she must be encouraged to express the milk to maintain lactation. Levonorgestrel is not excreted to milk to such an extent that the mother could not continue breastfeeding.

14.3.5.2 IUD

The most effective alternative in EC is copper-IUD. The general contraindications of IUD insertion are to be remembered. If, after resumption of menstruation, the bleedings are too heavy or painful, other options must be considered. If not, a long-term effective contraception can be continued.

14.3.6 Service Delivery System and Uptake of Post-Abortal and Postpartum Contraception

Motivation to initiate effective contraception is typically at its highest immediately after an induced abortion [34]. This has been highlighted in several recent studies comparing rapid vs. delayed initiation of various contraceptive methods, such as contraceptive implants [12, 13], LNG-IUS [15, 16], or DMPA [14]. Besides the higher uptake of these various methods immediately after abortion, patient satisfaction is higher and number of subsequent unwanted pregnancies lower. It is thus important to utilize this window-of-opportunity when providing effective post-pregnancy contraception. (Table 14.4).

Also, the service-delivery system has a significant effect on the uptake of various contraceptive methods after an induced abortion and childbirth [35, 36]. The value of free-of-charge contraceptive provision, especially regarding the uptake of LARC methods, has been shown repeatedly in different health care settings [35, 37]. In a randomized trial routine provision of intrauterine contraception as part of abortion, significantly reduced the need of subsequent abortion during 5 years of follow-up ([36]; Fig. 14.2). Thus, providing post-pregnancy contraception rapidly and as part of the overall pregnancy (either abortion or childbirth) care are important elements of successful post-pregnancy contraceptive care [38, 39].

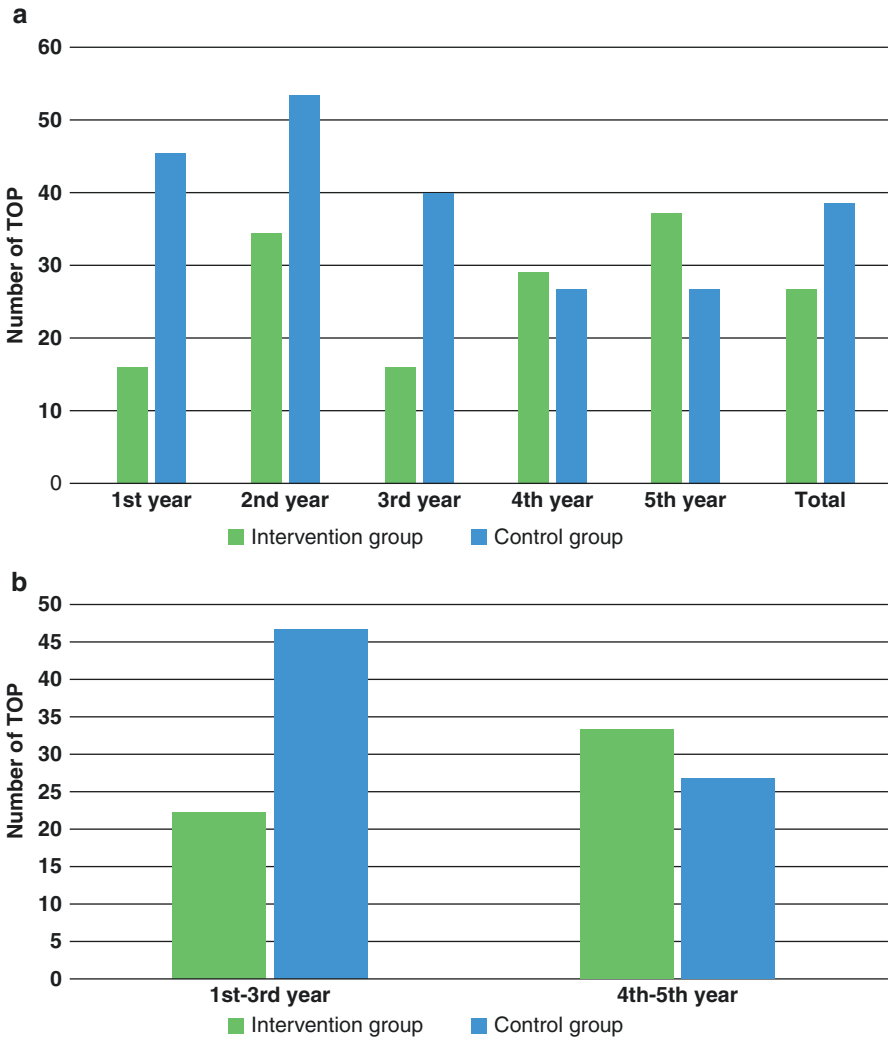

Fig. 14.2 Rate of subsequent TOP during follow-up following provision of IUD as part of first trimester abortion care (intervention) vs. provision of oral contraceptives with the possibility of obtaining free-of-charge IUD from the primary health care (control). Shown are (**a**) annual rate of subsequent TOP during the 5-year follow-up (/1000 years of follow-up) and (**b**) average rate of subsequent TOP during the 5-year follow-up (/1000 years of follow-up) [36]

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Contraception in Perimenopausal Women

15

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15.1 Background of the Perimenopausal

Since 1967, it has been reported that after 37–40 years of age, menstrual cyclicity undergoes important changes in frequency, duration and quantity, with characteristics similar to those commonly observed during adolescence, with absolutely different ethiopathogenesis [1]. In fact, if, during adolescence, menstrual irregularities are linked to the progressive maturation of the complex hypothalamic-pituitary-ovary axis, in the period that is today defined as perimenopausal transition, the exhaustion of ovarian follicles is the cause of disorder of the feedback mechanisms at pituitary-hypothalamus level. The stages of a woman's reproductive life have been classified [2]. The reduced ovarian reserve with the reduction of inhibin secretion triggers an increase in follicle stimulating hormone (FSH) concentration which, in turn, induces multiple and accelerated folliculogenesis. This is followed by an excessive secretion of estradiol (E2) by the residual granulosa cells, but in an absolutely inadequate period of the follicular cycle, so that the asynchronous secretion of E2 is followed by a scarce or absent secretion of progesterone (P4). All this has been well studied with the ultrasound visualization of the asynchrony of the size and number of ovarian follicles in older women compared to women in the middle reproductive age [3]. In this way, the imbalance between E2 and P4 is a risk factor for excessive endometrial stimulation by E2. Not only that, but the poor activity of P4 results in systemic changes which, ultimately, translate into predisposition to pathological metabolic changes that accelerate the process of endothelial damage

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already dependent on age. In fact, the lack of P4 is linked to a predisposition to weight gain. Progesterone increases energy expenditure [4]. The assessment of body composition documents an increase in fat mass in perimenopausal women [5]. To this we must add an increase in the bioavailability of androgens, caused by a decrease in the secretion of the sex-hormone binding globulin (SHBG) [6]. The evaluation of the waist/hip ratio documents an increase confirming the greater effect of androgens on the disposition of adipose tissue [5]. The visceral fat is characterized by macrophage infiltration and inflammatory cytokine secretion [7]. Through inflammatory cytokines, visceral adipose tissue induces the activation of the renin angiotensin aldosterone system (RAAS) and the secretion of cortisol. Cortisol and aldosterone, in turn, create a vicious cycle of stimulation on the same visceral adipose tissue [8]. We must not overlook that hyperandrogenism also changes the metabolism of insulin and creates predisposing factors for metabolic syndrome. The same inflammatory cytokines must be taken into consideration for a deleterious effect on the central nervous system. Neuro-inflammation is responsible for neurotransmitter and degenerative changes in neuronal cells, primum movens for brain degenerative diseases, as well as for psychological modifications [9, 10] and oncological stimulation on the breast and endometrium [11].

Figure 15.1 summarizes the metabolic changes that result from endocrine alterations of the perimenopause and the consequences on general health.

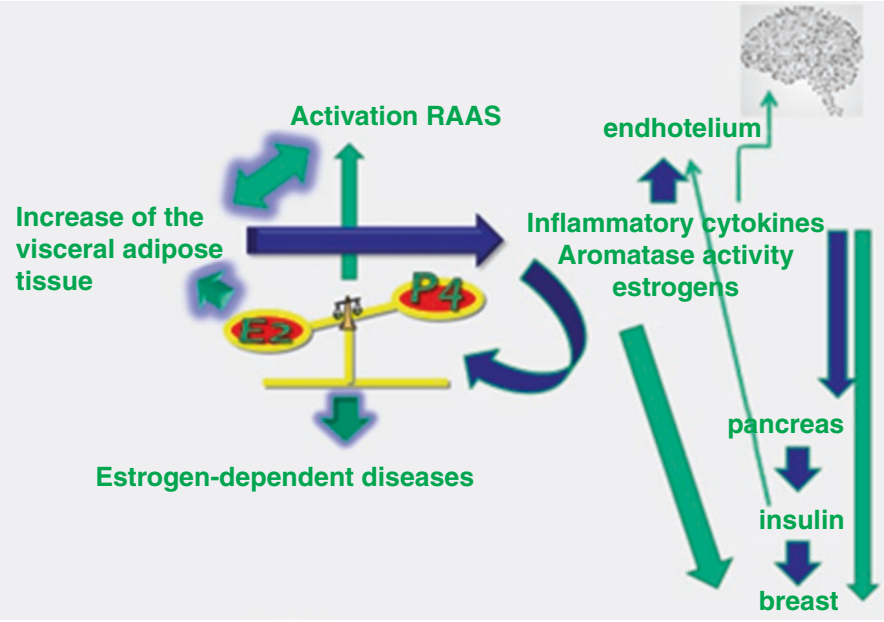

Fig. 15.1 Endocrinological and metabolic changes that appear in the perimenopause and predispose to consequences on general health

Furthermore, in the perimenopausal period, behavioural and psychological changes have been documented by several studies developed in meta-analysis, as the probable consequence of the reduction of hormonal level on the brain [12]. Before reaching the complete exhaustion of the ovarian reserve and the last menstruation (menopause), the ovarian function can be reversible [13], so much so that the problem of contraception arises.

15.2 Contraception After 40 Years

Contraception becomes extremely important because unplanned pregnancies that, although rare, occur in this age of the woman's life, are characterized by negative outcomes, which include early abortions, especially in relation to the high incidence of foetal aneuploidies, premature birth, preeclampsia, gestational diabetes, complications of childbirth and puerperium [14]. What kind of contraceptive can be indicated? No contraceptive method is really contraindicated in this age group; however, it is appropriate to consider the different risk profile in comparison to younger women. Beyond the contraceptive effect and the additional protection benefit of the endometrium, the use of the levonorgestrel-releasing intrauterine device (LNG-IUD) does not offer any further advantages regarding the endocrine-metabolic situation of perimenopause. Hormonal contraception (HC), on the other hand, antagonizes the imbalance between the secretion of E2 and P4, preventing the negative metabolic situation of this age, to which are added the well-known extra-contraceptive benefits of HC, such as: prevention of estrogen-dependent diseases, prevention of osteoporosis, ovarian cancer prevention. With this point of view, HC can be considered as a therapy. Concerns arise about the type of HC that we have today thanks to the pharmacological and clinical evolution in this field: what dose of estrogen? What type of progestin? Which estrogen? Which method of hiring? Which route of administration? The characteristics of E2 compared to ethinylestradiol (EE), in relation to the lower activity on RAAS and hepatic coagulation factors lead to prefer contraception with E2.

Recent data from the post-marketing epidemiological study, known as the INAS study [15] reinforce the data published so far on the non-negative effect of HC with E2. In fact, the study shows that HC with E2 does not interfere with arterial risk and its effect on thromboembolic risk is equal to that of HC containing EE and LNG, the progestogen with androgenic activity that counteracts the pro-coagulating action of estrogen. At the present, there are two contraceptive formulations containing natural estrogen, one of which containing estradiol valerate (EV) associated with dienogest (DNG) in a quadriphasic regime (EV + DNG) and the other containing micronized estradiol (E2) associated with nomegestrol acetate (NOMAc) (E2 + NOMAc) in continuous combined mode. Dienogest is a progestagen derived from nortestosterone, which, thanks to the double bond in position 9–10, has a powerful progestin action, and thanks to the cyan-methyl group in position 17 alpha exerts a powerful anti-androgenic action. Nomegestrol acetate, derived from 19 nor-progesterone, is characterized by high affinity for the P4 receptor, marked progestin and

Table 15.1 Pharmacological properties of compound contained in hormonal contraceptives with natural estrogen

Molecule	Pharmacological properties
Estradiol	• Lower induction of protein synthesis in the liver (coagulation factors, sex-hormone binding globulin, lipoproteins, angiotensinogen) in comparison with the ethinylestradiol • Weaker estrogen activity in comparison with ethinylestradiol
Dienogest	• Powerful progestogen activity • Absence of mineralocorticoid effect • Absence of glucocorticoid effect • Absence of androgenic effect • Anti-androgenic activity
Nomegestrol acetate	Powerful progestogen activity Absence of mineralocorticoid effect Absence of glucocorticoid effect Absence of androgenic effect Low anti-androgenic activity

anti-gonadotropic activity, no androgenic activity, no mineralocorticoid activity, minimal anti-androgenic effect. Table 15.1 summarizes metabolic properties of the hormones contained in HC with natural estrogen.

In the perimenopausal period, EV + DNG has been shown to counteract the increase in fat mass that occurs in this period of life with a reduction in the hip/waist ratio [16]. Hormonal contraception with E2 + NOMAc in women during their middle reproductive phase has been shown not to change body composition [17]. These data are highly comforting to indicate that both of these HCs can offer not only the contraceptive effect, but also additional benefits on the metabolic aspect. As regards the impact of these formulations on bone metabolism, it has been shown that a significant reduction in bone resorption parameters is evident in young women after 3 months of treatment with EV + DNG [18]. As regards NOMAc, it has been shown that this progestogen is capable of not antagonizing the anti-resorbing action of E2 [19, 20] and two-year clinical data of treatment confirmed that E2 + NOMAc does not change bone mineral density [21].

15.3 Future of Hormonal Contraception After 40 Years

The HC containing a powerful progestogen, drospirenone (DRSP), in association with another natural estrogen, the estetrol (E4), are currently under study. Estetrol is a steroid secreted by the fetal liver exclusively during pregnancy; E4 passes into amniotic fluid and maternal blood. From studies carried out with the aim of evaluating its biological effect in pregnancy, it has emerged that E4 plays an important role in regulating the fibrinolytic protein system in endothelial cells, showing a key action in the vascular system, with potential implications for the local control of blood clotting and vascular remodelling [22]. A recent study in rat hippocampal cell cultures shows that E4 exerts an antioxidant action mostly dependent on the estrogen receptors (ER) α and β [23]. The same study shows that E4 exerts an important

effect on neurogenesis and possible pro-myelination activity through its link with ERβ [23]. These characteristics would make it the ideal estrogen in all phases of a woman's life, but especially in the perimenopausal phase in which, in addition to the contraceptive effect, extra-contraceptive benefits are required, especially on the metabolic side. These metabolic benefits, that are already present with the two formulations EV + DNG and E2 + NOMAc, could be even more numerous with the use of E4 in association with a progestin, such as DRSP, which has long been known for its progestogenic, anti-androgenic, anti-mineralcorticoid and neurotrophic activities [24].

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Contraceptive Choice in Women with PCOS

16

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Abbreviations

17OHP	17-hydroxyprogesterone
A	Androstenedione
ACTH	Adrenocorticotropic hormone
BMI	Body mass index
C	Cortisol
CHCs	Combined hormonal contraceptives
COCPs	Combined oral contraceptive pill
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
EE	Ethinylestradiol
FAI	Free androgen index
FG	Ferriman-Gallwey
FSH	Follicle-stimulating hormone
HCs	Hormonal contraceptives
HDL	High density lipoprotein
HOMA	Homeostatic model assessment
IR	Insulin resistance
IUD	Intrauterine device
LDL	Low density lipoprotein
LH	Luteinizing hormone
LNG	Levonorgestrel
METS	Metabolic syndrome

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PCOS	Polycystic ovary syndrome
POCs	Progestogen-only contraceptives
SHBG	Sex hormone binding globulin
T	Testosterone
T2DM	Type 2 diabetes mellitus
VLDL	Very low density lipoprotein
VTE	Venous thromboembolism
WHO	World Health Organization

16.1 Background: What Is Polycystic Ovary Syndrome?

Polycystic ovary syndrome (PCOS) is a complex endocrinological disorder that affects women of reproductive age. It is characterized by clinical and/or biochemical signs of hyperandrogenism, chronic menstrual irregularities and polycystic ovaries, as defined by the 2003 Rotterdam criteria. The Rotterdam definition recognizes four phenotypes of PCOS: (1) severe or classic PCOS, where the three criteria are all present; (2) PCOS with hyperandrogenism and chronic anovulation; (3) ovulatory PCOS; (4) mild PCOS, with a normal androgenic profile [1, 2].

The epidemiological studies present significant variations in the reported prevalence of the syndrome and this could be due to differences in study populations, limitations within the sampling and protocols applied and to the lack of standardized definitions for the phenotypes. Also race, ethnicity and the fact that the ultrasound is an operator-dependent imaging technique contribute to increase the differences among the prevalence reported by various studies. Today, it is assumed that the prevalence of PCOS among women in reproductive age is about 10% when the Rotterdam criteria are used for diagnosis [3].

The clinical and biochemical profiles of women with PCOS are extremely variegated. Reproductive, hormonal and metabolic problems are strictly related to each other and the pathogenesis of the syndrome is complex.

16.1.1 Hyperandrogenism

Hyperandrogenism represents an important feature of PCOS and its clinical signs can significantly affect the quality of life of women suffering from this disorder. It is defined by the state characterized or caused by the excess production and/or secretion of androgens, which is usually manifested by acne, hirsutism or frontal (or androgenic) alopecia [4].

Androgens are steroidal hormones and they are mainly synthesized in ovary and adrenal glands. Cholesterol is the precursor for pregnenolone, which is then converted to steroid hormones after a series of enzymatic processes. Androgen secretion is regulated by autocrine and paracrine mechanisms that are stimulated by luteinizing hormone (LH) in the ovary and by adrenocorticotropic hormone (ACTH)

in the adrenal gland. In the ovary, the first step of androgen production is performed in LH-stimulated theca cells, as these cells express the cytochrome P450c17 gene. This is a key enzyme for androgen biosynthesis, and it can have two activities: 17-hydroxilase, that is needed to produce cortisol (C) throughout life, and 17,20-lyase, that is controlled independently in an age-dependent pattern [5, 6].

Thecal cells synthesize dehydroepiandrosterone (DHEA) and androstenedione (A) that will be then converted to estrogen by granulosa cells by means of the P450 aromatase. Ovaries also directly secrete androgens in circulation, mainly A and testosterone (T). Ovarian androgens do not regulate LH production through feedback mechanism: that's why in women, excess free T or A will not reduce ovarian production of these androgens [7, 8].

Women with PCOS have an altered production and metabolism of androgens and estrogens, with an abnormal function of the hypothalamus-pituitary-ovarian axis. Sixty percent of these androgens are produced by the ovary, while the other 40% is secreted by the adrenal gland [4]. The normal LH/FSH (follicle stimulating hormone) ratio is altered and LH level is often two to three times that of FSH level: this change can disrupt ovulation and the LH hypersecretion is found to be the primary abnormality in classic PCOS causing androgen excess [9–11].

In order to evaluate the hyperandrogenism in PCOS, both clinical observation and biochemical analysis are needed. The most frequently detected alteration is the presence of elevated levels of free T. The measurement of total and free T level is constrained by the available assay methods. This finding reflects the fact that sex hormone binding globulin (SHBG) levels are typically decreased in PCOS due to the ability of T and insulin to decrease hepatic production of SHBG [12]. Assays for total T lack precision and sensitivity in the female T range; moreover, age, body mass index (BMI) and drugs can affect the levels of circulating hormones. Direct measurement of free T is inaccurate. Measurements of total T by radioimmunoassay or liquid chromatography-mass spectrometry are currently the best available methodologies. Anyway, the only T level is not enough to describe the androgenic profile of PCOS women. A and dehydroepiandrosterone sulfate (DHEAS) can be frequently altered, sometimes constituting the sole abnormality in circulating androgens. As already said, besides the ovary, another important source of excess androgens is the adrenal gland: an increase in adrenocortical precursor steroids is frequently found, including pregnenolone, 17-hydroxyprogesterone (17OHP), DHEA, A, 11-deoxycortisol and C [2, 12–16].

The most common clinical sign of hyperandrogenemia is hirsutism and approximately 60% of women with PCOS are hirsute. Other signs of a disbalanced androgenic profile are the appearance of severe acne and androgenic alopecia [17].

Hirsutism is the abnormal growth of the terminal hair in a male-like pattern. Hyperandrogenism is strictly related to hirsutism. Within the hair follicle, the enzyme 5α-reductase converts T to its more active metabolite, dihydrotestosterone (DHT). DHT converts vellus hair into terminal hair. Increased activity of 5α-reductase, as well as high circulating androgen levels, can result in terminal hair growth in several areas that are not normally androgen-sensitive in women, particularly the face, neck, chest and lower abdomen [18]. The modified Ferriman-Gallwey

(FG) score is used to determine the density of terminal hairs at nine different body sites, (i.e. upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm and thigh); a total score of 8 is considered as hirsutism [19]. It is demonstrated that there is an association between levels of androgens and FG score, most of all considering the level of A and DHEAS [19], confirming the usefulness of the evaluation of the entire panel of circulating androgens, and not only of T, in order to have a complete profile of the hyperandrogenism of the patient.

Acne vulgaris is another common cutaneous manifestation of hyperandrogenism, even if the exact role of the androgens on the sebaceous gland is not completely clear. They enhance sebum production and cause abnormal follicular epithelial cell desquamation, both of which contribute to the development of a comedo. Subsequently, Propionibacterium acnes colonizes the comedone, leading to the formation of papules and pustules typical of acne vulgaris [18]. Anyway, there is not a clear positive correlation between the levels of circulating androgens and the severity of acne [20].

16.1.2 Metabolic Profile in PCOS

Besides the features described in the definition of the disease, PCOS is a risk factor for the development of metabolic dysfunctions. Obesity, insulin resistance (IR) and metabolic syndrome (METS) are often present in women with PCOS and all these features contribute to increased cardiovascular risk.

The prevalence of obesity in PCOS is estimated to be between 14 and 75% among different ethnic groups [21]. Women with PCOS not only have a higher BMI, but also a higher rate of longitudinal weight gain and central adiposity compared to women without PCOS [22]. Obesity negatively affects ovarian function and contributes to the development of IR, type 2 diabetes mellitus (T2DM), gestational diabetes and other pregnancy complications. It is demonstrated that a reduction of 5–10% of body weight has positive effects on both reproductive and metabolic features, even when women remain in the overweight or obese range [23, 24].

IR plays a pivotal role in the development of clinical and metabolic characteristics of PCOS. In PCOS there is a post-binding defect in insulin sensitivity in fibroblasts, adipocytes and skeletal muscle, resulting in reduced insulin-mediated receptor signalling: this defect is characterized by constitutive serine phosphorylation that affects the metabolic but not the mitogenic pathway of insulin receptor.

Insulin acts as a co-gonadotropin and increases LH-induced androgen synthesis in theca cells and FSH-induced estrogen production in granulosa cells; it can also increase LH receptor expression in follicles, leading to the arrest of follicular growth; it contributes to the alteration of the LH/FSH ratio and promotes premature luteinization of follicles; it determines a reduction in hepatic secretion of SHBG, causing a relative increase of free T [12]. Hyperinsulinemia is strictly related with the increase of circulating androgens and the possible link between these two phenomena is the insulin-stimulated hyperactivity of the P450c17, which is the key

enzyme that regulates the production of androgen precursors in the ovary and in the adrenal gland [5]. Consequently, hyperinsulinism can result in an increased 17OHP, A and T synthesis in ovaries and in an increased DHEAS synthesis in the adrenal gland.

PCOS is often associated with METS, too. It is diagnosed by the presence of at least three of the following criteria: waist circumference ≥88 cm, fasting serum glucose >100 mg/dl, triglycerides ≥150 mg/dl, cholesterol high-density lipoprotein (HDL) < 50 mg/dl and arterial pressure ≥130/85 mmHg [25, 26]. The prevalence of METS in PCOS ranges from 10 to 45% according to the regional area and the main predictive factors are the elevated plasma levels of free T and the low levels of SHBG. A mixed dyslipidemia is common, with higher levels of low density lipoproteins (LDL), very low density lipoproteins (VLDL) and triglycerides and lower levels of high density lipoproteins (HDL) than normal [27, 28]. The risk of METS increases with adiposity [29].

Many studies have found the evidence of the increased risk of cardiovascular risk: women with PCOS were found to have an increased carotid intima-media thickness, signs of endothelial dysfunction, an increased coronary artery calcification. Anyway, it's not yet clear which phenotype of PCOS is more correlated to this increased risk. Moreover, the increased cardiovascular disease risk observed in younger affected women plateaus in later life, while unaffected women continue to develop more cardiovascular risk, ultimately resulting in similar cardiovascular risk in PCOS and reproductively normal women during the postmenopausal years [30].

Women with PCOS also have an increased risk of obstructive sleep apneas, non-alcoholic fatty liver disease and they show alterations of the coagulation mechanisms, with an accentuation of thrombotic phenomena and an inhibition of fibrinolysis [30, 31].

16.1.3 Reproductive Features of PCOS

Menstrual irregularity constitutes an important issue related to the syndrome. It results from the effects of both androgens and insulin on the ovarian function.

More than half of the women with PCOS refer to have alterations of the menstrual cycle, mainly oligomenorrhea or amenorrhea (70–80% of the cases). This is due to the chronic oligoanovulation typical of the syndrome. Sometimes, women refer to have an apparently regular cycle, because chronic anovulation can bring to dysfunctional bleedings of the uterus that mimic a normal menstruation [32]. PCOS diagnosis is made in 80–90% of women referring oligomenorrhea, but only in the 40% of women referring complete amenorrhea [33]. An important matter related to the anovulation is the infertility. Women with a high BMI are more exposed to this problem than lean women: among women with PCOS and infertility, 90% are overweight. Moreover, women with PCOS and hyperinsulinemia have more frequent anovulatory cycles and, consequently, difficulties in conception [22, 32].

A recent study found that women with PCOS were less likely to use contraception compared to women not reporting PCOS [34]: this can be due to the perceived

difficulty in achieving a spontaneous pregnancy. However, women reporting PCOS had similar numbers of children compared to women without PCOS, reassuring women who may have concerns regarding future fertility [22]. The preconception counselling is very important for these women and it should be focalized on factors affecting fertility, in particular the impact of lifestyle, obesity and age [22].

Another important consideration is that oligoamenorrhea and anovulation are risk factors for the development of endometrial cancer. Approximately 5% of cases with endometrial cancer occur in women aged 40 years and younger with chronic anovulation. Obesity, diabetes and IR are other risk factors for endometrial cancer [35].

16.2 Rationale for the Use of Hormonal Contraceptives in PCOS

Since the introduction of hormonal contraceptives (HCs) into the market, they have been continuously modified in order to reduce the associated side effects and medical risks. Today, combined hormonal contraceptives (CHCs) and progestogen-only contraceptives (POCs) offer well-documented health benefits and are considered first-line treatment for many gynaecological diseases.

Women with PCOS may come to the clinician asking for contraception and the clinician has to be informed on how to choose the best contraceptive for that woman, customizing the choice according to what is the clinical and biochemical profile of the patient. Moreover, CHCs may constitute a valid treatment ally in this kind of patient, further demonstrating how much attention must be paid in the choice.

HCs have a wide range of use in PCOS. Women who are not looking for a pregnancy may want them for contraception, but they can also be used to approach clinical hyperandrogenism and menstrual irregularities. Moreover, they have a role in the prevention of endometrial cancer. The clinician should also pay attention to the possible contraindications to this treatment, considering the metabolic and cardiovascular risk of women with PCOS.

16.2.1 Overview of the Molecules Used in Contraception

Today, CHCs on the market contain low doses of estrogens and progestins in order to reduce the possible side effects without losing their therapeutic benefits.

The main synthetic estrogenic compound found in CHCs is ethinylestradiol (EE), but nowadays there are also some formulations with natural estrogens. The so-called modern "low-dose" CHCs must contain less than 50 μg of EE, but today virtually all CHCs contain 20–35 μg of EE, while the dose of synthetic progestin ranges between 0.1 and 3 mg [36]. Due to its high bioavailability, EE exerts a strong impact on the hepatic metabolism, displaying a more sustained biological activity than natural estrogens on angiotensinogen, SHBG, cortisol binding protein, coagulation factors and lipoproteins [37, 38]. To overcome these metabolic effects, more

physiological forms have recently been developed: these preparations with natural estrogens (17β-estradiol, estradiol valerate and estetrol) have negligible effects on carbohydrate and lipid metabolism and hemostasis, showing a safer profile than those containing EE [39, 40].

CHCs can be classified in three generations according to the timing of introduction of the progestin molecule. Progestins of the first and second generation CHCs are chemically related to T: they are able to bind androgen receptor causing different degrees of androgenic side effects (mainly oily skin, acne and hirsutism). Progestins of the third generation of CHCs show a higher affinity for the progesterone receptors, reducing the incidence of androgenic side effects [36].

Progestins can also be classified according to the molecule they derive from. The main families of molecules of progestins used in CHCs are: pregnanes derived from 17α-hydroxyprogesterone (i.e. chlormadinone acetate, cyproterone acetate); norpregnanes derived from 17α-hydroxynorprogesterone (i.e. nomegestrol acetate); estranes derived from 19-nortestosterone (i.e. norethisterone, norethisterone acetate, lynestrenol); gonanes derived from 19-nortestosterone (i.e. levonorgestrel, desogestrel, gestodene, norgestimate, dienogest); spironolactone derivatives (i.e. drospirenone) [41].

The affinity of the progestin for different receptors is important for many reasons. First of all, progestins can have different effects on the androgen receptor. The oldest have an androgenic activity (i.e. levonorgestrel). Some progestins (gestodene, norgestimate and desogestrel) have a minimal or any androgenic activity, while others (cyproterone acetate, dienogest, drospirenone, chlormadinone acetate and nomegestrol acetate) have an anti-androgenic activity. This last effect is maximum with cyproterone acetate, while dienogest and drospirenone are approximately 40% and 30% of its potency [35, 42]. Moreover, progestins are able to modulate and counteract the metabolic effects of the estrogens. In contrast to progestins with androgenic activity, CHCs containing progestins with no- or anti-androgenic activity do not counteract either the positive effect of estrogens on lipid and carbohydrate metabolism, nor their stimulatory effects on coagulation factor [43].

When the clinician decides to prescribe a CHC to a woman with PCOS, he or she has to accurately decide which is the best combination of molecules, customizing the therapy according to the characteristics and the metabolic profile of the patient. He has to balance the possible benefits and side effects of the treatment, also considering which is the main reason why the CHC is required.

16.2.2 General Contraindications of Hormonal Contraceptives

The World Health Organization (WHO) has developed evidence-based guidelines for the use of hormonal contraceptives, the “Medical eligibility criteria for contraceptive use”, whose most recent version was published in 2015 [44]. A new app was developed in 2018: this digital tool has been developed to facilitate the task of family planning providers in recommending safe, effective and acceptable contraception methods for women with medical conditions or medically-relevant characteristics.

Generally, women without relevant medical conditions can use CHCs and POCs without restriction, just paying some more attention for those women over 40 years. On the contrary, there are certain conditions in which the risks usually outweigh the advantages or represent an unacceptable health risk on using CHCs. The main conditions were CHCs should be advised against or totally avoided are [44, 45]:

- Previous or current thromboembolic event or presence of known thrombogenic mutations or risk factors for venous thromboembolism (VTE).
- Breastfeeding women ≤6 months postpartum and women who are <21 days postpartum and not breastfeeding, most of all if they have risk factors for VTE.
- Migraine with aura.
- Multiple risk factors for cardiovascular disease, history of ischemic heart disease or stroke and complicated valvular heart disease.
- Severe cirrhosis or malignant liver tumours.
- Breast cancer.

POCs and levonorgestrel-releasing intrauterine devices (LNG-IUD) usually have less contraindications in these cases [44]. Women with a history of superficial venous thrombosis, with a known dyslipidemia or with other known cardiovascular risk factors (obesity, smoking, diabetes, hypertension…) can generally use hormonal contraceptives because the benefits still outweigh the risks, but the clinician should pay attention to the possible association of multiple risk factors [35, 44]. Anti-phospholipid syndrome is the only absolute contraindication for the use of both POCs and CHCs.

As stated in the guidelines for PCOS published in 2018, PCOS "per se" is not a specific contraindication for the use of HCs. In this case, the choice of which HC to use has to be based on the clinical and metabolic profile of the patient and on the main reason why it is used (contraception, menstrual irregularities, hirsutism) [45].

16.2.3 How to Choose the Right Hormonal Contraceptive

The classic HC's formulation used in PCOS is the combined oral contraceptive pill (COCPs), because it can conjugate the advantages of the contraception and those due to the presence of both an estrogen and a progestin at a systemic level that can ameliorate the clinical features of the syndrome.

Today, according to the most recent guidelines, CHCs can be used in women with PCOS also for the management of hyperandrogenism and/or irregular menstrual cycles [45].

Looking at the contraceptive effect, there is no recommendation on specific types or dose of progestins, estrogens or combinations to use as first line choice in adults and adolescents with PCOS. The clinician should base his choice on the patient's need, on practice and on general population guidelines [44, 45]. CHCs with routes of administration different than the oral one can also be used, as the intradermal patch and the intravaginal ring.

The lowest effective estrogen doses (such as 20–30 μg of EE or equivalent) and natural estrogen preparations need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability [45]. Moreover, there are other kinds of HCs that contain only progestins (POCs and LNG-IUD) and other not-hormonal contraceptives (such as the mechanical IUD). These formulations can be a choice for those PCOS women who ask for a long-acting contraceptive method and/or for those with contraindications to the use of CHCs.

16.2.4 Other Non-Contraceptive Benefits of the Combined Oral Contraceptive Pills

HCs are often requested by PCOS women that are not looking for a pregnancy to treat menstrual irregularity and hyperandrogenism. Both ESHRE/ASRM-sponsored PCOS Consensus Group recommendations [46] and The Endocrine Society's clinical practice guidelines [46] suggest CHCs as first-line management for amelioration of clinical and biochemical androgen excess and menstrual irregularity. They also emphasize that there is no definitive evidence for any difference in efficacy of various COCPs. In presence of IR or severe hirsutism and acne, COCPs can be administered in association with other therapies, like metformin and antiandrogens [45].

The Endocrine Society guidelines suggested that CHCs should be used from late adolescence onwards [47] and a longer duration of treatments with CHCs seems to lower the chance of developing signs of hyperandrogenism during adulthood [48].

Considering the pharmacological profile of the different progestins and estrogens present in CHCs, some considerations must be done at the time of prescription. The specific features of the CHCs can constitute an advantage for the therapy, but sometimes they can cause also side effects that will be discussed later.

Hyperandrogenism is often approached with COCPs containing antiandrogenic progestins. On the basis of recent data, preparations with cyproterone acetate should not be considered first-line in PCOS as well as in general population due to adverse effects, including VTE risk. Table 16.1 summarizes the effects of the main progestins on androgenic parameters.

16.2.4.1 Sex-Hormone Binding Globulin

SHBG is typically decreased in PCOS due to the effects of androgens and insulin on its secretion. Low plasma levels of SHBG are considered a risk factor for the development of cardiovascular disease and non-alcoholic fatty liver disease [55, 56]. Estrogens, including those contained in COCPs, can increase its synthesis, while progesterone and progestins have variable androgenic effects and counter the beneficial effects of estrogens (Table 16.1). The highest effect on SHBG is displayed by preparations with 35 μg EE associated with cyproterone acetate [57]. The effects induced by pills with 30 μg EE depend on the type of progestin present in the combination, being higher for associations containing progestins with antiandrogenic properties and causing an increase between 200% and 400% over basal values. Due to the potency of EE, a significant increase in SHBG is induced also by pills with

Table 16.1 Comparison of effects of different progestins on sex hormone binding globulin (SHBG), free and total testosterone (T) and 5α-reductase activity. Their antiandrogenic activity is compared to the most antiandrogenic one, the cyproterone acetate (CPA). For each target, progestins are ordered from the most to the least efficient. References are in the Table

Target	Progestin	Effect
Increase of SHBG [39, 49, 50]	Cyproterone acetate (+35 μg EE)	+300–400% over basal values
	Drospirenone (+30 μg EE)	+250–300% over basal values
	Dienogest (+30 μg EE)	+250–300% over basal values
	Desogestrel (+30 μg EE)	+200–300% over basal values
	Gestodene (+30 μg EE)	+200–300% over basal values
	Contraceptive patch	+260% over basal values
	Norgestimate (+35 μg EE)	+150% over basal values
	Vaginal ring	+150% over basal values
	Desogestrel (+20 μg EE)	+100–150% over basal values
	Levonorgestrel (+30 μg EE)	+50–110% over basal values
	Dienogest (+1–3 mg estradiol valerate)	+60–90% over basal values
Inhibition of skin 5α-reductase [51]	Norgestimate	+++
(compared to finasteride)	Levonorgestrel	++
	Dienogest	++
	Cyproterone acetate	+
	Gestodene	+
Decrease of free T [52, 53]	Drospirenone	−63.6% than basal values
(when associated to 30 μg EE)	Cyproterone acetate	−59.2% than basal values
	Chlormadinone acetate	−52.4% than basal values
	Desogestrel	−42.1% than basal values
	Gestodene	−40% than basal values
Decrease of total T [52, 54]	Cyproterone acetate	−66% than basal values
(when associated to 30–35 μg EE)	Drospirenone	−61.9% than basal values
	Chlormadinone acetate	−51.2% than basal values
	Gestodene	−41.7% than basal values
	Desogestrel	−30.9% than basal values
Antiandrogenic activity [35, 38]	Cyproterone acetate	100%
(compared to CPA)	Dienogest	40% of CPA
	Drospirenone	30% of CPA
	Chlormadinone acetate	20–30% of CPA

EE: ethinylestradiol

20 μg of EE and also when EE is administered by non-oral route [49, 58, 59]. Natural estrogens show to have a lower impact on liver than EE, so they also have a weaker effect on SHBG, which shows an increase of about 60–90% over basal values [39, 50].

16.2.4.2 Testosterone and Free Androgen Index

Due to the inhibitory effect of CHCs on hypothalamus-pituitary-ovarian axis, all preparations are able to reduce androgen secretion. Conversely, different estroprogestin associations may have different effects on free T and free androgen index (FAI), based also on their potency to increase SHBG and their ability to compete with T for SHBG sites (Table 16.1) [49, 58]. The decrease of free T and FAI is higher for CHCs containing 30–35 μg of EE associated with progestins with antiandrogenic activity [52].

16.2.4.3 5α-Reductase Activity

CHCs can also reduce hyperandrogenism through the inhibition of 5α-reductase activity [60]. The effect is progestin-dependent. An in vitro study by Rabe et al. demonstrated that the most efficient inhibitor of 5α-reductase compared to finasteride was norgestimate, followed by levonorgestrel, dienogest, cyproterone acetate and gestodene (Table 16.1). Norgestrel, norethisterone and 3-keto-desogestrel were less potent. No effect on 5α-reductase was seen with EE alone [51].

The extent to which the change of one of the above parameters, induced by a CHC, may really contribute to the clinical effect on hyperandrogenism is not clear. No data is available showing that 30 μg EE are really better than 20 μg EE in the treatment of hirsutism [61]. As for progestins, comparative and non-comparative studies in literature show the usefulness of the combination with cyproterone acetate, drospirenone, chlormadinone acetate and dienogest in reducing mild to moderate acne and hirsutism [62–64]. Other progestins, such as desogestrel, levonorgestrel and gestodene, can be considered among these patients as alternatives. A review of 31 studies of the Cochrane Library of 2012 evidenced that CHCs containing chlormadinone acetate or cyproterone acetate improved acne better than levonorgestrel; moreover, CHC with drospirenone appeared to be more effective than the norgestimate or nomegestrol acetate, but less effective than cyproterone acetate [63]. They also showed that CHCs are more effective than placebo in the treatment of acne [63]. However, large placebo-controlled studies and comparative studies are in general scanty. The evidences supporting that CHCs with a specific antiandrogenic progestin are more recommended than others are not conclusive.

16.3 Metabolic Effects of Hormonal Contraceptives and Cardiovascular Risk

PCOS women are very heterogeneous. They have different cardiovascular risk profiles. At present, there are no data in literature showing the effects that CHCs may have on PCOS women.

16.3.1 Body Weight

High BMI is an important issue for women with PCOS. As for the effects of HCs on body weight in this population, the studies are scanty. A comprehensive review showed that it is not possible to state with certainty the negative effect of CHCs on BMI, waist circumference and waist-to-hip ratio: many studies demonstrated a non-significant change of these parameters [58].

Anyway, the clinician should consider this possible side effect when prescribing the CHC, advising the patient to improve her lifestyle to avoid weight increase. Metformin users experience less effects on body weight with CHCs [45, 65].

16.3.2 Lipid Profile

PCOS may show an altered lipid profile, with a low plasma level of HDL and an increase of LDL, VLDL and triglycerides levels. According to the WHO, women in reproductive age with known dyslipidemias and without other known cardiovascular risk factors can generally use any hormonal contraceptive method [44]. The effects of CHCs on lipid profile are very heterogeneous and it will be better clarified later in the text. In general, estrogens increase VLDL and HDL cholesterol and tryglicerides and they reduce LDL cholesterol. Progestogens, in turn, has a modest interference in the LDL reduction induced by estrogens, but play a significant modulatory role in the elevation of triglyceride and HDL cholesterol levels promoted by estrogens. Progestogens alone don't have significant effects on lipids [66].

Many studies have tried to better characterize the positive effects of specific COCPs on HDL plasma levels. The COCP containing 35 μg EE and 2 mg cyproterone acetate showed a significant increase of HDL levels in many of the studies performed, and similar results were obtained with COCPs containing drospirenone, even if some studies reported not significant changes for HDL levels with both the associations. The associations of EE + chlormadinone acetate and EE + desogestrel also had similar effects on HDL concentrations, but at the moment, fewer studies have been carried out. On the contrary, COCPs containing gestodene seem not to affect HDL levels. In general, CHCs with antiandrogenic progestins have a positive impact on HDL levels, and this should be considered a benefit of the treatment [58]. Lipid profile should be monitored during contraception. In case of deterioration, contraception should be interrupted, or statins should be added in those cases where CHC cannot be interrupted [67].

16.3.3 Carbohydrate Metabolism

It is assumed that IR is present in the majority of women with PCOS, with a higher risk of developing T2DM than general population. This is why many studies have tried to demonstrate if CHCs affected carbohydrate metabolism in order to clarify whether using them or not in this category of women. According to a

comprehensive review with meta-analysis, the use of CHCs for at least 3 months was not associated with negative effects on glucose metabolism, as measured by the hyperinsulinemic euglycemic clamp, fasting glucose to insulin ratios, and homeostatic model assessments (HOMA) [68]. The major difficulty in understanding the real impact of CHCs in carbohydrate metabolism is the extreme heterogeneity of the results of the studies in literature. The main causes for this heterogeneity could be the differences in BMI, age and study duration, while estrogen dose and progestin type could not explain the differences. This is an interesting result, because it shows that the lack of side effects on carbohydrate metabolism is not dependent on the kind of CHC used [68, 69]. An improvement of insulin sensitivity has been described during administration of estradiol valerate plus dienogest to PCOS women [70].

So, CHCs are not contraindicated in women with PCOS and IR. CHCs with low doses of EE should be recommended [65]. Also WHO guidelines for the use of contraceptives confirm that the use of CHCs are indicated in women with associated PCOS and diabetes [44]. Carbohydrate metabolism should be monitored during contraception. In case of deterioration, metformin should be prescribed [67].

16.3.4 Arterial Pressure

In the years, it has been hypothesized that CHCs could have an effect on arterial blood pressure, because EE exacerbates the production of the hepatic angiotensinogen, which in turn causes an elevation of arterial pressure via the renin–angiotensin–aldosterone system; among progestins, only drospirenone has anti-mineralocorticoid activity. In spite of the possible effect of steroids on blood pressure, no or minimal change only has been reported with CHCs in non-PCOS women. The check of blood pressure before and during contraception should be recommended [58]. Hypertension "per se" is a contraindication to CHCs [44].

16.3.5 Effects on Hemostasis and the Risk of Thrombosis

PCOS is associated with a twofold increase in the risk of non-fatal stroke [71] and with a 1.5-fold increase in the risk of VTE [72]. The risk is higher in presence of METS [73]. CHCs may impair the hemostatic system both in healthy and in PCOS subjects. The risk is associated in a dose-dependent manner with the estrogen component of the CHC and it causes both an increase in the risk of arterial events and of VTE. The risk of arterial events (myocardial infarct and cerebrovascular accidents) is mainly evident for "high-dose" CHCs (≥50 μg EE) [74], while the risk with "low-dose" CHCs seem to be not relevant [75]. Arterial events are mainly reported when high doses of EE are associated with progestins with androgenic activity [76].

The use of COCs is associated with a two- to six-fold increase in the risk for VTE development [77], depending on the dose of the estrogen used [66]. EE induces significant changes in the coagulation system. It provokes an enhancement in coagulation factors (fibrinogen and factors VII, VIII, IX, X, XII and XIII) and a

reduction in the inhibitors of coagulation (protein S and antithrombin), with a consequent mild procoagulant effect [66].

The risk of VTE also depends on the type of progestin used, but POCs are not associated with an increased risk. Users of CHCs with antiandrogenic progestins (gestodene, desogestrel, cyproterone acetate, or drospirenone) seem to have higher risk than that of users of COCPs with levonorgestrel [78]. In women with no additional risk of VTE, dienogest, and antiandrogen progestin carry a VTE risk similar to that of levonorgestrel when associated to natural estrogen [79]. Despite the difference in thrombogenic potential according to the antiandrogen effect of progestogens, the absolute risk for VTE is small among healthy women in reproductive age. The studies about a possible increase of VTE risk in PCOS women during HCs are scanty.

Since obesity can further increase the risk, caution should be taken for PCOS obese women [66].

Screening for thrombophilia before prescribing a hormonal contraceptive is not recommended [80].

16.4 Final Considerations: How to Approach the Patient with PCOS

PCOS women may use all kinds of contraceptives. CHCs may be a good choice. The approach to the patient is the same as suggested in general population. Anyway, women with PCOS can have more risk factors than general population and the clinician should be aware of what to investigate. As recommended, before prescribing any kind of CHC, blood pressure and body weight must be checked. A laboratory assessment may be advisable to verify the presence of dyslipidemia or IR and glucose intolerance. The use of contraceptives devoid of metabolic effects should be preferred. A thrombophilia screening is not recommended routinely. A positive family history for VTE can guide towards the choice of POCs or IUDs instead of COCPs.

Because of the possible presence of oligo-amenorrhea, a pregnancy must be excluded before starting. Moreover, a correct counselling about possible side effects of CHCs and about eventual symptoms of alarm should be done, and the patient must be informed that a long-term treatment is safe. The possible benefits on their hyperandrogenism must be also stressed, underlining that all signs of hyperandrogenism take time to improve. In those women with signs of hyperandrogenism, preparations with antiandrogenic progestins should be preferred.

A follow-up visit must be scheduled after some months of use for evaluation of compliance and for assessment of blood pressure and eventual problems of the patient. In the following visit, metabolic profile should be controlled, mainly in those women with high cardiovascular risk. The treatment should be interrupted in case of a further deterioration and alternate contraceptive method must be suggested [67].

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Part IV

Management of Female Contraception in Women with Medical Conditions

Contraception and Cardiovascular Diseases

17

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Abbreviations

ACOG	American College of Obstetricians and Gynaecologists
AF	Atrial Fibrillation
AHA	American Heart Association
AMI	Acute Myocardial Infarction
AT	Antithrombin
BP	Blood Pressure
C	Continuation
CHC	Combined Hormonal Contraception
CHD	Coronary Heart Disease
COC	Combined Oral Contraception
Cu-IUD	Copper-Intrauterine Device
CVD	Cardiovascular Disease
CVR	Combined Vaginal Ring
DMPA	Progestogen-only injectable: depot medroxyprogesterone acetate
DVT	Deep Vein Thrombosis
EPT	Oestrogen Plus Therapy
ET	Oestrogen alone Therapy
HDL	High Density Lipoproteins
HRT	Hormone Replace Therapy
I	Initiation
ICH	Intracerebral Haemorrhage

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IMP	Progestogen-only Implant
IUD	Intrauterine Device
LDL	Low Density Lipoproteins
LNG-IUS	Levonorgestrel-Intrauterine System
MEC	Medical Eligibility Criteria
MI	Myocardial Infarction
MTHFR	Methylene Tetrahydrofolate Reductase
NSTEMI	Non-ST elevation Myocardial Infarction
P	Transdermal Patch
PE	Pulmonary Embolism
POC	Progestogen-only Contraception
POP	Progestogen-only pill
SAH	Subarachnoid Haemorrhage
STEMI	ST elevation Myocardial Infarction
TG	Triglycerides
TIA	Transient Ischemic Attack
TOAST	Trial of Org 10,172 in Acute Stroke Treatment
UKMEC	UK Medical Eligibility Criteria
USCDC	US Medical Eligibility Criteria
VHD	Valvular Heart Disease
VLDL	Very Low-Density Lipoproteins
VTE	Venous Thromboembolism
WHO	Wold Health Organization

17.1 Preface About International Guidelines Categories

The UK [1], US [2] and WHO [3] Guidelines refer to Medical Eligibility Criteria for Contraceptive Use (MEC) to classify the recommendations about the possible methods that could be used safely by individuals with certain health conditions or characteristics to prevent an unintended pregnancy. For each of the personal characteristics or medical conditions considered a Category 1, 2, 3 or 4 is given (Table 17.1).

Table 17.1 Definition of MEC categories

	Definition
Category 1	A condition for which there is no restriction for the use of the method
Category 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
Category 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
Category 4	A condition which represents an unacceptable health risk if the method is used

Table 17.2 Initiation and continuation of a method by women with a medical condition

Initiation (I)	Starting a method by a woman with a specific medical condition
Continuation (C)	Continuing with the method already being used by a woman who develops a new medical condition

Table 17.3 The WHO MEC categories for contraceptive use

Category	With good resources for clinical judgement	With limited resources for clinical judgement
1	Use method in any circumstances	Yes (Use the method)
2	Generally use the method	Yes (Use the method)
3	Use of method not usually recommended unless other more appropriate methods are not available or not acceptable	No (Do not use the method)
4	Method not to be used	No (Do not use the method)

The different methods of contraception considered are: Intrauterine Device (IUD), that includes Levonorgestrel-Intrauterine System (LNG-IUS) (generally the 52 mg LNG-IUS) and copper-Intrauterine Device (Cu-IUD); Progestogen-Only Contraception (POC), that includes Progestogen-only pill (POP), Progestogen-only Implant (IMP) and Progestogen-only injectable: depot medroxyprogesterone acetate (DMPA); Combined Hormonal Contraception (CHC) that includes the Combined Oral Contraceptive (COC), the transdermal Patch (P) and the Contraceptive Vaginal Rings (CVR). Each method is analysed in relation to the medical health condition, assuming that no other risk factor for cardiovascular disease exists, otherwise the risk may increase.

The Initiation (I) and Continuation (C) of a method of contraception can sometimes be distinguished and classified differently (Table 17.2). The duration of use of a method of contraception prior to the new onset of a medical condition may influence decisions regarding continued use.

In addition to the four categories, the WHO [3] distinguishes a proper clinical judgment from a limited resource that limited the medical history differentiate between the clinical judgement with good and with limited resources (Table 17.3).

17.2 Hypertension

17.2.1 Definition

Hypertension is a condition characterized by blood pressure (BP) above the normal range. The American Heart Association (AHA) categorizes hypertension in five ranges (Table 17.4): blood pressure values of less than 120/80 mmHg are considered within the normal range; elevated when systolic consistently ranges from 120–129 mmHg with a diastolic less than 80 mmHg; hypertension Stage 1

Table 17.4 Blood pressure categories (AHA)

Blood pressure category.	Systolic mmHg		Diastolic mmHg
Normal	<120	and	<80
Elevated	120–129	and	<80
High blood pressure—stage 1	130–139	or	80–89
High blood pressure—stage 2	140 or higher	or	90 or higher

when blood pressure consistently ranges from 130–139 mmHg systolic or 80–89 mmHg diastolic; hypertension Stage 2 when blood pressure consistently ranges at 140/90 mmHg or higher. A single reading of BP level is not enough to classify a woman as hypertensive. If elevated, the BP should be reassessed at the end of the consultation [1–3].

17.2.2 Guidelines

Comparing the different types of contraceptive methods, there are no specific restrictions (Category 1 or 2) linking to hypertension except for CHC. CHCs are contraindicated in hypertension, adequately controlled or not, and in vascular disease. The health risk using CHC in women with vascular disease and systolic ≥160 mmHg or diastolic ≥100 is unacceptable (Category 4): in these women, CHC should be banned. If the blood pressure is adequately controlled or if the systolic is >140–159 mmHg or diastolic >90–99 mmHg CHC are not usually recommended unless other more appropriate methods are not available or not acceptable (Category 3). As well, DMPA are categorized as 3 with vascular disease and with systolic value ≥160 or diastolic ≥100 mmHg. Concerning vascular disease (coronary heart disease presenting with angina, peripheral vascular disease presenting with intermittent claudication, hypertensive retinopathy and transient ischemic attack), there are no restrictions about Cu-IUD (Category 1) (Tables 17.5, 17.6, and 17.7).

Women adequately treated for hypertension are at a reduced risk of acute myocardial infarction (MI) and stroke compared to untreated hypertensive women. Although there are no data, POC and CHC users with adequately controlled and monitored hypertension should be at reduced risk of acute MI and stroke compared to untreated hypertensive POC and CHC users [4, 5]. Limited evidence suggests that among women with hypertension, those who used POP, DMPA and COC have a small increased risk of cardiovascular events compared with women who do not use these methods [6–27]. Discontinuation of COC in women with hypertension may improve BP control [28]. Women who did not have a BP check before initiation of COC use had an increased risk of acute MI and stroke [14, 29, 30]. It is desirable to have BP measurements taken before initiation of POC use. However, in some settings, BP measurements are unavailable. In many of these settings, pregnancy-related morbidity and mortality risks are high, and POC are among the few types of methods widely available. In such settings, women should not be denied the use of POC simply because their BP cannot be measured (Category 2) [3].

Table 17.5 UKMEC 2016

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
Adequately controlled hypertension	1	1	1	2	1	3
Consistently elevated blood pressure levels (properly taken measurements)						
Systolic >140–159 mmHg or diastolic >90–99 mmHg	1	1	1	1	1	3
Systolic ≥160 mmHg or diastolic ≥100 mmHg	1	1	1	2	1	4
Vascular disease	1	2	2	3	2	4

Table 17.6 USCDC 2016

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
Adequately controlled hypertension	1	1	1	2	1	3
Elevated blood pressure levels (properly taken measurements)						
Systolic 140–159 mmHg or diastolic 90–99 mmHg	1	1	1	2	1	3
Systolic ≥160 mmHg or diastolic ≥100 mmHg	1	2	2	3	2	4
Vascular disease	1	2	2	3	2	4

Table 17.7 WHO 2015

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
History of hypertension, where blood pressure CANNOT be evaluated (including hypertension in pregnancy)	1	2	2	2	2	3
Adequately controlled hypertension, where blood pressure CAN be evaluated	1	1	1	2	1	3
Elevated blood pressure levels (properly taken measurements)						
Systolic 140–159 or diastolic 90–99 mmHg	1	1	1	2	1	3
Systolic ≥160 or diastolic ≥100 mmHg	1	2	2	3	2	4
Vascular disease	1	2	2	3	2	4

The following tables (Tables 17.8–17.11) show the differences between the UKMEC, USDCD and WHO guidelines. The most evident differences are concerning LNG-IUS, IMP and POP. Each three contraceptive methods with systolic ≥160 mmHg or diastolic ≥100 mmHg are considered as Category 2 by USDCD and by the WHO and as Category 1 by UKMEC. That is because there is a theoretical or proven concern about the effect of LNG on lipid. There are no substantial differences: no specific restrictions are reported, but USCDC and WHO specify that the advantages of using the method generally outweigh the theoretical or proven risks.

Table 17.8 LNG-IUS

	UKMEC	USCDC	WHO
Systolic ≥160 or Diastolic ≥100 mmHg	1	2	2

Table 17.9 POP

	UKMEC	USCDC	WHO
Systolic ≥160 or Diastolic ≥100 mmHg	1	2	2

Table 17.10 DMPA

	UKMEC	USCDC	WHO
Systolic 140–159 mmHg or diastolic 90–99 mmHg	1	2	2
Systolic ≥160 or Diastolic ≥100 mmHg	2	3	3

Table 17.11 IMP

	UKMEC	USCDC	WHO
Systolic ≥160 or Diastolic ≥100 mmHg	1	2	2

17.3 History of High Blood Pressure During Pregnancy

17.3.1 Definition

The definition of hypertension during pregnancy includes different conditions, divided into four categories by the American College of Obstetricians and Gynecologists (ACOG): preeclampsia–eclampsia, chronic hypertension (of any cause), chronic hypertension with superimposed preeclampsia; gestational hypertension.

Preeclampsia–Eclampsia. Preeclampsia is the most common form of high BP with multisystem involvement that complicates pregnancy. It is defined by the occurrence of new onset hypertension plus new onset proteinuria after 20 weeks of gestation. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/μL), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease), pulmonary oedema, or new-onset cerebral or visual disturbances. It is recommended that a diagnosis of hypertension requires at least two determinations at least 4 hours apart, although, on occasion, especially when faced with severe hypertension, the diagnosis can be confirmed within a shorter interval (even minutes) to facilitate timely antihypertensive therapy. Proteinuria is diagnosed when 24-h excretion equals or exceeds 300 mg in 24 h or the ratio of measured protein to creatinine in a single voided urine measures or exceeds 3.0 (each measured as mg/dL), termed the protein/creatinine ratio.

Eclampsia is the convulsive phase of the disorder and is among the more severe manifestations of the disease. It is often preceded by premonitory events, such as severe headaches and hyperreflexia, but it can occur in the absence of warning signs or symptoms.

Chronic Hypertension. During pregnancy, chronic hypertension is defined as high BP known to predate conception or detected before 20 weeks of gestation.

Chronic Hypertension with Superimposed Preeclampsia. The diagnosis is made by of the following seven scenarios: women with hypertension only in early gestation who develop proteinuria after 20 weeks of gestation and women with proteinuria before 20 weeks of gestation who (1) experience a sudden exacerbation of hypertension, or a need to escalate the antihypertensive drug dose especially when previously well controlled with these medications; (2) suddenly manifest other signs and symptoms, such as an increase in liver enzymes to abnormal levels; (3) present with a decrement in their platelet levels to below 100,000/μL; (4) manifest symptoms such as right upper quadrant pain and severe headaches; (5) develop pulmonary congestion or oedema; (6) develop renal insufficiency (creatinine level doubling or increasing to or above 1.1 mg/dL in women without other renal disease); and (7) have sudden, substantial, and sustained increases in protein excretion. If the only manifestation is elevation in BP to levels less than 160 mmHg systolic and 110 mmHg diastolic and proteinuria, this is superimposed preeclampsia without severe features. The presence of organ dysfunction is superimposed preeclampsia with severe features.

Gestational Hypertension. Gestational hypertension is characterized most often by new onset of BP elevation after 20 weeks of gestation, often near term, in the absence of accompanying proteinuria. The failure of BP to normalize postpartum requires changing the diagnosis to chronic hypertension. Gestational hypertension, although transient in nature, may also be a sign of future chronic hypertension.

17.3.2 Guidelines

There are no contraindications to the use of IUD and POC (Category 1). CHC are fixed as Category 2: their use in case of high BP during pregnancy is still safe [1–3].

There are no differences between the different guidelines about this clinical situation. The history of high BP during pregnancy doesn't indicate any restrictions for the use of contraceptive methods, all of them are safe. UKMEC [5, 12, 15, 16, 18, 31–36] USCDC [18, 29–38] and WHO [18, 29–33, 36–38] stress that users of COC with a history of high BP in pregnancy have an increased risk of MI and venous thromboembolism (VTE), compared with COC users who do not have a history of high BP during pregnancy, but the absolute risks of acute MI and VTE in this population remained small (Tables 17.12, 17.13, 17.14).

Table 17.12 UKMEC 2016

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
History of high BP during pregnancy	1	1	1	1	1	2

Table 17.13 USCDC 2016

Condition.	IUD		POC			
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
History of high BP during pregnancy	1	1	1	1	1	2

Table 17.14 WHO 2015

Condition	IUD		POC			
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
History of high BP during pregnancy	1	1	1	1	1	2

17.4 History of Ischaemic Heart Disease

17.4.1 Definition

The term acute myocardial infarction (AMI) should be used when there is evidence of myocardial injury (defined as an elevation of cardiac troponin values with at least one value above the 99th percentile upper reference limit) with necrosis in a clinical setting consistent with myocardial ischaemia [24]. For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate patients with persistent chest discomfort or other symptoms suggestive of ischaemia and ST-segment elevation in at least two contiguous leads as STEMI. In contrast, patients without ST-segment elevation at presentation are usually designated as having a non-ST-segment elevation myocardial infarction (NSTEMI). In addition to these categories, MI is classified into various types, based on pathological, clinical, and prognostic differences, along with different treatment strategies.

17.4.2 Guidelines

There are no differences between the guidelines about this clinical situation. With current and history of ischemic heart disease, the Cu-IUD can be prescribed without contraindication (Category 1). The LNG-IUS can be started by a woman with a history of ischemic heart disease (Category 2) but is not usually recommended unless other more appropriate methods are not available or not acceptable if the event develops during his utilization (Category 3), because there is a theoretical concern about the effect of LNG on lipids. The same considerations are made with POC methods, POP and IMP: they are categorized as 2 if the ischemic problem is in the medical history of

Table 17.15 UKMEC 2016

Condition	IUD			POC					CHC
	Cu-IUD	LNG-IUS		POP		DMPA	IMP		
		I	C	I	C		I	C	
Current and history of ischaemic heart disease	1	2	3	2	3	3	2	3	4

Table 17.16 USCDC 2016

Condition	IUD			POC					CHC
	Cu-IUD	LNG-IUS		POP		DMPA	IMP		
		I	C	I	C		I	C	
Current and history of ischemic heart disease	1	2	3	2	3		2	3	4

Table 17.17 WHO 2015

Condition	IUD			POC					CHC
	Cu-IUD	LNG-IUS		POP		DMPA	IMP		
		I	C	I	C		I	C	
Current and history of ischemic heart disease	1	2	3	2	3	3	2	3	4

the woman and as 3 in case of new event during the use of contraception. DMPA are categorized as 3. UKMEC specifies that the duration of use of POC in relation to the onset of disease should be carefully considered when deciding whether or not continuation of the method is appropriate [15, 39]. Otherwise, CHC represents an unacceptable health risk with ischemic heart disease, current or past (Category 4) and they should be avoided (Tables 17.15, 17.16 and 17.17).

17.5 History of Cerebrovascular Accident

17.5.1 Definition

A stroke is an acute neurologic injury that is a real medical emergency. It is classified into two major types: brain ischemia, the most common, due to thrombosis, embolism, or systemic hypoperfusion; brain haemorrhage due to intracerebral haemorrhage (ICH) or subarachnoid haemorrhage (SAH).

Brain Ischemia. There are three main subtypes of brain ischemia [40]: thrombosis generally refers to local in situ obstruction of an artery due to disease of the arterial wall, such as arteriosclerosis, dissection or fibromuscular dysplasia; embolism refers to particles of debris originating elsewhere that block arterial access to a particular brain region; systemic hypoperfusion is a more general circulatory problem manifesting itself in the brain and perhaps other organs.

Table 17.18 TOAST classification of subtypes of acute ischemic stroke

Large-artery atherosclerosis (embolus/thrombosis)
Cardioembolism (high risk/medium risk)
Small-vessel occlusion (lacune)
Stroke of other determined aetiology
Stroke of undetermined aetiology
(a) Two or more causes identified
(b) Negative evaluation
(c) Incomplete evaluation

Blood and coagulation disorders are an uncommon primary cause of stroke and transient ischemic attack (TIA), but they should be considered in patients younger than age 45, patients with a history of clotting dysfunction, and in patients with a history of cryptogenic stroke. The blood disorders associated with arterial cerebral infarction include: sickle cell anaemia, polycythaemia vera, essential thrombocytosis, heparin induced thrombocytopenia, protein C or S deficiency, acquired or congenital, prothrombin gene mutation, factor V Leiden (resistance to activated protein C), antithrombin III deficiency, antiphospholipid syndrome, hyperhomocysteinemia.

A system for categorization of subtypes of ischemic stroke mainly based on aetiology has been developed for the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) (Table 17.18) [41]. It assigns ischemic strokes to five subtypes based upon clinical features and the results of ancillary studies, including brain imaging, neurovascular evaluations, cardiac tests, and laboratory evaluations for a prothrombotic state.

Brain Haemorrhage. There are two main subtypes of brain haemorrhage: intracerebral haemorrhage refers to bleeding directly into the brain parenchyma from arterioles or small arteries and subarachnoid haemorrhage refers to bleeding into the cerebrospinal fluid within the subarachnoid space that surrounds the brain. The most common causes of ICH are hypertension, trauma, bleeding diatheses, amyloid angiopathy, illicit drug use (mostly amphetamines and cocaine), and vascular malformations; less frequent causes include bleeding into tumours, aneurysmal rupture, and vasculitis. The two major causes of SAH are rupture of arterial aneurysms that lie at the base of the brain and bleeding from vascular malformations that lie near the pial surface; bleeding diatheses, trauma, amyloid angiopathy and illicit drug use are less common.

17.5.2 Guidelines

There are no differences between the guidelines about this clinical situation. The only real contraindication is the use of CHC, which are considered not safe (Category 4) in case of stroke by UKMEC, USCDC and WHO. The continuation of POP and IMP after a cerebrovascular accident requires expert clinical judgment since the use of them is not usually recommended unless other more appropriate methods are not available or acceptable (Category 3). DMPA are categorized as 3. The advantages of using LNG-IUS and to start POP or IMP with a history of stroke outweigh the risk (Category 2) and Cu-IUD has no restrictions at all (Category 1) (Tables 17.19, 17.20 and 17.21).

Table 17.19 UKMEC 2016

Condition	IUD			POC					CHC
		LNG-IUS		POP			IMP		
	Cu-IUD	I	C	I	C	DMPA	I	C	
Stroke (history of cerebrovascular accident, including TIA)	1	2	3	2	3	3	2	3	4

Table 17.20 USCDC 2012

Condition	IUD		POC					CHC
			POP			IMP		
	Cu-IUD	LNG-IUS	I	C	DMPA	I	C	
History of cerebrovascular accident	1	2	2	3	3	2	3	4

Table 17.21 WHO 2015

Condition	IUD		POC					CHC
			POP			IMP		
	Cu-IUD	LNG-IUS	I	C	DMPA	I	C	
Stroke (history of cerebrovascular accident)	1	2	2	3	3	2	3	4

17.6 Dyslipidaemia

17.6.1 Definition

Dyslipidaemias are a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. They may be manifested by elevation of the total cholesterol, the low-density lipoprotein cholesterol and the triglyceride concentrations, and a decrease in the high-density lipoprotein (HDL) cholesterol concentration in the blood.

Dyslipidaemias were traditionally classified in five Fredrickson phenotypes by patterns of elevation in lipids and lipoproteins (Table 17.22). A more practical system categorizes dyslipidaemias as primary and secondary and characterizes them by the type of lipoprotein elevated: increases in cholesterol only (pure or isolated hypercholesterolemia), increases in triglycerides only (pure or isolated hypertriglyceridemia), increases in both cholesterol and triglycerides (mixed or combined hyperlipidaemias).

This system does not consider specific lipoprotein abnormalities (e.g., low HDL or high LDL) that may contribute to disease despite normal cholesterol and TGs levels. Dyslipidaemias may be primary and secondary, caused by lifestyle and other

Table 17.22 Fredrickson phenotype

Phenotype	Elvated lipoprotein	Elevated lipids
I	Chylomicrons	TGs
IIa	LDL	Cholesterol
IIb	LDL and VLDL	TGs and cholesterol
III	VLDL and chylomicron remnants	TGs and cholesterol
IV	VLDL	TGs
V	Chylomicrons and VLDL	TGs and cholesterol

LDL low-density lipoprotein, *TGs* triglycerides, *VLDL* very-low-density lipoprotein

factors. Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of TGs and LDL, or in underproduction or excessive clearance of HDL. Secondary causes contribute to many cases of dyslipidaemia in adults and the most important cause is the sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans fats that characterized the developed countries. Other common secondary causes of dyslipidaemia include diabetes mellitus, alcohol overuse, chronic kidney disease, hypothyroidism, primary biliary cirrhosis and other cholestatic liver disease; drugs, such as thiazides, beta-blockers, retinoids, highly active antiretroviral agents, cyclosporine, tacrolimus, oestrogen and progestins, and glucocorticoids. Secondary causes of low levels of HDL cholesterol include cigarette smoking, anabolic steroids, HIV infection, and nephrotic syndrome.

17.6.2 Guidelines

Routine screening for these genetic mutations is not cost effective because of the rarity of the condition and the high cost of screening [1, 3]. Increased levels of total cholesterol, LDL and TGs, as well as decreased levels of HDL, are known risk factors for CVD. Women with known, severe, genetic lipid disorders are at a much higher lifetime risk for CVD and may warrant further clinical consideration. Limited evidence on use of CHC among women with dyslipidaemia and risk of cardiovascular outcomes provided inconsistent results. One study suggested an increased risk for MI among COC users with hypercholesterolaemia compared to non-users without hypercholesterolaemia [10]; one study suggested an increased risk for VTE and for stroke among COC users with dyslipidaemia compared to COC users without dyslipidaemia [42]; and one study suggested no worsening of lipid abnormalities among CHC users with dyslipidaemia compared to non-users with dyslipidaemia [43]. No evidence of risk for pancreatitis was identified.

There are no specific restrictions about the use of contraceptive methods with known dyslipidaemias without other cardiovascular diseases (Category 1 or 2) (Tables 17.23, 17.24 and 17.25).

Table 17.23 UKMEC 2016

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
Know dislipidaemia	1	2	2	2	2	2

Table 17.24 USCDC 2012[a]

Condition	IUD		POC			**CHC**
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
Hyperlipidaemias	1	2	2	2	2	2/3

[a]Not reported in USCDC 2016

Table 17.25 WHO 2015

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
Known dyslipidaemias without other known cardiovascular risk factors	1	2	2	2	2	2

17.7 Valvular Heart Disease

17.7.1 Definition

Valvular heart disease (VHD) is characterized by damage to or a defect in one of the four heart valves: the mitral, aortic, tricuspid or pulmonary. Normally functioning valves ensure that blood flows with proper force in the proper direction at the proper time. In VHD, the valves become too narrow and hardened (stenotic) to open fully or are unable to close completely (incompetent). There are many different types of valve disease; some types can be present at birth (congenital), such as aortic stenosis, atrial septal defects, atrioventricular septal defect, cardiomyopathy (hypertrophic or dilated), coarctation of the aorta, complex transposition of the great arteries, Ebstein's anomaly, Eisenmenger syndrome, patent ductus arteriosus, pulmonary atresia, pulmonary stenosis, tetralogy of Fallot, total anomalous pulmonary venous connection, tricuspid atresia, truncus arteriosus, ventricular septal defect, while others may be acquired later in life, such as aortic stenosis, mitral regurgitation, tricuspid valve abnormalities, pulmonary stenosis.

The severity of VHD varies. In mild cases, there may be no symptoms, while in advanced cases, valvular heart disease may lead to congestive heart failure and other complications. Treatment depends upon the extent of the disease.

VHD accounts for substantial morbidity and mortality in developed countries. Furthermore, the incidence increases with age, reaching approximately 13.2% in patients 75 years and older. Because of the predominance of degenerative aetiologies, the prevalence of valvular disease increases markedly after the age of 65 years, in particular regarding aortic stenosis and mitral regurgitation, which account for 3 in 4 cases of valvular disease. Rheumatic heart disease still represents 22% of valvular heart disease in Europe. The incidence of infective endocarditis is approximately 30 cases per million individuals per year. In developing countries, rheumatic

heart disease remains the leading cause of VHD. The temporal and geographical heterogeneity illustrates the effect of socioeconomic status and changes in life expectancy on the frequency and presentation of VHD [44].

Increasing numbers of women of reproductive age are affected by cardiac disease, partly because more children with congenital heart disease are surviving to adulthood and because of the rise in obesity and unhealthy behaviours [45].

17.7.2 Guidelines

According to the UK and WHO medical eligibility criteria for contraceptive use, the use of CHC in women with uncomplicated VHD is possible as a Category 2, because it is a condition where the advantages of using the method generally outweigh the theoretical or proven risks. Uncomplicated cases could be where there is no requirement for cardiac medication, the woman is asymptomatic, and a cardiology review is required annually or less. If in doubt, discussion with a specialist cardiologist is advised [1]. While, in case of complicated VHD (pulmonary hypertension, risk of atrial fibrillation, history of subacute bacterial endocarditis) is more arduous because it's a condition which represents an unacceptable health risk if the contraceptive method is used [3].

According to the US medical eligibility criteria for contraceptive use, uncomplicated and complicated cases are equally included in Category 1 so there isn't any restriction for the use.

Regarding IMP, DMPA and POP, uncomplicated and complicated cases are both conditions for which there is no restriction for the use of the contraceptive methods (Tables 17.26, 17.27 and 17.28).

Table 17.26 UKMEC 2016

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Valvular heart disease						
Uncomplicated	1	1	1	1	1	2
Complicated	2	2	1	1	1	4

Table 17.27 USCDC 2016

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Valvular heart disease						
Uncomplicated	1	1	1	1	1	2
Complicated	1	1	1	1	1	4

Table 17.28 WHO 2015

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Valvular heart disease						
Uncomplicated	1	1	1	1	1	2
Complicated	2	2	1	1	1	4

The UKMEC and WHO guidelines, concerning IUD say that uncomplicated VHD have no restriction for the use of the methods; while complicated cases are conditions where the advantages of using the method generally outweigh the theoretical or proven risk [1].

Prophylaxis against bacterial endocarditis is no longer indicated for women with artificial heart valves or previous endocarditis when inserting or removing IUD. However, this does not necessarily mean that there is no risk [45, 46]. Instead, according to the USCDC, both Cu-IUD and LNG-IUS are methods that can be used without restrictions.

Choosing the most appropriate contraceptive for women with cardiac disease requires consideration of the level of risk should the woman become pregnant, the method's efficacy, the risks associated with administration and long-term use, the contraceptive benefits and the woman's own personal choice. In many cases, balancing these risks will require a multidisciplinary and individualised approach.

Among women with VHD, CHC use may further increase the risk of arterial thrombosis and women with complicated VHD are at greatest risk. Women with valvular diseases require special considerations when selecting an appropriate method of contraception. A detailed history and risk assessment are required before prescribing contraception [3, 45]. For all women, history taking should include: medical conditions (past and present) and procedures, menstrual and gynaecological history, including cervical screening, obstetric history, family history of medical conditions, drug history (prescription, non-prescription, herbal remedies and supplements), sexual history, specific enquiry about cardiovascular and cerebrovascular risk factors like migraine, smoking and personal or family history of hypertension, VTE, thrombophilia, hyperlipidaemia, stroke or diabetes [47].

For those with cardiac conditions, a clinician should also seek to enquire specifically about cardiac diagnosis, cardiac operations or catheter interventions, history of rhythm disturbance, functional status, for example, history of breathlessness, fatigue, oedema, presyncope/syncope (New York Heart Association Classification) and advice of the woman's cardiologist on use of oestrogen and degree of risk associated with pregnancy.

A recording of BP, weight and body mass index should be documented. It may also be appropriate to review recent cardiac clinic correspondence and results if this information is accessible and the patient consents.

The following tables show the differences between the different methods of contraception according to the UKMEC, USDCD and WHO guidelines about the condition of VHD (Tables 17.29 and 17.30).

Table 17.29 Cu-IUD

	UKMEC	USCDC	WHO
Valvular heart disease			
Uncomplicated	1	1	1
Complicated	2	1	2

Table 17.30 LNG-IUS

	UKMEC	USCDC	WHO
Valvular heart disease			
Uncomplicated	1	1	1
Complicated	2	1	2

17.8 Arrhythmia

17.8.1 Definition

An arrhythmia is a disorder of the heart that affects the rate or rhythm at which the heart beats. It describes an irregular heartbeat. Heart arrhythmia, also known as irregular heartbeat or cardiac dysrhythmia, is a group of conditions where the heartbeat is irregular, too slow, or too fast. Arrhythmias occur when the electrical signals to the heart that coordinate heartbeats are not working properly. For instance, some people experience irregular heartbeats, which may feel like a racing heart or fluttering. Arrhythmias are broken down into: slow heartbeat: bradycardia, fast heartbeat: tachycardia, irregular heartbeat: atrial flutter or fibrillation (AF) and early heartbeat: premature contraction. Many heart arrhythmias are harmless; however, if they are particularly abnormal, or result from a weak or damaged heart, arrhythmias can cause serious and even potentially fatal symptoms.

It is known that the QT interval is longer in women than men and, in many studies, it has been shown that sexual hormones changed the myocardial repolarization and is thought to play a role by influencing the regulation of cardiac ion channels. Throughout puberty, the QTc interval in males shortens by 20 ms, whereas the QTc of females remains unchanged, resulting in a 6% shorter QTc in males compared to females [48].

A prolonged QT interval is a marker for an increased risk of ventricular tachyarrhythmias. Both endogenous and exogenous sex hormones have been shown to affect the QT interval. Endogenous testosterone and progesterone shorten the action potential, and oestrogen lengthens the QT interval.

During a single menstrual cycle, progesterone levels, but not oestrogen levels, have the dominant effect on ventricular repolarization in women. Studies of menopausal hormone therapy in the form of oestrogen-alone therapy (ET) and oestrogen plus progesterone therapy (EPT) have suggested a counterbalancing effect of exogenous oestrogen and progesterone on the QT. Oestrogen is reported to account for the QT interval prolongation in several studies conducted with hormone replacement therapy (HRT) in postmenopausal women. Along with this, there are conflicting data as regards the effects of HRT on QT interval and dispersion. Moreover, there is no evidence about the effect of HRT on exercise QT parameters [49].

Specifically, ET therapy lengthens the QT, whereas EPT therapy has no effect [48].

Moreover, there is evidence demonstrating that the resection of ovaries shortens the QT interval, while estradiol and dihydrotestosterone prolong it. Therefore, it can be considered that HRT leads to early after-depolarizations and consequently leads

to ventricular tachycardia by prolonging the QT interval [49]. A small increase in heart rate was demonstrated in women using oestrogen-containing contraceptives, but not with estradiol alone [48]. Theoretically, an increase in heart rate could reduce myocardial perfusion and promote cardiac arrhythmias; however, the rise in heart rate in these studies was minor and is therefore unlikely to be of clinical significance [50]. There is no other evidence that contraception of any kind triggers the occurrence of arrhythmias [51, 52].

There is a lack of evidence on the effects of hormonal contraceptives on cardiac rhythm. Because of the potential increased risk of thrombosis, CHC is generally not recommended for women who are at risk of thrombosis from cardiac arrhythmias such as AF, particularly if the woman is not on anticoagulant treatment. There is evidence to suggest that the QT interval is prolonged by endogenous oestrogen and oestrogen-only HRT, whereas combined oestrogen and progestogen HRT has been shown to have no significant effect. No studies were identified in relation to the effects of hormonal contraceptives, and there is no specific contraindication to the use of CHC in women with congenital familial or acquired arrhythmias [45]. A known long QT syndrome is a condition where the advantages of using the method generally outweigh the theoretical or proven risks.

17.8.2 Guidelines

Considering CHC, including COC, P and CVR, according to the UKMEC 2016 [1], a disorder of heart rate as AF is a condition that represents an unacceptable health risk if the method is used (Category 4) and a long QT syndrome is a condition where the advantages of using the method generally outweigh the theoretical or proven risks.

Regarding POC, including IMP and POP, AF is a condition that represents an unacceptable health risk if the method is used (Category 4). However, known long QT syndrome isn't a condition for a restriction of the use of the method of contraception (Category 1) (Tables 17.31, 17.32 and 17.33).

Table 17.31 UKMEC 2016

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Arrhythmia						
Atrial Fibrillation	1	2	2	2	2	4
Long QT syndrome	3 (I) 1(C)	3 (I) 1(C)	1	2	1	2

Table 17.32 USCDC 2016

	IUD		POC			
Condition	Cu-IUD	LNG-IUD	POP	DMPA	IMP	CHC
Arrhythmia	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]

[a]*NR* not reported

Table 17.33 WHO 2015

	IUD		POC			
Condition	Cu-IUD	LNG-IUD	POP	DMPA	IMP	CHC
Arrhythmia	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]

[a]*NR* not reported

Furthermore IUD, including CuIUD and LNGIUS, is a method that can be used in women who have these diseases: in particular, for Cu-IUD, AF is a condition for which there isn't any restriction for the use (Category 1), but in case a long QT syndrome exists, a Category 1 is assigned if the method is already used. In case of initiation, the theoretical or proven risks of using the method generally outweigh the advantage (Category 3). Regarding LNG-IUS, AF is a condition where the advantages of using the method generally outweigh the theoretical or proven risks (Category 2). Instead, in case of a woman with long QT syndrome, the initiation in using LNG-IUS can be less safe because it's a condition where the theoretical or proven risks of using the method generally outweigh the advantage (Category 3), then the provision of an IUD requires expert clinical judgement and/or referral to a specialist contraceptive provider. However, if the woman already has the LNG-IUS and she wants to continue using the method, there isn't any restriction (Category 1). The most important issue is the elevated thrombo-embolic risk with use of combined contraceptives in women with an arrhythmia. In women with isolated arrhythmias (isolated supraventricular or ventricular extra beats, atrioventricular nodal re-entry tachycardia, or ventricular tachycardia in long QT-syndrome), combined contraceptives can be used. However, when atrial flutter or fibrillation is present, either paroxysmal or permanent, caution in the use of combined hormonal contraceptives is advised, because of elevated risk of thrombo-embolism [51, 52]. The safety of hormonal contraceptives is unclear with regard to conditions, such as Brugada syndrome and congenital or acquired (drug induced) long QT syndrome, which are associated with arrhythmia and sudden cardiac death. Women have a lifelong higher risk of sudden cardiac death associated with long QT syndrome than men. Women with arrhythmias often use medication that is teratogenic (amiodarone), consequently, effective contraception is essential. When a change of antiarrhythmic medication is decided upon, it should be implemented when the mother is still using contraception, since this allows time to judge the tolerance and effectiveness of the new medication. In the case of anticoagulant medication, the change can be made in early pregnancy.

17.9 History of Deep-Vein Thrombosis

17.9.1 Definition

The American Society of Haematology describes VTE as a term referring to blood clots in the veins, which is a highly prevalent and far-reaching public health problem that can cause disability and death. Despite effective new options for prevention

and treatment, VTE remains a threat underappreciated by the general public, causing up to 100,000 deaths annually in the United States alone and the estimated annual incidence rates among people of European ancestry range from 104 to 183 per 100,000 person-years, rates that are similar to that of stroke.

VTE includes deep-vein thrombosis (DVT), a blood clot that typically forms in the deep veins of the leg, and pulmonary embolism (PE), a life-threatening condition that occurs when a blood clot breaks free and becomes lodged in the arteries of the lung.

Stasis, endothelial injury and hyperviscosity (Virchow's triad) increase the risk of clot formation. Impaired cardiac function and/or dilated heart chambers or arrhythmia increase the risk of stasis. Closure of a cardiac defect within the last 6 months or presence of a mechanical heart valve increases the risk of thrombus formation. Cyanotic defects are associated with hyperviscosity because of increased haemoglobin [45].

Patients with contributory factors, such as obesity, smoking, hypertension, diabetes, high cholesterol, poor nutrition, and stress, already have an increased risk of VTE. However, these risk factors can be modified through various methods, including counselling, exercise, medication, and weight loss. Other factors that increase a patient's risk of VTE include advancing age, cancer, prior VTE, venous insufficiency, pregnancy, trauma, frailty, immobility and thrombophilia.

Women from thrombophilic families have increased risk of VTE, which increases further during COC use and pregnancy postpartum.

The baseline risk can be further increased by underlying conditions like cancer and obesity, by exogenous risk factors, such as surgery and trauma, and, in women of reproductive age, using COC and the pregnancy- postpartum period [53].

Thrombophilia testing is often proposed in women of childbearing age before the initiation of contraception. However, the presence of a familial history of VTE has the potential to be more accurate than the presence of inherited thrombophilia [54].

The association between the use of COC and an increased risk of VTE has been known about for many years, it being related mainly to the dose of oestrogen; however, recent research has also shown the influence of the type of progestin. When compared to COC containing levonorgestrel, norgestimate or norethisterone, those containing desogestrel or gestodene present a two-fold greater risk of VTE; for COC containing cyproterone acetate, the risk is four-fold greater, while there are no or insufficient data for those containing chlormadinone acetate or drospirenone [55]. Limited data from a single transatlantic prospective study suggests that the quadriphasic association between estradiol valerate and dienogest may have a risk of VTE in the same range of ethinylestradiol- and levonorgestrel-based products [56]. The VTE risk for non-oral CHC like CVR or P is as high as for COC of third or fourth generation. POC methods do not increase VTE risk significantly [57].

Moreover, several studies have explored the impact of positive family history and it is considered an independent risk factor of VTE with reported odds ratios varying between 2.2 and 2.7 [58].

Although further research is needed, findings suggest that a family history originating from a female patient, that is, a mother or sister, especially when that patient

experienced a COC- or pregnancy-related VTE may further increase VTE risk in her female relatives. This information could be important in the counselling of women on contraceptive options [54].

17.9.2 Guidelines

According to the UKMEC 2016 and the WHO 2015, VTE is rare among women of reproductive age. All types of CHC are associated with an increased risk for VTE compared to non–use. Studies have found differences in risk for TVE associated with COC containing different progestogens. Current evidence suggests that COC containing levonorgestrel, norethisterone and norgestimate or products containing estradiol are associated to the lower risk. However, the absolute differences are very small.

The UKMEC 2016 and the WHO 2015 medical eligibility criteria for contraceptive use say that, in case of history of DVT, the condition represents an unacceptable health risk if the CHC (Category 4), including COC, CVR, P and combined injectable contraceptive, is used. A family history of VTE, instead, may alert the clinicians as the woman may have an increased risk but alone cannot identify with certainty an underlying thrombophilia. According to the USCDC 2016, in women with lower risk for recurrent DVT, the theoretical or proven risks usually outweigh the advantages of using CHC. In women with higher risk for recurrent DVT, it's incorrect using CHC (Tables 17.34, 17.35 and 17.36).

For USCDC 2016 and WHO 2015, an episode in a first degree relative is in Category 2, independently by the age, though some conditions that increase the risk for VTE are heritable. On the other hand, according to UKMEC 2015 concerning a first degree relative episode at an age lower than 45 years, the theoretical or proven risks usually outweigh the advantages of using a CHC (Category 3). If the history of VTE is about a first degree relative at an age of over 45 years, the advantages of using the method generally overcome the theoretical or proven risk (Category 2).

Table 17.34 UKMEC 2016

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
Venous thromboembolism						
History of VTE	1	2	2	2	2	4
Current VTE (on anticoagulants)	1	2	2	2	2	4
Family history of VTE						
First-degree relative age < 45 years	1	1	1	1	1	3
First-degree relative age ≥ 45 years	1	1	1	1	1	2
Major surgery						
With prolonged immobilization	1	2	2	2	2	4
Without prolonged immobilization	1	1	1	1	1	2
Minor surgery without immobilization	1	1	1	1	1	1
Immobility (unrelated to surgery)	1	1	1	1	1	3

Table 17.35 USCDC 2016

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
Deep vein thrombosis/pulmonary embolism						
History of DVT/PE, not receiving anticoagulant therapy						
Higher risk for recurrent DVT/PE (one or more risk factors)	1	2	2	2	2	4
Lower risk for recurrent DVT/PE (no risk factors)	1	2	2	2	2	3
Acute DVT/PE	2	2	2	2	2	4

Table 17.36 WHO 2015

Condition	IUD		POC			CHC
	Cu-IUD	LNG-IUS	POP	DMPA	IMP	
Deep vein thrombosis/pulmonary embolism						
History of DVT/PE	1	2	2	2	2	4
Acute DVT/PE	1	3	3	3	3	4
DVT/PE and established on anticoagulant therapy	1	2	2	2	2	4
Family history (first-degree relatives)	1	1	1	1	1	2
Major surgery						
With prolonged immobilization	1	2	2	2	2	4
Without prolonged immobilization	1	1	1	1	1	2
Minor surgery without immobilization	1	1	1	1	1	1

Regarding POC, including POP and IMP, the UKMEC 2016, WHO 2015 and USCDC 2015 recommendations belong to Category 2: previous DVT is a condition where the advantages of using the method generally outweigh the theoretical or proven risk. If there is a family history of DVT (first-degree relatives) the indications refer to Category 1: there is no restriction for the use of the contraceptive method.

Concerning the use of IUD in women with history of DVT, the recommendations are different: concerning Cu-IUD, there isn't any restriction for the use (Category 1), and concerning LNG-IUS, the advantages generally overcome the theoretical or proven risks (Category 2). In case of family history of DVT, the condition is the same as the first one, so there is no restriction of the use.

The key procedures in terms of ensuring the safe use of this contraceptive method are a full clinical, personal and family history, in order to evaluate risk factors for VTE and cardiovascular disease, along with the recording of BP and body mass index prior to the prescription of COC [55].

There are no substantial differences between the UKMEC, USDCD and WHO guidelines about the using of contraceptive methods with history of DVT.

17.10 Thrombogenic Mutations

17.10.1 Definition

Thrombophilia is a predisposition to arterial or venous thrombotic complications as a result of congenital or acquired haemostatic system defects. Thrombophilia increases risk of fatal complications, disability of patients. In the 1990s, several gene mutations were found to substantially increase the risk of thrombosis [59].

There are six key thrombogenic mutations to be concerned about in the risk of thrombosis:

Factor V Leiden Mutation. About 80% of women with activated C-reactive protein resistance have this mutation, the most common genetic risk factor for VTE. It activates protein C resistance, inhibiting the blood's anticoagulant system and thereby enhancing the blood's susceptibility to thrombosis. Globally, the highest prevalence of factor V Leiden is among European populations, ranging from 2.0% to 7.0%; prevalence is lower among Africans and Asians. In the United States, the factor V Leiden mutation is carried in heterozygous form by about 5% of the white population and is less frequent among Hispanic-Americans (2.2%), African Americans (1.2%) and Asian-Americans (0.45%). Both men and women with factor V Leiden mutation face a 30% lifetime risk of VTE. However, this risk remains low in asymptomatic heterozygotes, at 0.2%, whereas the risk is far higher in homozygotes, at 16–17%. Therefore, activated protein C resistance due to the factor V G1691A polymorphism and the G20210A polymorphism in the prothrombin gene are well-characterized genetic variants causing thrombophilia [60].

Prothrombin Gene Mutation. Patients with this mutation also face a 30% lifetime risk of VTE; the prevalence is 2–3%. The risk of VTE in heterozygotes is just 0.5%, but the risk in homozygotes is 15%.

Antithrombin Deficiency. Antithrombin (AT) belongs to the serpin superfamily and regulates coagulation by inhibiting thrombin, activated factor X (FXa), and to a lesser extent FIXa, FXIa, FXIIa and FVIIa. Hereditary AT deficiency is classified as type I (quantitative) and type II (qualitative). In type II deficiency, the defect may affect the reactive site (IIRS), the heparin-binding site (IIHBS) or it can exert pleiotropic effect (IIPE) [61]. Patients with this deficiency face a 70–90% lifetime risk of VTE.

Protein C Deficiency. Protein C deficiency is a rare disorder, characterized by a reduction in the activity of protein C, a plasma serine protease involved in the regulation of blood coagulation. The active form of protein C, activated protein C, exerts potent anticoagulant activity. A deficiency in protein C is characterized by the inability to control coagulation, resulting in the excessive formation of blood clots (thrombophilia). Patients with this deficiency face a 30% lifetime risk of VTE. The prevalence ranges from 0.2% to 0.5%. The risk of VTE during pregnancy is 4%.

Protein S Deficiency. Protein S (also known as S-Protein) is a vitamin K-dependent plasma glycoprotein synthesized in the liver. In the circulation, Protein S exists in two forms: a free form and a complex form bound to complement protein C4b-binding protein (C4BP). In humans, protein S is encoded by the PROS1 gene. It functions as a cofactor to Protein C in the inactivation of Factors Va and VIIIa.

Only the free form has cofactor activity. Mutations in the PROS1 gene can lead to Protein S deficiency, which is a rare blood disorder that can lead to an increased risk of thrombosis.

Nowadays, Leiden mutation and mutation in prothrombin G20210A contributing to congenital thrombophilia are routinely tested. These mutations have a high prevalence in the population. Congenital deficiencies of protein S, protein C and antithrombin III are rare thrombophilia with lower population frequency, but higher risk of thromboembolic event [62].

17.10.2 Guidelines

According to UK medical eligibility criteria for Contraceptive Use (2016), WHO medical eligibility criteria for contraceptive use (2015) and the U.S. Medical Eligibility Criteria for Contraceptive Use (2016), among women with thrombogenic mutations, COC users had a 2- to 20-fold higher risk of thrombosis than non-users. Moreover, women with known thrombogenic mutations (factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies) should not use combined hormonal contraceptive methods (Category 4). Whereas, concerning the use of POC, in case of thrombogenic mutations, it can be used because there are less risks and the advantages are higher than theoretical or proven risks. Concerning IUD, Cu-IUD relates to Category 1 having no restriction for the use, while LNG-IUS relates to Category 2 so it can be used because the advantages overcome the theoretical or proven risks. Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening (Tables 17.37, 17.38 and 17.39).

There are no differences between the UKMEC, USDCD and WHO guidelines about the indication of the use of contraception with thrombogenic mutations (factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies).

Table 17.37 UKMEC 2016

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Thrombogenic mutations	1	2	2	2	2	4

Table 17.38 USCDC 2016

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Thrombogenic mutations	1	2	2	2	2	4

Table 17.39 WHO 2015

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Thrombogenic mutations	1	2	2	2	2	4

17.11 Multiple Risk Factors for Arterial Cardiovascular Disease

17.11.1 Definition

In the 1950s, several epidemiological studies were set in motion with the aim of clarifying the cause of cardiovascular disease. Four years after the Framingham Heart Study started, researchers had identified high cholesterol and high blood pressure levels as important factors in the development of cardiovascular disease. In subsequent years, the Framingham study and other epidemiological studies have helped to identify other risk factors, which are now considered classical risk factors [63].

The independent risk factors for coronary heart disease (CHD), defined as major risk factors by the AHA, are cigarette smoking of any amount, elevated BP, elevated serum total cholesterol and LDL, low serum HDL, diabetes mellitus, and advancing age (Table 17.40) [64].

Lipids. When epidemiological studies began, there were some prior evidence that suggested a relationship between total cholesterol and atherosclerosis based on animal studies and clinical observations. This association was confirmed by epidemiological studies showing a strong relation between serum total cholesterol and cardiovascular risk [65] and that changes in cholesterol levels due to migration or interventions where associated with changes in CVD incidence rate. These findings were confirmed when LDL, the principal lipoprotein transporting cholesterol in the blood, was also directly associated with CVD. Moreover, LDL cholesterol levels in young adulthood predict development of CVD later in life, supporting the idea that the relationship between LDL and development of CVD should be viewed as a continuous process beginning early in life. Current guidelines identify LDL as the primary target for high blood cholesterol therapy. Meanwhile, raising HDL levels has become an accepted therapeutic strategy for decreasing CHD incidence rate; in fact, it is estimated that a 1 mg/dL increase in HDL level is associated with a decrease in coronary risk of 2% in men and 3% in women [66].

Hypertension. Hypertension is the medical term for high BP. Around 85 million people in the United States have high BP. Medical guidelines define hypertension as a BP higher than 130 over 80 millimetres of mercury (mmHg), according to guidelines issued by the AHA in November 2017. Hypertension is a leading cause of CVD. There are very few studies dealing with the incidence of hypertension and changes in BP over time. The systolic and diastolic blood pressure has a continuous, independent, graded, and positive association with cardiovascular outcomes and even high-normal BP values are associated with an increased risk of CVD [67].

Table 17.40 Major independent risk factors

Cigarette smoking
Elevated blood pressure
Elevated serum total (and LDL) cholesterol
Low serum HDL cholesterol
Diabetes mellitus
Advancing age

Smoking. Smoking represents one of the most important preventable risk factors for the development of atherosclerosis; in fact, it is a major cause of CHD, stroke, aortic aneurysm, and peripheral vascular disease. Smokers have a two- to fourfold increase in coronary artery disease and about a 70% higher death rate from coronary artery disease than do non-smokers [68].

Diabetes. That diabetes mellitus is a major risk factor for CVD is well established. Diabetes is a condition that impairs the body's ability to process blood glucose, otherwise known as blood sugar. In the United States, the estimated number of people over 18 years of age with diagnosed and undiagnosed diabetes is 30.2 million. Diabetes is associated with a 2- to 3-fold increase in the likelihood of developing CVD [54], this increase being higher in women than in men [69]. Both type 1 and type 2 diabetes confer a heightened risk for CVD. Type 2 diabetes is of particular concern because it is so common and usually occurs in persons of advancing age, when multiple other risk factors coexist.

The quantitative relationship between these risk factors and CHD risk has been elucidated by the Framingham Heart Study [70] and other studies. These studies show that the major risk factors are additive in predictive power. Accordingly, the total risk of a person can be estimated by a summing of the risk imparted by each of the major risk factors. Other factors are associated with increased risk for CHD (Table 17.41). These are of 2 types: conditional risk factors and predisposing risk factors.

The conditional risk factors are associated with increased risk for CHD, although their causative, independent, and quantitative contributions to CHD have not been well documented. The predisposing risk factors are those that worsen the independent risk factors. Two of them, obesity and physical inactivity, are designated major risk factors by the AHA. The adverse effects of obesity are worsened when it is expressed as abdominal obesity, an indicator of insulin resistance.

The Framingham report defined low risk as the risk for CHD at any age that is conferred by a combination of all the following parameters: blood pressure 120/80 mmHg, total cholesterol 160–199 mg/dL (or LDL 100 to 129 mg/dL), and HDL 45 mg/dL for men or 55 mg/dL for women in a non-smoking person with no diabetes.

Table 17.41 Others risk factors

Predisposing risk factors
Obesity
Abdominal obesity
Physical inactivity
Family history of premature coronary heart disease
Ethnic characteristics
Psychosocial factors
Conditional risk factors
Elevated serum triglycerides
Small LDL particles
Elevated serum homocysteine
Elevated serum lipoprotein(a)
Prothrombotic factors (fibrinogen)
Inflammatory markers (C-reactive protein)

17.11.2 Guidelines

The recommendations of the UK's 2016, WHO's 2015 and the US's 2016 MEC for contraception use in condition of multiple risk factors for arterial cardiovascular disease between the different methods are similar: the UKMEC give a Category 3 to CHC methods (a condition where the theoretical or proven risks usually outweigh the advantages of using the method), Category 2 for POP and IMP methods (a condition where the advantages of using the method generally outweigh the theoretical or proven risks), Category 1 for Cu-IUD (no restriction for the use of the method) and a Category 2 also for LNG-IUS. The WHO 2015 and the USCDC 2016 give Category 3/4 to the CHC that includes injectable contraception, P and CVR. Concerning POC, that includes POP and IMP, it is assigned a Category 2, so the method can be used because the advantages of using it generally outweigh the theoretical or proven risks. Regarding IUD, Cu-IUD is considered as a method that can be used without restrictions in condition of multiple risk factors for arterial cardiovascular disease (Category 1) while LNG–IUS, in the same condition, as a Category 2 method (Tables 17.42, 17.43 and 17.44).

According to the UK and the WHO medical eligibility criteria, when a woman has multiple major risk factors, any of which alone would substantially increase the risk of CVD, use of CHC may increase her risk to an unacceptable level. A simple addition of categories for multiple risk factors is not intended; for example, a combination of two risk factors assigned a Category 2 may not necessarily warrant a higher category.

The following tables show the differences between the different methods of contraception according to the UKMEC, USCDC and WHO guidelines about the condition of Multiple risk factors for arterial cardiovascular disease (Table 17.45).

Table 17.42 UKMEC 2016

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Multiple risk factors for arterial CVD	1	2	2	3	2	3

Table 17.43 USCDC 2016

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Multiple risk factors for arterial CVD	1	2	2	3	2	4

Table 17.44 WHO 2015

	IUD		POC			
Condition	Cu-IUD	LNG-IUS	POP	DMPA	IMP	CHC
Multiple risk factors for arterial CVD	1	2	2	3	2	4

Table 17.45 CHC

	UKMEC	USCDC	WHO
Multiple risk factors for arterial CVD	3	4	4

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The Effect of Hormonal Contraceptives on Metabolism

18

Angelo Cagnacci and Anna Biasioli

18.1 Introduction

Planning reproductive events has changed women life in the last century. The social revolution, brought by the possibility of dissociating sexuality from reproduction, should haven't been possible without the public marketing of hormonal contraception (HC). HC is now used by millions of women worldwide. HC is prescribed only to prevent the physiological consequence of a sexual intercourse, and for this reason any induced complication or side effect is of concern and hardly tolerated.

Cardiovascular diseases represent the leading cause of death, and cardiovascular prevention an implemented strategy by all health organizations. Accordingly, it is important to know whether HCs exert any effect on a woman lifetime risk of developing a cardiovascular disease [1]. Since a 1963 report [2] documenting an altered metabolism in users of HC, many investigators focused their studies in establishing the metabolic impact of different HC formulations. Obviously, the risk of cardiovascular disease is very low in young women, but also at this age, a prolonged exposition to risk factors could accelerate atherosclerosis and lead to an earlier manifestation of events. Events occur late in life, years after the initiation of a HC, and are not picked up by epidemiological studies that are limited to the period of HC use. In the absence of an appropriate epidemiological evidence, modifications of surrogate markers can give an advice on possible future cardiovascular risk and should be wisely considered when prescribing a HC.

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18.2 HC Formulations

In order to improve safety, HC formulations were progressively changed by reducing ethinyl estradiol (EE) doses, by introducing other estrogen molecules, newer progestins, new treatment schedules, and alternative routes of administration.

For decades only one estrogenic molecule, EE, was used in HC, but its dose was reduced from more than 50 μg up to 15 μg daily. More recently new molecules, estradiol (E2), its valerate form (E2V), and estetrol (E4), were marketed.

Three generations of progestins derived from testosterone were synthesized, and progestins derived by other molecules were introduced. Besides the molecule from whom they derive, progestins can be classified accordingly to their activity: estrogenic (or anti), androgenic (or anti), glucocorticoid, or anti-mineralocorticoid. Progestins with androgenic activity are those related to testosterone, such as norethisterone acetate (NETA), levonorgestrel (LNG), desogestrel (DSG), gestodene (GSD), and norgestimate. Progestins with mild or antiandrogenic activity are those related to progesterone, such as nomegestrol acetate (NOMAC), nestorone, chlormadinone acetate (CMA), and cyproterone acetate (CPA), or are those related to spironolactone, i.e., drospirenone (DRSP). Dienogest (DNG) is the only progestin related to testosterone with antiandrogenic properties. At the dose used in HC, DRSP is the only progestin with anti-mineralocorticoid activity.

In this chapter we will focus on the effect that different molecules alone or in combination may exert on surrogate markers of cardiovascular disease, i.e., on those factors that contribute to the metabolic syndrome, such as carbohydrate and lipid metabolism, blood pressure, and body weight.

18.3 Carbohydrate Metabolism

Analysis of glucose-insulin metabolism and of its modification induced by HC is rather complex the final effect deriving by the contribution of different systems and hormones. Part of glucose is metabolized independently from insulin in the brain and, depending on the levels, also in peripheral tissues. Circulating glucose is regulated by deposition and mobilization of liver glycogen and modification of insulin sensitivity in peripheral tissue. The gastrointestinal tract is activated during oral carbohydrate ingestion and via its hormones and substances controls and modulates glucose utilization and insulin secretion. Accordingly, in order to understand completely how HCs influence glucose-insulin metabolism, almost all these components should be investigated.

An initial study performed in the 1970 reported that when the whole system is challenged by an oral glucose administration (OGTT), glucose tolerance is impaired in women receiving HC [3]. It was reported that during HC fasting glucose is frequently maintained within normal limits, by an elevation of fasting insulin, but that following OGTT, the rise of glucose and insulin is higher [4]. In 2014 a Cochrane review [5] concluded that few studies evaluated the effect of HC on carbohydrate metabolism but that the evidence shows a small effect, clinically irrelevant, in

Table 18.1 Effect of estrogens and progestins on metabolic factors

	EE	E2	Androgenic progestin	Antiandrogenic progestin
HDL	Increase	Not significant	Decrease (related to potency)	None
LDL	Decrease	Not significant	Increase (related to potency)	None
TG	Increase	Not significant	Decrease (related to potency)	None
Insulin resistance	None	None	Deteriorated (related to potency)	None
Blood pressure	Increase	None	None	None (except DRSP)

Table 18.2 Effect of combined hormonal contraception on metabolic factors

	EE+ androgenic P	EE+ antiandrogenic P	E2 + nomac E2V + dng
HDL	Decrease (related to androgenic potency)	Increase	Not significant
LDL	Increase (related to androgenic potency)	Decrease	Not significant
TG	Decrease (related to androgenic potency)	Increase	Not significant
Insulin resistance	Deteriorated (related to androgenic potency)	None	None
Blood pressure	Increase	Increase (except DRSP)	None

women without diabetes. One of the limits of most of these studies is that the effect on carbohydrate metabolisms was frequently considered as a secondary outcome, often evaluated only by modification of fasting glucose.

Presumably, the impact of different HC compounds on carbohydrate metabolism differs on the basis of the type and dose of estrogen, type of progestin, and route of administration (Tables 18.1 and 18.2).

18.3.1 Estrogens

When studying the metabolic effect of estrogens, it is necessary to consider the potency, dose, and route of administration.

EE replaced mestranol and was initially used at doses of 150 μg per pill and then progressively decreased to 50, 30, 20, and even 15 μg. EE undergoes a slow metabolization in the liver, and independently on its route of administration, it exerts a strong hepatic effect that on a weight basis is approximately 300–500 times more potent than that of E2 [6].

Studies evaluating the effect of mestranol or EE on carbohydrate metabolism failed to show any major effect [7, 8]. It appears that different estrogen preparations, either given for 6 months (1.25 mg of conjugated estrogens, 0.08 mg mestranol, or

either 0.05 mg or 0.5 mg EE) or for 2 years (mestranol), did not consistently alter carbohydrate metabolism. A similar conclusion was reached by the analysis of three studies with different estrogenic compounds [9].

Other studies did not find any effect on glucose metabolism of different doses of EE [4, 6, 10, 11]. For example, a detrimental effect on insulin sensitivity was observed with a HC containing a low dose of EE and a neutral effect with a HC containing a higher EE dose, but the two associations contained progestins with a different androgenic potency. When the progestin molecule is kept fix, the dose of EE used is irrelevant and does not change insulin sensitivity or the glucose-insulin response to an OGTT [11, 12].

Neutral metabolic effect was also observed with HC containing E2 or E2V in association with a non-androgenic progestin. Response of insulin and glucose measured during OGTT remained unaffected by E2V/DNG treatment [13] or E2/NOMAC [14]. Similarly, HC containing E2 or E2V did not affect insulin sensitivity, as measured by the HOMA index [15].

The development of new estrogens such as E4 holds promise for the safety and tolerability of future HC. E4 is synthesized by human fetal liver and is therefore present only during human pregnancy. In a preliminary evaluation, E4 seems to have a neutral metabolic profile that is conditioned by the associate progestin molecule [16].

18.3.2 Progestins

Most progestins, which bind and transactivate progesterone receptor (PR), modify insulin half-life that is directly related to insulin resistance. This effect depends upon the structure of the molecules and in particular to its androgenic potency. Testosterone decreases insulin sensitivity by an action exerted at a post-receptor level [17]. Indeed, insulin sensitivity is decreased by androgen supplementation [17, 18] and is low in women with hyperandrogenism [19, 20]. In the latter, it can be improved by abolition of hyperandrogenism [21, 22] or by administration of antiandrogens [23, 24]. HC formulations containing potent (LNG) or less potent (GSD and DSG), androgenic progestins decrease insulin sensitivity and increase glucose response to an OGTT [3, 25]. GSD has an androgenic activity higher than that of DSG [26]. In a trial [27] evaluating the effect of GSD 60 μg/EE 15 μg versus those of DSG 150 μg/EE 20 μg, an increased glucose response to OGTT was observed with both treatments, but the response of insulin was increased more with the GSD/EE association. Another trial [28] compared the effects of preparations containing the same dose of EE (20 μg) and either LNG or its derivatives, DSG, and GSD that are characterized by a reduced androgenic action. Fasting levels and response to OGTT of glucose increased after administration of either DSG or GSD, by 10–12% (for fasting glucose), but the effects were milder than those observed with LNG.

Cagnacci et al. [11] compared oral administration of DSG and vaginal delivery of its metabolic active component ETN, both associated with EE. A decrease of insulin sensitivity was observed with the oral but not with the vaginal route of

administration. Because EE, whatever is its route of administration, affects the liver to the same extent, it seems that DSG exerts a different effect on insulin sensitivity when given in similar doses but with different routes of administration.

When androgenic progestins are substituted by non-androgenic or antiandrogenic progestins, the effect of HC on carbohydrate metabolism is neutral.

In a study comparing the administration of the androgenic progestin DSG and the non-androgenic progestin CMA, it was shown that DSG plus 20 μg EE decreases insulin sensitivity and that this effect is not observed with the administration of CMA associated with 30 μg EE [10]. Other antiandrogenic progestins show the same neutral effect. DRSP in different formulations does not modify glucose, insulin, and C-peptide response to an OGTT [12, 29]. A neutral effect on insulin sensitivity or to an OGTT was observed also for other two non-androgenic progestins, such as NOMAc and DNG associated with either E2 or E2V, respectively [13, 14].

18.3.3 Progestin-Only Contraception

The effect of DSG alone was observed in comparative studies with LNG. In a multicenter study performed in Finland [30], a minimal effect on carbohydrate metabolism was observed for both treatments with a trend for higher glucose and insulin values in the LNG group. Really carbohydrate metabolism was not adequately studied [31, 32]. In a single-center open randomized study, the effect of the ETN implant was compared to that of the LNG implant [33]. Within each group, there was a significant increase in the area under the curve of both glucose and insulin response to an OGTT. The effect increased with duration of use, from 6 to 12 and 24 months. No statistical difference was observed between ETN and LNG. In a comparative study evaluating the difference between the administration of ETN implant and GnRH agonist to patients with endometriosis, insulin sensitivity tended to decrease, although not significantly, in the GnRH-agonist group and significantly in the ETN implant group [34].

Some studies assessed the possible effects of LNG-releasing intrauterine system (LNG-IUS) on carbohydrate metabolism. The LNG-IUS produces a very high local but low plasma concentrations of LNG. Nevertheless, blood LNG levels may reach values of 150–200 pg/ml. After 12 months of LNG-IUS use, fasting glucose was reported to be significantly increased [35]. These data are in contrast to those of a study in which glucose levels were reported to be significantly reduced during LNG-IUS [36]. Both studies did not perform any extensive evaluation of carbohydrate metabolism. In premenopausal women LNG-IUS did not affect insulin sensitivity evaluated 12 months after insertion [37].

18.3.4 Women with Diabetes

In diabetic women pregnancy should be accurately programmed. The WHO Medical Eligibility Criteria for Contraceptive Use [38] states that for any diabetic patient, without cardiovascular or microvascular complications, advantages of using HC

generally outweigh the theoretical or proven risks. A Cochrane review performed in 2006 [39] investigated whether in women with diabetes progestin-only, combined hormonal or nonhormonal contraceptives differ in terms of their side effects on carbohydrate and lipid metabolism or in long-term complications, such as micro- and macrovascular disease. Although the three randomized controlled trials included in this systematic review were insufficient to provide definite conclusions, no difference was found after 12 months of contraception in daily insulin requirement, glycated hemoglobin (HbA1c), or fasting blood glucose. Accordingly, HC seems to represent a safe and effective option for diabetic women, at least for those women with an uncomplicated diabetes [40]. Recent guidelines [38] underline the need to avoid the use of HC in case of associated cardiovascular risk factors, cardiovascular diseases, or severe microvascular complications, such as nephropathy with proteinuria or active proliferative retinopathy. Furthermore, HC must be used with caution in type 2 diabetic women with associated obesity or other risk factors that increase both the thromboembolic and the arterial risk. Progestin-only HC can be a good option in these women.

18.3.5 Women with Polycystic Ovary Syndrome

HC is the first-line management option for the clinical manifestations of PCOS, specifically for menstrual irregularity, and symptoms of hyperandrogenism, like hirsutism and acne. In addition, its use may reduce the risk of endometrial cancer [41]. PCOS is associated with clinical and metabolic comorbidities that may limit HC prescription. Insulin resistance and hyperinsulinemia play an important role in the pathogenetic mechanism of PCOS [20, 42], and risk factors for cardiovascular diseases, such as systemic arterial hypertension, obesity, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus (DM2), develop more frequently in women with PCOS. Alteration of carbohydrate metabolism is accelerated by overweight and obesity and ultimately contributes to an excess risk of cardiovascular events [43]. In women with PCOS, the high prevalence of disturbance and risk factors require a specific phenotype-based HC prescription [44, 45]. Because of remarkable induced decrease in androgen and increase in SHBG concentrations, hyperandrogenic PCOS phenotype patients may have greater benefits by the administration of EE and antiandrogenic progestins. Collectively [23, 45] randomized or observational studies indicate that in hyperandrogenic PCOS, administration of HC containing CPA, CMA, DRSP, and NOMAc does not negatively affect or may even slightly improve carbohydrate metabolism. Additional studies strongly indicated that HC containing CPA or DRSP do not worsen insulin metabolism in PCOS patients [46–48].

The effect of HC vs. metformin was evaluated in a systematic review with meta-analysis of four randomized controlled trials [49]. Metformin was found to be superior in terms of reduction of fasting insulin, albeit the two treatments showed no significant difference in fasting glucose levels or in the onset of type 2 diabetes. An ongoing clinical trial [50] is aimed to compare the effects of HC containing LNG

with products containing antiandrogenic progestins (DRSP, CPA) or less androgenic progestins (DSG). In women at risk, HC with natural estrogens may have a safer cardiovascular profile. Association of E2V and the antiandrogen progestin DNG did not alter glucose levels in PCOS but improved insulin sensitivity and reduced insulin response to an OGTT [51].

Progestin-only contraception can be a safe option in PCOS. In observational, prospective, controlled study, 6 months after LNG-IUS insertion, glycemia only slightly increased in women with PCOS [52].

18.4 Lipid Metabolism

Increases in the ratio of LDL to HDL cholesterol, and particularly in the apoprotein (apo)-B/apo-A1 ratio, are considered major cardiovascular risk factors [53, 54]. Elevation of triglycerides may contribute to the cardiovascular risk, but only in the presence of reduced HDL [55].

Estrogens and progestins can act on lipid metabolism. The final effect depends upon the estrogen-progestin dose and the relative balance between the estrogenic potency and the androgenic activity of the progestins [1, 6]. Yet it is not clear whether HC-induced modifications of lipid metabolism do really translate into clinically significant effects on the risk of cardiovascular diseases [56] (Tables 18.1 and 18.2).

18.4.1 Estrogens

Estrogens stimulate free fatty acid, apoproteins, and HDL synthesis. Free fatty acid synthesis elevates VLDL rich in triglycerides [57]. The magnitude of such effect is related to the potency of the estrogen molecule. Because HC-induced VLDL is not transformed in LDL and because of the elevated levels of HDL, this estrogen-induced increase of triglycerides is believed to be not harmful [55]. Accordingly, estrogen-induced lipoprotein modifications are considered to be protective for the development of atherosclerosis [58]. The introduction of E2-based contraceptives has highly reduced the estrogenic potency of HC, avoiding significant effects on lipid metabolism [59]. In a prospective trial, the effect of a four-phasic oral contraceptive containing E2V/DNG was compared to that of EE/CMA. E2V/DNG did not impact on lipid metabolism [15]. HDL, LDL, total cholesterol/HDL, LDL/HDL ratio, Apo-A1, Apo-B, and Apo-B/Apo-A1 ratio remained unmodified after three cycles of treatment. Instead, in women receiving EE/CMA, a significant increase of HDL cholesterol (p .0.001) and triglycerides (p .0.003) and a significant decrease of LDL/HDL ratio (p .0.039) were observed. No modification of LDL cholesterol and total cholesterol/HDL ratio was observed. Apo-A1 and Apo-B significantly increased with a stable Apo-B/Apo-A1 ratio.

The lipid effect of E2-based HC, where the estrogen effect is not counterbalanced by an androgenic progestin, is similar and probably better than that exerted

by EE-based HC containing LNG, a potent androgenic progestin [13, 14]. Mawet et al. [16] compared the impact of several dosages of estetrol (E4)/DRSP and E4/LNG with EE/DRSP on lipid metabolism. Both the E4/DRSP and E4/LNG combinations showed light effects on lipid levels (HDL, LDL cholesterol, TG). In comparison with EE/DRSP, the pooled E4/DRSP group was associated with a nonsignificant increase of HDL and LDL cholesterol and triglycerides. In accordance with data of the literature, EE/DRSP increased levels of HDL cholesterol, decreased levels of LDL cholesterol, and increased levels of triglycerides (approximately 60%). All E4/LNG regimens reduced plasma triglycerides by approximately 30% (statistically significantly different from EE/DRSP), reduced HDL, and not significantly increased LDL.

18.4.2 Progestins

The effect of HC on lipids seems to be related to the androgenic activity of the progestin. Progestins with androgenic properties may counteract the effect of estrogens on lipoprotein metabolism. When the balance of a HC is toward estrogen, the lipoprotein profile is likely protective, whereas it becomes neutral or pro-atherosclerotic as the balance shifts toward androgens [1]. Indeed, in primates on a high-fat diet, administration of estrogen inhibits the extent of atherosclerosis by 67%, but this effect is reduced to 28% when the androgenic progestin LNG is co-administered with estrogens [60].

Third-generation progestins have a lower metabolic impact than those containing LNG, because of the reduced androgenic potency [61]. Godsland et al. [17] showed that the androgenic potency of a progestin can be documented by modification of HDL_2 levels. HCs with LNG reduce HDL_2 by 15–43%, with the highest LNG dose inducing the greatest effect. HCs with a high dose of norethindrone decrease HDL_2 by 27%, whereas HCs with DSG have no effect. The combination of high doses of LNG with EE may cause a decrease of HDL and an increase of LDL [62, 63]. In contrast, triphasic oral contraceptives with low LNG dose exert a less unfavorable effect on lipid metabolism [64]. Modifications induced by the association of EE and DSG were more favorable and similar with the oral or intravaginal route, but related to the different dose of EE administered [11, 65, 66].

Antiandrogenic progestins do not counteract the effect of estrogens on lipids. Accordingly, association of 20 or 30 μg EE with DRSP [12] increased HDL levels by 9% and 23%, respectively. In parallel, triglycerides increased, and LDL slightly decreased. The lipid profile induced by 20 μg EE and DRSP tended to be also slightly more favorable than that observed with the association of the same dose of EE and DSG [67, 68]. Because of the lack of androgenicity of DNG, the effect of the estrogen component in the three DNG-containing formulations (30 EE/DNG, 20 EE/DNG, E2V) led to a significant rise in Apo A-I (10–15%) and triglycerides and to reduced LDL, with only a tentative increase of HDL and HDL2 [69]. The rise of TG and VLDL suggests an enhanced synthesis by the liver as a response to the hepatic effect of EE. Lack of a significant increase of HDL3 or HDL2 induced by

EE and vice versa may indicate a weak inhibitory action of DNG, even though this progestin is devoid of androgenic activity. Favorable metabolic effects on lipids were reported with CMA [10, 70]. EE and CMA elevated HDL cholesterol and triglycerides and in particular increased HDL/LDL ratio, Apo-A1, and Apo-A1/Apo-B ratio [10].

18.4.3 Progestin-Only Contraception

Androgenic progestins with a different androgenic potency are used as progestin-only contraception. A double-blind, randomized, multicenter study was performed to study the effects of two POPs (containing either DSG 75 μg/day or LNG 30 μg/day) on lipid metabolism. Both pills had minimal effects. No change was observed of LDL cholesterol and Apo-B, while a small decrease was observed for total cholesterol and triglycerides (TG). A decrease was observed for HDL, its subfractions, and APO-A1. The changes of lipid parameters were less pronounced with DSG than LNG [71].

ETN implant [72] significantly decreased HDL and total cholesterol. The change of TG was transient. In other three studies in comparison to LNG, implant of ETN did not appear to have any clinically meaningful effect on lipid metabolism [73–75]. In obese women after 12 months of LNG-IUS, a 10.8% increase of LDL levels ($p = 0.03$) and a decrease of HDL were observed [37]. However, no changes of lipid concentrations were observed after 12 [36] or 18 months [76] of LNG-IUS utilization.

18.5 Blood Pressure

Hypertension is the first risk factor for cardiovascular diseases, and HC is known to increase blood pressure (BP) both in hypertensive [77] and normotensive [78] women.

Evidence suggests that women who did not have blood pressure measurement prior to HC initiation have a higher risk for acute myocardial infarction and ischemic stroke [79]. In accordance with the WHO Eligibility Criteria for Contraceptive Use [39], women with adequately controlled hypertension or moderately elevated blood pressure (140–159/90–99 mmHg) should not use HC (category 3). Women with severely elevated blood pressure (≥160/100 mmHg) or with vascular consequences are forbidden to use HC (category 4).

18.5.1 Estrogens

EE or oral E2 enhance the liver synthesis of angiotensinogen [80]. Via the activation of the renin-angiotensin-aldosterone system (RAAS), estrogens may induce water retention and raise blood pressure. The increase of angiotensinogen depends on the

potency and dose of the estrogen stimulus [81]. Studies have shown that preparations containing higher (≥ 50 μg) doses of EE may increase office BP up to 15 mmHg [82]. Increases of about 4–5 mmHg of BP were documented with HC containing lower EE doses [83]. The effect is observed also when EE is administered by a vaginal route in a dose of 15 μg [84]. Because of the reduced EE dose, the effect on blood pressure is minimal and documented only by 24-h monitoring, but not by office measurements [84, 85]. An activation of RAAS was documented also with the use of the contraceptive patch [86]. The clinical implications of BP elevation induced by HCs with lower EE dose in healthy normotensive women are unclear [87].

It was recently demonstrated that E2-based HCs do not modify 24-h systolic, diastolic, and mean BP and also heart rate, even when daytime or nighttime values were separately considered [87]. Studies performed with office BP measurement also reported a neutral effect of E2-based formulations on BP [12, 88] (Table 18.1).

18.5.2 Progestins

The effect of estrogens on angiotensinogen synthesis is not counteracted by any progestin molecule [89]. Progestins do not possess a sodium-retaining effect, and most of them are devoid of anti-mineralocorticoid action. When given in combination, they are unable to control EE-induced sodium retention, and when given alone they do not influence blood pressure (Tables 18.1 and 18.2).

Isolated administration of LNG-IUS or subcutaneous ETN implant does not modify BP [90]. Among progestins, GSD possesses anti-mineralocorticoid properties, but these properties become evident at doses higher than those commonly used in HC [12]. The only progestin capable to antagonize the sodium-retention effect of EE is DRSP, a derivative of spironolactone, that possesses clear anti-aldosterone properties. Studies on the association of DRSP and EE are limited and mostly confined to the measurement of office blood pressure [12, 91, 92]. Cagnacci et al. [93] evaluated whether the association of 30 mcg EE plus 3 mg DRSP can modify blood pressure by a 24-h ambulatory monitoring. In that study EE-DRSP did not modify 24-h, nighttime, or daytime blood pressure values of normotensive healthy women. Similar data were reported in a study comparing DRSP associated with either 20 or 30 mcg EE [94].

In some studies it emerged that the administration of EE and either DSG (vaginally) [84] or EE and DRSP [93] increases heart rate. Studies performed in older men and women show that cardiovascular risk increases of 1% every five beats [95–97], but whether this may be of relevance in young women is unknown. The increase of heart rate during EE can be consequent to a stimulus of sympathetic nervous activity at the heart, via an increase of angiotensin II [98], further enhanced by DRSP. This is in accordance with similar effects exerted by spironolactone [99] and opposite effects exerted by aldosterone [100]. However, a prospective 6-month study [101] found no effect of EE and DRSP on blood pressure and on several autonomic parameters.

18.6 Body Weight and Composition

The effect of HC on body weight is still under debate. Weight gain is one of the most frequently cited side effects of HC that many women and clinicians believe to be consequential to HC administration [102]. Concern about weight gain limits the use of HC, especially in younger women, and can cause early discontinuation or poor compliance. In a report from the 2006–2010 National Survey of Family Growth, 63% of women who had ever used HC stated that they were dissatisfied by HC, mainly as the consequence of side effects, of which weight gain was one of the most cited [103]. Despite the popular notion that HC leads to weight gain, a recent Cochrane review (2014) of 49 randomized trials found that the available evidence is insufficient to determine whether HC has any real effect on weight [104].

Nevertheless, body composition can be affected by some estrogen-progestin associations. Estrogens may activate the RAAS and favor weight gain. The biological mechanism for contraceptive-induced weight gain, so, could be fluid retention [80]. Other hypothesized pathways are an effect on appetite, leading to an increase in food intake or even an androgen-mediated increase of muscle mass [80, 105]. Studies made in primates kept on a fixed diet showed that HC use leads to a reduced weight and a selective reduction of body fat, via an increase of resting metabolic rate [106].

In general, most studies that evaluated the effect of HC on women considered a variation of 1 kg from baseline, as negligible [107].

Short-term administration of both 20 μg/100 μg and 30 μg/150 μg HC association of EE/LNG had little effect on weight and body composition, both in normal-weight and obese women [108]. Small but significant increases of body weight of 0.4–0.6 kg over 6 months were documented with EE/norelgestromin, mainly as the consequence of water retention [109–111]. The same was observed with the administration of a pill containing LNG 50/75/125 μg and EE 30/40/30 μg [110]. Water retention is dependent on EE dose and can be counteracted by the anti-mineralocorticoid progestin DRSP [112]. Women receiving DRSP combinations showed reduction of body weight ranging from 0.7 to 1.7 kg, either when compared to baseline [113] or other HC combinations [114, 115]. The effect of the vaginal ring on body weight (+0.37 kg in 12 months) was similar to that of HC containing DRSP [116]. Similar data with the ring were obtained in another European trial [117]. This may indicate that EE-related fluid retention can be avoided or minimized by using HC with a low EE dose (15 μg).

The effect on body weight of HC seems to be further reduced by substitution of EE with E2V or E2.

No modification of BMI and body composition was reported after 6 months of treatment with E2V/DNG [13], and this association even counteracted the increase of fat mass and body weight observed in perimenopause [118]. Similarly, no effect on body weight and composition was observed in 48 fertile women after 12 months of E2/NOMAC administration [119].

18.6.1 Progestin-Only Contraception

A recent Cochrane review [120] by evaluating 22 studies concluded that there is limited evidence of change in weight or body composition with use of progestin-only HC. Mean weight gain at 6 or 12 months was less than 2 kg for most studies. Changes of body weight are most consistently reported in users of depot medroxyprogesterone acetate (DMPA). A prospective, controlled study demonstrated that DMPA use is associated with a significant increase of weight (4.4 kg after 24 months and 5.1 kg after 36 months) and central fat deposition [121–123]. Likely the effect of DMPA is mediated both by its glucocorticoid-like activity and by the profound hypoestrogenism (similar to menopause) that its administration induces.

In a prospective cohort sub-study of the Contraceptive CHOICE Project (CHOICE), the use of LNG-IUS, ETN implant, or copper IUD did not induce a significant effect on body weight or fat deposition [124]. After 12 months of continuous use, mean body weight increased by 0.5 and 0.1 kg in users of LNG-IUS or ETN implant, respectively. Additionally, at 6 months there was no significant difference in BMI between women continuing and discontinuing treatment. In contrast to these data, two prospective studies showed a weight gain of 2.9 kg [125] and 4.1 kg [126] after 12 months of LNG-IUS or ETN implant use, respectively. In both cases the increase of body weight was associated with an increase of body fat of about 2.5%. An observational study performed in 102 perimenopausal women treated with 75 μg DSG pill or 52 mg LNG-IUS or with no treatment showed that fat mass did not change in the control group but significantly increased in the LNG-IUS and DSG group [37].

18.7 Conclusions

Contribution of HC-induced metabolic changes to the woman lifetime risk of coronary heart disease is uncertain. Different HC formulations show a different risk profile and may impact differently on the future occurrence of cardiovascular disease. Epidemiological studies at the moment are unable to give a definite confirmation of this possibility. Nevertheless, cardiovascular risk factors leading to the metabolic syndrome are known to translate in the epidemiological evidence of increased cardiovascular events. There is no strong argument to sustain that a similar translation does not apply to women on HC. Accordingly, in the absence of a clear epidemiological evidence, it seems wise to consider HC-induced modification of risk factors as predictive of future cardiovascular disease and to select those formulations that may minimally endanger or even protect the cardiovascular system of the woman.

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Contraception in Women with Rheumatologic Disease and After Organ Transplantation

19

Jan Brynhildsen

19.1 Rheumatoid Arthritis

The prevalence of rheumatoid arthritis (RA) in women is between 0.2 and 1% of the population [7]. As most autoimmune disease, RA is predominant in the female population. Active disease at conception most often continues to be active during pregnancy and might even increase the risk for a postpartum flare [6], and consequently women with RA should be encouraged to use highly effective contraceptive methods. Most studies concerning effectiveness and safety of contraception in relation to RA have focused on oral contraceptives (OC). A systematic review [8] concluded that use of oral contraception, both combined hormonal methods (CHC) and progestin-only methods, was unlikely to affect RA disease progression; however these conclusions were based mainly on old studies of low quality.

Because inflammation may affect the risk of thromboembolism, several studies have investigated the relation between RA and deep venous thromboembolism (DVT). There is a consistency between studies that patients with RA have an approximately twofold increased risk of venous thromboembolism [9–12]. This seems to be true also for other rheumatologic diseases such as psoriatic arthritis and Sjögren's syndrome [10, 13]. In general, this increase can be considered as small and from a contraceptive counselling point of view nonsignificant. It may, however, be of significance if other relative contraindications are present.

Patients with RA have an increased risk of developing osteoporosis and fractures [14, 15]. It is today unsure if this risk is increased by the use of corticosteroids [16]. Use of depot medroxyprogesterone acetate (DMPA) should not be recommended to women with an increased risk of osteoporosis [17]. As the use of DMPA might be

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followed by a reduction in bone mineral density [18], use of DMPA is not recommended to women with RA.

19.2 Systemic Lupus Erythematosus (SLE)

Women with SLE constitute a high-risk pregnancy group [5], and optimally pregnancies should be planned and disease activity low in order to minimize the risk for both mother and fetus.

Pregnancy-related risks, as DVT risk, increase already during early pregnancy [19] and may lead to an increased risk for the SLE patient even if there will be a termination of pregnancy. Consequently, safe and high effective contraception is of outmost importance for this group of women.

Use of CHC may initiate or exacerbate manifestations of SLE [20] and was for long considered as contraindicated. These effects are dependent of the estrogen component in CHC and seem to act in a dose-dependent way. Use of progestin-only methods can be safely used by women with SLE.

In the beginning of the twenty-first century, however, questions were raised whether women with SLE could safely use low-dose CHC. Two randomized controlled trials (RCTs) were undertaken and published in 2005 [21, 22]. The first trial [21] compared use of three different methods: combined OC (COC), progestogen-only contraceptive Pills (POP), and copper intrauterine devices (Cu-IUDs). There were no differences in disease activity or use of medication over 1 year. No exacerbations of SLE symptoms were noted in the COC group. Neither was there any difference in the occurrence of DVT, but notably there were four DVTs (two in COC user, two in POP users) in 162 patients which give an annual incidence of 246/10,000/year which is considerably higher than usually reported during CHC use in healthy women.

A second RCT [22] was undertaken in the USA [21] where women with SLE were double-blindly randomized to either a COC or placebo. There were no differences in lupus flares or DVT between the groups.

The conclusion from these two studies has usually been that CHC can be used by women with stable or inactive SLE and with low risk of DVT [23]. However, it must be noted that in the second RCT (the SELENA study [22]), the patients were strongly selected as patients with high titers of anticardiolipin antibodies, lupus anticoagulant, or a history of DVT were excluded.

Presently, guidelines [5, 23] state that CHC can be safely used in women with low disease activity not positive for antiphospholipid antibodies. However, from a contraceptive counsellor's point of view, other methods seem to be better and safer alternatives (Table 19.1). Firstly, it is today well known that use of LARC offers higher efficacy, fewer unwanted pregnancies, and more satisfied users than CHC. LARC can also be used safely by SLE patients. Moreover, in most settings, the counsellor might not have access to all relevant information on the disease activity in the SLE patient which is a prerequisite for prescription and use of CHC. Therefore, the SLE patient in the first place should be recommended LARC,

Table 19.1 Overview of contraceptive methods and recommendations in persons with RA or SLE

Method	Recommendation	Comment
LARC		
Copper IUD LNG-IUD Progestin implant	Recommended Recommended Recommended	• First choice. Highly effective • Can be used safely by women with rheumatic disease including SLE
Progestin-only pill	Recommended (second choice)	• Can be used safely by women with rheumatic disease including SLE • Lower efficacy than LARC
Combined hormonal methods	Relative contraindication	• Can be used safely by women with RA or other rheumatic disease (except SLE) • Might exceptionally be used by women with SLE, stable disease, and no anticardiolipin antibodies and no other cardiovascular risk factors. Collaboration with rheumatologist recommended and most often needed
DMPA	Relative contraindication	• Should be avoided due to negative effects on bone mineral density
Diaphragm Condom Fertility awareness-based methods	Safe Safe Safe	• Methods with higher efficacy should be recommended in the first place

secondly other progestin-only methods, and thirdly, if no such method could be accepted, in collaboration with the responsible rheumatologist, CHC could be considered.

19.3 Organ Transplantation

Most female transplant patients are sexually active, and ovulation and menstruation usually resume within months after transplant surgery [24–26]. Coordination of sexual and reproductive health care between other specialists and staff dealing with contraceptive counselling and/or prescription may minimize unintended pregnancy and optimize the safety of intended pregnancy among transplant patients. The unintended pregnancy rate among transplant patients has been reported as high as 93% and the rate of contraceptive use only 48–72% [27]. To reduce the risks of unintended pregnancy and to address the unmet need for contraception, contraception must be incorporated into the clinical care of transplant patients [28].

Clinical studies of contraception in transplant patients are limited in both number and size. So far, we have to rely on case series and small prospective studies. For all patients, the underlying condition as well as ongoing medication must be taken into consideration. When choosing appropriate contraception, comorbidities and medications must be considered along with the patient's clinical status. Certain risks of medical conditions can influence choice of contraceptive method, for example, hypertension or an increased risk of venous thromboembolism which precludes use

of exogenous estrogen. Immunosuppressive therapies may affect or be affected by contraceptive hormone metabolism.

Renal and liver transplant patients using combined hormonal contraception for more than 12 months did not become pregnant and maintained stable transplant functions [29, 30]. However, in one of these studies, antihypertensive regimens (sic!) did require adjustment in some patients, and two patients discontinued the pill because of lower extremity thromboembolism and acute graft rejection. Consequently, combined hormonal contraception should be considered as contraindicated for women with complicated solid organ transplants [23]. On the other hand, women with complicated solid organ transplants, defined as acute or chronic graft failure, rejection, or cardiac allograft vasculopathy, may safely initiate progestin-only methods such as the progestin implant, progestin injection, and progestin pills. LNG-IUS can also be recommended as more recent case series report high contraceptive efficacy and safety, with no unintended pregnancies or pelvic infections [31, 32]. Most probably also Cu-IUDs can be safely used as Cu-IUD has been shown to be both safe and effective in the immunosuppressed population [33].

19.4 Hematopoietic Stem Cell Transplantation

The hematopoietic stem cell transplantation (HCT) patient means several challenges with regard to contraceptive choice and gynecological treatments. Most often the underlying condition may be a malignant disease with associated risk of thromboembolism [34]. But also thrombocytopenia-associated menorrhagia may be a consequence of the conditioning regimen for HCT.

The conditioning treatment usually results in pancytopenia. The thrombocytopenia may in women of fertile ages result in profound menstrual blood loss, and menstrual suppression is considered as needed [35]. Even though the absolute majority of HCT patients lose fertility due to the conditioning treatment, effective contraception is required in order to avoid the small but existing risk of pregnancy both during and after treatment. These two requirements can favorably be combined into one single treatment. Because of the increased VTE risk, combined hormonal methods should be avoided. Cu-IUDs should not be used because of the risk of profound uterine bleeding. Instead, progestin-only methods with high likelihood of amenorrhea should be the methods of choice [35].

LNG-IUS, implants, or injectables that the woman already uses before treatment can continue. However, caution for deep intramuscular injection may be advisable. Caution with initiation of progestin-only methods close to treatment may as well also be recommended because of common irregular bleeding pattern. High-dose progestin-only methods with a high probability of amenorrhea should be recommended in the first place before treatment starts.

Although infertility is common after HCT, contraception is advisable if fertility status is unknown, pregnancy is not advised, or the women do not have any pregnancy wish. If the VTE risk and risk of profound bleeding are considered as low, the woman can use any method if no other contraindication is present.

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Drug Interactions with Contraceptives

20

Milo Gatti and Fabrizio De Ponti

20.1 Drug Interactions: Pharmacological Considerations

Drug interaction is defined as a clinical meaningful alteration in the effect of one drug (*object drug*) as a result of co-administration of another (*precipitant drug*) [1]. Although some drug interactions may be used for therapeutic benefit, usually interactions may increase or inhibit the effects of a drug, leading, respectively, to toxicity or a diminished therapeutic efficacy [1]. The probability of any drug interaction increases on the basis of the number of agents used [2]. Drug interactions may represent a major issue at any age in life, and up to 7% of hospital admission to medical wards and prolonged hospital stays are caused by serious drug interactions [3].

Drug–drug interactions may broadly be categorized as *pharmacokinetic* or *pharmacodynamic* [2]. Pharmacokinetic (PK) interactions occur when the exposure of the object drug is modified by the precipitant agent and may be caused by changes in absorption, distribution, metabolism and elimination. Conversely, pharmacodynamic interactions occur when medications cause additive, synergistic or antagonistic pharmacological effects influencing efficacy or leading to adverse effects [2]. The inhibition or induction of the activity of cytochrome P450 (CYP450) enzymes and the influence on transporters represent generally the most common and important mechanisms of drug interactions [2, 4].

An overview of the main pharmacokinetic mechanisms causing drug interactions is provided in the next section.

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Absorption
Three distinct mechanisms may be responsible for absorption-related drug interactions: (i) absorption may be affected by chelation with a cation (calcium or iron); (ii) changes in gastric pH may impair the absorption of agents requiring low gastric pH for dissolution; (iii) first-pass intestinal metabolism may be affected by inhibition or induction of CYP450 enzymes (especially the CYP3A4 isoform, representing almost 80% of CYPs expressed in small intestinal mucosa) or the P-glycoprotein (P-gp) efflux transporter in the intestinal epithelium [2]. Drugs affecting first-pass metabolism play an important role in interactions concerning hormonal contraceptives; particularly the induction of intestinal CYP3A4 may lead to reduced hormone levels and consequently impaired efficacy.

Distribution
Distribution of agents to the sites of action is mediated by drug influx and efflux transporters and influenced by protein binding, as only the free fraction is able to penetrate across tissue membranes [2]. Drug interactions may be caused by interference with different transporters or protein binding displacement. Protein binding displacement shows clinical relevance when the two drugs are highly protein bound (as in the case of hormonal contraceptives that have >90% binding protein), competing for the same binding site, and one of them has a low volume of distribution and narrow therapeutic window.

Metabolism
Metabolic interactions are mostly caused by CYP450 isoforms, a superfamily of microsomal enzymes playing a major role during phase I liver reactions [2]. Food, environmental features, other drugs and genetics influence cytochrome activity and consequent drug metabolism [2]. Medications interacting with the CYP450 pathway may be classified as substrates, inhibitors or inducers. Inhibitors may be further subdivided into weak, moderate or potent [2]. A summary of the main inhibitors and inducers for each CYP450 isoform is provided in Table 20.1. Glucuronidation, a phase II metabolic reaction, may be involved in clinically relevant drug interactions caused by inhibition or induction of this process.

Elimination
Inhibition of influx or efflux transporters in renal cells may impair tubular reabsorption or secretion of different medications, leading to enhanced or decreased clearance.

20.1.1 Clinical Relevance of Drug–Drug Interactions

Drug interactions should be considered clinically relevant if they lead to modified efficacy or increased toxicity and adverse effects [2]. A potential drug interaction is an occurrence in which two drugs known to interact are concurrently prescribed, regardless of the onset of adverse events [2].

Table 20.1 Summary of the most important inducers and inhibitors of CYP450 (+ weak; ++ moderate; +++ strong inhibition)

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5
Inhibitors				
Ciprofloxacin +++ Levofloxacin + Amiodarone + Fluvoxamine +++	Amiodarone ++ **Fluconazole +++**	Fluoxetine + Omeprazole ++	Fluoxetine +++ Paroxetine +++ Amiodarone + Quinidine +++	**HIV protease inhibitors +++** **Clarithromycin +++** **Azole antifungals +++** Verapamil ++ Amiodarone + Diltiazem +
Inducers				
Tobacco smoke + Omeprazole +	**Rifampicin +++**	–	–	**Carbamazepine +++** **Efavirenz +++** **Nevirapine ++** **Etravirine ++** **Phenobarbital +++** **Phenytoin +++** **Rifampicin +++**

Relevant drug interactions with hormonal contraceptives are highlighted in bold. (Adapted from [8])

Although it was known since the 1970s that drug interactions could lead to serious clinical adverse events, only in 1997 was the first guidance regulatory document to industry on the conduct of premarketing drug metabolism and drug interaction studies drafted [2, 5, 6]. This occurred as a consequence of reports of sudden cardiac death in patients treated concurrently with terfenadine (able to prolong QT interval causing torsade de points) and ketoconazole (a strong inhibitory of CYP450 activity, leading to toxic plasma levels of terfenadine) [7]. Despite a large number of potential drug interactions are detected in vitro or in studies performed in healthy volunteers, predicted interactions lead to discernible toxicity or therapeutic failure only in few cases [2]. Actually, there is no consistent rating system to assess the severity and likelihood of potential drug–drug interactions, leading to a lack of consensus on decision whether to change therapy [2]. Only few drug–drug interactions may be considered clinically relevant, resulting in serious and life-threatening adverse events or in therapeutic failure. The concept of *interaction iceberg* can be put forward to underline the fact that in a real-world setting, clinically relevant drug interactions occur only when several concomitant factors concur in increasing the actual risk bypassing the "filters" encountered at each stage from the bottom (where potential drug interactions are found) to the top (where actual interactions are listed; Fig. 20.1).

The clinical relevance of a potential drug interaction depends on several factors, including the pharmacokinetic/pharmacodynamic relationship, the therapeutic index of the object drug, the proportion of the object drug affected by the specific metabolic, elimination or transport pathway that is inhibited or induced by the precipitant agent and pharmacogenomics issues (poor or extensive metabolizers of the different CYP450 isoforms are common in world population) [2]. Increased or

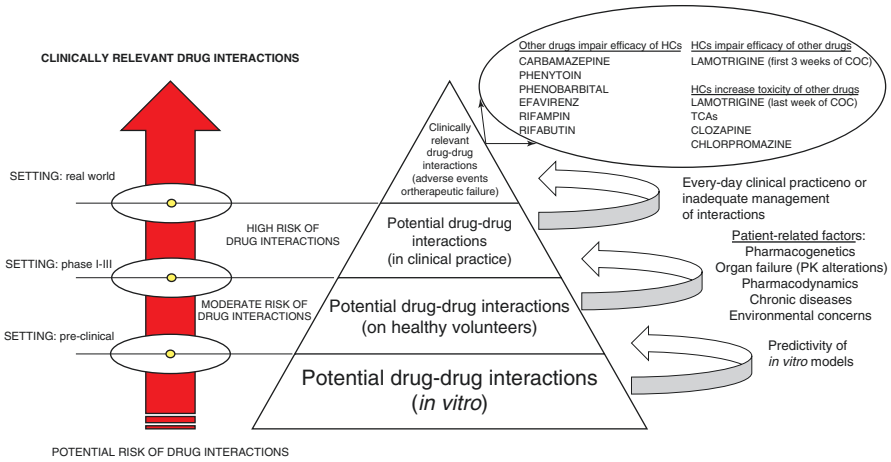

Fig. 20.1 The "interaction iceberg". Only some drug–drug interactions have clinical importance: in a real-world setting, clinically relevant drug interactions occur only when several concomitant factors concur in increasing the actual risk bypassing the "filters" encountered at each stage from the bottom (where potential drug interactions are found) to the top (where actual interactions are listed). Examples of those involving HCs are shown

decreased plasma concentrations of the object drug may be considered clinically relevant for agents characterized by narrow therapeutic window and subjected to rapid metabolism [8].

The clinical relevance of any drug interaction is closely dependent on the duration of treatment with the precipitant agent. For short-term therapies (e.g. antibiotic prophylaxis for dental procedure with once-only amoxicillin or a macrolide), the probability of affecting the bioavailability of the object drug (i.e. hormonal contraceptives – HCs) is very scarce. Conversely, for long-term (e.g. anticoagulants for management of deep vein thrombosis or rifampicin in tuberculosis) and lifelong treatments (e.g. anticonvulsant or antiretroviral agents), the risk of occurrence of clinically relevant drug interactions is higher. These different scenarios must be considered in the management of a woman treated with hormonal contraceptives.

Substitution of drugs with the same therapeutic indications or within the same drug class that are metabolized by different isozymes or separate pathways may be useful strategies to avoid potential interactions. When substitution is not feasible, careful dosing adjustment can minimize drug interactions [2].

20.1.2 Drug–Herbal Interactions

Use of herbal preparations and complementary and alternative medicine therapies is common across the globe, with no substantial difference among countries [9, 10]. In the USA, the use of herbal products is reported in approximately 20% of women of reproductive age [11]. Despite popular belief, herbal preparations and

complementary medicine therapies (food, micronutrients and dietary supplements) are not completely harmless and may affect the pharmacokinetics and pharmacodynamics of co-administered conventional drugs, leading to enhanced toxicity or therapeutic failure [12]. The most important causes of clinically relevant herbal-drug interactions are inhibition or induction of the activity of intestinal and hepatic CYP450 and influence on transporters with consequently potential alterations in absorption, distribution, metabolism and elimination of conventional drugs [12, 13].

It is important to recognize that the most clinically relevant drug–food and drug–herbal interactions are not limited to co-administration of grapefruit juice or the Saint John's wort herbal extract, but several other over-the-counter products may cause severe and life-threatening events [13]. Examples of herbal and dietary supplement capable to produce interactions with conventional drugs are provided in Table 20.2.

Table 20.2 Summary of over-the-counter products causing clinically relevant interactions with conventional drugs

Over-the-counter products	Interaction mechanisms	Clinical consequences
Fruits-vegetables-juices-other beverages		
Grapefruit—grapefruit juice—fruit derived from grapefruit (Seville orange, lime, pomelo) (*Citrus paradise—Citrus sinensis*)	Inhibition of metabolism of drugs by CYP3A4 with increasing in peak plasma concentrations	**Estrogen and progestin plasma levels may be higher and lead to enhanced toxicity** Caution with the use of oral drugs with low bioavailability (<50%) due to an extensive first-pass intestinal metabolism Risk is significant when the interval between the consumption of grapefruit and drug intake is less than 4 h
Cranberry juice (*Vaccinium macrocarpon*)	Inhibition of CYP3A4 and CYP2C9	**Estrogen and progestin plasma levels may be higher and lead to enhanced toxicity** Caution with warfarin (eight cases of bleeding) and midazolam (one case of drowsiness)
Herbal medicines		
Gingko (*Ginkgo biloba*)	Inhibition of CYP2C9 Platelet anti-aggregant activity	**Ethinylestradiol and desogestrel plasma levels may be higher and lead to enhanced toxicity** Increased bleeding risk with warfarin and nonsteroidal anti-inflammatory drugs
Garlic (*Allium sativum)*	Inhibition of intestinal first-pass extraction	**Estrogen and progestin plasma levels may be higher and lead to enhanced toxicity** Caution with warfarin (increased risk of bleeding) and saquinavir (loss of efficacy)

(continued)

Table 20.2 (continued)

Over-the-counter products	Interaction mechanisms	Clinical consequences
Echinacea (*Echinacea purpurea*)	Induction of intestinal and hepatic CYP3A4	**Potential decreased efficacy of HCs** Increased clearance of drugs metabolized by CYP3A4
St. John's wort (*Hypericum perforatum*)	Strong dose-dependent induction of intestinal and hepatic CYP1A2 – 2C9 – 3A4 – 2E1 and P-gp	**Decreased efficacy of HCs** Increased risk of therapeutic failure with drugs metabolized via CYP450
Ginseng (*Panax ginseng*)	Decreased intestinal warfarin absorption	**Use of HCs containing estrogen may enhance the risk of thrombotic events** Impairment of efficacy (warfarin) and increased risk of thrombotic effects
Goldenseal (*Hydrastis canadensis*)	Strong inhibitor of CYP2D6 and CYP3A4	**Ethinylestradiol and progestins plasmatic levels may be higher and lead to enhanced toxicity** Increased risk of toxicity with concomitant drugs metabolized via CYP450
Salvia (*Salvia officinalis*)	Inhibition of CYP2C9	**Ethinylestradiol and desogestrel plasmatic levels may be higher and lead to enhanced toxicity** Increased risk of bleeding with warfarin
Micronutrients and dietary supplements		
Calcium	Hypercalcemia	Avoid combination with digoxin
Calcium, iron, magnesium, zinc, aluminium	Chelation and reduced bioavailability of different drugs	Avoid combination with tetracyclines, fluoroquinolones and bisphosphonates
Tyramine	Enhanced activity in case of inhibition of MAO and increasing risk of life-threatening hypertensive crisis	Avoid combination with linezolid and antidepressants inhibiting MAO
L-Tryptophan	Precursor of serotonin	Increased risk of serotoninergic syndrome in combination with selective serotonin reuptake inhibitors
Vitamin B6	Pharmacodynamic stage impaired	**Decreased efficacy of oral contraceptives**

Relevant interactions with hormonal contraceptives are highlighted in bold. (Data retrieved from [12, 13])

Interactions between over-the-counter products and conventional drugs are probably underreported. Although the use of herbal products is rapidly increasing, there are only few national surveillance systems monitoring and evaluating adverse reactions associated with their use [12]. Pharmacovigilance studies are essential in order to assess safety profile and clinical relevance of interaction with conventional drugs.

20.2 Hormonal Contraceptives: Pharmacological Classification, Pharmacokinetic Issues and Impact on Drug–Drug Interactions

HCs represent one of the most common prescription classes of medications used by women of reproductive age, playing an unequivocal role in improving contraceptive efficacy and minimizing the risk of unintended pregnancies [14]. Despite the high efficacy of HC, almost 0.2–0.3% of women experience an unintended pregnancy within the first year even when usage "follows the book" [15]. Drug–drug interactions involving HCs could partially explain the impaired efficacy reported in real-life setting, so it is important to underline the pharmacokinetic issues of the different types of HC and the relationship with the mechanisms of drug interactions.

Several formulations of HCs are currently available, including either a progestin alone or a combination of estrogen and progestin, and characterized by different PK features depending on the drug used and the route of administration. PK features may explain the different likelihood for an interaction with each HC method. Drug–drug PK interactions may depend on alterations in absorption, distribution, metabolism or elimination causing impaired efficacy or toxicity of hormonal contraceptives, although the role of intestinal and hepatic first-pass metabolism represents the main issue. An overview of the different potential sites of drug interactions involving hormonal contraceptives is provided in Fig. 20.2.

HCs may be responsible for bidirectional drug interactions, which may influence effectiveness and safety of both contraceptives and concomitant drugs. Currently,

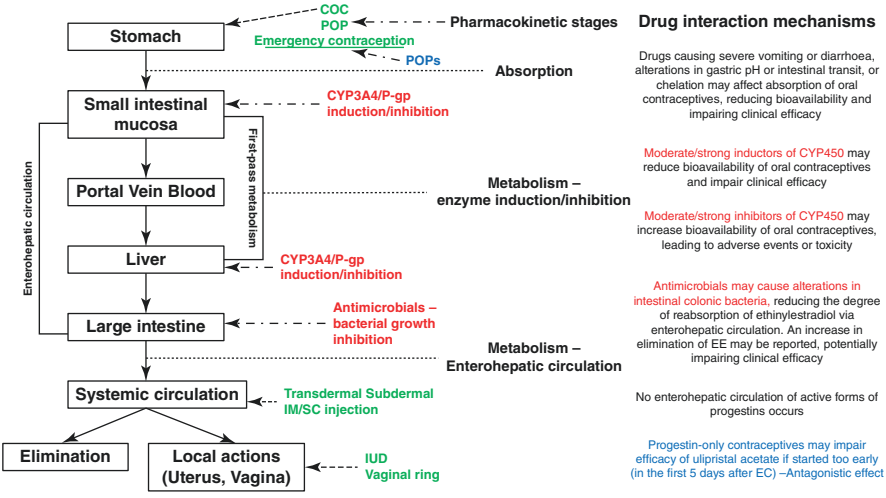

Fig. 20.2 Pharmacokinetic features of different administration routes of hormonal contraceptives and site of potential drug–drug interactions. Green, different routes of administration; red and blue, respectively, mechanisms of PK and PD drug interactions. *COC* combined oral contraceptive, *POP* progestin-only pill, *IM* intramuscular, *SC* subcutaneous, *IUD* intrauterine device; *P-gp* P-glycoprotein, *EE* ethinylestradiol. (Adapted from [71])

HC methods approved by the Food and Drug Administration (FDA) and European Agency of Medicines (EMA) included at least ten categories, of which eight are reversible contraceptive methods and two are emergency contraceptive methods (Table 20.3) [16].

Table 20.3 Classification and pharmacological consideration on different methods of HC approved by the FDA and the EMA. (Adapted from [16])

Hormonal contraceptives	Route of administration	Dosing frequency	Pharmacological consideration
Combined oral contraceptive (COC)	Oral	A pill every day for a complete cycle of 28 days (placebo in the fourth week)	First-pass metabolism with inter- and intra-variability in bioavailability **Higher risk of drug interactions compared to nonoral route**
Progestin-only pills (POPs)	Oral	A pill every day at the same daytime for a complete cycle of 28 days (placebo in the fourth week)	First-pass metabolism with inter- and intra-variability in bioavailability **Higher risk of drug interactions compared to nonoral route. Low-dose progestin in POPs may be responsible for contraceptive failure in concomitant treatment with moderate or strong inducers of CYP450**
Levonorgestrel 1.5 mg – emergency contraception	Oral	Within 3 days after unprotected intercourse	First-pass metabolism with inter- and intra-variability in bioavailability **Relevant drug interactions may occur only in case of ongoing long-term treatments with moderate or strong inducers of CYP450**
Ulipristal acetate – Emergency contraception	Oral	Within 5 days after unprotected intercourse	First-pass metabolism with inter- and intra-variability in bioavailability **Relevant drug interactions may occur only in case of ongoing long-term treatments with moderate or strong inducers of CYP450**
Contraceptive patch – ethinylestradiol/ norelgestromin	Dermal	Put on a new patch each week for 3 weeks (21 total days). No patch during the fourth week	Similar to COC, but gastrointestinal absorption and first-pass metabolism is avoided. Following the first application of the patch, serum hormone levels increase gradually over the first 48–72 h reaching a plateau and then remain constant up to 21-day period **High risk of drug interactions with strong inducers of CYP450**

Table 20.3 (continued)

Hormonal contraceptives	Route of administration	Dosing frequency	Pharmacological consideration
Levonorgestrel-releasing intrauterine devices (LNG-IUDs)	Intrauterine	Up to 3–5 years according to the type	Lack of gastrointestinal absorption and first-pass metabolism. Contraceptive activity mainly at local level **Lower risk of relevant interactions compared to oral route**
Etonogestrel implant	Subdermal	Up to 3 years	Lack of gastrointestinal absorption and first-pass metabolism **Lower risk of relevant interactions compared to oral route, but higher with respect to parenteral HCs or LNG-IUDs**
Depot medroxyprogesterone acetate (DMPA)	Intramuscularly	Every 3 months	Lack of gastrointestinal absorption and first-pass metabolism **Lower risk of relevant interactions compared to oral route**
Vaginal contraceptive ring – ethinylestradiol/ etonogestrel	Vaginal	3 weeks	Similar to COC, avoiding gastrointestinal absorption and first-pass metabolism. Serum hormone levels increase immediately after ring insertion and then decrease slowly over the cycle **High risk of drug interactions with strong inducers of CYP450**

Intestinal and hepatic first-pass metabolism may lead to profound PK variations of oral contraceptives, involving absolute and relative bioavailability, resulting in wide and different levels of steroids that reach systemic circulation and sites of action. After ingestion, steroids enter the stomach and undergo dissolution. The dissolved drugs pass into the intestine where they are subjected to transformation by bacterial enzymes and enzymes in the intestinal mucosa (especially CYP3A4). The mixture of metabolized and unmetabolized drug passes the intestinal mucosa and through the portal vein blood reaches the liver [17]. At this stage, estrogens and progestins undergo additional phase I and II metabolic reactions, mainly via CYP450 and glucuronidation pathways, before reaching systemic circulation. Extensive first-pass metabolism mediated by intestinal and/or hepatic CYP450 is a key stage of metabolic pathway of oral contraceptives, leading to potential occurrence of drug–drug interactions with concomitant agents (conventional drugs, herbal products, dietary supplements) [17]. On the contrary, administration of HCs via nonoral routes effectively bypasses first-pass metabolism, thereby avoiding possible drug interactions occurring at this stage.

Apart from few exceptions, the estrogenic component of virtually all currently marketed HCs (combination oral contraceptive, transdermal patch and vaginal ring) consists of ethinylestradiol (EE) [17]. EE is absorbed from the stomach and the upper intestine during the first hour after ingestion, reaching peak concentration after 1–2 h in most women, despite that wide variability is reported [17]. EE is subjected to intestinal and hepatic metabolism (first-pass metabolism), where the 2-hydroxylation catalysed by the hepatic CYP3A4 and CYP2C9 is the most important metabolic pathway. EE is then rapidly conjugated in part to an inactive glucuronide via glucuronosyltransferase isoenzymes (UGT1A1) and is subjected to renal elimination, and in part to sulphate metabolites, which may partially deconjugate during enterohepatic recirculation to EE, adding to the active circulating levels of EE [17]. Bioavailability and elimination half-life show wide intra- and inter-variability between women, ranging from 25% to 65% and from 6 to 27 h, respectively [17]. Intestinal and hepatic first-pass metabolism plays a key role in establishing bioavailability of EE, while enterohepatic recirculation may affect elimination half-life. While oral administration of EE shows a peak-trough fluctuating pattern in serum levels, transdermal and vaginal dosing are not affected by first-pass metabolism, leading to more constant levels [17].

Progestins contained in HCs may be classified into four generations based on chemical structure (related to progesterone or testosterone). They present larger inter- and intra-variability in metabolism, blood levels and pharmacokinetic parameters [17]. Many of the progestins used for oral contraception are prodrugs requiring to be metabolized for activation [17]. They are subjected to intestinal and hepatic first-pass metabolism and are well absorbed, although differences in bioavailability among different progestins are reported. The major metabolic transformation consists in reduction via CYP3A4. Successively, the unreduced and reduced progestins are subjected to hydroxylation and conjugation to form sulphates or glucuronides, which will be eliminated by the kidney [17]. Norethindrone and dienogest have relatively low half-lives, ranging from 8 to 12 h, while cyproterone acetate shows the longest half-life (50–80 h), followed by drospirenone (almost 30 h) [17]. Other progestins show half-life ranging from 12 to 24 h [17, 18]. A summary of pharmacokinetic parameters of EE and progestins, with a focus on the role of CYP450 in their metabolism, is provided in Table 20.4.

Emergency contraception includes levonorgestrel and ulipristal acetate. Levonorgestrel is a synthetic progestin available in a single dose of 1.5 mg for emergency contraception [19]. It does not undergo first-pass metabolism and has 100% bioavailability [19]. Levonorgestrel is highly protein bound (almost 99%), and any displacement to the bound protein could potentially lead to adverse events (drug–drug interactions with other highly bound agents) [19]. It is metabolized by CYP450 and metabolites are excreted in urine and faeces (terminal half-life almost 24 h).

Ulipristal acetate is a selective progesterone receptor modulator, available in a single dose of 30 mg [19]. It is highly bound to plasma proteins (>98%), including albumin, and it is metabolized by hepatic CYP3A4 [19]. Ulipristal acetate has a terminal half-life of almost 30 h. Induction or inhibition of the activity of CYP450 with ulipristal administration is not reported; however it may be a strong inhibitor

Table 20.4 Summary of pharmacokinetic aspects of HCs. (Adapted from [32, 35]; data retrieved from [17])

Hormonal contraceptive	Available delivery routes	Bioavailability	Protein binding	Clearance	CYP substrate	CYP inhibitor	CYP inducer	UGT1A1
Estrogen								
Ethinylestradiol	Oral Transdermal Vaginal ring	25–65% (oral)		Urine Faeces	3A4 2C9 *Minor pathway* 1A2, 2C19, 3A5	2B6 2C19 3A4 (only in vitro)	2A6 (only in vitro)	Substrate Inducer
Estradiol valerate	Oral	3–5% High first-pass metabolism (>95%)	97–98%	Urine (90%)	3A4, 1A2, 2C8, 2C9, 3A5	1A2 (unknown strength)	3A4 (unknown strength)	Substrate
Progestins								
First generation: derived from 17-hydroxyprogesterone or testosterone								
Medroxyprogesterone acetate	IM SC	100%		Faeces	3A4	–	3A4 (almost 25%)	–
Norethisterone	Oral	49–73%	>95%	Urine	3A4	2C9 (weak and only in vitro) 3A4 (modest)	–	Substrate
Second generation: derived from testosterone								
Levonorgestrel	Oral IUD Subdermal	100% (no first-pass metabolism)	98.5%	Urine Faeces	3A4	3A4 2C19 (weak and only in vitro)	-	Substrate (minor)
Norgestrel	Oral	100%	>98%	Urine Faeces	3A4	–	–	–

(continued)

Table 20.4 (continued)

Hormonal contraceptive	Available delivery routes	Bioavailability	Protein binding	Clearance	CYP substrate	CYP inhibitor	CYP inducer	UGT1A1
Third generation: derived from levonorgestrel								
Desogestrel	Oral	70% prodrug converted to etonogestrel	96–99%	Urine Bile Faeces	2C9 (only data in vitro)	–	–	Substrate
Etonogestrel	Vaginal ring Subdermal	70%	96–99%	Urine	3A4	3A4 (weak and only in vitro)	–	Substrate
Gestodene	Oral	99%	98–99%	Urine Bile	3A4	3A4 (potent in vitro – no clinical relevance at usual doses)	–	–
Norgestimate	Oral	95–100% prodrug converted to norelgestromin and norgestrel	>97%	Urine Faeces	3A4	3A4 (weak and only in vitro)	–	–
Norelgestromin	Transdermal	95–100% undergoes hepatic metabolism to norgestrel	>97%	Urine Faeces	3A4	–	–	–
Fourth generation: non-ethylated estranges (antiandrogen and antimineralocorticoid activity)								
Drospirenone	Oral	76–85%	95–97%	Urine Faeces	3A4 (minor)	3A4 2C19 1A1 2C9 (in vitro – not relevant)	–	–

IM intramuscular, *SC* subcutaneous, *IUD* intrauterine device, – available data show no inducing or inhibitory activity on CYP450 or UGT1A1

of P-gp at clinically relevant concentration [19]. Pharmacodynamic interactions between ulipristal acetate and progestin-containing HCs are reported [19]. Quickly starting hormonal contraceptives after ulipristal acetate administration may reduce effectiveness of emergency contraception. Hormonal contraception may not be started until 12 days following ulipristal acetate administration, as reported in the Summary of Product Characteristics (antagonistic pharmacodynamic interactions between progestins and ulipristal) [19].

20.3 Clinically Relevant Drug Interactions Involving HCs

Several classes of drugs may potentially interact with HCs, leading to enhanced toxicity caused by higher estrogen and progestin plasma concentrations or impairment of efficacy and occurrence of unintended pregnancies. Women of reproductive age requiring HCs may face different scenarios with specific concerns to be addressed.

First, it is expected that strong or moderate inducers of CYP3A4, namely, carbamazepine, phenytoin, phenobarbital, efavirenz, rifampicin and St. John's wort (see Table 20.1), may lead to clinically relevant interactions and affect efficacy of HCs.

Second, women of reproductive age may require therapeutic management with drugs able to cause teratogenicity (e.g. isotretinoin, carbamazepine, valproate, phenytoin, warfarin). In this case, effective contraceptive strategies must be provided to these patients, in order to avoid the consequences of unintended pregnancies. Clinicians should be aware of potential efficacy-impairing drug interactions between teratogenic agents and HCs. Particularly, different antiepileptic drugs with teratogenic potential (carbamazepine and phenytoin) are also strong inducers of CYP3A4. It is important that clinicians manage potential interactions, prescribing agents having lower teratogenic risk or unable to interact with hormonal contraceptives whenever possible. In case a teratogenic agent with strong or moderate induction activity on CYP3A4 cannot be withdrawn, alternative contraceptive methods must be implemented.

Third, women of reproductive age may be affected by different disease conditions requiring long-term or lifelong treatment. Indeed, several chronic diseases may lead to organ failure and consequently increase the risk of clinically relevant drug interactions. Epileptic disorders, tuberculosis, HIV infection and psychiatric illnesses are common worldwide, with women of reproductive age representing a non-negligible subgroup. Different therapeutic strategies may be implemented in low- and middle-income countries, based on the difference in drug access (see below Sect. 22.3 concerning HIV treatment). Women living in developing countries may have limited access to alternative compounds characterized by reduced teratogenic risk or relevant interactions with HCs. Therefore, long-term or lifelong treatments lead to higher risk of drug–drug interactions, particularly when inducers of CYP450 are chronically utilized.

Finally, drug interactions may be bidirectional, and HCs may impair the efficacy or lead to severe toxicity of concomitant drugs. Poor control of the underlying diseases may be an occurring risk.

It is important to underline that the most important and relevant drug interactions involving HCs are caused by agents raising one or more of the concerns listed above. For example, carbamazepine and phenytoin are strong inducers of CYP3A4 and may lead to teratogenic events, and a long-term treatment is required with these agents. A second example, efavirenz, exhibits the same issues: lifelong treatment, strong induction of CYP3A4 and a non-negligible teratogenicity. Finally, treatment including rifampicin and rifabutin is required for several months, and the agents are strong inducers of CYP3A4. High risk of relevant drug interactions affecting contraceptive efficacy is expected in women of reproductive age treated in these settings.

20.3.1 Antiepileptic Agents

Epilepsy may have major impacts on several important aspects of life. The severity of the diseases ranges from good seizure control up to absence of seizures, to a debilitating disease requiring polytherapy that may lead to severe adverse events and drug interactions [20]. Antiepileptic agents are widely used, not only as standard treatment of epilepsy but also in the management of several non-epileptic disorders, including neuropathic pain, generalized anxiety disorders, fibromyalgia, migraine prophylaxis and bipolar spectrum disorders [21]. In many countries, women of reproductive age constitute the majority of users of anticonvulsants [22].

Because of the long-term nature of epilepsy and non-epileptic disorders requiring antiepileptic agents, the treatment is continued for many years and commonly for a lifetime. Consequently, patients will use several medications for the management of concurrent or intercurrent disorders, leading to higher risk of pharmacokinetic and pharmacodynamic drug interactions [23]. Clinicians should be aware that women in reproductive age taking hormonal contraceptives and requiring antiepileptic agents may experience bidirectional drug interactions, resulting in unintended pregnancy or increased seizure activity [24]. Although drug interactions involving hormonal contraceptives are well-established with the concomitant use of older antiepileptic agents, interactions may occur also with the use of second-generation anticonvulsants [25]. Failure rate with oral contraceptives is higher in women affected by epilepsy in comparison to healthy subjects (3–6% vs. 1%), and lack of efficacy of hormonal contraceptives is the cause of one in four unplanned pregnancies in women taking antiepileptic agents [26, 27]. Contraceptive inefficacy may represent a critical issue for women treated with anticonvulsant drugs, considering their teratogenic potential. Consequently, it is important to prevent the occurrence of clinically relevant drug interactions between hormonal contraceptives and antiepileptic agents. A brief overview of the potential bidirectional drug interactions between hormonal contraceptives and antiepileptics is provided in Table 20.5.

20.3.1.1 Effects of Antiepileptic Agents on HCs

"First-generation" antiepileptic agents including carbamazepine, phenobarbital, phenytoin and primidone are strong enzyme inducers enhancing the metabolism of both ethinylestradiol and progestins. These drugs cause also an increased amount of

Table 20.5 Bidirectional drug interactions (DDIs) between HCs and antiepileptic agents (AEDs) (green, reported no interaction; yellow, some concerns with concomitant use and increased risk of treatment failure; red, avoid concomitant use; grey, no available data; COCs, combined oral contraceptives; POPs, progestin-only pills; LNG-IUD, levonorgestrel-releasing intrauterine device). (Data retrieved from [23–25])

Antiepileptic agents	Reduction in Ethinylestradiol serum levels caused by AED	Reduction in Progestins serum levels caused by AED	Reduction in AED serum levels caused by HC	Route of HCs administration involved in DDIs
First-generation antiepileptic drugs				
Carbamazepine				COCs, POPs, progestin subcutaneous implants, LNG-IUD
Phenobarbital				COCs, POPs, progestin subcutaneous implants, LNG-IUD
Phenytoin				COCs, POPs, progestin subcutaneous implants, LNG-IUD
Valproate				COCs, vaginal ring, dermal patch
Second-generation antiepileptic drugs				
Eslicarbazepine				COCs
Felbamate*				Low-dose COCs
Gabapentin				
Lacosamide				
Lamotrigine				COCs, vaginal ring, dermal patch (for reduction in AED serum levels) COCs and POPs (for reduction in progestins serum levels)
Levetiracetam				
Oxcarbazepine				COCs, POPs
Perampanel				COCs, POPs
Pregabalin				
Retigabine/ezogabine				
Rufinamide				COCs, POPs
Stiripentol				
Tiagabine				
Topiramate				COCs
Vigabatrin				COCs
Zonisamide				

*Orphan drug

sexual hormone binding globulin, leading to decrease in free active proportion of endogenous and exogenous sexual steroid hormones. Increased risk of unplanned pregnancy is reported with the concomitant use of carbamazepine, phenytoin, phenobarbital and primidone and hormonal contraceptives, including combined oral contraceptives (COCs), progestin-only pills (POPs), levonorgestrel and etonogestrel subcutaneous implants and levonorgestrel-releasing intrauterine device (LNG-IUD) [26]. Available data suggest that the metabolism of hormone-releasing contraceptives is not affected by concomitant use of valproate [26].

As regards "second-generation" or newer antiepileptics, oxcarbazepine, eslicarbazepine, felbamate and rufinamide are moderate inducers and may reduce serum concentrations of both ethinylestradiol and progestins, leading to contraceptive failure [23, 24]. Breakthrough bleeding is reported with felbamate in women taking low-dose COCs [27]. Dose-dependent topiramate showed to induce the metabolism of ethinylestradiol, although no clinical relevance was reported with low doses used for migraine prophylaxis [24]. Lamotrigine and high-dose perampanel showed to induce progestins metabolism, leading to the possible occurrence of contraceptive failure, particularly with low-dose POPs [23, 24]. Breakthrough bleeding and increased levels of follicular stimulating hormone (FSH) and luteinizing hormone (LH) were reported in women concomitantly treated with lamotrigine and low-dose COCs [28]. Reduced ethinylestradiol levels were reported in 2 of 13 healthy women taking COCs and vigabatrin, although clinical relevance is unknown [26].

Available data suggest that metabolism of HCs is not significantly affected by the concomitant administration of gabapentin, lacosamide, levetiracetam, retigabine, zonisamide or tiagabine, as reported also in Summary of Product Characteristics.

In order to improve contraceptive efficacy in women treated with antiepileptic agents inducing CYP450 enzymes, it is often recommended the use of COCs containing at least 50 μg of ethinylestradiol. However, there are no published data to prove the efficacy of this therapeutic strategy, and unintended pregnancies occurred also with the use of older COCs containing more than 100 μg of ethinylestradiol (in any case, this dosage is no longer used today) [29]. The use of a COC containing a progestin dose well above the dose required for inhibition of ovulation and the continuous use of oral contraceptives without a pill-free interval (the so-called long cycle) may be useful strategies to reduce contraceptive failure [29]. However, full oral contraceptive efficacy cannot be guaranteed in women treated with strong inducer anticonvulsants. In this setting, also POPs and etonogestrel/levonorgestrel subcutaneous implants may lead to contraceptive failure. High-dose injectable progestin-only formulation (despite the several possible side effects) and LNG-IUD may be practicable alternatives for epileptic women taking strong inducers of CYP450.

20.3.1.2 Effects of HCs on Antiepileptic Agents

Ethinylestradiol may affect the metabolism and serum concentrations of some antiepileptic agents through inhibition of CYP450 isozymes or induction of UGT enzymes. Clinically relevant drug interactions were reported with the concomitant use of lamotrigine. Ethinylestradiol may enhance the metabolism of lamotrigine via

an action on UGT 1A4, leading to lower serum concentrations during the phase of HC intake, causing consequently an increased seizure frequency and seizure recurrence [23]. An increase in lamotrigine dosing of almost 50–75% may be required in women taking HCs containing ethinylestradiol [30]. Significant increasing in serum lamotrigine concentrations during the washout contraceptive week was found, leading to intermittent lamotrigine-related toxicity [23].

The concomitant administration of lamotrigine and valproate may lead to avoidance of the above interaction, because of the potent inhibitory activity of valproate on lamotrigine metabolism [23, 24]. Clinically relevant drug interactions involving lamotrigine are reported with the use of COCs, vaginal ring and transdermal patches containing ethinylestradiol, while metabolism of lamotrigine is not affected by the use of progestin-only contraceptive methods, thereby resulting in the best choice in order to improve seizure control while maintaining contraceptive efficacy.

Ethinylestradiol showed to modestly reduce serum valproate concentrations. However, the clinical relevance of this interaction is unclear [24].

Potential effects of HCs on other antiepileptic agents were studied only in few cases. Metabolism and activity of levetiracetam, zonisamide, lacosamide and retigabine are not affected by the concomitant use of hormonal contraceptives; however no data are available for the remaining anticonvulsants [23].

Overall, a high risk of bidirectional drug interactions is reported with the concomitant use of HCs and antiepileptic agents. However, the large number of alternatives for both anticonvulsants (almost 20 drugs showing different metabolic pathways) and HC strategies (characterized by different PK features) allows to avoid relevant and serious drug interactions in most cases.

Currently, no data are reported concerning potential interactions between emergency contraception, which implies once-only administration, and antiepileptic agents.

20.3.2 Antiretroviral Agents

Currently, more than 17 million women are affected by HIV worldwide, mainly living in low- and middle-income countries [31]. The well-proved efficacy antiretroviral therapy (ART) shifted HIV infection from a disease presenting high lethality to a chronic condition requiring lifelong treatment. The largest proportion of HIV-infected women are of reproductive age, and hormonal contraceptives play a key role in avoiding unintended pregnancy and in decreasing perinatal HIV transmission. The prevention of perinatal HIV transmission is important considering that vertical transmission actually represents a significant infection route worldwide and the teratogenic potential of several antiretroviral agents, particularly efavirenz [32].

Several classes of antiretroviral agents in different combination ART regimes are used: nucleotide reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), CCR5 inhibitors, fusion inhibitors, integrase strand transfer inhibitors (INSTIs) and pharmacokinetic enhancers (boosters) [31, 32]. In Europe and the USA, the recommended first-line

regimens include an INSTI or PI in association with two NRTIs, while in low- and middle-income countries, efavirenz is recommended as the third drug in first-line ART. Nevirapine and dolutegravir represent alternative options [33].

Based on these guidelines, ART containing efavirenz is the most widely used regimen in HIV-positive women, representing a major issue in management of drug–drug interactions including HCs, given the peculiar pharmacokinetic of efavirenz.

Additionally, HIV infection is associated with high risk of several opportunistic and non-opportunistic infections, including tuberculosis and other non-tuberculous *mycobacteria*, leading to a more complex scenario concerning the occurrence of drug interactions with rifamycins [34].

The impact of different classes of antiretroviral agents on CYP450 causing potentially relevant drug–drug interactions (including co-administration of HCs) is reported in Table 20.6.

Given the relatively large number of women with HIV and the widespread use of HCs in this setting, clinicians should be aware of the significant risk of relevant drug–drug interactions, potentially impairing treatment efficacy (contraceptive failure and antiretroviral ineffectiveness).

20.3.2.1 Effects of Antiretroviral Agents on HCs

Efficacy of HCs does not seem to be affected by the concomitant use of NRTIs, INSTIs and CCR5 inhibitors, while enfurtivide is not expected to impair the pharmacokinetic of contraceptives [35, 36].

As regards NNRTIs, although studies evaluating pregnancy as main outcome are few, evidence showed a slightly higher pregnancy rate in women subjected to co-administration of oral contraceptives and efavirenz as compared to nevirapine. Also surrogate markers of ovulation were found to be higher in patients taking oral contraceptives and efavirenz [35, 36]. PK studies demonstrated that progestin levels decreased by approximately 60% in women treated with efavirenz, while ethinylestradiol concentrations were not significantly altered. Concomitant administration of nevirapine leads to decreased ethinylestradiol concentrations of almost 30–60%, while progestin levels were not affected. Additionally, no changes in hormone levels with co-administration of COCs and etravirine, rilpivirine or fosdevirine were reported [35, 36]. Contraceptive efficacy of intramuscular medroxyprogesterone acetate was not affected by co-administration of efavirenz or nevirapine, while pregnancy rates were higher among women using levonorgestrel subdermal implant concomitantly with efavirenz [36]. Significant reduction in etonogestrel levels (almost 50–70% lower) was found in women using subdermal implant and concomitantly taking efavirenz-containing ART. No difference in pregnancy rate was reported with the use of levonorgestrel implant and nevirapine. Finally, significant reduction in levonorgestrel levels was reported in emergency contraceptive pills users when efavirenz was administered [36].

As regards PIs, in women taking COCs, POPs or combined transdermal patches, no difference in surrogate markers of ovulation was reported with the concomitant administration of different PI regimens (darunavir/ritonavir or

Table 20.6 Activity on CYP450 isoforms of the different antiretroviral agents used in HIV management (–, available data show no inducing or inhibitory activity on CYP450; green, no or low potential risk of relevant drug–drug interactions; yellow, moderate risk; red, elevate risk) (data retrieved from [31, 32, 35, 36])

Antiretroviral agents	CYP450 inducer	CYP450 inhibition	Potential implication in relevant drug-drug interactions
NRTIs			
Zidovudine	-	-	
Abacavir	-	-	
Tenofovir	-	-	
Emtricitabine	-	-	
Didanosine	-	-	
Lamivudine	-	-	
Stavudine	-	-	
NNRTIs			
Efavirenz	3A4 – 2B6	3A4 – 2C9 – 2C19	
Etravirine	3A4 (weak)	2C9 – 2C19	
Nevirapine	3A4 – 2B6	-	
Rilpivirine	3A4 (weak)	-	
Delaviridine	-	3A4 – 2C9 – 2D6 – 2C19	
Fosdevirine	-	3A4 – 2D6 – 2C9 – 2C19	
PIs			
Ritonavir	3A4 – 1A2 – 2C9 – 2C19	3A4 – 2D6	
Atazanaivr	-	3A4	
Darunavir	-	3A4 – 2D6	
Fosamprenavir	3A4	3A4	
Saquinavir	-	-	
Tipranavir	1A2 –2C19 – 3A4	3A4 – 1A2 – 2C9 – 2C19– 2D6	

(continued)

Table 20.6 (continued)

Nelfinanivr	-	3A4	
Indinavir	-	3A4 – 2D6	
CCR5 inhibitors			
Maraviroc	-	2D6 (high dose)	
Vicriviroc	-	-	
Fusion inhibitors			
Enfurtivide	-	-	
INSTIs			
Dolutegravir	-	-	
Elvitegravir	2C9	-	
Raltegravir	-	-	
Pharmacokinetic enhancers			
Cobicistat	-	3A4 – 2D6 (weak)	

NRTIs nucleotide reverse-transcriptase inhibitors, *NNRTIs* nonnucleoside reverse-transcriptase inhibitors, *PIs* protease inhibitors, *INSTIs* integrase strand transfer inhibitors

lopinavir/ritonavir) [35, 36]. PK studies showed lower ethinylestradiol levels, but higher progestin concentrations, in women taking COCs, POPs or combined transdermal patches and treated with different PIs (ritonavir, atazanavir/ritonavir, lopinavir/ritonavir and darunavir/ritonavir) [35, 36]. Concurrent use of COCs or combined transdermal patches with PIs does not impair contraceptive efficacy despite the observed decreasing in estrogen levels, as the progestin component is primarily responsible for contraceptive efficacy [36]. Additionally, the higher progestin levels reported with the concomitant use of COCs, POPs or combined transdermal patches and PIs compared to controls may better preserve from unintended pregnancies.

The efficacy of depot medroxyprogesterone acetate and of etonogestrel subdermal implants are not affected by the co-administration of PIs (lopinavir/ritonavir and nelfinavir) [36]. In these women, levels of progestins administered through intramuscular or subdermal route were higher than in patients not treated with PIs. Despite the high concentrations of progestin in women treated concomitantly with HCs and PIs, enhanced toxicity was not reported [36]. However, clinicians should

carefully monitor women at high risk of increased hormone exposure for excess hormone-related toxicities, including thrombosis and hypertension.

Limited observational data suggest that the contraceptive efficacy of LNG-IUD is not impaired in women taking concomitantly ART, based on localized delivery and action of the progestin released from the device. ART is not expected to significantly affect hormone concentration in the genital tract and may be used with relative safety in well-controlled women affected by HIV infection [35].

A summary of relevant drug–drug interactions between HCs and antiretroviral agents is shown in Table 20.7.

Management of relevant drug–drug interactions reported with the co-administration of HCs and NNRTIs and/or PIs includes the following: (i) the use of combined contraceptives with minimum 30 μg of ethinylestradiol or additional methods or contraception in women taking PIs (excluded indinavir) [31], (ii) the use of intramuscular medroxyprogesterone in women taking efavirenz [31, 35] and (iii) the use of 3 mg levonorgestrel for emergency contraception (off-label use) in women treated with efavirenz [31, 32]. No specific action is required for other antiretroviral agents.

20.3.2.2 Effects of HCs on Antiretroviral Agents

A systematic review reported no effects of HCs, particularly with the use of combined oral contraceptives, levonorgestrel implants or injectable medroxyprogesterone acetate, on the efficacy of NNRTI-containing or PI-containing ART [36]. Outcomes evaluated were death, $CD4^+$ cell count or plasma viral load. Although the use of injectable medroxyprogesterone acetate may lead to immunosuppression based on the high affinity of binding to glucocorticoid receptor, clinical significance of this finding is currently unclear, and available data suggest that medroxyprogesterone acetate does not affect HIV disease progression [35].

Pharmacokinetic studies reported lower concentrations of efavirenz with the concomitant use of COCs (potentially caused by inducing activity of ethinylestradiol on CYP3A4 involved in efavirenz metabolism) and slightly higher nevirapine concentrations in women after the administration of medroxyprogesterone acetate, although clinical relevance is unknown and HIV disease progression was not affected [36].

As regards PIs, co-administration of COCs led to slight increase in atazanavir levels, while combined transdermal patches may decrease concentrations of lopinavir and ritonavir, although clinical significance remains unknown [36]. Concentrations of saquinavir and darunavir were not affected by concomitant use of COCs.

No alterations in pharmacokinetic parameters were found with the concomitant use of NRTIs and maraviroc with COCs or medroxyprogesterone acetate [35, 36].

Overall, the most clinically significant drug–drug interactions with the concomitant use of antiretroviral agents and HCs involved efavirenz-containing ART. This is

Table 20.7 Effects of antiretroviral agents on efficacy of different hormonal contraceptive methods (green, no or low risk of significant drug–drug interactions; yellow, some concerns; red, high risk, avoid association; grey, no available data) (data retrieved from [31, 32, 35, 36])

Antiretroviral agents	COC	POP	IM/SC injection	Progestin implants
NRTIs				
Zidovudine				
Abacavir				
Tenofovir				
Emtricitabine				
Didanosine				
Lamivudine				
Stavudine				
NNRTIs				
Efavirenz				
Etravirine				
Nevirapine				
Rilpivirine				
Delaviridine				
Fosdevirine				
PIs				
Ritonavir				
Atazanaivr				
Darunavir				
Fosamprenavir				
Saquinavir				
Tipranavir				
Nelfinanivr				
Indinavir				

Table 20.7 (continued)

CCR5 inhibitors				
Maraviroc				
Vicriviroc				
Fusion inhibitors				
Enfurtivide				
INSTIs				
Dolutegravir				
Elvitegravir				
Raltegravir				
Pharmacokinetic enhancers				
Cobicistat				

NRTIs, nucleotide reverse-transcriptase inhibitors; NNRTIs, nonnucleoside reverse-transcriptase inhibitors; PIs, protease inhibitors; INSTIs, integrase strand transfer inhibitors; COC, combined oral contraceptive; POP, progestin-only pill; IM, intramuscular; SC, subcutaneous

a major issue in women living in low- and middle-income countries given that efavirenz-containing ART is recommended as first-line therapy for HIV infection. Clinicians should be aware of this significant drug interaction, strictly monitoring women treated with efavirenz and HCs and recommending additional and/or alternative contraceptive strategies.

20.3.3 Antitubercular Agents

Approximately ten million people every year develop new cases of tuberculosis worldwide (especially in low- and middle-income countries), of which about one third are women mostly of reproductive age. Tuberculosis requires long-term treatment with a combination regimen including isoniazid, rifampicin, pyrazinamide and ethambutol, while infections caused by non-tuberculous *mycobacteria* require management with rifampin or other rifamycin antibiotics [34]. It is important to underline that rifamycins are moderate to strong inducers of CYP450, leading to several clinically relevant drug interactions, also involving HCs. Given the relatively large number of women with tuberculosis and the widespread use of HCs in this setting, clinicians should be aware of the significant risk of relevant drug–drug interactions, potentially impairing treatment efficacy (contraceptive failure and antitubercular ineffectiveness).

20.3.3.1 Effects of Antitubercular Agents on HCs

A recent systematic review assessed the risk of significant drug interactions between rifamycins and COCs [37]. No studies evaluated nonoral formulations of HCs. Although no evidence directly assessing the risk of pregnancy are reported, surrogate markers of contraceptive efficacy showed more common events of breakthrough bleeding in women affected by tuberculosis and managed with concomitant COCs and rifampicin [37]. PK studies confirmed these findings, showing reduction in estrogen and progestin levels when COCs were co-administered with rifampicin.

Additionally, rifabutin caused significant reduction in estrogen and progestin exposure. However, rifampicin resulted in larger reduction concentrations for both ethinylestradiol and norethisterone compared to rifabutin [37]. PK parameters of COCs were not affected by co-administration of rifamixin (as expected on the basis of PK features, since rifamixin is only poorly absorbed) and rifalazil, while no studies evaluated potential interactions between rifapentine and HCs. Rifapentine shows intermediate level of CYP3A4 induction with respect to rifampin and rifabutin, so a similar degree of interaction would be expected [38].

Overall, the risk of clinically significant interactions leading to contraceptive failure appears to be different between rifamycins: rifampin > rifabutin > rifapentine > rifalazil ≈ rifamixin [37].

A PK study showed no variation in estrogen and progestin levels in women treated with isoniazid or streptomycin [37].

20.3.3.2 Effects of HCs on Antitubercular Agents

COCs do not appear to affect the clinical course of tuberculosis in women treated concomitantly with rifampin-containing regimes [37]. Additionally, PK parameters of rifampin were unchanged with the concomitant use of COC containing ethinylestradiol and norethindrone [37].

20.3.4 Other Antimicrobials

Antimicrobials are commonly used in reproductive-aged women. Short-term (e.g. prophylaxis for dental procedures or treatment of uncomplicated cystitis) and long-term antimicrobial treatments (e.g. outpatient treatment of community-acquired pneumonia or candidiasis vulvovaginitis) exhibit different risks in terms of potentially relevant drug interactions, since a longer length of therapy exposes to greater chance of interactions with concomitant agents. Theoretical mechanisms leading to contraceptive failure in association with antimicrobial treatment include decreasing in intestinal bacteria (implicated in enterohepatic recirculation of ethinylestradiol) and alterations in HC metabolism via CYP450. However, the contribution of enterohepatic recirculation on active ethinylestradiol circulation is limited, so the reduction in estrogen reabsorption is unlikely to produce significant effect on systemic levels. Additionally, rifampicin is the only antimicrobial known to induce CYP450 enzymes, causing relevant decrease in HC levels and possible unintended pregnancies. However, treatment with rifampicin is mainly used in tuberculosis management (see 22.3.3).

Clinical concerns of drug interactions between antimicrobials and HCs are based primarily on case reports of unintended pregnancies or on surveys limited severely by recall bias [39, 40]. Additionally, most pharmacists recommend alternative and/or additional contraceptive methods with respect to hormonal strategies in women treated with antibiotics [40, 41]. However, these alerts may result in interruption of HCs or poor compliance with antimicrobial regimens, leading to possible treatment failure with either drug. In the event that no relevant drug interaction is present, risks of treatment failure caused by poor adherence are assumed unnecessarily [40]. The existence of drug interactions between HC and non-rifamycin antibiotics is not supported by evidence reported from a recent review [40]; thereby clinicians should be aware that most women may expect no reduction in HC efficacy with the concomitant use of antimicrobials. Currently, evidence evaluated only the potential interactions with COCs, emergency contraceptives and vaginal ring. No data exist on the combination between antimicrobials and other nonoral hormonal formulations [40].

20.3.4.1 Effects of Antimicrobials on HCs

Two studies [42, 43] found no increased risk of pregnancy in oral contraceptive users treated with any type of antibiotics in comparison with women taking oral contraceptives and not treated with antimicrobial agents. Additionally, two studies [44, 45] found no higher odds of antibiotic use at the time of conception in women taking oral contraceptives experienced unintended pregnancies. However, it is important to underline that all these studies were retrospective characterized by case-control or crossover design and showed fair to poor quality and several biases, so the strength of the evidence is questionable.

Surrogate markers of contraceptive efficacy and pharmacokinetic data support the evidence of the absence of relevant effects caused by the most important classes of antimicrobials (penicillins, cephalosporins, macrolides, fluoroquinolones, tetracyclines, metronidazole, azoles) currently used in outpatient treatment on hormonal contraceptives [40, 46, 47]. Breakthrough bleeding in COCs users was reported in two women treated with ampicillin and in two taking trimethoprim/sulfamethoxazole, while a PK study reported a significant decrease in ethinylestradiol levels during co-administration with dirithromycin, a macrolide no longer available in Europe and the USA [40].

Some antimicrobials, including ciprofloxacin, macrolides, metronidazole, trimethoprim and azole antifungals, are known inhibitors of CYP450. Concomitant use of these agents and HCs may lead to increase in ethinylestradiol and progestin levels, theoretically exposing women to toxicity. Increased estrogen concentrations were found with the co-administration of erythromycin, dapsone and voriconazole, while progestin levels augmented with the co-administration of tetracycline or voriconazole (norethindrone) and erythromycin (dienogest and ulipristal acetate) [40, 47]. However, no adverse effects were reported correlating with the increasing in HC levels. In any case, clinicians should be aware of potential risks produced by estrogen or progestin exposure (e.g. thrombotic risk, weight gain, dyslipidemia).

20.3.4.2 Effects of HCs on Antimicrobials

COCs could affect the metabolism of co-administered antimicrobials, potentially leading to alterations in safety or efficacy profile. Increased azithromycin and voriconazole levels were reported with co-administration of ethinylestradiol, which may moderately inhibit several CYP450 enzymes [40, 47]. Although ethinylestradiol is not known to induce CYP450 enzymes, decreased exposure of ampicillin, cephaloridine, trovafloxacin and moxifloxacin was reported [40]. However, the clinical relevance of these potential drug interactions in terms of toxicity or treatment failure is unknown.

Overall, although current evidence is limited and incomplete, no clinically relevant drug interactions between HCs and the most common antimicrobials used in outpatient settings were reported [40]. However, clinicians should carefully monitor HC users requiring long-term antimicrobial regimens or treatment with newer antibiotics.

20.3.5 Antidepressants and Antipsychotics

Depression is a leading cause of global disability and morbidity. Almost 15% of women of reproductive age in developed countries are affected by depression, and half of them is treated with antidepressant agents [48]. Additionally, concurrent or isolated anxiety is the most common mental health disorder, and women are 60% more likely than men to experience an anxiety disorder [49]. Finally, unintended pregnancies in women with a diagnosis of schizophrenia or other psychotic disorders may have a major impact on the health of women and children and on the cost of healthcare [50]. Psychiatric disorders in women of reproductive age are associated with inconsistent or misuse of HCs [51, 52]. Clinicians should be aware of the potential drug–drug interactions involving co-administration of HCs with psychotropic medications.

A recent systematic review reported clinical and pharmacokinetic studies evaluating drug interactions between HCs and selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), oral benzodiazepines, bupropion, atypical antipsychotics and chlorpromazine [52]. To the best of our knowledge, no studies reported the assessment of potential drug interactions between HCs and serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, trazodone, buspirone, monoamine oxidase inhibitors (MAOIs) or other traditional antipsychotics. Actually, no published data on the potential drug interactions between psychotropic agents and progestin-only oral contraceptives or nonoral hormonal methods are reported.

20.3.5.1 Effects of Antidepressants and Antipsychotics on HCs

Although some psychotropic agents may inhibit different CYP450 isozymes, only fluvoxamine (a SSRI) is a known inhibitor of CYP3A4 and 2C9, which are involved in hepatic metabolism of ethinylestradiol and several progestins. Additionally,

moderate or strong inhibitory effects on CYP3A4 or 2C9 enzymes were not reported for any psychotropic drugs. Consequently, limited theoretical concern exists for any of the antidepressant or antipsychotic drugs to significantly inhibit the metabolism of HCs, leading to clinically relevant interactions responsible to affect contraception-related safety [52]. A clinical study found slightly increased odds of headache in women taking HCs concomitantly with fluoxetine compared to HCs plus placebo users [52, 53]. Moreover, a greater psychomotor performance impairment was produced with the co-administration of alprazolam, lorazepam or triazolam in hormonal contraceptive users, although a correlation between symptoms and pharmacokinetic changes was not found [52–54]. Dysmenorrhoea was reported in a case of concurrent assumption of lurasidone and association of ethinylestradiol and norgestimate, despite no changes in pharmacokinetic parameters of the two hormones [55].

The potential for antidepressant and antipsychotic agents to induce the CYP450 enzymes, thus theoretically decreasing steroid hormone concentrations leading to impaired efficacy, is currently unknown [52]. Four studies (one clinical and three pharmacokinetic) investigated the potential decrease in contraceptive effectiveness caused by drug interactions [52]. No significant differences were reported in women treated concomitantly with HCs and fluoxetine, vortioxetine, ziprasidone or lurasidone in terms of unintended pregnancies or reduction in pharmacokinetic parameters predictive of hormonal efficacy (namely, AUC or C_{Max}). A study [56] reported breakthrough bleeding with the concomitant use of HCs and benzodiazepines, especially chlordiazepoxide and meprobamate. Breakthrough bleeding may be used as surrogate marker for HC efficacy, suggesting low serum hormone levels and possibly impaired suppression of ovulation.

20.3.5.2 Effects of HCs on Antidepressants and Antipsychotics

Considering possible effects of HCs on psychotropic agents, it is important to underline that ethinylestradiol inhibits CYP3A4, 1A2, 2B6 and 2C19 isozymes and induces the glucuronidation pathway, while several progestins are weak inhibitors of 3A4 and 2C19 isozymes, despite that their inhibitory activity was assessed only in vitro [17].

HCs may potentially increase the exposure of different antidepressants (duloxetine, TCAs, mirtazapine) and antipsychotics (olanzapine, clozapine, ziprasidone) metabolized via hepatic CYP1A2 [52]. Pharmacokinetic studies [57, 58] showed increased exposure and decreased clearance of amitriptyline and imipramine in women taking HCs, although the clinical relevance of these findings is unknown. Despite that TCAs are replaced by SSRIs as first-line therapy of depression, they are used for the management of chronic pain disorders (particularly neuropathic) and chronic migraine, commonly affecting women of reproduction age. Given the narrow therapeutic window and the serious events related to TCAs toxicity, clinicians should be aware of the potential relevance of drug interactions in women taking HCs. Clinically significant adverse events are reported with the use of clozapine or chlorpromazine in association with oral contraceptives, caused by metabolic inhibition of antipsychotics and increased exposure [59, 60].

Although there is no known theoretical concern for HCs to induce CYP450 enzymes and consequently affect the efficacy of psychotropic agents [52], pharmacokinetic studies [61, 62] showed significant decrease of bupropion, lorazepam and temazepam. Ethinylestradiol may inhibit CYP2B6 isozyme, involving in metabolism of bupropion from prodrug compound to active metabolite. Additionally, ethinylestradiol may induce glucuronidation via UGT1A1, increasing the metabolism and clearance of oxazepam-like benzodiazepines (such as lorazepam and temazepam), reducing serum concentrations and potentially clinical efficacy of these agents.

Overall, the limited evidence on drug interactions between psychotropic agents and HCs suggests low concern for clinically relevant interactions, although a case-by-case risk assessment should be performed, especially with the use of TCAs and clozapine.

20.3.6 Anticoagulants

The co-administration of anticoagulants (warfarin or direct oral anticoagulants – DOACs) and HCs is relatively uncommon, as several conditions requiring anticoagulant treatment occur following reproductive age [63]. However, venous thromboembolism, including drug vein thrombosis and pulmonary embolism, may affect also women of reproductive age, thereby needing limited or chronic management with anticoagulants [64]. In these women, the teratogenic effects of warfarin impose the implementation of contraceptive strategies in order to avoid the consequences of unintended pregnancies. Finally, it is important to underline that estrogen component of combined HCs may increase the thrombotic risk, possibly leading to impaired efficacy of anticoagulant treatment.

20.3.6.1 Effects of Anticoagulants on HCs

Both warfarin and DOACs are not known to show inducer or inhibitory activity on any enzymes of CYP450 system; consequently these agents are not expected to cause clinically relevant drug interactions causing impaired efficacy or toxicity of HCs [64].

Currently, there are no studies reporting negative effects of anticoagulants on HCs [64].

20.3.6.2 Effects of HCs on Anticoagulants

Warfarin is metabolized by CYP450 (mainly 2C9 isozymes), and several DOACs (namely, rivaroxaban and apixaban) are metabolized mainly via 3A4 isoform. Ethinylestradiol inhibits in vitro CYP2C9 and other microsomal isoforms, so theoretically concern exists on potential relevant drug interactions leading to enhanced anticoagulant effect and increased risk of bleeding [64]. Two case reports [63, 65] showed significantly increased international normalized ratio (INR) without concomitant bleeding in women requiring anticoagulant therapy and taking COCs or emergency contraception containing high-dose levonorgestrel. In a case series of 13 women on chronic anticoagulation for prosthetic heart valves and concomitantly

treated with injectable medroxyprogesterone acetate, sporadic increase of INR in 3 of them was reported [66]. Finally, a PK study in ten healthy women found no relevant interaction concerning CYP2C9 activity between a triphasic COC and warfarin, although plasma clearance of warfarin was reduced [67]. However, the clinical relevance of this finding is unclear.

Currently, there are no known PK drug interactions involving heparin, low molecular weight heparin (LMWH) or DOACs and HCs [64]. Treatment with heparin and LMWHs is usually limited to the first week after diagnosis of venous thromboembolism, so it is unlikely that clinically relevant interactions with HCs occur [64]. A potential PD interaction may occur with the use of HCs containing ethinylestradiol and anticoagulant agents, considering the increased thrombotic risk caused by estrogen. In this setting, ethinylestradiol may potentially affect the efficacy of anticoagulants, although no cases are reported and clinical relevance is unknown.

Overall, despite limited data, there is little evidence showing the occurrence of significant drug interactions with the concomitant use of HCs and anticoagulants, including warfarin.

20.3.7 Interactions with Herbal Products and Dietary Supplements

Use of herbal preparations and complementary/alternative medicines is common in women of reproductive age concomitantly taking HCs [11]. Several products may affect HC efficacy and safety. Additionally, for most herbal preparations or dietary supplements, the effects on HCs and the impact on contraceptive failure are still unknown [12, 13].

Unfortunately, St. John's wort (*Hypericum perforatum*) is considered worldwide a remedy for the treatment of depression, and it can induce cytochrome 3A4 isozymes, leading to relevant drug interactions when co-administered with CYP450 substrates, including hormonal contraceptives [13, 68]. Evidence showed increased risk of ovulation and breakthrough bleedings caused by decreased contraceptive efficacy in association with *Hypericum* [68]. Of the 55 drug–food interactions reported to the Netherlands Pharmacovigilance Centre Lareb, 13 reports showed the concomitant use of *Hypericum* with oral contraceptives, leading to their reduced effectiveness [13, 69].

Estrogen-containing oral contraceptives may reduce the serum levels of vitamin B6, folic acid and magnesium [13]. Decreased absorption and increased metabolism and clearance due to estrogen activity may cause drug–food interactions.

Several drug–herbal and drug–food interactions involving HCs may be predicted on the basis of pharmacokinetic and pharmacodynamic of different products used in complementary medicines, leading to impaired efficacy and unintended pregnancies [12, 13]. Clinicians should be aware that not only conventional drugs but also herbal preparations and dietary supplements may be responsible for relevant drug interactions and adverse effects. Additionally, clinicians should carefully check all ingredients contained in each herbal product or dietary supplement, considering that

some may be undeclared, and the dosage in order to assess the risk of relevant interactions and the safety profile.

20.4 Sources of Information on Drug–Drug Interactions

As new drugs and new indications for marketed medications are introduced and pharmacological knowledge expands, the recognition of occurrence of drug–drug interactions and their clinical relevance has become more difficult for clinicians. Additionally, the high number of drug interactions makes it impossible to be aware of all potential interactions. To fill this gap, several sources of information on drug–drug interactions have been developed and updated regularly as clinical decision support tools, as reported in Table 20.8 [70].

In the field of drug–drug interactions, regulatory alerts including FDA boxed warning (in the USA; https://www.levinlaw.com/fda-black-box-warning), reports of EMA concerning safety signals discussed each month in Pharmacovigilance Risk Assessment Committee (PRAC) meeting (in Europe; https://www.ema.europa.eu/en/committees/pharmacovigilance-risk-assessment-committee-prac) and Italian Medicines Agency (AIFA; http://www.agenziafarmaco.gov.it/content/note-aifa) remarks may provide useful and updated information. Tertiary sources may provide established information in terms of drug interactions [70, 71]. They include the *Stockley's Drug Interaction* (the most relevant and accurate drug interaction resource; www.medicinescomplete.com/mc/index.htm), the *Meyler's Side Effects of Drugs* (international textbook discussing adverse drug reactions and drug–drug interactions; https://www.elsevier.com/books/meylers-side-effects-of-drugs/aronson), *Hansten and Horn Drug Interactions* (producing different textbooks on the most common drug interactions and how to manage them; www.hanstenandhorn.com/index.html) and *Facts and Comparison* (presenting detailed monographies of drug interactions; www.factsandcomparison.com). *Up-to-date* (www.uptodate.com/crlsqul/interact) is the most important electronic sources evaluating clinical relevance and management of drug–drug interactions, characterized by close updating. *Medscape* (reference.medscape.com/druginteractionchecker), *Micromedex* (www.micromedex.com) and *Drugs* (www.drugs.com/drug_interactions.html) may provide useful information on drug interactions. Despite that *Medscape Drug Interaction Checker* is widely used, caution must be exercised because it is based primarily on drugs used in the USA and it may highlight interactions with contraceptive hormones of which the clinical relevance is unknown, leading to possible wrong decisions. Finally, specific electronic sources including *Online HIV Drug Interaction Checker* (www.hiv-druginteractions.org) highlight potential drug interactions between antiretroviral drugs and other agents, including HCs.

Clinicians should remember that when using any third-party resources, the decision to follow the advice rests on individual clinical judgement about the specific risk-benefit ratio in each woman requiring treatment with HCs [71].

Table 20.8 Advantages and disadvantages of the different sources of information on drug–drug interactions

Source of information on drug–drug interactions	Advantages	Disadvantages
Regulatory alerts (FDA boxed warning, EMA reports, AIFA remarks)	– Adverse drug reactions or relevant drug interactions based on large number of cases – "Real-life" data	– It is difficult to maintain an updated overview – Scant information concerning management when both drugs are needed for compelling clinical reasons
Stockley's drug interaction	– Management of several drug interactions is proposed – Drug interactions with herbal products and dietary supplements are reported	– Resource available only upon paid subscription
Meyler's side effects of drug	– Most important drug interactions and adverse drug reactions are reported	– Textbook: may not be updated as compared to electronic sources (last edition 2016) – Resource available only upon paid subscription
Hansten and Horn drug interaction	– Monographies of relevant drug interactions – Management of common drug interactions is covered	– Textbook: may not be updated as compared to electronic sources (last edition 2019) – Resource available only upon paid subscription
Facts and comparison	– Data concerning drug interactions of several classes are reported	– Resource available only upon paid subscription
Up-to-date	– Frequent update – Assessment of clinical relevance of drug interactions – Management of drug interactions is covered	– Resource available only upon paid subscription
Micromedex	– Support to clinical decision is proposed	– Subscription resource
Drugs.com	– Free of charge – User-friendly interface – Data concerning adverse drug reactions and drug interactions of the most important classes are reported – Assessment of relevance of interaction	– Based on drugs used in the USA and may highlight drug interactions with medications not labelled in EU or characterized by unknown clinical relevance
Medscape drug interaction checker	– Free of charge – Used-friendly interface	– Based on drugs used in the USA and may highlight drug interactions with medications not labelled in EU or characterized by unknown clinical relevance
Online HIV drug interaction checker	– Free of charge – Used-friendly interface	– Only drug interactions involving antiretroviral agents

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Hormonal Contraception and Bone

21

Martin Birkhaeuser

21.1 Introduction

The first combined oral contraceptive (COC) was introduced in 1960 (Enovid-Searle) and unleashed a social revolution. According to the estimates of international organizations, all over the world the pill is used by about 9% of women of reproductive age. It is the most common method of contraception in industrialized countries and the third most common in developing countries [1]. Currently available oral contraception makes it possible to choose between formulations based on oestrogens and progestins and those containing only a progestin. Combined preparations vary in dose and type of oestrogen, dose and type of progestin, regime (monophasic, biphasic, triphasic or quadriphasic, progestin-only) and route of administration (pill, patch, vaginal ring or subcutaneous implant).

Over the past 60 years, research aimed at the reduction of the side effects and risks of combined (COC). The modern advances in oral contraception include:

- Mestranol used formerly for oral contraceptives has been replaced by ethinyloestradiol.
- Reduction in hormone doses: pills are now available containing 35, 30, 20 and 15 μg of ethinyloestradiol (Fig. 21.1).
- Development of more selective progestogens with high anti-gonadotrophic activity, e.g. gestodene, desogestrel, nomegestrol, dienogest or nestorone.
- Changes in dosing regimens.

In addition, the introduction of formulations using oestetrol (E4) or natural oestradiol (17β-oestradiol (E2) or E2-valerate) instead of synthetic ethinyloestradiol (EE) aims at decreasing further the metabolic risks and serious adverse events such

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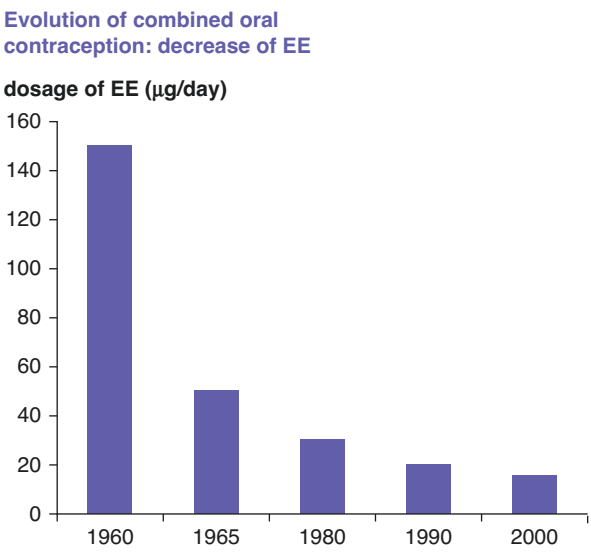


Fig. 21.1 Evolution of combined oral contraception. Decrease of ethinyloestradiol dose since 1960

as cancer and cardiovascular events. All these improvements increase safety and tolerability profiles of combined hormonal contraceptives (CHCs) and increase acceptance and compliance.

Unfortunately, most older studies on the metabolic activity of EE have neglected to look at its effect on bone. In the celebration papers written for the 50th anniversary of "The Pill" [2, 3], BMD and fracture rate in CHC users are not mentioned. Although the few earlier studies done in adult women with low-dose oral preparations ≤35 µg EE daily have reported a normal bone metabolism, increasingly, doubts came up in the last 30 years if the modern low-dose 15–20 µg COCs exert a functionally adequate oestrogenic activity at the bone in all age groups of pill users. These doubts have been enhanced by dose-dependent effects of EE in the postmenopause. In women after menopause, a net loss of bone mass was observed using EE doses below 15 µg EE daily, whereas no loss occurred using doses between 15 and 25 µg EE daily; a net bone gain occurred with doses of ≥25 µg EE [4]. Newer studies suggest that in premenopausal women, the influence of different contraceptives on female bone is closely related to age at the start of intake, the type and the dose of oestrogen used, the progestin added and the duration of the therapy. In adult life, BMD remains practically stable until menopause, as long as there are no diseases or drug therapies influencing bone metabolism. Due to the increasing lack of oestrogens, a physiological gain in bone loss occurs with menopausal transition.

In all age groups, use of combined hormonal contraception (CHC) may influence bone metabolism and bone mineral density (BMD). Peak bone mass (PBM) is built up until the age of 20–35 years [5]. The prospective population-based Canadian Youth and Adult CaMos Cohorts [6] calculated that peak BMD at both the femoral neck and the total hip may be gained in women between ages 16 and 19 years and lumbar spine peak BMD is achieved between ages 33 and 40. The acquisition of PBM in adolescence seems to be a key factor for the effect of COCs on BMD in

younger women. This effect might be different up to and beyond peak bone mass (PBM). Newer data suggest that an increased incidence of osteoporosis or osteoporosis-associated fractures in later life can be derived from these findings. EE, E2, E4 and synthetic progestins affect the bone to different degrees. There is raising evidence that bone protection and the acquisition of peak bone mass seem not to be assured in adolescent users of low-dose pills with 15–20 μg EE daily and of some progestin-only preparations.

21.2 Oestrogens and Progestins Used for Contraception

21.2.1 Oestrogens

The combined preparations hold both an oestrogen and a progestin component. In CHC, the dominant oestrogen still used today is the synthetic EE. The metabolism of EE is in part similar to that of native endogenous oestradiol. Both undergo oxidation at various carbon atoms [7–11] and are focused on hydroxylation at C2 and C4, resulting in the formation of catechol-oestrogens. But there is a major metabolic difference in EE compared to E2. 17ß-Oestradiol is oxidized at position 17. This oxidation is responsible for the conversion of natural E2 into the far less potent oestrone (E1) [11]. E1 has approximately 4% of the oestrogenic activity of E2. In contrast, in synthetic EE, position 17 is blocked. The 17α-ethinyl group prevents the oxidation of the 17ß-hydroxy group (Fig. 21.2). In consequence, EE is not inactivated in organs such as the liver expressing 17ß-hydroxysteroid dehydrogenase so

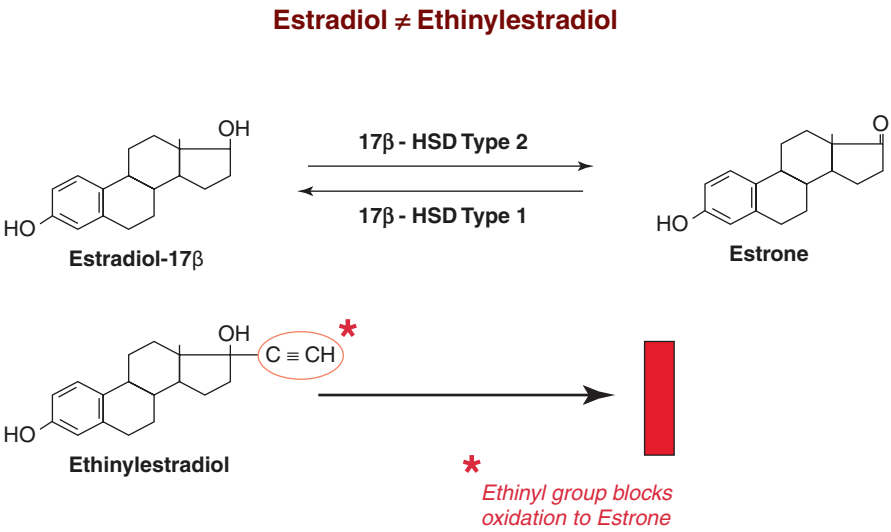


Fig. 21.2 Metabolism of 17β-oestradiol compared to ethinyloestradiol (EE). 17ß-Oestradiol is oxidized at position 17. In synthetic EE, position 17 is blocked. The 17α-ethinyl group present in EE prevents the oxidation of the 17ß-hydroxy group

Table 21.1 Relative potency of estrogens

Estrogen	FSH	HDL-C	SHBG	CBC	Angio
E2	100	100	100	100	100
Estriol	30	20			
Estrone sulfate	90	50	90	70	150
CEE	110	150	300	150	500
EE	12,000	40,000	50,000	60,000	35,000

Angio angiotensinogen, *CBC* cortisol-binding globulin, *CEE* conjugugated estrogens, *EE* ethinyl estradiol, *HDL-C* high density lipoprotein-cholesterol, *HF* hot flushes, *SHBG* sex hormone-binding globulin. Data from Kuhl H [13], Mashchak et al. [12] and Sitruk-Ware et al. [8]
Relative potency of estrogens (%) concerning various clinical and metabolic parameters. As compared to E2, EE exerts a stronger effect on hepatic proteins
When compared to estradiol (E2), the relative potency is organ-dependent

that EE has a much stronger relative oestrogenic activity compared to E2 and is metabolically significantly more active than the natural oestrogen E2. The half-life of E2 and E1 is 20–30 min, whereas the half-life of EE is much longer, due to the metabolic block at position 17. Its half-life cited in the literature ranges from 13.1 to 27.0 h [12]. The relative potency of oestrogens is presented on Table 21.1.

In the liver, EE is dramatically more potent than E2 and exerts very strong effects on hepatic protein production. Whereas the pharmacological principle of the hepatic first-pass effect is valid for oral versus nonoral administration of native 17ß-oestradiol so that nonoral E2 has little influence on hepatic parameters, this principle does not apply to synthetic EE with its significantly longer half-life. Oral and nonoral EE increase both dose-dependently circulating levels of lipoproteins and triglycerides and other liver-derived proteins such as sex-hormone-binding globulin (SHBG), corticosteroid-binding globulin (CBG) and thyroxine-binding globulin (TBG). Both ways have an impact on the renin-angiotensin-aldosterone system (RAAS) and coagulation factors. The result is a greatly increased risk for cardiovascular events and VTE in EE compared to oestradiol users. EE affects triglyceride levels at a dose as low as 1 µg/day and LDL and HDL cholesterol levels at a dose as low as 2.5 µg/day [14].

The specific effects of EE-COCs in comparison to the impact of E2 on bone have been insufficiently studied. Natural endogenous oestrogens increase bone formation and permit the acquisition of an optimal peak bone mass (Fig. 21.3). Inversely, suppression of endogenous E2 in adolescents by modern pills with 15–20 µg EE daily or depot medroxyprogesterone acetate (DMPA) may hinder the achievement of the predetermined optimal peak bone mass with long-term consequences for fracture risk. It might be that the use of EE instead of E2 has consequences for bone, e.g. through growth factors [15].

To minimize unfavourable metabolic changes induced by EE, combined oral contraceptives having E2 or oestetrol (E4) instead of EE as their oestrogen component have been developed. E2 and E2-valerate are both metabolically identical to endogenous E2. E4 is an oestrogen produced by the liver of the foetus from

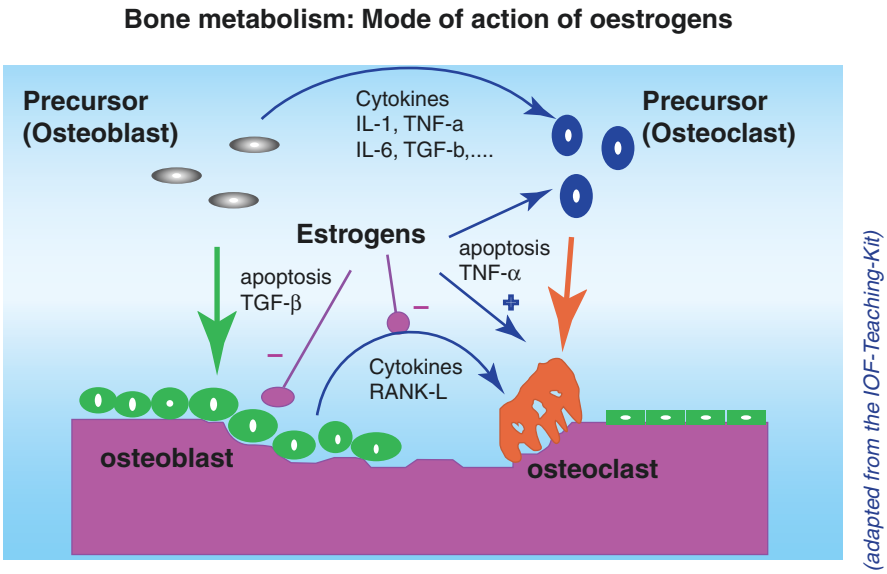


Fig. 21.3 Bone metabolism: mode of action of oestrogens (simplified, adapted from IOF). Green: stimulation. Red: inhibition

maternal oestriol (E3) and is considered an end-product as it is not further metabolized. E4 is 18–20 times less active than EE and is orally bioavailable with a long half-life of more than 24 h. E4 has been synthesized and successfully studied as a new oestrogen for use in contraception and hormone replacement therapy. Its efficiency is confirmed by hot flush models and by tests of ovulation inhibition. E4 acts as an oestrogen agonist for the bone, brain, vagina and endometrium and has an excellent metabolic profile [16–20].

21.2.2 Progestins

Today, many progestins with different partial activities (Table 21.2) are available for contraception. As for oestrogens, the dose and the endocrine and metabolic characteristics of progestins have changed over time. According to the period of their introduction into the market, progestins used in hormonal contraception have been attributed to so-called generations: first, second, third and a badly defined fourth generation (in this review called newer progestins). Unfortunately, this purely marketing-driven denomination says nothing about the hormonal properties of the molecules. It would be wiser to classify progestins in function of their chemical origin and their partial activities (Table 21.2) that determine their pharmacodynamic and pharmacokinetic properties [7, 8, 10, 11, 21–23]. "Generations" are no real help for the clinician. Modern oral contraceptives still use today the classical and well-tolerated levonorgestrel. The newer progestins used for hormonal contraception

Table 21.2 Partial activities and use of progestins compared to progesterone

	Use/ Generation	Progestogen	Anti-gonadotrop	Anti-estrogen	Estrogen	Androgen	Anti-androgen	Gluco-corticoid	Anti-miner-alocorticoid	Procoagulatory
Progesterone	MHT-pref	+	+	+	–	–	+/–	+	+	–
Dydrogesterone (retrosteroid)	MHT-pref	+	–	+	–	–	+/–	–	+/–	–
17a-Hydroxy-Progesterone derivatives										
Medrogestone	MHT	+	+	+	–	–	+/–	–	–	
Chlormadinone acetate	n-a	+	+	+	–	–	+	+	–	–
Cyproterone acetate	AA	+	+	+	–	–	++	+	–	–
Megestrol acetate	cat	+	+	+	–	+/–	+	+	–	+
Medroxyprogesterone acetate	MPA	+	+	+	–	+/–	–	+	–	
19-Nor-Progesterone derivates										
Nomegestrol acetate	n	+	+	+	–	–	+/–	–	–	–
Promegestone	MHT	+	+	+	–	–	–	–	–	–
Trimegestone	MHT	+	+	+	–	–	+/–	–	+/–	–
19-Nortestosterone derivates										
Norethisterone = Noreth-indrone (N orethisterone acetate = NETA)	MHT	+	+	+	+	+	–	–	–	+

Lynestrenol	1	+	+	+	+	+	–	–	–	–
Norethinodrel	Out of use	+/–	+	+	+	+	–	–	–	–
Levonorgestrel	2	+	+	+	–	+	–	–	–	–
Norgestimate (active metabolite: Norelgestromin)	2	+	+	+	–	+	–	–	–	–
Desogestrel (active metabolite: 3-keto-desoges-trel = Etonogestrel)	3	+	+	+	–	+	–	–	–	–
Gestodene	3	+	+	+	–	+	–	–	–	–
Dienogest	n-a	+	+	+/–	+/–	–	+	–	–	–
Nestorone	n	+	+	+	–	–	–	–	–	–
Spirolonactone derivate										
Drospirenone	n-a	+	+	+	–	–	+	–	+	–

1 = 1. generation 2 = 2. generation, n = newer progestins used in hormonal contraceptives; n-a = newer progestins with anti-androgenic partial activity used in hormonal contraceptives; cat: used in cats for contraception

MHT used in menopausal hormone therapy, *AA* anti-androgen, *MHT-pref* first choice for use in menopausal hormone therapy, *MPA* used for hormonal contraception and for MHT

include gestodene, desogestrel, norgestimate, drospirenone, dienogest, nomegestrol acetate, chlormadinone acetate and nestoron. These progestins show an improved metabolic neutrality in terms of insulin sensitivity and lipid parameters and intend to improve older progestins with clinically relevant androgenic partial activities. However, with the loss of an androgenic partial activity, newer progestins lose also part of their beneficial impact on bone metabolism and peak bone mass accrual. The effect of newer progestins on bone is poorly studied and has not been compared in humans alone to the ones of levonorgestrel or norethisterone acetate in controlled randomized prospective head-to-head trials lasting ≥24 months.

On the other hand, the arrival of the newer progestins was a genuine turning point because they greatly reduced major side effects, such as water retention. Their anti-androgenic properties are used in treating most forms of hyperandrogenism associated with acne and mild hirsutism. The use of new progestins characterized by a high anti-gonadotrophic activity can ensure excellent suppression of ovarian activity and permits the reduction of the EE component to 15–20 μg per day. This is problematic in younger subgroups of COC users as illustrated later. New combinations of 17β-oestradiol with dienogest and nomegestrol acetate are highly suitable contraceptives for women with abundant menstrual bleeding. However, their effect on BMD is still largely unknown.

Today, a great variety of contraceptive pills is available and allows to tailor hormonal contraception to patient's needs, including her needs for bone protection and BMD accrual.

Effect of Progestins Alone or in Combination with an Oestrogen on Bone

Animal Data In Vitro and In Vivo

Progesterone and promegestone (at pico- to nanomolar concentrations) are capable of stimulating the number of human osteoblastic cells derived from the iliac crest cells and to increase the concentrations of TGF-β, IGF-1 and IGF-2 [24]. Under similar in vitro conditions, nomegestrol is active on bone at concentrations of 1–100 nM [25]. Dydrogesterone and its active 20α-dihydro-metabolite stimulate human osteoblast-like cells, comparable to natural progesterone [26, 27]. Norethindrone in picomolar concentrations influences an osteosarcoma cell line; at nanomolar concentrations, norethindrone stimulates collagen synthesis in chicken calvarian organ cultures [28]. Other studies show that progesterone stimulates the proliferation of osteoblasts from foetal rat calvaria [29] and influences the proliferation of progenitor cells for osteoblasts derived from female but not from male rats [13]. The majority of published *in vitro* and *in vivo* studies in animals investigate older progestins and COCs.

There is a major limitation to *in vitro* studies: the metabolism of the progestins *in vivo* has not been respected. It is well known that studies comparing natural progesterone with synthetic progestins can be biased because progesterone undergoes a metabolic degradation and can disappear much more rapidly from cell cultures than synthetic compounds [30].

A 30 μg pill (30 μg EE + 0.15 mg desogestrel) has been tested in skeletally immature female rats. The results suggest that COC administration allows normal bone accrual and may improve bone geometry [31]. This experiment has not been repeated with low-dose pills (15 μg or 20 μg of EE). These data are in contradiction to an earlier study in skeletally immature adolescent female monkeys [32]. The monkeys received a triphasic pill containing 30 μg resp. 40 μg of EE combined with levonorgestrel. In these primates, prolonged continuous oral contraceptive use led to a lower peak bone mass.

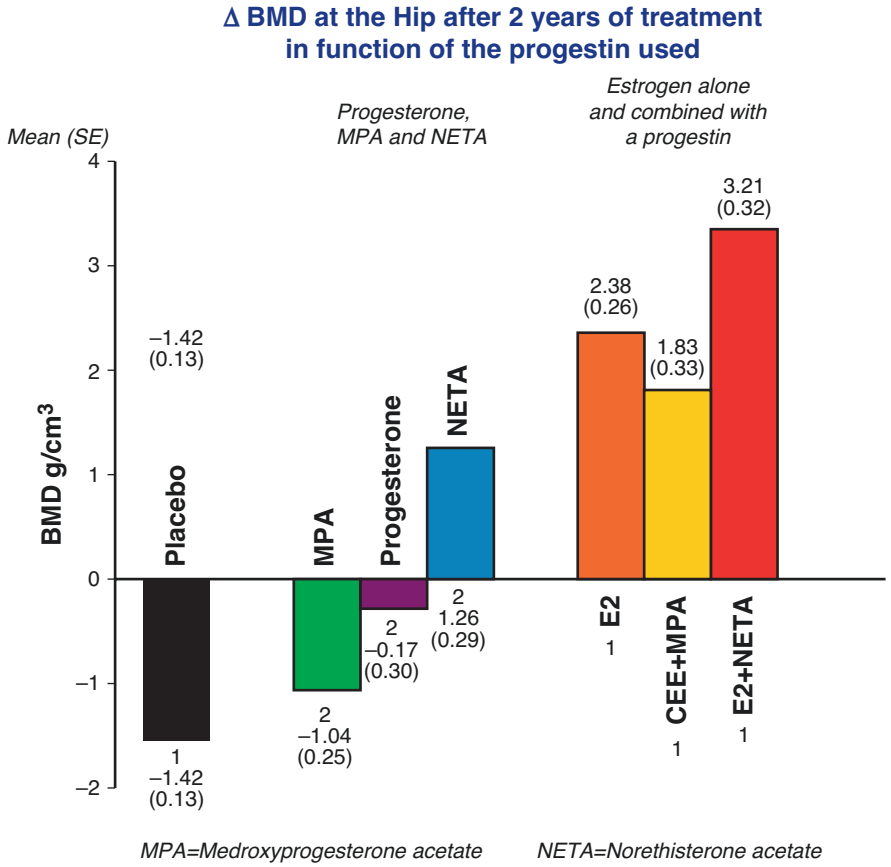
Effect of Progestins in Humans

Only a few progestins have been compared in human studies with bone as the primary study goal or compared in head-to-head studies. The 2-year results from the EPIC trial, a RCT, are shown on Fig. 21.4. Whereas MPA (5 mg/day perorally) induced at the hip a significant bone loss, NETA (1 mg/day perorally) resulted in a significant increase of BMD at the same site [33]. Similar results have been observed with the administration of LNG-Implants versus DMPA where the LNG-Implant but not DMPA led to an increase of BMD [34]. When NETA is combined with 17β-oestradiol (1–2 mg/day perorally), the stimulatory effect of E2 alone is increased. The combination of conjugated equine oestrogens (CEE 0.625 mg/day perorally) with MPA is inferior to E2 alone. The stronger effect of NETA compared to MPA on bone might be explained by the oestrogenic partial activity of NETA, but also by the fact that 0.35% of NET is aromatized into EE in the liver. This metabolization is clinically relevant [11]. The EPIC trial confirms that there is no class effect for progestins and that each progestin might act differently on bone.

The studies available suggest that progesterone and progestins modulate bone remodelling and may reduce bone loss. The postulated beneficial effect appears to be mediated, at least partly, by progesterone receptor expression in osteoblasts and also through androgen receptors as well as glucocorticoid receptors. Binding to the glucocorticoid receptor might reduce competitively the impact of glucocorticoids on bone [30].

The contradictory observations gained from animals and from basic human studies and the lack of RCTs investigating progestins alone in women let many questions open that might be relevant for a better understanding of the effect of different progestins alone on bone metabolism. There are no RCTs and no head-to-head studies in women comparing the effect on bone of newer progestins with the effect of older ones such as NETA or MPA without the concomitant administration of an oestrogen.

A review on RCTs comparing in head-to-head trials several COCs where EE has been combined with different progestins (levonorgestrel, norethindrone, desogestrel, gestodene, drospirenone; 50, 59–65) found no obvious and clinically relevant differences in their effect on BMD and bone markers. Although the evidence is limited, it might be that in user subgroups the different progestins exert due to their variable specific metabolic characteristics beneficial or neutral effects on BMD in an age-dependent way. It should be remembered that in primates, prolonged continuous oral contraceptive use leads to a lower peak bone mass [32].



Data from:

1) *Hosking DJ, McClung MR, Ravn P, Wasnich RD, Thompson OE. Dalev MS, Yates AJ for the EPIC Study Group. alendronate in the prevention of osteoporosis: EPIC study two-year results. J Bone Min Res 1996, 11, S1: p.133*
2) *Hosking DJ, McClung MR, Ravn P et al., data presented at the 18th ASBMR Annual Meeting 1996*

Fig. 21.4 Comparison of the effect on BMD in users of progesterone, medroxyprogesterone acetate (MPA), norethisterone acetate (NETA) alone or in combination with an oestrogen in comparison to placebo. E2 = 17β-oestradiol. CEE = conjugated equine oestrogens (data from [33])

21.3 Clinical Data in Postadolescent Women

21.3.1 Combined Oral Contraceptives Containing Ethinyloestradiol

21.3.1.1 Randomized Controlled Trials

In terms of methodology, the most valid studies for answering pharmacological questions are randomized placebo-controlled trials and direct comparative studies ("head-to-head" studies) of two or more COCs. Although placebo-controlled,

randomized double-blind studies are the gold standard for clinical pharmacological studies, their use for the investigation of COCs reaches natural limits because of the in contraception particularly problematic placebo arm. In the absence of RCTs, the best evidence comes from observational studies, cross-sectional studies and direct comparative studies reviewed below.

In spite of this limitation, several randomized controlled trials (RCTs) investigating the influence of COCs on bone metabolism and BMD have been published. It has been shown in a RCT that combined oral contraceptives exert a positive influence on bone turnover in young postadolescent women [35]. An early systematic review on the effect of COC on BMD in perimenopausal women [36] concluded that there is good evidence for a positive effect of COC on bone density in the perimenopause and fair evidence for a positive effect in "hypothalamic" oligo−/amenorrhoeic premenopausal women. However, fracture data are missing.

In 2014, a Cochrane analysis has been consecrated to RCTs looking at the effect of steroidal contraceptives on bone fractures in women [37]. The evidence varied in quality but was overall low. Eligible interventions included comparisons of a hormonal contraceptive with a placebo or with another hormonal contraceptive that differed in terms of drug, dosage or regimen. The analysis also included studies where a supplement has been provided. Nineteen RCTs were eligible. Eleven of these 19 trials compared different combined oral contraceptives (COCs) or different regimens of COCs. Only three RCTs provided evidence of moderate or high quality. One of these three trials showed no difference for the COC group versus placebo. The second reported a BMD decrease for the group with gestodene plus 15 μg EE per day. The third indicated a significantly lower bone resorption in the group with gestodene plus 30 μg EE per day than in users of COCs with EE 20 μg daily. However, there was overall no clearly demonstrable and clinically relevant difference in the change in BMD or in markers of bone metabolism between the examined combinations.

More recent RCTs are discussed below.

21.3.1.2 Observational Studies

Two early and very large prospective epidemiological studies of fracture in premenopausal women revealed a higher risk ratio for incident fracture in ever users of COCs compared with those who had never used a contraceptive pill [38, 39]. The Royal College of General Practitioners' Oral Contraception Study reported that COC users experienced a 20% increased relative fracture risk (RR 1.20, 95% CI 1.08–1.34) [39]. A comparable relative fracture risk (RR 1.3, 95% CI 1.1–1.5) was reported in the Oxford-Family Planning Association Contraceptive Study where fracture risk increased with longer use of COC [40]. However, both early observational studies had several methodological biases. They did not consider confounding factors for fracture such as a low body weight linked to alimentation and lifestyle, alcohol use or current smoking. Furthermore, they included younger women who might have had reproductive and skeletal immaturity.

Age at the time of COC use might have a decisive influence on later fracture risk [41]. A population-based Swedish case-control study in postmenopausal women (50–81 years of age) reports in 1327 COC past users and 3312 controls odds ratios for hip fractures depending from the age at use. The odds ratios for hip fracture (past

users vs. never users) were 0.69 (0.51–0.94) for use after age 40, 0.82 (0.57–1.16) for use at ages 30–39 and 1.26 (0.76–2.09) for use before age 30. These results imply that in postmenopausal women, oral contraceptive use late in reproductive life may reduce the risk of hip fracture.

A Cochrane review of observational studies published in 2015 [42] selected good evidence for its analysis of the effect of steroidal contraceptives on bone. Out of the initial 559 references, only 24 met the inclusion criteria. Finally, 14 original trials were included (7 case-control and 7 cohort studies), but only 6 studies provided moderate- or high-quality evidence (Table 21.3). In these six studies, possible associations between COCs and fracture risk have been analysed. A cohort study [39] reported an increased risk for all fractures (RR 1.20, 95% CI 1.08–1.34) in COC ever users. However, a case-control study of a subset of these data reported no association except for those with 10 years or more since use (OR 1.55, 95% CI 1.03–2.33) [43]. A UK cohort study [40] compared OC users and nonusers after having adjusted the relative risks (RRs) for age. Increased fracture risk was only noted for long-term users (97 months or longer) of OCs. For fractures of the radius and all fractures, the reported RRs were 1.5 (95% CI, 1.1–2.1) and 1.2 (95% CI, 1.1–1.4), respectively. When the interval since OC use was examined, two groups revealed an increased risk. For recent users (interval of 12 months or less), the reported RR for all fractures was 1.3 (95% CI 1.1–1.5). For an interval of 73–96 months, the RR for radius fracture was 2.5 (95% CI, 1.5–4.0).

The increased relative fracture risk of earlier studies has not been confirmed by the later findings of the WHI prospective observational cohort study in 93,725 postmenopausal women [44]; hazard ratios were adjusted for a number of important potential confounders. The investigators examined any oral contraceptive (COC) use, years of COC use and years of COC use after excluding women with a prior fracture. The adjusted relative hazard (HR) for fracture among past COC users was 1.07 (95% CI, 1.01–1.15). Small increased risks for first fracture were found for any COC use (HR 1.07; 95% CI 1.01–1.15) and for use ≤5 years. After excluding women with prior fractures, the latter finding was not evident (HR 1.09; 95% CI 1.01–1.18). Past use of COCs >5 years showed no significant difference between users and never users of COCs. A Danish case-control study [47] found an increased risk only for those who had filled in ten or more prescriptions (OR 1.09, 95% CI 1.03–1.16). A case-control study published in 2010 used the UK-based General Practice Research Database and examined the use of COCs and of depot medroxyprogesterone acetate (DMPA) [45]. Cases were 20–44 years old and had between 1995 and 2008 a first-time fracture diagnosis. Controls were randomly selected from the base population and matched on several variables including age. There was only one subgroup in the COC arm with a very modest but significant increase of fracture risk, similar to the Danish study. These three newer studies do not support earlier data suggesting that former COC use might protect against fractures in later years. On the other hand, it has to be stressed that the increased risks found in COC users are very low.

Table 21.3 Combined oral contraceptive (COC) use compared with nonuse for contraception (from sensitivity analysis [moderate to high quality evidence]); significant difference in fracture risk)

Patient or population: women			Setting: hospital or clinical site	
Intervention: OC use			Comparison: no use of OC	
Outcomes	Relative effect 95% CI	Participants (study)	Quality of evidence (GRADE)	Participant ages comparison
All fractures	RR 1.20 (1.08–1.34)	1365 [39]	⊕⊕⊕◯ Moderate	Mean age 29 years; ranged from <25 to >65 OC use ever vs never
First fracture	OR 1.55 (1.03–2.33)	819 [43]	⊕⊕⊕⊕ High	Age 20–87 years Last OC use >10 years vs. never
First fracture: radius or ulna; all sites	RR 1.5 (1.1–2.1); RR 1.2 (1.1–1.4)	17,032 [40]	⊕⊕⊕⊕ High	Recruited age 25–39 years; followed to 45 years; OC use >97 months vs no use
First fracture: radius or ulna; all sites	RR 2.5 (1.5–4.0); RR 1.3 (1.1–1.5)	17,032 [40]	⊕⊕⊕⊕ High	Recruited age 25–39 years; followed to 45 years; Interval since use: 73–96 months vs no use (radius or ulna); <12 months vs no use (all fractures)
First fracture	HR 1.07 (1.01–1.15); HR 1.09 (1.01–1.18)	80,947 [44]	⊕⊕⊕◯ Moderate	Recruited age 50–74 years; OC use: any vs none; <5 years vs none
First fracture	OR 1.09 (1.03–1.16)	87,627 [45]	⊕⊕⊕◯ Moderate	Age 20–44 years; Current OC use >10 prescriptions vs no use
Fracture, any	OR 1.50 (1.03–2.18); OR 1.30 (1.05–1.61)	258,189 [46]	⊕⊕⊕◯ Moderate	Mean age 51.7 years OC daily dose 0.3–0.99 tablet vs never user; <15 years old; 15.1–17 years old
Fracture, any	OR 1.42 (1.09–1.84); OR 1.13 (1.05–1.22)	258,189 [46]	⊕⊕⊕◯ Moderate	Mean age 51.7 years; OC ethinyl estradiol dose changed between 20 μg and > 30 μg vs no OC use: 15.1–17 years old; > 19 years old

Adapted from [42]; data from [39, 40, 42–47]
Ci confidence interval, *RR* relative risk, *0Fi* odds ratio, *HR* hazard ratio
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

The Cochrane review [42] concluded in 2015 that observational studies do not suggest an overall association between oral contraceptive use and fracture risk but that some specific subgroups may have an increased risk. However, a later retrospective case-control study from the UK in 12,970 women (mean age 37.8 years) again supports the hypothesis of a bone protective effect of COCs. 6485 women with and 6485 women without fractures from 135 general practitioner offices in the UK have been compared [48]. The use of oral contraception was associated with a significantly lower risk of bone fracture (OR 0.81, 95% CI 0.74–0.90). This effect was strongest in the age groups 18–25 and 26–35 and in patients having used COCs for more than 1 year. In this retrospective case-control study, women without bone fractures were significantly more likely to have had exposure to COCs, especially when the duration of pill use was ≥5 years. These and some older data in adult women suggest that in healthy users ≥30 years of age, COCs may not increase fracture risk and might actually protect against bone loss in subgroups. This discrepancy can only be solved by prospective randomized long-term studies.

The clinically relevant data in adolescents using pills with 15–20 μg EE is discussed below.

21.3.1.3 Cross-Sectional Studies

Cross-sectional studies on the influence of COCs on bone density show no clinically significant differences in adult women compared to controls [49–59]. A subanalysis of a large cross-sectional study was performed in a group of women between the ages of 19 and 30 using COCs with doses of <35 μg EE for more than 12 months. This subgroup shows significantly lower BMD measurements at all sites [55]. Compared to controls without COC, COC users showed a nonsignificant, 5% lower bone density on the femoral neck. An open, nonrandomized cross-sectional study in COC users (daily administration of 20 μg EE and 0.15 mg desogestrel) showed no BMD increment, whereas nonusers had a BMD increase of 7.8% after an observation time of 5 years. These data point to the possibility that in adolescents starting early long-term use of low-dose COCs (20–35 μg EE per day), the expected normal peak bone mass (PBM) may not be reached or might be delayed [57] (see below).

21.3.2 Combined Oral Contraceptives Containing 17β-Oestradiol or 17β-Oestradiol Valerate

The first natural oestrogen introduced into hormonal contraception was oestradiol valerate (E2V) associated with dienogest (DNG) in a quadriphasic regime in which the dose of oestrogen and progestin followed the physiological pattern of the ovarian and endometrial cycle for 26 days plus 2 days of placebo (E2V/DNG-containing COC). The four hormonal phases of E2V/DNG-containing COC extend over 28 days as follows: 3 mg E2V for 2 days, 2 mg E2V + 2 mg DNG for 5 days, 2 mg E2V + 3 mg DNG for 17 days and 1 mg E2V per 2 days and placebo for 2 days. The early oestrogenic dominance (3 mg E2V for 2 days) ensures good initial endometrial proliferation, while the association of E2V and DNG and the dominance of the latter in the

middle to late part of the cycle, followed by modest oestrogenic activity in the final phase, ensure satisfactory endometrial stability [60, 61]. In the second E2-COC approved, natural E2 (1.5 mg) is associated with nomegestrol acetate (2.5 mg) in a monophasic formulation following a 24/4 day regime [60–62]. Surrogate parameters suggest that E2-COCs are metabolically better tolerated than EE-COCs.

COCs. The more favourable clotting parameters observed might be a clinical advantage. If these new hormonal settings have a specific impact on bone has not been studied. For both preparations, there is no evidence available for their influence on BMD, peak bone mass accrual and fracture risk.

21.3.3 Combined Oral Contraceptives Containing Oestetrol

As phase II and phase III studies have shown, E4 can be used as an oestrogen for MHT as well as for contraception. E4 acts as an oestrogen agonist for the bone, but long-term bone data are still missing. Clinical studies demonstrated that the combination of E4 with drospirenone is reliable and safe and that its metabolic profile is better than the one of COCs containing EE [16–20]. The first preparation should soon be approved. It combines E4 with drospirenone [16]. No data have been published yet on the effect on BMD, peak bone mass accrual and fracture risk.

21.4 Influence of Low-Dose COCs (15–20 μg EE Daily) on Bone Metabolism

21.4.1 Adult Women

In adult women, two early RCTs revealed no negative effect of low-dose COCs delivering 15–20 μg EE daily on bone metabolism and BMD when compared with COCs delivering 30 μg EE. A prospective randomized trial in 48 volunteers aged 20–35 years compared 2 COCs which administered 30 μg respectively 20 μg EE per day [63]. After 3 years of treatment, BMD had not changed, and no significant difference has been observed between the two treatment groups in the change of bone markers. The second RCT included 56 healthy young women aged 22–34 years. It compared two low-dose COCs releasing 15 μg EE and 30 μg EE [64]; 19 healthy fertile women were used as untreated controls. At 12 months, no statistically significant difference in spinal BMD values was detected between the three groups. There was no difference between end-of-study and basal BMD values. In both COC groups, urinary levels of bone markers (urinary pyridinoline (PYR) and deoxypyridinoline (D-PYR)) have been significantly reduced in comparison with basal values and with controls ($p < 0.05$). These metabolic results confirmed an older RCT studying the effect of two groups of COC users (20 μg resp. 30 μg EE daily) on bone resorption markers (PYR and D-PYR) in young adult women aged 22 and 30 years; there was no difference between the two COC preparations [65]. In healthy perimenopausal women [51], BMD measurements increased significantly ($p < 0.05$) in users of two of the three 20 μg pills tested compared with nonusers [51].

This evidence of moderate quality leads to the conclusion that in young postadolescent women >30 years of age and in perimenopausal women, preparations containing 15–20 and 30 μg EE are both capable of maintaining BMD and should be sufficient for bone protection. Unfortunately, these conclusions have been inadvertently applied to adolescent women using a pill before the acquisition of peak bone mass although the results from some published studies performed in younger women might have raised suspicion.

21.4.2 Adolescent Girls

Observational studies and RCTs in adolescents have frequently inherent limitations such as small sample size, inclusion of smokers and poor accounting for other confounders. Up to 2015, the evidence available for the effect of COCs administering 15–20 μg EE per day on the skeleton in adolescent girls was unequal and mostly of low quality [53, 57, 59, 66–77]. In RCTs, a placebo arm is ethically highly problematic in girls of the age group between menarche and 18 years. Therefore, the evidence available is limited.

As early as in 1995, a prospective observational study in young women (10–22 years) suggested that long-term treatment with an oral monophasic contraceptive formulation (EE 20 μg + desogestrel 0.150 mg) prevents the occurrence of the physiologic peak of bone mass in adolescents [57]. This and later observations in adolescents between 12 and 18–20 years have been raising the suspicion that administration of low-dose COCs administered before peak bone mass has been reached might decrease BMD accrual and compromise bone quality in adult life [38, 78, 79].

Earlier smaller observational studies, done in adolescent girls below the age of 19 years and using different pills containing EE from 15 to 35 μg EE, are contradictory [75–77]. One of these studies found no difference in BMD changes between COC users and controls [77]. Another prospective observational study compared three groups of healthy adolescent girls aged 16–19 years (n = 92). Group 1 and group 2 used COCs (15 resp. 30 μg EE), and group 3 had no hormonal contraception (controls). The results demonstrate a nonsignificant superiority of BMD accrual in controls compared with users of both groups taking COCs [75]. A prospective cohort study in a population-based sampling strategy recruited adolescent girls aged 14–18 years. They have been classified by the EE content of the COC (30–35 μg EE, n = 241, and < 30 μg EE, n = 241). Women aged 14–18 years on the higher EE dose of current COC formulations showed approximately 1% less bone gain over 2 years in the spine and total body than did the adolescents without hormonal contraception or on the lower-dose COCs [76]. Finally, in a nonrandomized parallel-control study in 67 adolescents aged 12 to 19 years, divided into COC users (20 μg EE, n = 41) and controls (nonuser, n = 26), pill users presented with lower bone mass acquisition in the lumbar spine compared with controls, confirming an older suspicion [80]. The difference between users and nonusers was statistically

significant ($p < 0.05$) [74]. These smaller observational studies suggest that the association between COC formulations and bone density is influenced by age, oestrogen dose, length of use and skeletal site.

Four larger studies (>120 COC users each) included in the meta-analysis of 2015 [42] support a clinically relevant inhibiting effect of low-dose COCs on peak bone mass accrual:

- A prospective controlled study [66] in 370 adolescents (mean age at baseline 16.0 ± 1.4, range 12–18 years) reports that long-term receipt of an oral monophasic contraceptive formulation (EE 20 μg + desogestrel 0.150 mg) lowers significantly the increase in mean percent change in lumbar spine BMD compared with controls ($n = 79$). BMD gain in COC users (2.3% [95% CI 1.49–3.18]) was significantly inferior to the increase seen in controls [$n = 107$] (3.8% [95% CI 3.11–4.57]; p = 0.03).
- In a prospective controlled comparative study (DMPA vs. COC, $n = 703$) over 36 months [72], BMD measurements of DMPA and users of a COC (20 μg EE daily) declined from baseline values. Age was found to be an important determinant of BMD change by contraceptive methods. COC users 16–24 years old lost significantly more bone density at the spine (0.4% vs. 0.8%, $p = 0.013$) than women 25–33 years of age.
- An open-label randomized comparative trial of 2 CHC agents with nonrandomized controls [73] included 450 women 16–18 years of age. One hundred fifty women were using a 30 μg EE pill combined with desogestrel, 150 women were using a 35 μg EE pill combined with cyproterone acetate (CPA), and 150 women were using nonhormonal contraception as control subjects. The increase in mean percent change in lumbar spine and femoral neck BMD in the EE/CPA group were smaller than those in the control group (1.88% vs. 0.30% and 0.98% vs. 0.49%, respectively). At 24 months of treatment, lumbar spine and femoral neck mean BMD values in women who used EE/desogestrel ($n = 127$) were slightly but not significantly lower compared with baseline ($p = 0.837$ and $p = 0.630$, respectively) [73].
- A 4-year follow-up in 122 adolescent women aged 12–19 years using COCs delivering ≤35 μg EE daily for more than 2 years revealed a significantly smaller increase in mean-adjusted lumbar and femoral BMD in COC users (1–2 years) compared with nonusers suggesting that low-dose EE preparations suppress normal BMD accrual in adolescent women [53].

These studies point to the conclusion that pills having ≤20 μg EE inhibit in adolescents bone accrual more than COCs containing 30–35 μg EE.

Recent evidence confirms such a diminished BMD accrual and an increased risk for any fracture among adolescents (12–24 years) using low-dose pills (15–20 μg EE daily) before PBM is reached [67–74, 81] (Figs. 21.1, 21.2, 21.3 and 21.4):

- A randomized prospective open-label trial with nonrandomized controls examined the skeletal effect of 20 vs. 30 μg EE-COC vs. control subjects [71]. This RCT compared bone accrual in 829 adolescent girls (12–18 years) using a 20 μg or a 30 μg COC with BMD accrual in nonusers (reference group). Mean changes in lumbar spine BMD were + 2.26% with EE 30 μg/LNG, +1.45% with EE 20 μg/LNG and + 2.50% in the reference group. A statistically significant difference was found between 20 μg EE/LNG and the reference group (1.05%; 95% CI, 0.61–1.49%), but not between LNG/30 μg EE and the controls (0.23%; 95% CI, −0.20% to 0.67%). Noninferiority of the EE 30 μg/LNG regimen compared with the reference group was confirmed. This RCT demonstrates that bone accrual is significantly lower only among EE 20 μg/LNG users compared to untreated controls. There is no difference between EE 30 μg/LNG users and controls.
- A nonrandomized prospective parallel-control study with a 1-year follow-up in 67 adolescents aged from 12 to 19 years [74] divided 67 volunteers into COC users ($n = 41$) taking 20 μg EE/desogestrel and COC nonusers (controls, $n = 26$). BMD by DEXA has been evaluated at baseline and after 12 months. The COC users presented with low bone mass acquisition in the lumbar spine. BMD and BMC median variations between the measurements at baseline and 12 months were of −2.07% and − 1.57%, respectively. The control group had median variations of +12.16% and + 16.84% for BMD and BMC, respectively, over the same period. The total body BMD and BMC showed similar evolutions during the study in both groups. Statistical significance ($p < 0.05$) was seen for the BMC percentage variation between COC users and nonusers. The authors conclude that use of a low-dose COC containing 20 μg EE/desogestrel is associated with lower bone mass acquisition in adolescents during the intake period.
- In a prospective longitudinal population-based cohort study in 527 randomly selected adolescent girls and young adults, COC users (average age at starting COC, 16.6 years) demonstrated in the hip region less peak BMD accrual than nonusers [70]. However, adjusted 2-year BMD change was not significantly associated with average EE doses of <30 μg ($n = 119$) compared with average doses ≥30 micrograms ($n = 71$) at any site. The following two studies putting the limit at 20 and not 30 μg EE reveal a different picture.
- In a recent prospective observational study, adolescents (<20 years) were divided into three groups: oral contraceptives 1 ($n = 42$; 20 μg EE/desogestrel), oral contraceptives 2 ($n = 66$; 30 μg EE/drospirenone) and a control group ($n = 70$). Both pill groups 1 and 2 were associated with lower bone gain and lower bone formation markers than group 3 (untreated controls). Comparison of BMD at baseline and after 1 year showed no significant difference between the 20 μg and the 30 μg pill groups, but a trend to lower BMD values in the 20 μg EE group [69]. Unfortunately, no measurements have been taken after 2 years.
- The purpose of the most recent study in female college students was to compare bone mineral density (BMD) and bone turnover markers between combined oral contraceptive (COC; age = 19.2 ± 0.5 years) and COC nonusers (age = 19.3 ± 0.6 years) over 12 months [67]. COC users were taking medications containing 20–35 μg of EE, combined with various progestins. Nonusers of

COCs increased whole-body BMD, while COC users demonstrated elevated bone turnover, a decline in spinal BMD and lack of whole-body bone acquisition over 12 months. Users of low-dose pills (20 μg EE) showed a significant decline in BMD of the lateral spine ($p = 0.046$) over 12 months, whereas users of pills releasing 30–35 μg EE daily did not.

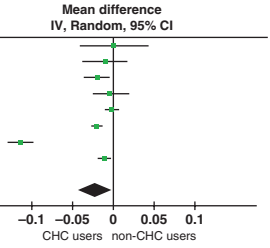
A **meta-analysis** published in 2019 reviewed the effect of low-dose CHCs on peak bone mass in adolescent girls [68]. The 12-month and the 24-month weighted mean differences in mean absolute change from baseline in g/cm for spinal areal BMD in adolescent CHC users and nonusers resp. in controls have been assessed in two random effects forest plots (Fig. 21.5). The weighted mean differences are significant at 12 months (IV, random −0.02; 95% CI −0.05, −0.00) and at 24 months (IV, random −0.02; 95% CI −0.04, −0.01). This strong review points out that low-dose COCs delivering 15–20 μg EE per day are of eminent concern in adolescents starting to use COC early. The most critical group are starters of COCs delivering 15–20 μg EE per day within the first 3 years after menarche.

Random-effects forest plots assessing the 12-mo and 24-mo weighted mean difference in mean absolute change from baseline in g/cm for spinal areal bone mineral density (BMD) in adolescent-combined hormonal contraceptives (CHC) users and nonusers/controls

a

Study or subgroup (Reverence)	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
Cromer (84)	0.016	0.055	9	0.015	0.041	17	9.4%	0.00 [−0.04, 0.04]	1996
Lara-Torre (80)	0.013	0.034	16	0.023	0.036	10	11.4%	−0.01 [−0.04, 0.02]	2004
Cromer (83)	0.02	0.056	62	0.04	0.04	95	12.9%	−0.02 [−0.04, −0.00]	2008
Berenson (75)	0.008	0.042	36	0.011	0.032	14	12.3%	−0.00 [−0.02, 0.02]	2008
Scholes (79)	0.007	0.041	115	0.008	0.014	75	13.6%	−0.00 [−0.01, 0.01]	2011
Gai (76)	−0.01	0.027	277	0.01	0.035	136	13.7%	−0.02 [−0.03, −0.01]	2012
Biason (77)	−0.01	0.03	26	0.104	0.03	35	13.0%	−0.11 [−0.13, −0.10]	2015
Gersten (74)	0.015	0.06	240	0.026	0.036	372	13.6%	−0.01 [−0.02, −0.00]	2016
Total (95% CI)			**781**			**754**	**100.0%**	**-0.02 [-0.05, -0.00]**	

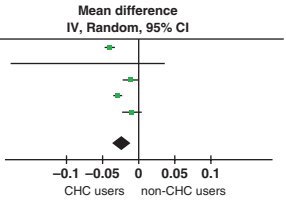
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 175.38$, $df = 7$ ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 2.08$ ($P = 0.004$)



b

Study or subgroup (Reference)	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
Cromer (83)	0.02	0.023	62	0.06	0.025	95	26.2%	−0.04 [−0.05, −0.03]	2008
Berenson (75)	−0.039	0.29	29	0.032	0.02	8	1.6%	−0.07 [−0.18, 0.04]	2008
Scholes (79)	0.011	0.037	93	0.0216	0.032	55	23.9%	−0.01 [−0.02, 0.00]	2011
Gai (76)	−0.01	0.027	261	0.019	0.035	115	26.5%	−0.03 [−0.04, −0.02]	2012
Braijic (73)	0.002	0.035	113	0.011	0.047	54	21.9%	−0.01 [−0.02, 0.01]	2017
Total (95% CI)			**558**			**327**	**100.0%**	**-0.02 [-0.04, -0.01]**	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 26.29$, $df = 4$ ($P < 0.00001$); $I^2 = 85\%$
Test for overall effect: $Z = 3.41$ ($P = 0.0006$)



a This random-effects forest plot assessed the 12-mo weighted mean difference in mean absolute change from baseline in g/cm for spinal areal bone mineral density (BMD) in adolescent-combined hormonal contraceptives (CHC) users and nonusers/controls

b This random-effects forest plot assessed the 24-mo weighted mean difference in mean absolute change from baseline in g/cm^2 for spinal areal bone mineral density (BMD) in adolescent-combined hormonal contraceptives (CHC) users and nonusers/controls

Fig. 21.5 Random effects forest plot assessing the 12-month and 24-month weighted mean difference in mean absolute change from baseline in g/cm for spinal areal bone mineral density (BMD) in adolescent combined hormonal contraceptive (CHC) users and nonusers/controls. (adapted from [68])

21.5 Nonoral Combined Hormonal Contraceptives

21.5.1 Combined Vaginal Ring

In a cross-sectional multicentre study in women aged 18–35 years, the effect of a vaginal ring ($n = 76$) on BMD was compared with that of a nonhormonal intrauterine device (IUD) ($n = 31$) over 2 years. While there was no change in bone density under the vaginal ring releasing 15 μg of EE and 120 μg of etonogestrel daily, there was a significant increase in bone density in the nonhormonal comparison group (difference between groups $p < 0.0001$) [82]. No data in adolescent girls <18 years and no comparative studies with COCs are currently available. There is an urgent need for research on the effect of combined vaginal rings on the accrual of PBM in young adolescent girls.

21.5.2 Combined Contraceptive Patch

No published epidemiological data or results of comparative studies on COCs are currently available for combined contraceptive patches. There is only one RCT comparing a combined contraceptive patch with a combined vaginal ring [83]. It did not find any significant differences in bone metabolism between transdermal contraception (20 μg EE + norelgestromin 150 μg) and a vaginal ring (15 μg EE +120 μg of etonogestrel), but in the two treatment arms, urinary levels of PYD and D-PYD and osteocalcin decreased significantly from basal levels ($p < 0.05$), in contrast to the control group. More data on contraceptive patches are urgently needed, particularly on the accrual of PBM in young adolescent girls.

21.6 Progestin-Only Ovulation Inhibitors

21.6.1 Oral Preparations

21.6.1.1 Classical "Minipill" (30 μg Levonorgestrel per Day)

There are currently no epidemiological data or results of RCTs available comparing BMD or fracture rate in "minipill" vs. COC users. A British study [84] had shown that during regular peroral administration of 30 μg levonorgestrel/day, the mean oestradiol concentration decreases only moderately, from 653 pgmol/L to 500 pgmol/L, in contrast to the stronger E2 suppression observed with the progestin-only pill administering desogestrel 0.075 mg per day. If the higher E2 concentration in users of the classical "minipill" might guarantee a normal bone metabolism and the acquirement of a normal peak bone mass in adolescents is not known.

The effect of the classical "minipill" on bone metabolism and BMD has not been studied in young women although this progestin-only pill could be of particular interest for the use in adolescents <18 years. Long-term studies in adolescent girls are needed for the 30 μg levonorgestrel pill.

21.6.1.2 Desogestrel Tablets (0.075 mg per Day)

There are currently no published epidemiological data from comparative studies with COCs available. The product information of the original preparation (Cerazette®) states that Cerazette® leads to a reduced oestradiol serum level, which corresponds to that of the early follicular phase. So far it is unknown whether this decrease has a clinically relevant effect on bone mineral density and the acquisition of a normal peak bone mass in adolescents, particularly on the accrual of PBM in young adolescent girls.

21.6.2 Hormonal Implants

21.6.2.1 Etonogestrel Implants

The original product Implanon NXT® releases 60–70 µg etonogestrel/day at 5–6 weeks after administration, 35–45 µg/day after 2 months, 30–40 µg/day after 24 months and 25–30 µg/day after 36 months. There is no RCT or observational study comparing the effect in users of etonogestrel implants on bone metabolism with untreated controls. The only direct comparative RCT available compares BMD changes at the forearm in users of the etonogestrel implant Implanon® with users of the LNG implant Jadelle®. 111 women aged 19–43 years used either Implanon® ($n = 56$) or Jadelle® ($n = 55$) [85]. In all volunteers, BMD at the mid-shaft of the ulna was significantly lower at 18 months of use compared with baseline. There was no difference between Implanon® (−3.75%; $p < 0.001$) and Jadelle® users (−3.36%; $p < 0.002$). In both groups, there was no BMD difference compared to baseline at the distal radius [85]. A cross-sectional study in 100 women for at least 2 years reports that long-term users of Implanon® had a significantly lower BMD at the distal radius and ulna than the controls [86]. These data are in contradiction to the product information of Implanon NXT® declaring that "In a two-year study in 44 users, the bone density was compared to a control group of 29 users of a non-hormonal IUD, and no undesirable influences on the bone mass were observed". The evidence available does not allow to draw any conclusions for the long-term effect of etonogestrel implants on fracture rate in adults and old age.

21.6.2.2 LNG Implants

There are several LNG implants on the market, but there exists just one RCT comparing the original product Norplant® to one of its generics in young women [87]. For Norplant® and its generic, no decrease of BMD and no significant adverse effect on achieving maximum bone mass in young women have been found [87, 88]. No RCTs comparing LNG implants with healthy untreated controls are available. This poor evidence does not allow to draw any conclusions for the long-term effect of LNG implants on fracture rate in adults and old age.

21.6.3 Levonorgestrel Intrauterine System (LNG-IUD)

Today, there are a variety of intrauterine systems releasing LNG available. The serum levels published by the manufacturer are listed on Table 21.4. For LNG-IUDs, no RCTs or comparative studies with COCs are currently available. A Danish case-control study [42, 47] reports a reduced fracture risk for ever use and for longer use of different LNG-IUDs (OR 0.75, 95% CI 0.64–0.87). Fracture risk is also reduced for those who used the hormonal IUD for 1.6 to 4 years (reported OR 0.77, 95% CI 0.59–0.99). From the LNG-serum levels on Table 21.4, it may only be concluded that the effect of LNG-IUDs on bone should not be inferior to the one of the classical "minipill".

21.6.4 Depot Medroxyprogesterone Acetate (DMPA)

Depot preparations are injected every 3 months. In most countries, there are two original preparations available: DMPA (150 mg i.m.) and DMPA (104 mg s.c.).

21.6.4.1 DMPA (150 mg i.m.) and DMPA (104 mg s.c.) After Acquisition of Peak Bone Mass

Effect on Fracture Risk: In 2015, a Cochrane review analysed the effect of DMPA (150 mg i.m.) on fracture rate [42]. Although there is a large body of literature available with BMD as an outcome in DMPA users, there have been only a few reports on fracture risk. A Cochrane analysis ([42], Table 21.5) identified two observational studies [45, 89] having a moderate quality of evidence. In these studies, current and past users of DMPA were generally more likely to have had a fracture than nonusers. The odds increased slightly with the number of prescriptions. Vestergaard et al. [89] reported a slightly but significantly increased fracture risk for DMPA (150 mg

Table 21.4 Mean serum levels of levonorgestrel (LNG) in users of intrauterine devices releasing LNG (original preparations only)

Preparation	Mean serum levels	
Name	At 3 yrs	At 5 yrs
Mirena® (5 yrs) (Bayer)	n.i.	131 pg/ml (range 113–161)
Levosert® (5 yrs) (Gedeon Richter)	127 pg/ml (CI 41.2%)	110 pg/ml (CI 38.8%)
Kyleena® (5 yrs) (Bayer)	91.3 pg/ml (CI n.i.)	83.1 pg/ml (CI n.i.)
Jaydess® (3 yrs) (Bayer)	59 pg/ml (CI n.i.)	

n.i. no information

The maximal serum LNG levels in users of Microlut® (30 µg levonorgestrel per tablet) listed for comparison are 7–10 times higher

All data are taken from the product information published by the manufacturers

For comparison

Microlut® (30 µg levonorgestrel per tablet)

- Maximal plasma levels at 60 min. After intake: approx. 800 pg/ml
- Half-life (first phase): approx. 1 h
- Half-life (second phase): approx. 20 h
- Steady state reached after 2–3 weeks

Table 21.5 Progestin-only contraceptive use compared with nonuse for contraception (adapted from [42]; data from [42, 45, 89])

Patient of population: women			Setting: hospital or clinical site	
Intervention: OC use			Comparison: no use of OC	
Outcomes	Relative effect 95% CI	Participants (study)	Quality of evidence (GRADE)	Participant ages comparison
Fracture [47, 89]	OR 1.44 (1.01–2.06); OR 2.25 (1.14–4.42); 1.94 (1.09–3.45); OR 2.16 (1.32–3.53)	258,189	⊕⊕⊕◯ Moderate	Mean age 5.17 years DMPA use vs no use; ever use; use among women >50 years old; daily dose >1; use >4 years
Fracture [47, 89]	OR 0.75 (0.64–0.87); OR 0.77 (0.59–0.99)	258,189	⊕⊕⊕◯ Moderate	Mean age51.7 years Hormonal IUD use vs no use; ever use; 1.6–4 years
Fracture [45]	OR 1.36 (1.15–1.60); OR 1.54 (1.33–1.78)	87,627	⊕⊕⊕◯ Moderate	Age 20–44 years DMPA current use vs no use; use 3–9 years; use >10 years
Fracture [45]	OR 1.17 (1.07–1.29); OR 1.23 (1.11–1.36); OR 1.30 (1.09–1.55)	87,627	⊕⊕⊕◯ Moderate	Age 20–44 years DMPA past use (prescriptions) vs no use; 1–2; 3–9; >10

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

i.m.) in users compared to nonusers; the reported global OR was 1.44, 95% (95% CI 1.01–2.06). Increased risk was more apparent among women over 50 years of age (reported adjusted OR 2.25, 95% CI 1.14–4.42), those with regular use (reported OR 1.94, 95% CI 1.09–3.45) and those who used DMPA for more than 4 years (reported OR 2.16, 95% CI 1.32–3.53). Meier et al. [45] reported in females aged 20–44 years an increased risk for any past use, including after only one or two prescriptions (OR 1.17, 95% CI 1.07–1.29). For current users with three to nine prescriptions, the reported adjusted OR was 1.36 (95% CI 1.15–1.60). For current users with one to seven DMPA injections, the adjusted OR was 1.47 (95% CI 1.40–1.54) and for those with ten or more prescriptions, 1.54 (95% CI 1.33–1.78). DMPA users have a significantly higher fracture risk than COC users. A direct comparison of users of ten or more prescriptions of DMPA with users of ten or more prescriptions of other hormonal contraceptives yielded an OR of 1.46 (95% CI = 1.15–1.85) [45].

A retrospective cohort study not included in the Cochrane analysis [90] compared in 312,395 contraceptive users the fracture incidence of women under DMPA to that of women who were known not to use DMPA. The relative incidence rate ratio (IRR) for all fractures in women with first-time use of DMPA (n = 166,367) occurring in the observation period and the last 6 months before and after the first contraceptive use was evaluated. When comparing the users of DMPA with the women who did not use DMPA, the IRR for all fractures before use (IRR 1.28; 95% CI 1.07–1.53) against current use was comparable to that after application (IRR 1.37; 95% CI 1.29–1.45). A recent case-control study in women aged 22–44 years [91] compared the adjusted OR for first-time fractures in 4189 DMPA users (150 mg i.m.) with 4189 matched controls. The adjusted OR in current users was 0.97 (95% CI 0.51–1.86), 2.41 (95% CI 1.42–4.08) and 1.46 (95% CI 0.96–2.23) for 1–2, 3–9 and ≥ 10 prescriptions, respectively, and the adjusted OR for developing a fracture in past users of DMPA compared to nonusers 0.96 (95% CI 0.73–1.26), 1.14 (95% CI 0.86–1.51) and 1.55 (95% CI 1.07–2.27) for 1–2, 3–9 and ≥ 10 prescriptions.

Effect on BMD Many older studies published on adult current users of DMPA have been cross-sectional. Those measuring central sites such as the lumber spine and femoral neck have mostly shown negative effects of DMPA on BMD, while those that have shown no effect of DMPA have generally measured the forearm. No study has shown a positive effect of DMPA on BMD [92].

There is strong evidence from longitudinal data demonstrating that DMPA compromises BMD in adult current users. Berenson et al. confirmed an earlier RCT over 12 month of the same group [93] by conducting a 3-year follow-up study in women aged 16–33 years. DMPA users lost 3.7% BMD in the spine and 5.2% in the femoral neck compared with BMD increases in controls. The loss was greatest in younger users (16–24 years) [72]. Kaunitz et al. [94] presented data from a 5-year prospective cohort study in women aged 25–35 years. BMD changes in new DMPA users (n = 248) were compared with those in women using nonhormonal contraception (n = 360) for up to 240 weeks of treatment and 96 weeks of posttreatment follow-up. At week 240 of treatment, mean percentage changes from baseline in DMPA vs. nonhormonal subjects were − 5.16% in *users* (n = 21) vs. +0.19% in controls (n = 65) at the total hip ($p < 0.001$) and − 5.38% in users (N = 33) vs. +0.43% in controls (n = 105) at the lumbar spine ($p < 0.001$). For the subgroup who received more than four injections over a 60-week period, the average decrease in bone density in the hip and femoral neck was −6.4% and −5.4%, respectively. In the follow-up period after the end of the treatment, the baseline values for the bone density at the lumbar spine were again reached within about a year and for the bone density in the hip after about 3 years. However, a large number of participants did not complete the study so that the final results are based on a smaller number of participants (71 women at 60 weeks and 25 women at 240 weeks after the end of therapy).

In perimenopausal women aged 45–53 years (103, cited in 58), a controlled clinical study showed an average decrease in bone density at the lumbar spine and hip on DMPA treatment (150 mg at 12-week intervals). Over a period of up to 5 years, there was a decrease of −6% in the DMPA, but none in the control group. After 1, 2, 3, 4 and 5 years, the average cumulative decrease in bone density at the lumbar

spine was −2.86%, −4.11%, −4.89%, −4.93% and −5.38%, respectively, in DMPA users. The average values measured at the hip and the femoral neck were comparable. The decrease in bone density was more pronounced in the first 2 years than in the later years of use.

Several trials included DMD changes in BMD after discontinuation of the treatment. When DMPA (150 mg i.m.) treatment is discontinued and ovarian oestrogen production increases, the decrease in bone density appears to be reversible in both adult and adolescent women [94–96]. However, prolonged treatment was associated with a lower bone density restitution rate. It has not yet been completely clarified whether the possible structural changes in bone architecture are reversible.

DMPA (104 mg s.c.) users of all ages may also experience a decrease in bone density. The results of a comparative study [97] on the changes in bone density within two test groups (DMPA (104 mg s.c.) vs. DMPA (150 mg i.m.)) showed a total decrease in BMD after 24 months at the lumbar spine of −4.3% resp. −5.0% and at the total femur of −3.3% resp. −3.6%. After 36 months, there was an average drop in the lumbar spine of −5.4% resp. –4.6% and in the total femur of −5.5% resp. −5.2%. After a treatment period of 2 years, there was no significant difference between the two groups.

21.6.4.2 Changes in Bone Density and Fracture Rate in Adolescent DMPA Users Before the Acquisition of Peak Bone Mass

A loss of BMD is of particular importance in adolescence and early adulthood, as this is the crucial phase for the formation of the peak bone mass [98]. The two observational studies of Meier et al. [45] and Vestergaard et al. [89] did not include young women below the age of 20 years, so that we have to rely on smaller studies. In the recent case-control study of Kyvernitakis et al. [91], the highest fracture risk was identified in young patients less than 30 years with longer DMPA exposure (≥10 prescriptions) (DMPA vs. controls, OR 3.04; 95% CI 1.36–6.81), as well as in patients in the late reproductive years with past use of DMPA (DMPA vs. controls, OR 1.72, 95% CI 1.13–2.63). All but one study confined to the adolescent age group of 12–18 years revealed BMD losses in DMPA users that contrasted with significant increases observed among control participants not receiving hormone treatment [77, 99–101]. Odds increased slightly with the number of prescriptions. Edwards et al. [100] report after 18 months of treatment a BMD decrease from baseline by −3.8% in the DMPA group (n = 10) and BMD increases by +6.1% in COC users (n = 4; $p < 0.05$) resp. by +2.0% in normally menstruating untreated adolescents [100]. In prospective study by Busen et al. [101] in 17 DMPA users between the ages of 15 and 19 years (mean = 16.7, SD = 1.6), BMS decreased after 12 months by (mean ± SD) -3.31% ± 0.16 at the femoral neck (p = 0.013) and by −3.52 ± 2.4 at the lumbar spine [101]. When these three longitudinal studies [77, 100, 101] performed in adolescent users of DMPA (12–18 years of age) are pooled, the mean loss of BMD at the lumbar spine ranges from −1.59% to −3.52% after 1 year and from −3.44% to −5.99% after 2 years of treatment [99]. In contrast, untreated control adolescents of the same age experienced concurrent mean BMD increases of +1.20% to +2.45% over 1 year and up to +5.89% over 2 years of treatment.

A first study published by Cromer et al. [102] has been performed in 48 postmenarcheal, adolescent girls aged 12–21 years. After 1 year, BMD decreased by 1.5% in Depo-Provera users, compared with increases of 2.5% in Norplant users, 1.5% in oral contraceptive users and 2.9% in control subjects ($p < 0.02$). After 2 years, bone density increased a total of 9.3% in Norplant users and 9.5% in control subjects but decreased a total of 3.1% in DMPA users ($p < 0.000$ I) [102]. A longitudinal study by Cromer et al. [38, 78] in 370 adolescent girls aged 12–18 compared the effect of DMPA or a COC containing 20 μg EE/100 μg levonorgestrel on BMD with the BMD changes in girls who received no hormonal treatment (control group). The results contribute to the increasing body of evidence indicating not only a negative impact of COCs containing 15–20 μg EE on bone health in young women but also of DMPA. Results of an open, nonrandomized study with 150 mg DMPA every 12 weeks for up to 240 weeks (4.6 years) with one follow-up observation phase in female adolescents between 12 and 18 years also showed that the use of DMPA leads to a significant decrease in bone density [103]. Again Cromer et al. [104] investigated 433 adolescent girls aged 12–18 years in a more recent observational, prospective cohort study. The effect of DMPA has been compared with COC users (containing 20 μg of EE and 100 μg of levonorgestrel) and controls. Over 24 months, mean percentage change in spine BMD was for DMPA −1.5%, for COC +4.2% and for untreated controls +6.3%. Mean percentage change in femoral neck BMD was for DMPA −5.2%, for COC +3.0% and for untreated controls +3.8%. At the femoral neck, but not at the spine, there was an accelerated loss in the second year. Statistical significance was found between the DMPA group and the two other groups.

None of the DMPA users experienced ≥5% gain in bone density, but almost 60% of the untreated girls did [104]. Bone density loss increases with longer duration of use and may not be completely reversible. It might be, at least in the subgroup of adolescents (12–18 years), that DMPA reduces definitively the final peak bone mass and increases the risk of osteoporotic fractures later in life.

For DMPA (104 mg s.c.), there are currently no studies in adolescents available. The long-term effects of DMPA (104 mg s.c.) on bone density during the critical period of bone growth are not known. However, due to the equivalent BMD changes described above in adults for DMPA (104 mg s.c.) and for DMPA (150 mg i.m.), the same selection criteria should apply in adolescents for the use of DMPA (104 mg s.c.) and for the administration of DMPA (150 mg i.m.). Both DMPA preparations have to be used in adolescent girls (12–18 years) only after that all other contraceptive methods have been discussed and evaluated as inappropriate (e.g. because of the absence of compliance), unsuitable or unacceptable.

21.6.4.3 Use in Women with Increased Risk of Osteoporosis

In patients with increased risk for osteoporosis (e.g. metabolic bone disease, chronic alcohol and/or nicotine consumption, eating disorders, low BMI, family history of osteoporosis and long-term use of drugs that can reduce bone density, such as anticonvulsants, GnRH therapy or corticosteroids), DMPA treatment can create an additional risk [105–107]. Other contraceptive methods should be considered when the benefit-risk of DMPA treatment is evaluated [96, 99].

21.6.5 Norethisterone Enanthate

200 mg Noristerat® intramuscularly provides contraception for 8 weeks. There is no evidence in the literature or in the product information that bone metabolism would be affected in an adverse or in a beneficial way.

21.7 Discussion

Evidence defining the effect of hormonal contraceptive methods on BMD and fracture risk is in general of poor quality and, worse, for several hormonal contraceptive methods not existing. Evidence is best for COC. In early studies, quality of evidence has been mostly low and in part contradictory. The two Cochrane reviews on the effect of steroidal contraception on bone fractures in premenopausal women (RCTs, 34; observational studies, 38) concluded from the selected studies that the evidence existing does not suggest an overall association between oral contraceptive use and fracture risk but that some specific subgroups may have an increased risk. This latter assumption has since been confirmed for adolescent users of low-dose COCs containing 15–20 μg EE and for DMPA users [42].

COCs (≤35 μg EE) inhibit bone remodelling in all age groups as far as the biochemical parameters are considered. COC intake after age 40 and in the perimenopause might protect against fractures in later life. This is not the case for the intake of a contraceptive pill in younger years. The effect of COCs on bone metabolism and BMD is not the same before and after that peak bone mass has been completed. Evidence from 11 RCTs [37] and 14 observational studies (7 case-control and 7 cohort studies) [42] indicates a dose- and age-dependent association between oral contraceptive use, BMD and fracture risk. In adult fertile women starting contraceptive use after the age of 30 years, the effect on BMD seems to be positive, although this age group is already in a state of bone loss. In perimenopausal women, COCs reduce bone destruction, stimulate bone rebuilding and may, depending on the starting point, induce actually an increase in BMD. In untreated adult subjects, bone destruction primes over bone rebuilding in the constant process of bone remodelling. The existing evidence leads to the conclusion that in young postadolescent women >30 years of age and in perimenopausal women, preparations containing 15–20 to 35 μg EE are capable of maintaining BMD and should be sufficient for bone protection.

Adverse skeletal effects of COCs are of particular concern in adolescents compared with adult women. Low-dose COCs (15–20 μg EE combined with a strongly anti-gonadotropic progestin) have been shown to affect negatively BMD in young women. The available evidence points to a significantly lower bone accrual among users of COCs with 15–20 μg EE compared to nonusers and to users of ≥30 μg EE pills although some studies in adolescents (menarche up to 18–20 years of age) have inherent limitations such as small sample size, inclusion of smokers and poor accounting for other confounders. COCs (15–20 μg EE) might reduce bone rebuilding in the constant process of bone remodelling and impede the formation of physiological peak bone mass (PBM) in adolescent girls. In a recent US study (mean age

(SD) for COC users 19.2 ± 0.5, for controls 19.3 ± 0.6), young women who did not use COCs increase whole-body BMD, while COC users possess an elevated bone turnover, a decline in spinal BMD and a lack of bone acquisition of whole-body BMD over 12 months [67]. A recent meta-analysis in 1535 young women [68] supplies the final evidence for potential impairment of peak spinal BMD accrual at 12 and 24 months of use (Fig. 21.5) and concludes that the evidence for impairment of spinal peak bone mass accrual might result in a relevant public health problem because low-dose COCs are not only used for contraception but also for therapy. The reduced peak bone mass might lead to a reduced BMD at the age of menopause and an increased fracture risk in later life. Whether bone density remains reduced after low-dose COC intake has been discontinued, or whether a subnormal development of the bone structure, bone architecture and BMD can be made up for is unanswered. It should also be remembered that 50% of the final peak bone mass is genetically determined.

DMPA administration is associated with increased fracture risk. A number of cross-sectional as well as retrospective and prospective cohort studies have examined the influence of DMPA therapy on BMD and on fracture. The vast majority of all studies performed in adult women showed an accelerated bone loss and a significant decrease in BMD when using DMPA (150 mg and 104 mg). A Cochrane analysis on fracture risk identified two placebo-controlled studies having a higher quality of evidence [42]. It concludes that DMPA users possess a higher fracture rate than nonusers. In adult women, the BMD decrease was at least in part reversible after discontinuation. Long-term adolescent users of DMPA may not reach the expected peak bone mass, or peak bone mass might be delayed. It is not known if a reduced peak bone mass could be made up for in later life.

An increased fracture rate particularly affects smokers, women who are heavily underweight, adolescents under the age of 18 and women over the age of 45. The highest fracture risk has been identified in young patients less than 30 years with longer DMPA exposure having started to use DMPA before their peak bone mass has been acquired. DMPA should only be used for contraception over a longer period of time (longer than 2 years) if other methods of contraception are not indicated, not possible or not accepted. If possible, DMPA should not be used in young women before peak bone mass has been acquired. BMD should be checked with long-term use of DMPA.

The common denominator for the negative effect of COCs and DMPA on bone mass accrual and peak bone mass in adolescents is inappropriately low endogenous E2 levels. The use of COCs containing 15–20 μg EE or of DMPA results in adolescents and in women with hypothalamic amenorrhoea or an instable cycle [36] in an "over-suppression" of the gonadal axis and to a reduction of endogenous oestrogen serum levels to the peri- and postmenopausal range. In adolescent girls receiving DMPA, 17β-oestradiol levels have been found to be as low as 25 (+9.41 SD) pg/ml, ranging from 10 to 35 pg/ml [101]. In adult fertile women using DMPA, the mean serum oestradiol levels fell to 18.9 (+12.9) pg/ml, ranging from 7.9 to 69 pg/ml [108], consistent with perimenopausal levels. Since bone metabolism correlates

with endogenous serum E2 levels [109], such a decrease leads to a significant loss of BMD. Healthy untreated perimenopause women typically lose 1–2% of bone mass per year, loss rates similar to those reported in DMPA users of all ages. The critical serum oestradiol level to maintain bone mineralization in adults is 40–50 pg/ml [110]. In adolescents before the acquirement of peak bone mass, administration of 15–20 μg EE daily delivered by a COC is insufficient to compensate the missing endogenous E2. Subtotal suppression of ovarian oestrogen production associated with COCs containing 15–20 μg EE and with DMPA treatment is one of the putative mechanisms in subnormal peak bone mass acquirement and osteopenia in adult women. Another putative mechanism for bone loss in DMPA users might be the glucocorticoid partial activity of MPA (Table 21.2).

Because of the decrease of E2 levels in DMPA users, some studies added 17β-oestradiol or CEE as a back-up [103, 111]. Since the oestrogen administered and the routes of administration differed, the two studies cannot be combined in a meta-analysis although both trials showed BMD increases for the women who received DMPA (150 mg i.m.) plus oestrogen supplement and decreases for those who had DMPA (150 mg i.m.) plus placebo.

Although the oestrogen activity delivered by combined pills using natural 17β-oestradiol or oestetrol should be sufficient for bone protection and a normal peak bone mass, there is no evidence available for the influence on BMD, peak bone mass accrual and fracture risk by these preparations.

Evidence is insufficient to formulate any recommendation on bone protection for users of nonoral combined hormonal contraceptives such as vaginal rings and patches. There seems to be no change in bone density under the vaginal ring, but in the untreated control group, a highly significant increase in bone density has been observed (difference between groups $p < 0.0001$). Contraceptive patches might follow the same pattern. A pilot study discusses the theory that different effects of oral and vaginal contraceptives on bone formation in young women might be mediated via the growth hormone-IGF axis [15].

For most progestin-only contraceptive methods, such as norethisterone enanthate injections, desogestrel-only tablets and etonogestrel as well as LNG implants, there is no good evidence about their effect on bone. However, a cross-sectional study reports that long-term users of Implanon® had a significantly lower BMD at the distal radius and ulna than the controls. Levonorgestrel intrauterine systems are said to possess a reduced fracture risk for some long-term users, but this hope is based on only one acceptable study. It is astonishing that nearly no data exist about a possible association of bone metabolism with the classical “minipill” (releasing 30 μg levonorgestrel per day). We know that the “minipill” decreases mean oestradiol concentration only moderately, in contrast to the stronger E2 suppression induced by the desogestrel-only pill releasing 0.075 mg desogestrel per day. This might be a good point for the use of the “minipill” in adolescents, but the acquirement of a normal peak bone mass in adolescent minipill users has not been explored. Long-term RCTs comparing the effect on peak bone mass of minipill users with users of low-dose COCs in adolescents below the age of 20 years are needed.

Why such an incredible lack of evidence so that too many questions related to the effect of hormonal contraception on bone cannot be answered? It might be that bone is not or only insufficiently studied because FDA and EMA do not demand fracture data for approval and that marketing has never been interested in bone so that the RCTs aiming at bone metabolism and fracture rate find no sponsors, particularly after that generics have been launched. RCTs are urgently needed to determine CHC/COC and progestin-only effects on adolescent bone health and the development of peak bone mass in order to understand better their influence on peak bone mass accrual in adolescents. In this age group (menarche up to approx. 18–20 years), not only the accrual of peak bone mass but also the prognosis for an increased risk of bone fractures in early postmenopause and old age should be investigated by prospective long-term studies. Whether losses of BMD due to hormonal contraception are fully reversible is unknown and merits investigation.

21.8 Summary

The evidence available allows to formulate some recommendations for the use of COCs and DMPA:

- In postadolescent women >30 years of age and in perimenopausal women, preparations containing 15–20 and 30–35 μg EE are both capable of maintaining BMD, and both guarantee bone protection. Combined oral contraception has no adverse impact on BMD when given during adulthood and may prevent the physiological bone loss that occurs in women >40 years of age and possibly increase BMD in the perimenopause.
- The strongly anti-gonadotropic progestins in COCs containing 15–20 μg EE suppress in adolescents the hypothalamic-pituitary-ovarian axis, hereby decreasing endogenous E2 production so that bone formation is reduced. Oral contraceptive use providing 15–20 μg EE per day might interfere with normal acquisition of peak bone mass in adolescents as does DMPA administration for the same reason, particularly when given early after menarche. When prescribing hormonal contraception to adolescent girls (≤18–20 years), we should consider that for low-dose COC administration (15–20 μg EE daily), the gain in bone density has been reported to be far smaller compared to nonusers and to users of 30 μg EE pills, so that a normal peak bone mass might not be reached. However, this evidence valid for pills releasing 15–20 μg EE daily should not lead to the consequence that a safe contraceptive method is refused to young women: in adolescents, 30 μg EE pills are safe for the acquisition of a normal peak bone mass. No data are suggesting that peak bone mass acquirement may be hindered by COCs delivering 30–35 μg EE per day.
- Oral contraceptive past use is associated with an increased risk of fracture in adult women. If this is also the case for women who started COC use below the age of 18 years is not known.

– There is strong evidence from longitudinal data showing that DMPA affects significantly BMD in adult current users. The decrease in bone density appears to be at least partially reversible in both adult and adolescent women.
– DMPA should be avoided in adolescents before peak bone mass is acquired. Initiation of DMPA within the first 3 years after menarche is of particular concern. DMPA should remain a reserve medication for patients where no alternative is possible.
– For all other contraceptive methods, good evidence is missing. In particular, it is not known if their use in adolescent girls is safe. Here, and in all questions related to the effect of hormonal contraceptives on bone metabolism and peak bone accrual, systematic research is urgently needed.
– The supply of sufficient calcium, vitamin D through food or with substitutes and proteins is important for the bone health in women of all ages needing contraception.

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Part V

Male Contraception: Current Options and Ongoing Research

The Male Role in Family Planning Today

22

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22.1 Introduction

Although contraception is currently a predominantly female responsibility, the male role in contraception has acquired different connotations over the centuries, progressively adapting to social and cultural changes.

Earlier contraceptive methods required the complete cooperation of men to be fully effective: in the Bible, it is written that men should withdraw before the end of intercourse to avoid pregnancy [1]. In ancient India, periodic abstinence was used to avoid pregnancy [1] and the Egyptians described the precursor of condom for the first time in 1350 B.C., as a decorative sheath that men could wear over the penis [2, 3].

After the Food and Drugs Administration (FDA) approval of the first oral hormonal pill in 1960, great changes happened in women's lives: sex became separate from procreation, pregnancy became a voluntary event, and safe motherhood became possible. Hormonal contraceptives empowered women and allowed them to achieve almost complete control of their own reproductive health: a reduction in the rate of abortions and a decrease in unwanted or high risk pregnancies have been some of the great successes of the "contraceptive revolution" [4]. The requirement of a doctor's prescription for the contraceptive pill or IUDs has led to a medical model of reversible female contraception based on the development of public family planning clinics throughout the United States, Europe, and the developing world [4]. Such services have been linked to maternal and child healthcare services and

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have given rise to a wider focus on women's reproductive health projects. Medical services are also needed for both tubal ligation and vasectomy, which do not require ongoing services or supplies, and reversible male methods such as condoms and withdrawal, do not require medical services for use. As a result, therefore, men have generally been left out of women's family planning services and no parallel system of reproductive healthcare for men has been developed. From the male perspective, men have been involved in a limited way, often only to ensure contraceptive continuation and acceptability.

More recently, the focus of family planning programs has started to include men. The inclusion of men in contraceptive decisions became even more important with the spread of HIV and other STDs in order to guarantee the sexual health of men and their partners and to cope with the high rates of unintended pregnancies among teenagers. None of the female methods available to date protects against sexually transmitted infections; therefore, the need for condoms has required the involvement of men in sexual and reproductive health programs. Men are gradually coming back into the picture [4, 5]. At the International Conference on Population and Development (Cairo 1994), men were recognized as legitimate targets for sexual and reproductive health promotion. **"…** *to emphasize men's shared responsibility and promote their active involvement in responsible parenthood, sexual and reproductive behavior, including family planning; prenatal, maternal and child health; prevention of sexually transmitted diseases, including HIV; prevention of unwanted and high risk pregnancies..."* [6].

For the first time, this conference explicitly supported the inclusion of men in women's reproductive health through three different approaches: (1) the promotion of men's use of contraceptives through educational programs and the distribution of male condoms. (2) Male involvement in the support of women's sexual and reproductive decisions, especially contraception. (3) The encouragement of responsibility in men's sexual and reproductive practices in order to control STDs [7].

Men have an important role to play in family planning, particularly in decisions about the number of children and which contraceptive method to use. Although data on men are limited, a growing body of research shows that involving men in family planning can increase modern contraceptive use, promote shared decision-making between couples, and help shift the belief that family planning is a woman's issue [7–9]. Involving males as contraceptive users and family planning clients is an opportunity to encourage the use of modern contraceptive methods and, at the same time, improve the health of men, women, and children. Furthermore, engaging boys from a young age through comprehensive sex education can have a positive effect into adulthood, promoting critical reflections on masculinity and on gender equality.

In the post-Cairo era, attention has been drawn to the absence of men from previous reproductive health initiatives and the need to incorporate them into any emerging programs [10–12]. Men are important actors who influence both positively and negatively, directly and indirectly, the reproductive health outcomes of women and children. The current challenge to the reproductive health framework is how to outline men's possible influences and to evaluate their impact on women's and children's health.

The introduction of health programs that involve men raise some important questions about the consequences of male participation in areas that have traditionally

been attributed to females, such as childcare, pregnancy, and fertility control [8, 13]. However, there is a fundamental question, as far as the strategy is concerned, about whether men's involvement increases their power over their female partners or whether it helps to empower women. In 1998, Cornwall cited evidence from Middle Eastern family planning programs that the involvement of men had probably increased their power over the fertility of women, rather than resulting in being an aid to the woman [14]. There is a need to evaluate the impact of the strategy and to ask a number of questions: does men's involvement in reproductive health empower women? Does this involvement empower men to resist social norms of male dominance? These and other important questions have yet to be answered [9].

Male involvement in reproductive health programs may be a way of increasing contraceptive adherence and supporting the woman's choice; however, the scarcity of male contraceptive methods represents a significant limit for male participation in family planning programs. Over the past few decades, a number of studies have been undertaken to develop male hormonal contraceptives that are safe and effective. A variety of new hormonal and non-hormonal molecules are under development and have provided very promising preliminary results.

In our overcrowded world, further research into the development of new male contraceptive methods is mandatory in order to widen contraceptive choices and allow men to take an active role in family planning programs.

22.2 The Male Role in Contraceptive Decision-Making

Both intrapersonal and interpersonal characteristics influence the use of effective contraceptive methods [15, 16]. Male condom use requires partner cooperation whereas most female contraceptive methods do not require the male partner's agreement. The involvement of both members of the sexual relationship is important [17]. It has been shown that partner involvement in hormonal contraceptive use is associated with lower discontinuation rates [18] and increased consistency of hormonal method use [19].

In 2003, Kerns et al. published an exploratory study in a mostly Hispanic (Dominican) population. The study aimed at identifying the variables associated with early pill discontinuation and showed that partner involvement in hormonal contraceptive use (even the simple knowledge of planned pill use) was associated with lower discontinuation rates [18].

Indeed sexual communication between partners is an interpersonal factor that has received attention for its association with contraceptive use: recent data support the idea that communication between partners is related to greater consistency of contraceptive use [20–22]. Johnson et al. showed that higher levels of sexual communication between partners had the most powerful impact on hormonal contraceptive use, in particular among women in steady relationship [19].

Relationship status is also considered to be another characteristic capable of influencing hormonal contraceptive use: steady sexual relationships increase compliance and adherence [23] and are also associated with long-term contraceptive use [24, 25]. If both partners are convinced they want to avoid a pregnancy, it has been demonstrated that their combined participation results in more consistent

contraceptive use [23]. On the other hand, when little or no discussion on contraceptive method takes place between partners in casual relationships, there seems to be more limited use of effective contraception [26].

A study by Grady et al. used data from the 2006 National Couples Survey (NCS) conducted in the United States to examine couples' contraceptive decision-making. This study investigated how each partner's contraceptive method preferences affected what method they used and determined whose preferences dominated. Data was gathered from both members of married, cohabiting and dating heterosexual couples. The results showed that women in married and cohabiting relationships appeared to have greater power over method choice than women in dating relationships. Male influence was equal to that of their female partners in dating couples only [27].

The male role in contraception acquires different connotations which changes according to the social and cultural background. In most low-income societies, especially in developing countries, the husband is usually the dominant decision-maker and the wife is economically dependent on the male figure. Men are responsible for financial support (e.g., by helping her pay for the contraceptive method); therefore, male involvement in family planning programs represents the first step for contraceptive use in these societies.

Men perform different roles in developed regions, where women are more often economically independent:

- **Emotional support and discussion regarding the method** (e.g., by accompanying her to the clinic, discussing the reasons for choosing one method over another and/or supporting her choice of method).
- **Help with the method chosen** (e.g., reminding her when to use it, helping with side effects and fears).
- **Support by using an alternative method** (such as condoms) in cases where she forgets to use or has an unexpected problem with her chosen method.

In February 2018, the World Health Organization published the third edition of the Global Handbook in order to offer clear, up-to-date information and advice to help providers meet clients' needs in family planning. For the first time, the WHO laid out some simple rules regarding contraceptives for clients' partners, highlighting the need to involve men in any emerging reproductive health programs.

In particular, the WHO says [28]: "A male partner can:

- Support a woman's choice of COCs.
- Help her to remember to take a pill each day and to start a new pack on time.
- Show understanding and support if she has side effects.
- Help her to make sure that she has a new pill pack on hand to start on time.
- Help to make sure she has ECPs on hand in case she misses pills or starts a new pill pack late.
- Use condoms consistently in addition to COCs if he has an STI/HIV or thinks he may be at risk of an STI/HIV."

22.3 Men's Knowledge of Contraception

In 2011, Fennel published an exploratory study conducted among 30 heterosexual couples that showed that both men and women learn about contraception through socialization; however, what they learn was markedly different. Information was freely available about condoms, whereas men reported receiving no information concerning female contraceptive methods, such as the hormonal contraceptive [29, 30]. They reported that lack of knowledge of contraceptive methods affected their ability to help their partners to choose and use contraceptives [24]. The lack of access to accurate information about contraception among men may inhibit communication within couples and promote the use of male-centered methods, such as withdrawal and condoms [26, 30].

Limited knowledge concerning reproductive health and an incorrect attitude towards contraception leads to ineffective and inconsistent contraceptive use among adults. Knowledge and attitudes toward contraceptive methods are first developed in adolescence [31]. In 2009, the Guttmacher Institute in the United States conducted a National Survey of Reproductive and Contraceptive Knowledge. The survey gathered detailed results from a nationally representative sample of 1800 unmarried men and women aged between 18 and 29. The survey included information on awareness of and knowledge about the various types of available birth control, the pervasiveness of popular myths, and the frequency of contraceptive use. Substantial proportions of young women and men who were sexually active and not trying to get pregnant were currently not using any contraceptive method. All data demonstrate lack of knowledge and awareness, in particular regarding the most effective hormonal methods such as LARC [32–35].

In 2013, Borrero et al. used data from this survey to examine racial and ethnic differences in male contraceptive knowledge and attitudes (Fig. 22.1) [32].

They found that men across all racial/ethnic groups had substantial lack of knowledge with regard to awareness of the full range of available contraceptive methods. While most men had heard of condoms and the pill (99% and 95%, respectively), only 64% had heard of IUDs, and only around one third had heard of

Knowledge	Total	White	Black (vs. White)		Hispanic (vs. White)	
	%	%	%	aOR[a]	%	aOR[a]
Awareness of methods (% who had heard of method)						
Female sterilization	58.3	65.6	41.0***	0.38**	49.7**	0.58*
Male sterilization	88.2	65.1	84.4*	0.34*	70.5***	0.21***
Implant	36.6	40.2	32.3	0.71	27.9*	0.63
IUD	64.5	71.8	55.7*	0.50*	51.0***	0.54*
Injection	68.7	74.0	67.9	0.53	61.3*	0.40***
OCPs	94.5	98.8	92.6**	0.16**	85.0***	0.11***
Patch	80.5	86.4	82.1	0.73	69.8***	0.39**
Ring	75.5	82.6	63.3**	0.39**	64.4***	0.50*
Condom	99.1	99.8	97.7*	[b]	97.9*	[b]
Female barrier	85.4	91.0	87.4	0.82	77.3**	0.50
Natural family planning	53.3	55.9	49.0	0.87	49.0	0.98
Emergency contraception	87.5	94.6	79.1***	0.26**	77.6***	0.32*

Fig. 22.1 Percentage distribution of men's responses to selected measures of contraceptive knowledge by race/ethnicity and aORs for racial/ethnic differences [32]

implants. Awareness of female sterilization (58%) was less common than the awareness of male sterilization (88%). Knowledge was studied through a series of true/false questions about the understanding of correct use, effectiveness, and facts about specific contraceptive methods. There were higher levels of knowledge about condoms while false myths and lack of information were common about long-acting and hormonal methods ("IUDs cannot be used in nulliparous women"). At the same time, results from statistical analyses assessing differences in contraceptive knowledge by race and ethnicity showed that Black and Hispanic men were less likely to have heard of many female contraceptive methods compared to White men. For many of the true/false questions, there was less knowledge among Black and Hispanic men compared to White men [32].

In 2012, Frost et al. analyzed data from the National Survey of Reproductive and Contraceptive Knowledge in order to measure the objective and subjective knowledge of contraceptive methods. It is common for young adults to have serious gaps in their objective knowledge about the main contraceptive methods. Only one in five young men achieved a high knowledge grade whereas 60% of young women and men underestimated the effectiveness of oral contraceptives. Objective and subjective knowledge about condoms, the pill, injectables, and the IUD was low. More than 50% of young men reported that they knew only a little or nothing at all about the methods analyzed. In particular, men in a stable relationship with a higher subjective knowledge of contraceptives had a lower probability of being non-users (odds ratio, 0.7); this data highlights the importance and need for information about contraception for males. One in five men thought one side effect of hormonal or long-acting methods was extremely likely, and 12% of each gender thought two or more were extremely likely; this greater expectation of negative side effects was associated with reduced use of hormonal or long-acting reversible methods [35].

In another study conducted by Raine et al. in the San Francisco Bay Area, young adult men (19–26 years old) from diverse racial backgrounds and from low-income communities were recruited for focus group discussions to examine social norms about sexual relationships and to evaluate their knowledge on contraceptive use. This study demonstrated how young men are confused and have little knowledge about highly effective hormonal methods: most participants were certain that women gained weight and many were concerned about future female infertility and the general safety of contraception for women. These false myths about hormonal methods may preclude young men from helping female partners in their contraceptive decision [26].

In 2009, Merkh et al. conducted a study on 41 ethnically diverse males aged between 18 and 25 using contraceptive life-history interviews focused on knowledge, attitudes, norms, and behavior regarding hormonal contraception use, decision-making, and communication. Most of these young males reported to have information only about condoms and no information about female contraceptive methods, [29, 30]. Low effectiveness and potentially exaggerated side effects were common myths in this population and knowledge related to how hormonal methods work and relative benefits and risks was generally limited.

22.4 Men's Perception of Contraceptive Responsibility

To understand the male role in family planning, we have to analyze what they think about contraception. Several studies have focused on the complexity of sexual decision-making for both boys and girls during adolescence when social norms around sexuality and relationships are formed and both sexes are exploring their sexuality. Data have shown significant differences regarding the perception of contraceptive responsibility between women and men [31]; furthermore decision-making and attitudes towards this responsibility may be affected by relationship status [31]. In 2000, Hooke et al. conducted a study exploring gender differences regarding the perception of sexual responsibility. An illustrated short story and questionnaire were used to survey a total of 129 Scottish 13–15-year-old teenagers. This study showed that while 73% of girls believed that contraception was a joint responsibility, only 46% of boys did. In addition, 27% of boys upheld the virtue of commitment in sexual relationships compared to 54% of girls [36].

These data were confirmed by Flood et al. who found that young Australian men considered the risk of pregnancy to be greater than the risk of sexually transmitted infections and saw it as their partner's responsibility to deal with that risk by using the contraceptive pill as condoms were reported to negatively influence the men's experience of intercourse [37].

With regard to the responsibility of pregnancy prevention, varying opinions were obtained from different countries: one study conducted in the United States by Merkh et al. [30], reported men regarding pregnancy prevention as being a shared role, while a study by Smith et al. [38] reported data from young Australian men who considered pregnancy prevention as being a woman's responsibility. Those who felt it was a "joint thing" were more likely to report dual method use (concurrent use of a condom and female contraceptive method) when compared to those who did not share this opinion [38].

Ekstrand et al. interviewed 17-year-old Swedish boys to gain deeper knowledge on how teenage males view sexual behavior and use of contraception. Some groups in this study considered the use of the condom to be more of a man's responsibility: "Usually the guy is the one who pulls out the condom'. Others regarded the condom foremost as a method of preventing STIs and secondarily for birth control: 'Condoms are for those who worry about diseases." The majority however, considered that the girl often has to take on greater responsibility in initiating or using contraception: "Girls are faced with the problem of becoming pregnant, whereas we're not" [38, 39].

Older married men and those who held more egalitarian attitudes were more likely to think that men and women have a shared responsibility for contraception [40].

Women, on the other hand, believed that attitudes towards the responsibility for contraception use among young people to be strongly gendered. Over 65% of women thought the responsibility for contraception fell too much on them [41]. Young women said that young men viewed contraception as "not their job." Young women are more serious about contraception mainly because the potential

consequences of unprotected sex are perceived to be worse for them than for young men [42].

Men perceive discussing reproductive health matters as a "waste of time" or "I am too busy generating income for the family" [43].

The man is the missing actor of family planning: we have to wonder why men perceive the responsibility for contraception to be so far from them and to identify the barriers that support their opinion.

Men's sexuality has been widely explored but reproductive health studies of their contraceptive practices are lacking. There are many specific barriers related to men; firstly, information about the male perspective is lacking in addition to the fact that the availability of contraceptive methods is still limited to methods such as condoms or vasectomy. Men do not like speaking about sexuality in their relationships and know little about their own or women's sexuality. Misinformation and negative beliefs such as "using contraception makes men less manly, limiting their power," or that "using contraception can cause infertility," help to create barriers to contraceptive access and use. Men also commonly refuse health checks and are undoubtedly more reluctant to avail themselves of medical care.

A review suggests that there is sufficient evidence demonstrating men's desire for information and services as well as their positive response to existing programming to warrant further programming for men and boys in family planning and contraceptive services [44].

22.5 Male Involvement in Contraception

Currently, women can choose from a large spectrum of contraceptive methods whereas for men essentially only few methods have been developed: the male condom, vasectomy, and the withdrawal method. Despite the scarcity of available options, male contraceptive methods account for only about seven percent of those used in developing regions, whereas this percentage increases to almost 30% in developed regions (Fig. 22.2) [45].

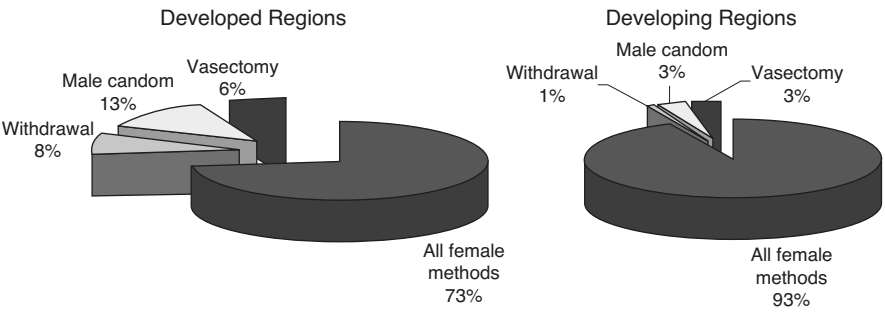


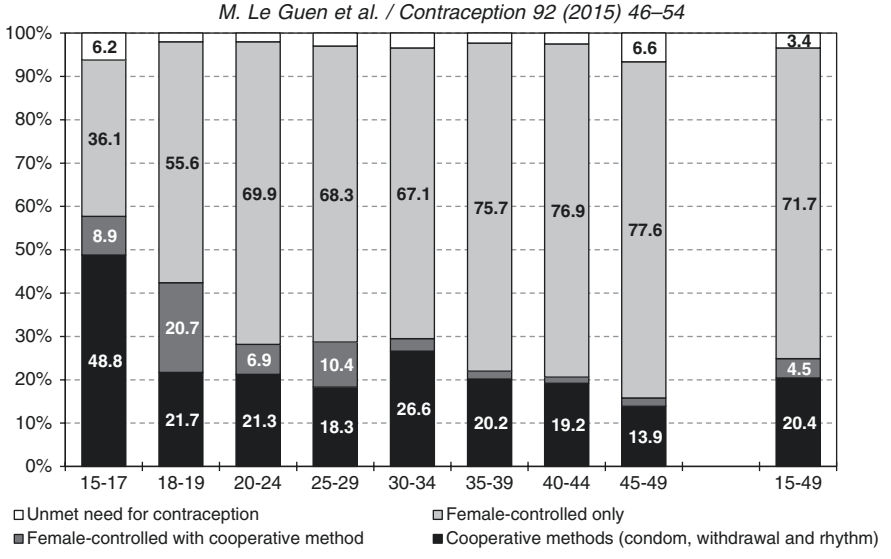
Fig. 22.2 Use of existing male contraceptives in developed compared to developing regions. (Data from the United Nations Population Division World Contraceptive Use 2003)

When analyzing men's involvement in contraception, we need to reconsider the methods used and to broaden the dualistic view of male or female methods to include the partners' awareness of use. Within this perspective, methods such as condoms or withdrawal, which require consent of both the man and woman, can be considered to be cooperative methods. However, this situation should not necessarily be interpreted as evidence of men's lack of interest in birth control because, despite the low effectiveness rate of the cooperative methods and the scarcity of male contraceptive options, the percentage of male contraceptive use is high.

Although men may want to be more involved in birth control programs, currently they have few and less effective contraceptive options being the male condom, withdrawal or the irreversible method of vasectomy.

A European study conducted in France confirmed data from developed regions regarding contraceptive use. This study showed that 3.4% of men aged between 15 and 49 were not using any contraceptive method, almost 70% of the men relied on a female-controlled method only, around 20% were using a cooperative method and 4.5% relied on a combined method (female-controlled method plus a cooperative method). The study showed that cooperative methods and combined female-controlled plus cooperative methods were mainly used at sexual debut but their use decreased as the age of this population increased [46] (Fig. 22.3).

Men may want to increase their involvement in contraceptive use and decision-making but policies and healthcare providers have primarily focused on women so men and boys are not particularly well served by family planning programs [47].



Source: FECOND Survey 2010 (Inserm-Ined)

* among male respondents aged 15-49 years who were not sterile and not trying to conceive, who had not had heterosexual intercourse in the last 12 months, and who had a female partner younger than 50 years who was not sterile or pregnant.

Fig. 22.3 Men's contraceptive use by age groups in France in 2010

Most programs are focused on women as contraceptive users and on men as supportive partners and there is insufficient effort in reaching men as contraceptive users in their own right. There are logistic constraints, such as insufficient numbers of male healthcare workers, inadequate training and support for male and female staff to engage men, and inflexible clinic opening hours [48].

Only a few providers of contraceptive counselling have ever discussed family planning with a client's male partner. Nevertheless, almost all providers thought that provision of reproductive health services for men would improve women's health [31, 48].

Ezenaloue et al. enrolled and conducted a cross-sectional survey of 2468 pregnant women and their male partners in Nigeria [49]. This study examined pregnant women and their male partners as a couple in order to identify the extent to which women's desires to use contraception were linked to their male partners' awareness and support of contraceptives. They found that men's awareness of and support for hormonal contraceptives was largely associated with their female partner's desire to use contraception, highlighting the dominant male role in family planning decisions in sub-Saharan Africa [50]. Therefore, especially in patriarchal countries where men are often the primary decision-makers about family size and their partner's use of contraceptive methods, male inclusion in birth control programs is crucial for success [51–53].

22.6 Effects of Male Involvement in Family Planning

Focusing on men's involvement and attitudes could have potentially both negative and positive effects. Men's sexual and reproductive well-being and behaviors directly affect the couple. It is necessary to bring men into positive decision-making with their partners because they play an important role in countering inequitable gender attitudes and encouraging positive norms [18, 19]. In developing regions especially, where men often have a dominant role in family planning, their involvement could increase contraceptive use and access to health services for women, children, and the men themselves.

Men's involvement could promote shared decision-making between couples, influence the spacing and timing of pregnancies resulting in an improvement of maternal and child health outcomes [54]. Moreover, involving young men through sexual education programs can have a positive effect into adulthood, promoting critical reflections on masculinity and on gender equality [55].

None of the available female-controlled contraceptive methods offers any protection against sexually transmitted diseases. The condom is the only contraceptive method to do that and requires male cooperation [56]; therefore, appropriate awareness and knowledge of this method is mandatory.

Another point of view is that men's involvement in family planning poses questions about the effects of involving men in areas that have traditionally been considered the preserve of women, such as childcare, pregnancy, and fertility control [8,

48]. There is a fundamental question about whether men's involvement increases their power over their female partner or whether it helps to empower women [9, 14].

We have to evaluate the possible risks related to men's engagement in maternal and child health. In 2016, Davis et al. collected data from Pacific regions regarding the attitudes and beliefs of maternal and child health professionals concerning the benefits, challenges, risks, and approaches of increasing men's involvement in maternal and child health programs [48]. Reproductive health professional expressed concerns about the potential for men's involvement to exert control over choices usually made by women who feel less able to talk about personal matters with practitioners. Other concerns include unintentionally dissuading single women from attending clinics alone when the presence of the couple is encouraged or the risk of violence or divorce when men obtain information about sexually transmitted infections or contraceptives [57].

Because of these potential risks, women should choose how and when male partners are involved in maternal health consultations and when personal health information should be provided to the male partner.

22.7 Ways to Engage Men in Family Planning Programs

Research suggests that men should be included in reproductive health decision-making in order to improve positive health outcomes for their partners [24]; however, women's rights to privacy and autonomy need to be maintained.

Given the lack of contraceptive knowledge observed among all men [26, 30, 32, 35] and the role that men can play in their partner's contraceptive choices, there is a need to educate men about effective contraceptive options and to increase the number of male contraceptive methods.

Certain initiatives may be effective in engaging boys and men of all ages in maternal and child health in both community and clinic settings. These include peer education programs, large-scale media campaigns and workplace and community health programs [9, 48].

There is reported evidence that the view of many expectant fathers is that they would be interested in participating in maternal and child services if they were invited to do so and that messages that build on traditional cultural roles and values would be more likely to be successful, especially in developing countries [48]. Furthermore, men's involvement early in life may be an effective strategy for improving knowledge and awareness of contraception since limited contraception knowledge reduces young men's sexual health communication [31].

Over the years, a number of research programs have been undertaken to develop safe and effective male hormonal and non-hormonal contraceptives. Oral or transdermal hormonal contraceptives for men are under development and commercialization of these methods will allow men to take an active role in family planning.

22.8 Conclusions

Men can potentially play an important role in family planning programs but awareness and knowledge levels of available contraceptives is still inadequate. Most men still believe that the responsibility for pregnancy and STI prevention is focused on the female. Family planning programs and healthcare providers should aim to educate men regarding effective contraceptive methods at the same time as continuing research should be undertaken in order to develop new male contraceptive options. These and other initiatives could be effective in giving men an active role in sexual and reproductive health decisions.

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Acceptability of Male Hormonal Contraception

23

Giulia Gava and Maria Cristina Meriggiola

23.1 Introductory Considerations

Since the 1970*s* several international studies have evaluated different hormonal regimens to provide men with safe and reversible contraception [1, 2]. These studies varied in molecules used and the number of participants, but they all demonstrated that the use of androgens alone or in combination with progestins can provide effective suppression of spermatogenesis. Despite the large number of studies published in this field, progress in the development of new products has been slow, and the commercialization of a hormonal contraceptive method for men is still far off. At the moment contraceptive methods available for men are only the male condom and the vasectomy [3], and the involvement of men in family planning is still limited with more than 70% of couples worldwide using female contraception [4].

Along with the assessment of the efficacy and safety of new methods, researchers in this field have continuously highlighted the need to explore the user's perspective and acceptability of potential new technologies, and they have worked to develop useful research tools for this purpose.

Acceptability can be defined as characteristics making a product satisfactory and attractive [5]. No existing method of contraception can be considered perfect, but an acceptable method should be effective quickly, reversible, safe without short- or

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long-term side effects, independent of sexual intercourse, without harming any offspring, and easily accepted by both partners. Apart from these universal characteristics, a method should also be acceptable for the single subject wishing to use it in a particular period of their life.

Acceptability of contraceptive methods can be evaluated indirectly through parameters such as its prevalence and continuation of use of the method or directly using questionnaires to evaluate the hypothetical acceptability before use and/or satisfaction after use. While studies of the acceptability of female methods focus on factors leading to contraceptive discontinuation, data regarding the acceptability of male hormonal methods comes from clinical trials assessing new methods and from surveys assessing male and female attitudes toward this form of contraception.

23.2 Acceptability Data from Surveys

Even though they only describe hypothetical behavior, surveys can provide significant perspectives underlining major differences across groups and continents. The acceptability of male hormonal contraceptive methods is influenced by cultural, economic, and religious factors and by relationship status.

A large multicenter study assessing men's opinions and attitudes regarding male hormonal contraception was published in 2000 [6]. A total of 1379 men were interviewed in different centers (493 in Cape Town, 450 in Hong Kong and Shanghai, and 436 in Edinburgh). In this study, the men interviewed reported that contraceptive choices were shared within the couple, in particular in Cape Town (80% of white men) and Hong Kong (80%). The majority of men stated that the responsibility of contraception still falls too much on the woman and that endorsement by the partner would be the most powerful motivation for method use.

The majority of men interviewed said that they would welcome new hormonal methods even though they were happy with their current choice. In all centers, but particularly in Edinburgh, the majority would prefer a male pill (44–83%), whereas 32–62% of men would be happy to use an injectable method.

In the case of the hypothetical use of an injectable method, most men would prefer injection intervals to be every 3 or 6 months in the majority of centers; only in Shanghai did nearly one in two men (42%) say they would prefer long-term implants lasting 3 years.

The authors also assessed if the need for repeated semen analysis and the 3-to-4-month delay before efficacy were considered a barrier to the use of a hormonal method. Globally 38.5% and 30.2% of men, respectively, considered these two steps acceptable.

In certain aspects, men's attitude varied greatly between centers reflecting cultural influences. For example, the Hong Kong center reported a lack of belief in the contraceptive efficacy of new methods but also of the male condom that was the principal method used being considered as highly convenient. In Edinburgh, men considered the condom not so convenient but highly effective. A hypothetical male pill or an injectable was considered more convenient than the male condom in all centers except for Hong Kong and Shanghai. Those considerations may have an

impact on the potential usage of those methods and on companies interested in the commercialization of these products.

Cultural influences also affected the evaluation of how the method would affect the perception of masculinity. For example, 34% of black men in Cape Town reported concerns regarding their masculinity with a hormonal pill, while only 3 percent of men interviewed in Edinburgh reported similar concerns. Other aspects assessed were instead more similar between the centers. Men were more concerned with lessening sexual desire and satisfaction with condoms than with a hormonal method. Age and educational levels were recognized as modifying men's attitude toward contraception.

In 2002 another cross-cultural survey was performed in over four continents to assess male attitudes toward contraception and factors influencing the use of a potential new male method [7]. The survey involved >9000 males aged between 18 and 50 in 9 countries on 4 continents. A large majority of participants (55–81.5%) reported shared decision-making regarding the choice of a contraceptive method, and the overall acceptance of male hormonal contraceptives was high (>55%). The willingness to use new male methods varied greatly between population groups ranging from 28.5% to 71.4%. An even more positive attitude was described in an Australian study where 75.4% of new fathers indicated that they would be willing to try a male method if available [8].

When taking into consideration the route of administration, the oral pill was the preferred route in all countries, except for Indonesia where long-acting agents were more desirable [7]. The second-best option in European countries was the yearly implant, which ranked lowest in Indonesia and Latin America. Daily application of hormonal gel was welcomed in Latin America but not widely accepted in Europe and North America. It should be remembered that the key factors influencing preferences are very similar to those found in women, and, for the future, it is hoped that couples will have access to different male methods with a variety of molecules and routes of administration to create tailored male contraception similar to female contraception. Further local investigations may be also needed to better assess factors related to family planning.

23.3 Female Partner's Perspective and Their Role in Male Hormonal Contraception

Multiethnic and multinational surveys investigating potential new hormonal male methods demonstrated that not only men but also their female partners would welcome such methods of contraception.

In several studies, the stable female partner's perspective and attitude to new male methods have been considered a strong predictor of initiation and continuation of male methods. In fact, participation in these studies was often prompted and supported by the partner [6, 9, 10]. Furthermore, the willingness of both partners to tolerate experienced side effects can affect acceptability. Motivated couples and those who are dissatisfied with other contraceptive methods may tolerate side effects more than couples who have had more positive experiences with other methods.

In 2000 Glasier et al. assessed attitudes toward male contraception in a study of 1894 women living in different countries (450 in Scotland, 900 in China, and 544 in South Africa). The majority of women agreed that the responsibility for family planning still fell too much on the woman [11].

Across the different countries, despite great cultural and interpersonal differences, a male hormonal method was considered a good option by the majority of women interviewed (more than 90% of women in Scotland and South Africa, 71% in Hong Kong, and 87% in Shanghai). Very few women (only 2%) stated that they would not trust their partner to use it. This may signify that even if women might not trust men in general to take the pill, they would be more trusting of their partner [9].

Cultural differences play a role not only in women's opinion toward male contraception but also in their attitude toward the use of these forms of contraception. For example, even if male contraception was generally considered to be a good idea, only 14% of women with a partner in Hong Kong would rely on a male method if available on the market, whereas in Shanghai 71% would use it [11].

In the United Kingdom, 134 female and 54 male users of contraceptives were interviewed regarding attitudes toward a proposed male contraceptive pill. The acceptability of the male method was high (49.5%); however 42% of participants, in particular women, were concerned that men would forget to take the pill [12].

In a survey published by Eberhardt et al. in 2009, attitudes toward a male pill were favorable with women having a more positive attitude than men although women did not completely trust men to use the male pill effectively. Men in stable relationships were more positive about the pill than those in casual sexual relationships [13].

23.4 Acceptability Data from Clinical Trials

In these studies, acceptability was assessed through questionnaires for the user and their partner administered before drug administration, throughout, and after the trials.

Men and couples taking part in these clinical trials offer a unique perspective regarding a method's ability to meet their needs also providing an interesting insight on the best steps toward improving its marketability. However, some limitations of data coming from the clinical trials should be acknowledged as there are several reasons why they cannot be considered as being fully representative of the acceptability in the general population. Firstly, all those who take part in clinical trials are carefully selected, and during the study, they receive care that is more intensive than that of a typical standard clinical service. Furthermore, questionnaires and interviews used to assess acceptability are often considered too simplistic. However, even though the information obtained from these studies may not accurately predict future behavior, they may provide a guide for scientists and other organizations in the planning of future research and product development [14].

As previously described, the acceptability of the method can depend on various factors: type of method, route and timing of administration, side effects, cultural aspects, and on the subject itself. Research on the acceptability of hormonal methods has helped organizations interested in this field to design methods with a route and administration timing increasingly more attractive for men, from pellets and long- and short-term injections to gel formulations.

One of the first reports to consider the acceptability of male hormonal methods investigated the use of testosterone implants (800–1200 mg every 3 months) in 29 men for 3–16 months [15]. This trial represented the first efficacy study using implants as they seemed to have a low acceptance rate due to the necessity of an implantation procedure and the substantially high frequency of extrusion. In this study, 70% of men achieved sperm suppression considered to be adequate for contraception (below 1 million/mL) without pregnancies in 214 exposure months. They reported no significant androgenic side effects. The acceptability of the method in the long term was considered good and only impaired by the need for pellet implantation and by the incidence of extrusions which was reported as being 10%.

As new hormonal formulations requiring injections had been researched and designed, in 2006 two new studies assessed the acceptability of injectable methods in China [16] and Italy [17]. In China in that period, the use of male methods was very uncommon with only 5.3% of men using the condom and 7.7% who had undergone vasectomy (http://www.npfpc.gov.cn/data/data-20,041,014-1.htm), and for this reason, the results of this study are particularly interesting. In the Chinese study, participants received testosterone undecanoate every month (1000 mg loading dose followed by 500 mg) [16]. The investigators interviewed male subjects at baseline, at 4 and 8 months of drug use, and at the end of the study. Their female partners were interviewed during the fourth and eighth months. Almost all participants (90%) stated that the possibility of sharing contraceptive responsibility was the main reason for participation in the trial. In this study, support of the wife was relevant with 58.8% of wives encouraging the man to join the study. Overall, the method was considered acceptable even though the once-a-month administration was considered too frequent. When considering the side effects of the method, the majority of participants did not notice any significant change in their well-being after 4 and 8 months (53 and 48%) or reported an increased feeling of physical power and libido.

In the Italian study, subjects were randomly assigned to no-treatment or treatment with norethisterone enanthate and testosterone undecanoate or placebo at 6-, 8-, or 12-week intervals for 48 weeks [17]. The majority of participants expressed the need to share the contraceptive choice. Seventy-nine subjects indicated that they would use the method if available on the market, and 74% thought that their partner would appreciate it. Sixty-one percent of participants using the studied injectable method rated it as excellent or good in terms of satisfaction, whereas dissatisfaction was expressed for the injectable route of administration and its lack of protection from sexually transmitted infections. Sexual function and mood were also investigated and no significant change was recorded in any group throughout the study periods.

Although those injective regimens seem to be tolerated, the injection schedule may be considered too frequent for long-term use, potentially reducing the acceptability of this contraceptive method. For this reason, further studies assessed if longer intervals were able to maintain adequate spermatogenesis suppression, reducing the total dose and improving safety, costs, and acceptability. As an example, norethisterone enanthate 200 mg (NETE) plus testosterone undecanoate 1000 mg (TU) administered at 8-week intervals was found to be effective [18].

The efficacy study using this formulation and the same injection interval confirmed high acceptability of the method: 87.9% of male participants and 87.5% of female partners would use this method [19]. At the end of the study, more than 75% reported being satisfied with this contraceptive method and interested in its use if marketed.

When considering the acceptability of a drug, side effects can of course play an important role. In the initial trials using only testosterone, the majority of side effects were associated with the high testosterone dose used, i.e., libido and mood fluctuations, night sweats, acne, and increased weight. The association of progestin to testosterone allowed for a reduction in the testosterone dose resulting in an improvement of side effects [20]. Persisting side effects were mainly related to the progestin molecule used. For example, androgenic side effects were still reported when a non-derived progestin was used such as levonorgestrel or side effects of androgen deprivation when a high dose of an antiandrogen was used such as cyproterone acetate (REF). Etonogestrel plus TU injections were also compared to placebo and the results were very interesting: adverse side effects were reported by 93% of men on active treatment but also by 81% of men on placebo [21].

In subsequent years, researchers made a concerted effort to avoid the need for intramuscular injections of testosterone increasing their research on the transdermal route of administration. Testosterone patches were investigated, but they were associated with a lower degree of sperm suppression than intramuscular testosterone [22–24]. Testosterone gels then became available on the market for the treatment of hypogonadism obtaining higher serum testosterone levels compared to testosterone patches and greater acceptability in hypogonadal men [25].

In 2007, *Amory et al.* reported that testosterone gel associated with depomedroxyprogesterone acetate (DMPA) injections every 3 months was a male contraceptive method considered to be acceptable by trial participants [26]. In this study, researchers treated 38 healthy men for 24 weeks with 100 mg testosterone gel daily and 300 mg every 3 months. Fifty percent of these men indicated that the method was acceptable considering it preferable to their previous methods. Forty-five percent of participants stated that they would use the regimen if commercially available. Some factors influenced acceptability: younger males and those with a partner using intrauterine devices expressed greater dissatisfaction with the method. Regimen acceptability was slightly lower than that reported in other male hormonal contraceptive studies using a long-acting injectable testosterone-progestogen combination. The reason for this may be due to the different study populations or to the differences between the appeal of the long-acting injectable T and the T-gel preparation. Cultural differences should also be acknowledged. Also in 2007, another

survey presented by *Heinemann et al.* showed that the gel-based approach was more appealing than injections in South American countries and less appealing than injections in Europe and North America [7]. One of the factors associated with the good acceptability of this method was believed to be the route of administration: 74% of men described the gel as easy to use with no skin irritation, although a large number of participants reported that the gel left a sticky sensation on the skin. Thirty-four percent of the men were dissatisfied with the method indicating that it interfered with their daily routine. Sexual function was also assessed and was largely well preserved during the trial although some decrease in sexual function was noted during the recovery phase.

Further research on gel formulations led to the production of a transdermal gel containing testosterone and Nestorone. The acceptability of the daily application of this gel-gel regimen was assessed in a 6-month trial where the product was administered as two separate gels, one in sachets and one in a pump. Fifty-six percent of participants were satisfied or extremely satisfied with this regimen with 51% stating that they would recommend it to others [27]. Although acceptability was high, only 34% of men stated that they would use it if available on the market, and the fear of sexually transmitted disease represented a factor that limited satisfaction of the method. Ethnicity was associated with the likelihood of using this contraceptive regimen with Afro-American men less interested than Asiatic or Caucasian men, while relationship status and age were not associated with method acceptability. In this study, acceptability was not significantly influenced by the daily gel routine, which did not seem to interfere with other activities.

A multicenter study enrolling 400 couples with a single gel containing both testosterone and Nestorone is ongoing as a phase IIb efficacy trial [28]. The single gel formulation with a reduced volume of gel and a simplified application is believed to further improve the acceptability of the regimen.

23.5 Conclusions

Several studies showed that contraceptive efficacy of currently studied hormonal male methods is high, with proven safety, low side effects, and a complete reversibility after discontinuation. Male hormonal methods appear to be easy to use with long- and short-term acting products (injections, gels, or pills).

In conclusion, available data from both surveys and clinical trials demonstrate a general willingness on the part of many men in different countries and continents to take more responsibility for using contraception. At the moment, the majority of men believe that the responsibility of contraception still falls too much on the woman and consider the idea of a male contraceptive acceptable. Even if the acceptability of male hormonal contraceptive methods can be influenced by several factors (cultural, economic, religious factors and relationship status), the majority of men reported that they would welcome new hormonal methods. The endorsement by the partner would be a powerful motivation for method use, and women would rely on their male partners to use a male contraceptive method. Currently, hormonal

methods require several weeks before they can be relied on, and we acknowledge that this can represent a limitation to their acceptability, although this is similar to vasectomy. It should also be considered that similarly to female hormonal methods, in the future men might be attracted to male hormonal contraceptives also for hypothetical non-contraceptive benefits that new methods may have considering bone and muscle health and prostate function that will need to be further investigated in population studies.

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Current Male Contraceptives and Experimental Nonhormonal Contraceptive Research

24

John K. Amory

24.1 Overview of Male Reproductive Physiology

Production of mature sperm (spermatozoa) in the human testes takes 64–72 days [1]. After a young man goes through puberty, sperm production is continuous and results in the production of approximately 1000 sperm a second. Spermatogenesis occurs in four distinct phases: (I) a mitotic phase in which the stem cells, the spermatogonia, divide to give rise to diploid spermatocytes; (II) a meiotic phase in which spermatocytes double their chromosome complement and undergo two rounds of cell division giving rise to haploid spermatids; (III) spermiogenesis, in which the spermatid undergoes condensation of its nuclei and the formation of the flagellum; and, lastly, (IV) spermiation, which involves release of the spermatozoa into the tubular lumen [2]. Essential further maturation of sperm takes place in the epididymis. For example, sperm aspirated from the cauda epididymis are capable of fertilizing an egg in vitro, while sperm from the caput epididymis are not [3]. The testes also synthesize testosterone, the main male sex steroid. Testosterone is necessary for sperm production and also maintains sexual function and muscle and bone mass among other functions [4]. Testosterone is produced by the Leydig cells in the interstitium of the testes, under the stimulation of luteinizing hormone (LH). Sperm production occurs in the seminiferous tubules, where the sperm are nurtured by Sertoli cells, which are stimulated by follicle-stimulating hormone (FSH) and high

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Capsule: This chapter reviews the two current, effective forms of male contraception, condoms and vasectomy, as well as efforts to develop new nonhormonal male contraceptives.

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concentrations of intratesticular testosterone [5]. Given the physiology of sperm production, male contraceptives can work in one of several ways:

1. By preventing sperm from reaching the egg by physical barriers such as condoms, vasectomy, and experimental vas occlusion methods
2. By preventing sperm production as is the case for experimental hormonal and nonhormonal methods
3. By killing or inhibiting a function of the sperm (e.g., capacitation) or interfering with the sperm's ability to bind and fuse with the egg (spermicides, experimental anti-motility agents)

This last category of contraceptives is usually intended to be used intravaginally in a woman and is therefore more properly considered female contraceptives, so it will not be discussed further. Instead, this chapter will describe the efficacy of existing methods of male contraception and then discuss the research directed toward the development of novel nonhormonal methods of male contraception that function either by inhibiting sperm production or by preventing sperm from reaching the female reproductive tract. The development of hormonal methods of male contraception will be discussed in the next chapter.

24.2 Currently Available Male Contraceptive Methods

24.2.1 Vasectomy

Vasectomy is an outpatient surgery in which the vas deferens is surgically interrupted bilaterally through a small scrotal incision. Approximately 500,000 vasectomies are performed in the USA annually, and over 50 million men worldwide have undergone the procedure [6]. In the USA, 10% of couples rely on vasectomy as their method of contraception [7]. In terms of contraceptive efficacy, vasectomy is highly effective with a failure rate under 1% and a low rate of complications [8]. The "no-scalpel technique," developed in China [9], relies on a single midline puncture in the scrotal raphe using scissors and has been widely adopted [10, 11]. The main drawback to vasectomy is the delay in the onset of azoospermia and hence contraceptive efficacy of 3–4 months. In addition, postoperative pain can be an issue. While most postoperative pain resolves quickly, 10–15% of men experience chronic testicular discomfort after their vasectomy [12]. In 1 study of such men, 27 of 33 had relief of their discomfort with reversal of the vasectomy [13], suggesting that obstruction of the vas was causing their pain. Lastly, cost and availability of vasectomy are factors that may limit use. In the USA, a vasectomy may cost upward of $1000, limiting the ability of some men to afford the procedure. In other parts of the world, there may not be providers trained in the procedure or facilities in which it can be performed.

Vasectomy is an appropriate form of permanent contraception for men who do not wish any future fertility. However, approximately 3–5% of men who have a vasectomy eventually request reversal, usually due to remarriage or the death of a child [14]. For this reason, some urologists recommend freezing a semen sample prior to the procedure, although this is not done commonly. Vasectomy can be

reversed by a procedure called a vasovasostomy, which restores fertility in most cases. However, rates of pregnancy after vasovasostomy vary from 50 to 75% depending on the length of time between the vasectomy and the vasovasostomy. In some of men, vasovasostomy is unable to restore patency of the vas, especially if more than 8 years have elapsed since the original vasectomy [15]. In addition, 20–30% of men remain infertile despite restored patency of the vas as documented by imaging techniques probably due to the presence of antisperm antibodies [16]. For these reasons, vasectomy cannot be recommended as a truly reversible method of contraception.

In terms of overall health, vasectomy is safe. Reports of associations between vasectomy and cardiovascular disease and vasectomy and prostate cancer initially reported in the 1980s have proven incorrect [17, 18]. In summary, vasectomy is highly effective and very safe. The major drawbacks are chronic testicular discomfort in a small subset of men and the inability of vasovasostomy to reliably restore fertility in all cases when desired. In the USA, 20% of couples rely on vasectomy as their method of contraception [7].

24.2.2 Condoms

Condoms have been used for contraception and as protection against sexually transmitted infections by men for several hundred years. Originally made of animal intestines, since 1920, most condoms have been made of latex rubber. Latex condoms are unique among currently available contraceptives in that they protect against many sexually transmitted diseases including the human immunodeficiency virus, syphilis, gonorrhea, papillomavirus, and the herpes simplex virus among others. Condoms are relatively free from side effects. The main drawback to condoms is their marginal contraceptive efficacy, which results mostly from improper or inconsistent usage, or breakage, which occurs in up to 4% of cases [19]. Pregnancy rates for couples using condoms as their sole means of contraception approach 10–15% per year [20, 21], and failure rates are likely higher in young couples with high fertility. In addition, some men dislike condoms because they feel that condoms either diminish sexual pleasure or are difficult to use [22]. Lastly, some men and women develop allergic reactions to the latex, which is allergenic and can lead to penile or vaginal irritation and, thankfully rarely, anaphylaxis [23]. Polyurethane condoms are available for couples in whom one of the partners has a latex allergy. These condoms are slightly less effective than latex condoms, however, mainly due to slippage from their looser fit [24–26].

24.2.3 Withdrawal

Lastly, “withdrawal” or coitus interruptus is sometimes considered a male method of contraception, is mentioned as the primary method of contraception by 3–5% of couples in the USA, and has been used at least once by 60% of individuals.

Withdrawal is not generally endorsed by the medical community as an effective method of contraception as the stated 1-year failure rate of withdrawal in couples using it as a sole method of contraception is 20–30% [21]. However, it must be noted that little research has focused on this method of contraception, and its true efficacy may be higher or lower depending on how it is practiced and how faithfully it is adhered to.

In summary, in the USA, 30–35% of couples use an existing male method of contraception (Table 24.1). This demonstrates that men are interested in contraception and willing to use available methods. However, as above, each of these methods has significant drawbacks. Therefore, novel approaches to male contraceptive development are needed. Research into novel methods of male contraception is underway. Hormonal approaches to male contraception are in clinical trials and are discussed in the next chapter. The remainder of this chapter will focus on attempts to develop a male contraceptive that do not involve the use of hormones, so-called "nonhormonal" male contraceptives.

24.2.4 Experimental Nonhormonal Male Contraceptives

Several research groups are examining approaches to nonhormonal male contraception, although to date, none of the current generation of candidates has been tested in men. Nonhormonal male contraception is defined as an approach to male contraception that doesn't involve the administration of hormones or compounds that block hormone secretion or hormone action [27]. Nonhormonal contraception may be more appealing to men than hormonal approaches currently in development as it would avoid any impact on testosterone concentrations and, hence, sexual function, muscle or bone mass, or sex drive. In addition, the use of testosterone or another anabolic steroid could lead to sports disqualification as individuals using testosterone or another steroid to suppress spermatogenesis would "test positive" in doping analyses. Lastly, nonhormonal contraceptives may be more easily dosed orally than most steroid preparations, which tend to be rapidly degraded due to extensive "first-pass" metabolism of testosterone by the liver.

Table 24.1 Percent of couples using a method of male contraception and efficacy of each of these methods in the prevention of unintended pregnancy in the USA (from Refs. [20, 21])

	Year				
Contraceptive method	1992	1995	2002	2008	Unintended pregnancy rate per year (%)
Vasectomy	11	11	9	10	0.1
Condoms	12	20	18	16	10–15
Withdrawal	2	3	4	5	20–30
Total male Contraceptive usage	25	34	31	31	–

24.2.5 Gossypol

One of the first examples of a nonhormonal male contraception was gossypol. Gossypol is a phenolic compound derived from the cotton plant (Fig. 24.1). It was extensively studied in China in the 1970s and 1980s, including in two large phase III studies that enrolled more than 8000 men [28–30]. Gossypol reduced both sperm production and sperm motility and induced abnormal sperm morphology by an unknown mechanism of action. After prolonged treatment a majority of men developed azoospermia. Gossypol had an approximately 90% efficacy in pregnancy prevention, but caused troubling hypokalemia and a 1% incidence of hypokalemic periodic paralysis [31]. In addition, approximately 20% of men did not have return of fertility. Despite attempts to lower the dose or chemically modify the structure of gossypol to improve efficacy and reduce the risk of side effects, this approach to male contraception has been largely abandoned [32].

24.2.6 Triptolide

Another avenue of male contraceptive research from China involved the use of the Chinese herb *Tripterygium wilfordii* which contains a diterpene epoxide called triptolide (Fig. 24.2) [33]. This herb had been used as a traditional Chinese medication for many centuries. In the 1980s an antisperm effect was identified. Specifically, *Tripterygium* administration impaired sperm motility and decreased sperm counts. As was the case with gossypol, however, several men taking this compound had irreversible sterility, leading to its abandonment as a male contraceptive [34].

24.2.7 Adjudin

A more recent example of a nonhormonal male contraceptive candidate is adjudin (Fig. 24.3), which was first described in the early 2000s [35]. Adjudin is an

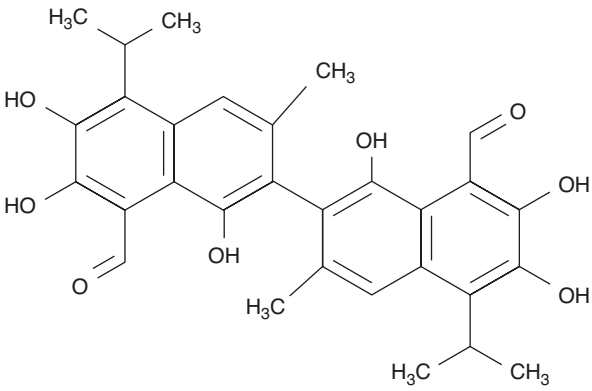


Fig. 24.1 Gossypol

Fig. 24.2 Triptolide

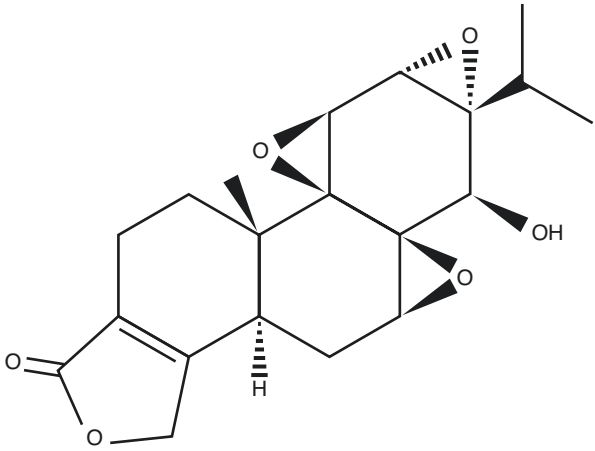
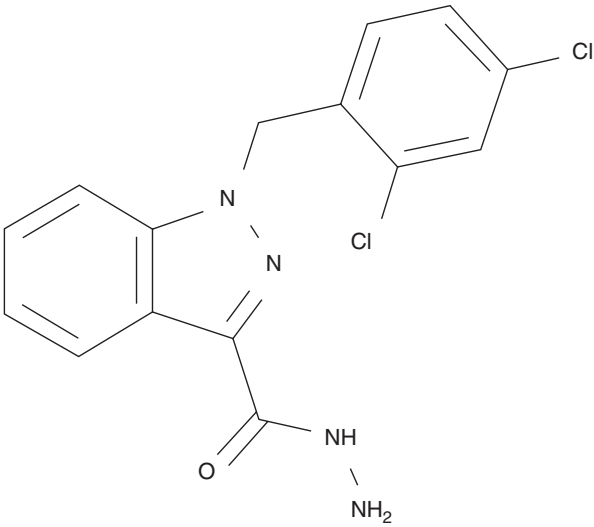


Fig. 24.3 Adjudin



antisperm compound that disrupts the adhesion of spermatids to Sertoli cells, causing premature spermiation and infertility. Administration of two doses of 50 mg/kg of adjudin weekly induced 100% infertility after 5 weeks of treatment in adult rats without changes in serum testosterone, FSH, or LH concentrations [36]. Because there was some liver inflammation observed in a 29-day study of adjudin administration [37], researchers conjugated adjudin to a FSHβ mutant specifically targeting it to Sertoli cells, thereby significantly reducing the dose necessary for contraception [38]. Unfortunately, the cost of this approach and the possibility of developing anti-FSH autoantibodies to the FSHβ mutant have stalled progress [39].

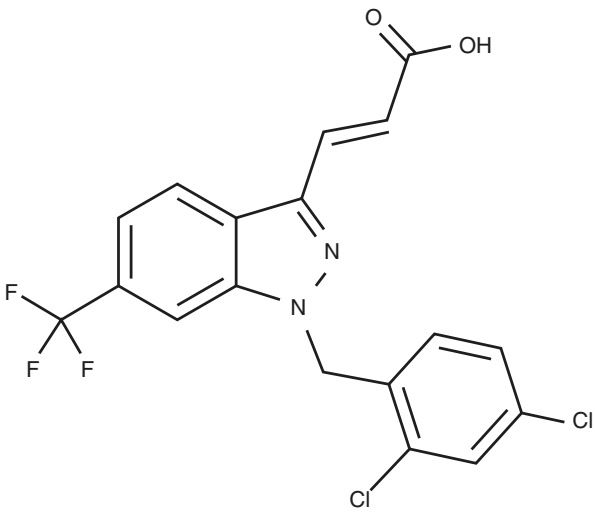
24.2.8 H2-Gamendazole

H2-gamendazole (Fig. 24.4) is an antisperm compound related to adjudin that also impairs the function of the apical ectoplasmic specialization [40]. All male rats who received a single oral dose of gamendazole at 6 mg/kg were infertile, but only 57% regained fertility [41]. In terms of toxicology, three out of five rats died after receiving a dose of 200 mg/kg of H2-gamendazole; however, no observable abnormalities including liver inflammation, necrosis, or hemorrhage were detected at dosages lower than 200 mg/kg. Initial work was performed in hopes of moving into human testing, but this work appears to have stalled, apparently due to toxicity.

24.2.9 EPPIN

EPPIN is a sperm surface protein that plays a role in liquefaction of the ejaculate [42]. It was initially demonstrated that seven of nine male nonhuman primates could be immunized against EPPIN and were unable to father pregnancies and the effect was reversible when the immunizations were stopped [43]. This group has now developing small molecular inhibitors of Eppin binding as a nonhormonal male contraceptive [44]. Intravenous administration of one compound, EP055, reduced sperm motility by 80% in a recently published paper [45]. The development of more potent, oral compounds that can fully suppress sperm motility will be an exciting area of future research.

Fig. 24.4 H2-gamedazole



24.2.10 BRDT Inhibition

A testicular bromodomain protein called BRDT, which is testes specific, is required for meiosis. Individuals with mutations in the *Brdt* gene have infertility from abnormal formation of sperm heads [46]. An exciting 2012 paper showed that the small molecule JQ1 (Fig. 24.5) could reversibly suppress spermatogenesis in mice by inhibiting the function of BRDT [47]. Unfortunately, this compound also inhibits other members of the bromodomain family, leading to toxicity. Therefore, this group is attempting to develop a BRDT-specific inhibitor, to minimize the potential for side effects from this approach [48].

24.2.11 Retinoic Acid Receptor Antagonists

It has been known since 1925 that vitamin A (retinol) is required for normal spermatogenesis [49]. Vitamin A and its active metabolite retinoic acid are required at puberty for the initiation of spermatogenesis and for the maintenance of spermatogenesis in adults [50, 51]. Retinoic acid produced from retinol in situ binds one of several retinoic acid receptors (RARs), which regulate gene expression. Because male RAR knockout animals are sterile due to various problems in spermatogenesis [52–55], blockade of retinoic acid function or biosynthesis is an appealing approach to male nonhormonal contraceptive development.

BMS-189453 (Fig. 24.6) is an orally active retinoic acid receptor pan-antagonist. At daily oral doses of 15, 60, or 240 mg/kg for 1 month, BMS-189453 produced marked testicular degeneration in rats but also lead to increases in leukocyte counts, alkaline phosphatase, and alanine aminotransferase levels [56]. One group has explored whether a lower dose of BMS-189453 might function as a contraceptive

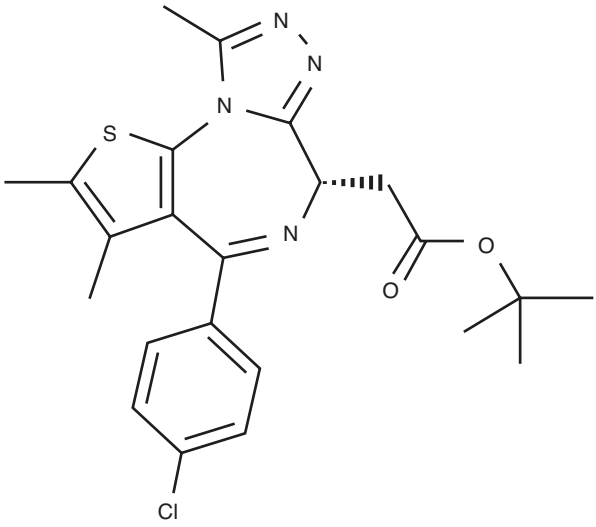


Fig. 24.5 JQ-1

without the toxicity seen at higher doses [57]. Two groups of 30 mice each were given BMS-189453 in oral dose of 5 mg/kg for 2 weeks and 2.5 mg/kg for 4 weeks. The study showed that the mice were completely sterile by 4 weeks after a dosing regimen of 5 mg/kg and by the end of treatment with a dose of 2.5 mg/kg for 4 weeks [58]. Twelve weeks after treatment was stopped, fertility was completely restored in all males. This compound, or a more specific retinoic acid-alpha antagonist under development [59], holds promise for nonhormonal male contraception.

24.2.12 Retinoic Acid Biosynthesis Inhibitors

Over 50 years ago, the oral administration of WIN 18,446 (Fig. 24.7) was shown to completely and reversibly inhibit spermatogenesis in man [60–62]. Unfortunately, subjects taking WIN 18,446 experienced a "disulfiram reaction" consisting of nausea, vomiting, palpitations, and sweating, when they took WIN 18,446 and drank alcohol. Because of this, further development of WIN 18,446 was abandoned without an understanding of its mechanism of action. In 2011, it was demonstrated that WIN 18,446 suppresses spermatogenesis by inhibiting testicular retinoic acid biosynthesis, via inhibition of the testes-specific aldehyde dehydrogenase ALDH1A2 [63, 64]. Using a rabbit model, it was observed that oral administration of WIN 18,446 induced reversible azoospermia, and reductions in spermatogenesis were preceded by a reduction in intratesticular retinoic acid. These findings suggest that inhibition of the testicular retinoic acid biosynthesis is a promising target for male contraceptive development. This work is focused on the development of novel,

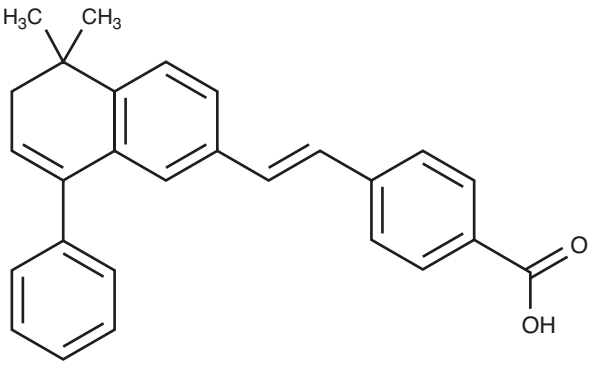


Fig. 24.6 BMS-189453

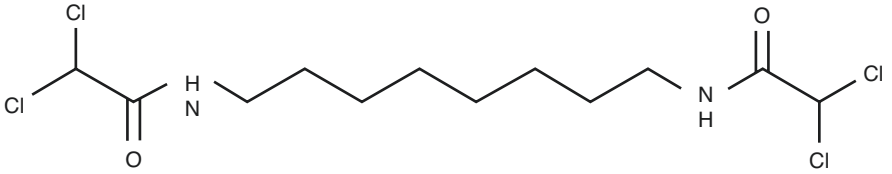


Fig. 24.7 WIN 18,446

specific compounds that inhibit testicular retinoic acid biosynthesis via ALDH1A2 without interfering with alcohol metabolism [65]. Hopefully, this work will result in compounds that reversibly inhibit spermatogenesis without significant side effects.

24.2.13 CatSper

In 2001, a novel sperm-specific calcium channel was identified [66]. Importantly genetic knockout of this protein leads to infertility [67]. One candidate CatSper antagonist, called HC-056456, has been reported in the literature [68]. In vitro, this compound significantly suppressed sperm motility; however, no in vivo data on this compound or other CatSper antagonists have been reported to date.

24.2.14 Gendarussa

A plant commonly used in an Indonesian traditional medicine called *Justicia gendarussa* has been used by men in Papua New Guinea. The active ingredient may be flavonoids called gendarusin A and B [69]. Efficacy for this compound has been reported in abstract form, but not published. In addition, the mechanism of action remains unclear. Therefore, additional information will be needed to determine whether this is a viable approach to developing a nonhormonal male contraceptive.

24.2.15 Vas Occlusion Methods

Since the 1970s, efforts have been underway in India and China to develop a temporary plug for the vas deferens, which could theoretically be removed or dissolved by an injection at a later date to provide reversibility. The Indian vas occlusion device is called RISUG for "reversible inhibition of sperm under guidance." Using ultrasound guidance, sterile styrene maleic anhydrate is instilled into the vas bilaterally occluding it and preventing the passage of sperm. Several small clinical trials in men have been performed using this technique [70, 71], showing excellent contraceptive efficacy over periods of up to 1 year. However, importantly, data on efficacy and reversibility from large-scale clinical trials are not available [72].

A nongovernmental organization called the Parsemus Foundation has acquired the rights to RISUG, now renamed "Vasalgel™." This reformulated styrene maleic anhydrate functioned effectively as a contraceptive for 1 year in rabbits [73] and also displayed efficacy in monkeys [74]. However, after reversal, the sperm of the rabbits lacked acrosomes, possibly due to residual inflammation in the vas [75]. No data on the fertility of these animals was reported. As a result, it remains unclear if this procedure is truly reversible.

Similar vas occlusion devices using medical-grade silicone and polyurethane plugs were studied in China in the early 1990s [76, 77]. Unfortunately, these devices

had problems with time to sperm suppression and recovery of sperm counts after reversal, leading the investigators to abandon this approach to male contraception.

24.3 Conclusions

Contraception is essential for the prevention of unintended pregnancy. Approximately 30% of couples currently rely on male contraceptive methods, specifically condoms and vasectomy and withdrawal. Shortcomings of these methods have led to efforts to develop new types of male contraceptives. Several nonhormonal methods in development appear promising in preclinical studies, but more testing and refinement of these approaches will be required before human studies can be performed to determine their efficacy for the prevention of unintended pregnancy.

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Male Contraception: Hormonal Methods

25

Carmen Abbe, Bradley D. Anawalt, and Stephanie T. Page

Abbreviations

11-βMNT	11β-methyl-19-nortestosterone17β
11-βMNTDC	11β-methyl-19-nortestosterone17β-dodecylcarbonate
DHT	Dihydrotestosterone
DMPA	Depot medroxyprogesterone acetate
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
IM	intramuscular
LH	luteinizing hormone
MENT	7α-methyl-19-nortestosterone
MHC	male hormonal contraception
T	testosterone
TE	testosterone enanthate
TU	testosterone undecanoate
WHO	World Health Organization

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25.1 Introduction

There is an urgent need for new contraceptives in order to decrease ongoing high rates of unintended and unwanted pregnancies globally. While numerous female contraceptive methods have been developed in the last century, no new male contraceptive methods have been introduced since the condom and vasectomy were developed hundreds of years ago.

Men want a role in family planning, and many desire control of their reproductive future. One quarter of contraceptive use worldwide is based on a male method [1], highlighting men's active role in family planning. A majority of men believe that women and men share responsibility for contraceptive decision-making and for family planning [2]. Availability of convenient, effective, reversible, and safe novel male contraceptive methods will permit men to further participate in these responsibilities. For couples, new male contraceptive methods will provide necessary options for family planning when the female partner is unable or unwilling to use female-based options. In addition, for couples who want to optimize contraceptive effectiveness, the use of a combination of an effective female and an effective male-based contraceptive would be synergistic.

More effective and acceptable male contraceptive methods might help decrease high rates of unwanted pregnancies and abortions across the globe. In the United States, 45% of pregnancies are unintended. Globally, it is estimated that 41% of pregnancies are unplanned, and at least 110 million married women face unmet family planning needs [3]. The global unsafe abortion rate is 14 per 1000 women aged 14–44 years, and 4700 female deaths annually are attributable to unsafe abortions [3]. In order to decrease the high rate of unintended and unwanted pregnancy and their consequences, men must be included in the solution.

The two effective male contraceptive options, condoms and vasectomy, are suboptimal. Condoms are inconvenient, decrease sexual pleasure for both partners, and have high failure rates [4]. Condoms have a 13% annual failure rate with typical use, a rate that is significantly higher than the most effective female-based contraceptives that have failure rates as low as 1–7% per year [5]. Vasectomies are very effective with failure rates <1% in the first year (and much lower failures thereafter) but require an invasive procedure and are not reliably reversible [6]. The withdrawal method, requiring the man to withdraw his penis prior to ejaculation, is inadequate, with a first-year failure rate of 18% [7].

To optimize family planning, there is a clear rationale for introducing new male contraceptives. Although there are novel hormonal and many nonhormonal male-based methods in the discovery phase, male hormonal contraception (MHC) is the furthest in clinical development and the closest to being available for widespread use. We review the mechanism, effectiveness, safety, and acceptability of male hormonal contraceptives in development.

25.2 Physiological Basis of Male Hormonal Contraception

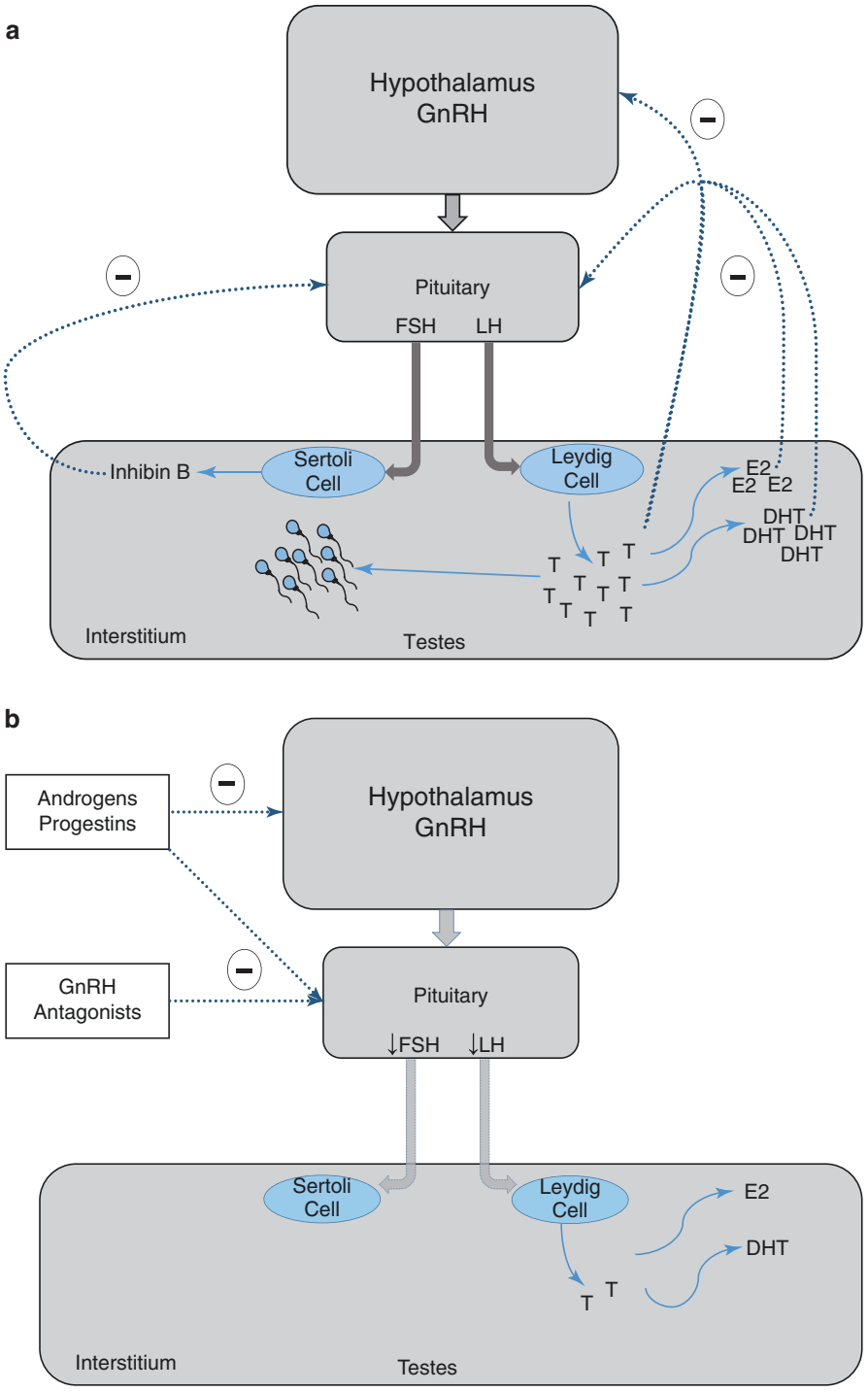
MHC takes advantage of negative feedback loops in the male endocrine system to suppress spermatogenesis and fertility. In normal men, the hypothalamic-pituitary-gonadal axis regulates sex hormone homeostasis and sperm production (Fig. 25.1a). In a classic feedback loop, gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus, leading to the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. Luteinizing hormone stimulates testosterone (and estradiol) production and secretion from Leydig cells resulting in high intratesticular testosterone (T) concentrations that are required for spermatogenesis. Follicle-stimulating hormone is necessary for quantitatively normal spermatogenesis, and it also stimulates the release of inhibin B from Sertoli cells. To complete the feedback loop, T and estradiol inhibit GnRH, LH, and FSH secretion, and inhibin B inhibits FSH secretion.

Similar to female hormonal contraceptives, male hormonal contraceptives inhibit GnRH, LH, and FSH. Administration of hormones such as GnRH analogs, T and other androgens, or progestins significantly suppresses circulating gonadotropin concentrations, thus suppressing endogenous T and sperm production (Fig. 25.1b). MHC regimens must include an adequate androgen dosage to ensure that the man does not develop manifestations of extra-gonadal androgen deficiency such as decreased libido, muscle weakness, reduced erythropoiesis, or loss of bone mineral density.

Male hormonal contraceptive research began as early as 1939 [8]. A variety of potential male hormonal regimens have been evaluated, including androgens alone and regimens that include various combinations of androgens plus progestins and/or GnRH analogs. We review the efficacy trials of MHC and novel compounds for MHC regimens that are under investigation.

25.3 Experimental Male Hormonal Contraceptives: Efficacy Studies

The published MHC efficacy studies have used regimens of androgens alone and androgens plus a progestin. MHC efficacy trials evaluate the method for the prevention of pregnancy within a couple, whereas phase 2 studies of MHC assess the suppression of sperm production as the primary endpoint. Published MHC efficacy studies have used injectable and implantable formulations administered by research personnel; the first efficacy study of a self-administered, transcutaneous MHC formulation is underway [9–14] (Table 25.1).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25.3.1 Androgen-Only MHC Approaches

25.3.1.1 World Health Organization Trials: Short-Acting Testosterone Injections

The World Health Organization (WHO) sponsored two international contraceptive efficacy studies of high-dosage testosterone enanthate (TE) that were published in the 1990s. In the first WHO TE study, 271 couples from Asian, European, and North American sites were enrolled. The male partners were injected with 200 mg of TE intramuscular (IM) weekly during an initial suppression phase [13]. When the male partners' sperm concentrations suppressed to azoospermia, couples entered into an efficacy phase in which the experimental hormonal contraceptive, IM TE, was the sole method of birth control. Fifty-eight percent (157/271) of enrolled couples entered the efficacy phase. One pregnancy occurred in the 119 couples who completed the efficacy phase. This study established that supraphysiologic dosages of IM TE induce azoospermia in the majority of men and that MHC-induced azoospermia provides highly effective contraception.

The second WHO T-alone efficacy study was designed to test whether T-induced severe oligozoospermia would be effective [9]. The study design of the second study was identical to the first WHO study: a 6-month suppression phase followed by a 12-month efficacy phase and a recovery phase. The original definition of severe oligozoospermia for this study was a sperm concentration ≤ 5 million/mL (azoospermia inclusive), but after 3 pregnancies occurred in couples whose male partners' sperm concentrations were 3–5 million/mL, the entry criterion for the efficacy phase was changed to ≤3 million/mL. Three hundred and ninety-nine couples enrolled from Asian, European, and North American sites. Eighty-six percent of the men had proven fertility prior to the study, and 77% had conceived children with their partners (with whom they had enrolled in the study). Of the men (89%) who completed the suppression phase, 98% suppressed to the target threshold (≤ 3 million/mL). The pregnancy rate for the couples whose male partner's sperm concentration suppressed to this target was 1.4 per 100 person-years. The combined pregnancy rate for the couples whose male partner's sperm concentration suppressed to ≤1 million/mL was 0.7 per 100 person-years. Based on this study, the benchmark for spermatogenic suppression in investigational male hormonal

Fig. 25.1 The feedback regulation loop of the normal hypothalamic-pituitary-gonadal axis. (**a**) In a classic negative feedback loop, the hypothalamus secretes gonadotropin-releasing hormone (GnRH), stimulating the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates Leydig cells to produce intratesticular testosterone (T) that normally has concentrations 100–200 times greater than serum T. Intratesticular T converts to dihydrotestosterone (DHT) and estradiol (E2). FSH, together with high intratesticular T, promotes quantitatively and qualitatively normal spermatogenesis. FSH stimulates Sertoli cells to release inhibin B. Completing the feedback loop, T and E2 inhibit GnRH, LH, and FSH secretion and inhibin B inhibits FSH secretion. (**b**) Administration of sex hormones or a GnRH antagonist suppresses the secretion of GnRH, LH, and FSH, resulting in decreased T, E2, and DHT production and suppressed spermatogenesis

Table 25.1 **(a)** An overview of male hormonal contraception efficacy trials. The reported number of pregnancies occurred during the efficacy phase of each study. The trials are listed in chronological order. The trials with no shaded background represent testosterone-alone regimens, and the trials with shaded backgrounds represent androgen plus progestin regimens. **(b)** An overview of additional male hormonal contraception trials that had pregnancy outcomes. Although these studies reported pregnancy outcomes, these trials were not designed to test efficacy. In addition to low enrollment numbers, the duration of the trials' efficacy phases was short and variable across participants

Trial	Method	Regimen	Participants enrolled/ completed	Criteria for entrance into efficacy phase	Duration of efficacy phase	Number of pregnancies
(a) Male hormonal contraception efficacy trials						
First WHO trial [13]	IM injection	200 mg testosterone enanthate weekly	271/119	0 million sperm/mL	12 months	1
Second WHO trial [9]	IM injection	200 mg testosterone enanthate weekly	399/349	≤ 3 million sperm/mL	12 months	4
First China-based trial [11]	IM injection	1000 mg testosterone undecanoate followed by 500 mg monthly	308/280	<3 million sperm/mL	12 months	1
Second China-based trial [12]	IM injection	1000 mg testosterone undecanoate followed by 500 mg monthly	1045/733	≤1 million sperm/mL	24 months	9
Australia-based trial [10]	IM injection + subcutaneous implants	200 mg testosterone pellets every 4 months; 300 mg depot medroxyprogesterone every 3 months	55/28	<1 million sperm/mL	12 months	0
Third WHO trial [14]	IM injection	1000 mg testosterone undecanoate every 8 weeks; 200 mg enanthate norethisterone	320/*NA*	≤1 million sperm/mL	Early termination of trial	4
(b) Additional male hormonal contraception trials with pregnancy outcomes						
McLachlan [49]	Implant	800 mg or 1200 mg T every 3 months	36/16	<1 million/mL	3–16 months	0
Soufir [26]	Oral pill + transdermal gel	20 mg oral medroxyprogesterone acetate +100 mg percutaneous testosterone	35/23	≤1 million/mL	9–11 months	1

Numbers in superscript provide the reference citation
NA "not applicable"

contraceptive regimens has been the percentage of men whose sperm concentration suppresses to ≤1 million/mL.

The WHO studies established that the suppression of spermatogenesis to concentrations ≤3 million/mL provides effective contraception that is comparable to most female-based methods. Common side effects in the two trials were weight gain, acne, injection site discomfort, and a decline in serum high-density cholesterol concentrations. In addition, weekly injections administered by clinic personnel would be impractical and was the cited reason for study discontinuation for several subjects.

25.3.1.2 China-Based Trials: Longer-Acting Testosterone Injections

The WHO trials demonstrated that an androgen-based MHC would provide effective contraception. However, these studies used weekly injections of TE at a dosage that is twice the usual replacement therapy for male hypogonadism resulting in supraphysiological T concentrations that might have contributed to side effects. It is unlikely that many men would be willing to use a contraceptive that requires weekly injections, and there have been concerns about the long-term safety of using high dosages of androgen in normal men.

Two studies in China tested a long-acting injectable formulation of testosterone undecanoate (TU) at a more physiological dosage. In the first study, 308 Chinese couples were enrolled, and the male partner received an initial injection of 1000 mg TU, followed by monthly injections of 500 mg TU [11]. Two hundred and ninety-six of the male partners (97%) suppressed to severe oligozoospermia (<3 million/mL) within 6 months and entered the 12-month efficacy phase. Nine men were non-suppressors whose sperm concentrations remained ≥3 million/mL. Spermatogenic rebound, a rise of sperm concentration to greater than the threshold target of suppression during the efficacy phase, occurred in six men during the efficacy phase. One pregnancy occurred during the efficacy phase that was attributed to spermatogenic rebound. The contraceptive regimen had a total efficacy of 94.8% with a failure rate of 5.2% (non-suppressors are included in the failure rate).

The second efficacy study of IM TU was designed to test the efficacy of spermatogenic suppression to ≤1 million/mL and enrolled 1045 healthy, young couples in stable relationships at 10 sites in China [12]. The male partners used the same TU injection regimen as the first China-based study. Of the original enrolled cohort, 95% of the male partners of the couples suppressed to the pre-specified target after completion of suppression phase. A total of 855 couples entered the 24-month efficacy phase. Ten men (1.3%) experienced spermatogenic rebound in the efficacy stage. There were nine pregnancies during the efficacy phase, six of which were attributed to spermatogenic rebound. In this study of TU-induced spermatogenic suppression (≤1 million/mL), the 2-year perfect use failure rate was 1.1 per 100 men over a 24-month period, but the TU regimen had a 6.1% contraceptive method failure rate if men who did not suppress to the target sperm concentration were included in the failure rate. Adverse effects in both China-based trials were similar to the WHO trials.

The China-based trials demonstrated two important findings. First, they confirmed the WHO findings that sperm concentrations ≤1 million/mL should be the criterion for entering into an efficacy phase of an MHC trial. Second, the studies in China confirmed a pattern initially observed in the WHO studies—that race (or an environmental factor associated with race) affects the rate of suppression to azoospermia. The WHO and Chinese trials demonstrated that Asian men were more likely to suppress to azoospermia than non-Asian men of European descent. An integrated analysis of several contraceptive studies confirmed that Asian men in China suppressed more rapidly and more uniformly to azoospermia than non-Asian men of European descent [15]. The reason for this variance is unknown, but possible explanations include differential gonadal-axis responsiveness, germ-cell apoptosis, and/or testicular morphology or environmental factors such as dietary differences [16].

25.3.2 Androgen plus Progestin MHC

Preliminary studies found that the combination of exogenous T and progestin causes more rapid and complete suppression of serum gonadotropins and spermatogenesis than T alone [15]. This combination approach also permits a more physiological dosage of testosterone that might decrease adverse androgenic side effects.

25.3.2.1 Australia-Based Trial: Long-Acting Testosterone plus Depot Medroxyprogesterone Acetate

An Australian group first tested the efficacy and safety of a long-acting androgen-progestin [10]. In this proof-of-concept study, 55 Australian couples were enrolled; the male partner received 200 mg T pellets every 6 months plus a 300 mg depot medroxyprogesterone acetate injection every 3 months. Fifty-one of the couples entered the 12-month efficacy phase after the male partner's sperm concentrations suppressed to <1 million/mL. The dosing schedule of the T pellets was changed to every 4 months after several men had symptoms of androgen deficiency and/or spermatogenic rebound. There were no pregnancies, and sperm concentrations suppressed more rapidly (1–3 months) than the T-only regimens used in the WHO and Chinese trials (up to 6 months). Adverse events were similar to the WHO trials.

25.3.2.2 WHO/Contraception Research and Development Trial: Long-Acting Testosterone plus Norethisterone

The most recently published efficacy study, sponsored by WHO and Contraception Research and Development, tested the combination of long-acting T undecanoate and norethisterone enanthate, a progestin with androgenic and progestogenic properties [14]. Three hundred twenty couples were enrolled at ten centers. In the 26-week suppression phase, intramuscular 200 mg norethisterone enanthate and 1000 mg T undecanoate were administered every 8 weeks, up to 4 times. Two hundred and sixty-six men met entry criteria (suppression of sperm concentrations ≤1 million/mL within 12 months) for couples to enter the efficacy phase. The Pearl

Index for the study was 2.18 per 100 person-years, but the true efficacy is difficult to measure due to the study's early termination. The study was terminated early based on the recommendations of an external safety review committee that cited a concern about adverse events (principally mood changes and depression). Other adverse events included site injection pain, myalgias, acne, and increased libido [14]. Over 90% of the reported emotional disorders occurred at one study center, all of which were reported as "mild." The majority of the reports of injection site pain, myalgias, and increased libido also occurred at this same center. There was one suicide that was judged not related to the study drug and one suicide attempt that was judged possibly related. There was also one case of depression that was deemed to be probably related to the study drug.

25.4 Studies of Other Potential MHC Regimens

Although only injectable formulations have been studied in published efficacy trials, pilot studies of oral and transdermal MHC formulations have been completed. In addition, some injectable regimens other than androgen plus a progestin show promise.

25.4.1 Oral Formulations

25.4.1.1 Oral T plus Cyproterone Acetate

An exploratory study in the 1990s tested a formulation of 80 mg T undecanoate and 12.5 mg cyproterone acetate administered orally, twice daily [17]. Out of the eight men enrolled, only one became azoospermic. The 16-week-long study was too short to accurately assess effects on spermatogenesis. There were no serious adverse events. This pilot study was the basis for additional studies of oral MHC although the twice daily-dosing regimen evaluated in this pilot study is likely impractical for effective contraception.

25.4.1.2 Oral Dimethandrolone Undecanoate

Dimethandrolone undecanoate is hydrolyzed in vivo to dimethandrolone, a derivative of 19-nortestosterone. Dimethandrolone binds to androgen and progesterone receptors to suppress gonadotropin secretion. This dual activity presents the potential for a single-agent male contraceptive [18, 19]. Oral and intramuscular dimethandrolone undecanoate formulations are under investigation. Phase 1 studies have demonstrated that oral dosages up to 800 mg are safe and well-tolerated [18, 20]. A phase 1b double-blind placebo study found that oral doses ≥200 mg, taken for 28 consecutive days, suppressed circulating gonadotropin and T concentrations with no serious adverse events [21]. To enhance bioavailability and absorption, dimethandrolone undecanoate must be taken with food [18]. Dimethandrolone is resistant to 5α-reduction, potentially decreasing the risk of prostate disease, and aromatization, which might increase body fat and decrease bone density [22, 23]. A

longer-term study of oral dimethandrolone undecanoate and its effects on spermatogenic suppression, as well as studies of IM dimethandrolone undecanoate, is being conducted by the National Institutes of Health-sponsored Male Contraceptive Clinical Trials Network.

25.4.1.3 11β-Methyl-19-Nortestosterone17β-Dodecylcarbonate

11β-Methyl-19-nortestosterone17β-dodecylcarbonate (11-βMNTDC) is the prodrug of 11β-methyl-19-nortestosterone17β (11-βMNT) [23]. With just one methyl group difference compared to dimethandrolone undecanoate, 11-βMNT similarly has androgenic and progestin activity in vitro. Oral formulation and long-acting injection formulations of 11-βMNTDC are under evaluation [24]. Oral doses of 11-βMNTDC have been safely administered in dosages up to 800 mg, leading to rapid suppression of serum gonadotropins and T concentrations [25]. Oral 11-βMNTDC absorption is increased with the co-ingestion of fatty food, and 11-βMNT is resistant to 5α-reduction and aromatization [25].

25.4.2 Transdermal Formulations

25.4.2.1 Testosterone Gel plus Oral Medroxyprogesterone

Transdermal gels and patches that are applied daily are available to treat hypogonadism in men, presenting possibilities for their use as potential male hormonal contraceptives. There has been one study of transdermal T gel and an oral progestin. In this descriptive study, 35 men in stable, heterosexual relationships self-administered 100 mg transdermal T with 20 mg of oral medroxyprogesterone acetate daily, and 80% achieved suppression of sperm concentrations to ≤1 million/mL within 3 months [26]. Twenty-five men whose sperm concentrations suppressed to ≤1 million/mL and their female partners were allowed to use this method as a sole contraceptive for variable amounts of time (1–17 months). Five subjects experienced spermatogenic rebound during this "efficacy" phase. One pregnancy occurred that was attributed to poor compliance by the male partner. The transdermal T gel maintained serum T concentrations in the normal range, potentially reducing long-term androgen-related adverse effects.

25.4.2.2 Transdermal Testosterone plus Nestorone Gel

Testosterone-nestorone gel is a transdermal formulation of T plus nestorone (segesterone acetate) in a single gel. Nestorone, a 19-nor-progesterone-derived progestin, binds specifically to the progesterone receptor, with very little androgenic nor glucocorticoid activity, and thus might have a more favorable side effect profile than other progestins [27]. The combination of T plus nestorone significantly suppresses circulating gonadotropins and endogenous testosterone production [28, 29]. A 20-day pilot trial among 140 men studied various doses of nestorone gel alone and T gel combined with nestorone gel [30]. The combined regimen of T gel and nestorone gel (6 or 8 mg) safely and effectively suppressed gonadotropin concentrations. Subsequently, 99 men enrolled in a 6-month-long study testing the

effectiveness of T gel alone (10 g) or combination of T gel and nestorone gel (8 mg) to suppress sperm production [28]. Of the men using the T gel and nestorone gel, 88.5% suppressed sperm concentrations to ≤1 million/mL, while only 23% of men using the T gel alone suppressed to ≤1 million/mL.

A recent randomized study compared gonadotropin suppression of T plus nestorone in a single gel vs. a T-alone gel, in a group of 44 normal men who self-applied the gel daily for 28 days [29]. The combination of nestorone and testosterone in a single gel suppressed serum gonadotropins significantly more than T-alone gel without significant safety signals. Based on these initial results, a multicenter phase 2b MHC efficacy study of self-administered, combined nestorone-testosterone transdermal gel has been initiated. Four hundred couples in 7 countries in Africa, Europe, North America, and South America are projected to enroll. Results are anticipated in 2022–2023.

25.4.3 Injectable and Implantable Regimens Other Than T plus Progestin

25.4.3.1 T plus GnRH Analogs (plus Progestin)

GnRH agonists and antagonists, initially candidate components for MHC, have proved to be disappointing as adjuncts. No efficacy trials have included a GnRH antagonist, but smaller studies of androgens plus GnRH antagonists generally have not revealed significant additive effects on spermatogenic suppression.

In a proof-of-concept study, daily subcutaneous Nal-Glu, a peptide GnRH antagonist, plus TE was compared to TE alone [19], but there is no significant difference in spermatogenic suppression, or time to suppression, between the two groups. Subsequent studies of acyline, a potent and longer-acting GnRH antagonist, demonstrated marked suppression of serum gonadotropins and T within 48 h after a single-dose injection, with maintenance of castrate serum T concentrations for up to 15 days after a single injection [31]. However, the combination of acyline plus T and depot medroxyprogesterone acetate (DMPA) did not significantly change the overall spermatogenic suppression compared to T plus DMPA alone [32]. Of note, a single study of another short-acting GnRH antagonist, cetrorelix, plus 19-nortestosterone (a non-aromatizable testosterone derivative) induced azoospermia by 12 weeks in 6/6 men, but this finding requires a much larger sample size [33].

25.4.3.2 7α-Methyl-19-Nortestosterone Subcutaneous Implants

7α-Methyl-19-nortestosterone (MENT) has not been studied in over a decade, but it remains a potential MHC. MENT is a potent androgenic-anabolic steroid and has tenfold higher potency than T to suppress pituitary gonadotropins [34, 35]. As an implant, it has the potential to only require replacement once a year or less [36]. Studies of MENT administered as a subcutaneous implant have shown no serious adverse events, affirmed its prostate-sparing quality, and demonstrated its ability to suppress spermatogenesis [37, 38]. Research on MENT has stalled due to an apparent decrease in bone density [39] and due to problems with implant hormonal release at higher doses.

25.5 Possible Mechanisms for Nonuniform Suppression of Spermatogenesis

About 5–10% of men have failed to suppress sperm concentrations to ≤1 million/mL during male hormonal contraceptive trials (Fig. 25.2). One hypothesis is that these "nonresponders" might have inadequate suppression of intratesticular T concentrations [40]. The possible role of intratesticular T in maintaining spermatogenesis in humans has been difficult to quantify; normal intratesticular T concentrations are very high – 100–200 times higher than serum concentrations [41]. A study of LH-reception knockout mice suggests that constitutive testicular T production (independent of gonadotropin concentrations) might suffice to preserve a low level of spermatogenesis [40]. This suggests that relatively low intratesticular T concentrations might support some degree of spermatogenesis even with maximal pituitary gonadotropin suppression. Human studies have shown no proportional relationship between intratesticular T concentration and sperm concentration [42, 43]. However, data from one study suggests that suppression of intratesticular T concentrations to below 10–15 nmol/L (100–200 times lower than normal) might cause uniform azoospermia [42]. A possible approach to inducing and maintaining more uniform spermatogenic suppression is the addition of T synthesis inhibitors to an androgen-progestin regimen. If low concentrations of intratesticular T are capable of maintaining spermatogenesis, the introduction of an inhibitor of testicular T production might induce more uniform spermatogenic suppression. One study demonstrated

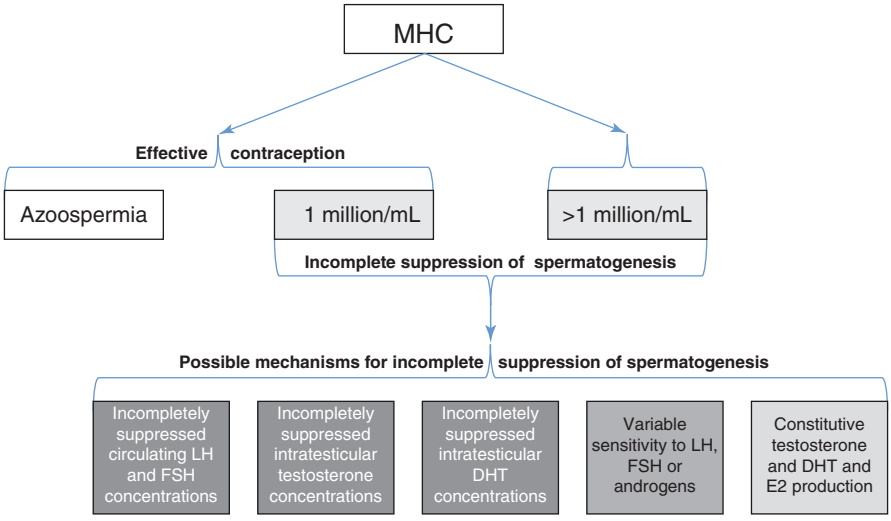

Fig. 25.2 Male hormonal contraception (MHC) leads to effective contraception in the majority of men. However, 5–10% of men fail to suppress sperm concentrations to ≤1 million/mL, the threshold often used as a marker for high contraceptive efficacy. This figure outlines the possible mechanisms for nonuniform suppression in MHC users who do not suppress to azoospermia. Possible mechanisms shaded in dark gray represent mechanisms of incomplete suppression

that gonadotropin suppression with a GnRH antagonist plus direct inhibition of testosterone synthesis with high-dosage ketoconazole resulted in very low intratesticular T concentrations, but the study was too short to measure effects on spermatogenesis [44]. Because high-dosage ketoconazole may cause glucocorticoid deficiency, testosterone synthesis inhibitors other than ketoconazole would be required for MHC [45].

Another hypothesis is that persistent, very low concentrations of circulating and intratesticular gonadotropins might maintain low-level spermatogenesis in some men; this could be due to variable expression of coactivators or receptor polymorphisms [42]. A very small amount of exogenous LH has large effects on intratesticular testosterone [46]. The finding suggests that low residual concentrations of LH might stimulate intratesticular T production enough to maintain low levels of spermatogenesis [46]. Although various male contraception studies have not shown differences in serum FSH and LH concentrations between men who suppressed and those who did not [15, 47], these results are not conclusive. Very low serum gonadotropin concentrations are difficult to measure even with modern assays, limiting the ability to discern possible differences in serum gonadotropin concentrations between MHC responders and nonresponders. It has also been suggested that persistent low concentrations of intratesticular dihydrotestosterone (DHT), a potent androgenic metabolite of T, might maintain spermatogenesis [48, 49]. One study of T pellets with or without a 5α-reductase inhibitor (to reduce intratesticular DHT) showed no difference in spermatogenic suppression [50], but the study did not measure intratesticular DHT concentrations.

25.6 Safety, Adverse Events, and Side Effects

MHC regimens have been generally well-tolerated. The most common adverse effects of androgenic MHC are acne, weight gain, and a decrease in serum high-density cholesterol (HDL-C). The decrease in serum high-density cholesterol is of uncertain clinical significance. Although serum HDL-C concentrations are inversely related to cardiovascular risk in epidemiological studies, this association might not pertain to drug-induced effects because HDL-C function (e.g., reverse cholesterol transport) might be more important to cardiovascular disease risk than HDL-C concentrations [51]. In addition to acne and weight gain, side effects of MHC include oily skin, increases in hematocrit and hemoglobin, and decreased testicular volume [52, 53]. Testicular volumes decrease about 25% on average, and most men do not notice the change [54]. Some MHC trials have reported changes in libido (mostly increased) and mood.

There is some question about whether MHC will lead to increased risk of sexually transmitted infections because of a potentially decreased incentive for condom use. Men using MHC would have to be educated and encouraged to use a condom in order to prevent sexually transmitted infections.

Some side effects of MHC regimens might be positive. For example, some men report increased libido, and some men gain weight that might be due to increased

lean body mass during MHC administration [55]; a subset of men might perceive these effects as beneficial. Increases in serum hemoglobin and hematocrit due to androgenic effects might increase exercise capacity in active men. Finally, MHC side effects vary based on the specific drugs administered; the sum of the androgenic, progestogenic, and estrogenic effects of the MHC regimen; the mode of delivery; and the dosage. For example, injectable T formulations are generally more likely to increase hemoglobin and hematocrit than transdermal T formulations [56], and transdermal MHC might be associated with less effect on serum high-density cholesterol concentration.

In the only placebo-controlled study of MHC (with sperm suppression as the endpoint), men receiving injectable T decanoate and etonogestrel reported a series of side effects more frequently than those in the placebo group. These included acne, increased body weight, mood changes, libido changes (mostly increases), and night sweats [57]. Studies comparing the effects of T plus a progestin versus T alone have demonstrated more weight gain and serum HDL-C suppression with the addition of a progestin [54, 58]. There might be differential effects in men from different genetic or environmental backgrounds; studies of Caucasian men demonstrate more suppression of serum HDL-C than Asian or African men, despite comparable drug concentrations [59, 60]. A short-term study comparing transdermal T plus several progestins versus each progestin alone demonstrated a more significant decline in serum HDL-C in the progestin-only groups compared to the T plus progestin groups and a significant decline in serum low-density cholesterol, insulin sensitivity, and hematocrit solely in the progestin-only groups. In progestin-alone groups, these differences might be attributable to suppression of serum T when progestin is administered alone (without T "giveback") and not due to the direct effects of progestin [61].

There is no evidence to date that MHC increases the risk for any long-term health outcomes including cardiovascular events or prostate disease. However, it is important to note that study participants have been healthy young men and the clinical trials have not exceeded 2–3 years and have not been adequately powered for cardiovascular and prostate disease outcomes. To fully understand potential long-term effects of MHC, longer, larger clinical trials with diverse cohorts of participants will need to be completed.

25.7 Acceptability of Male Contraception

Men's acceptance and desire for novel contraceptives has been demonstrated with numerous surveys [62–64]. The majority of men surveyed across Scotland, South Africa, and China wanted novel forms of MHC [63]. A multinational survey of over 9000 men in 9 countries [64] found that the majority of men have high overall acceptance of a hypothetical MHC, but there were significant variations between countries. Even men who have reported being mostly happy with their current contraceptive method still welcomed the idea of a novel hormonal method [63]. Additionally, women in committed relationships not only support introduction of MHC, but would trust their partners to use it [65, 66]. Moreover, men who

participate in MHC trials report high acceptability. A majority of men using experimental transdermal and injectable MHC reported satisfaction with the method and a willingness to recommend the method to others if it were available [67–70]. Further study regarding the acceptability and user and couple preferences for MHC formulations is needed to support further investment in these novel methods.

Multinational acceptability surveys provide a platform for exploring cultural differences in method acceptability. A multinational study in 1997 found that more than 60% of men in Cape Town and Edinburgh and about 50% of men in Hong Kong and Shanghai would be interested in taking a daily MHC contraceptive pill [66]. This study also found daily injections to be unpopular at every study site except Cape Town and implants to be universally less popular across all study sites. Another multinational study found implants to be the least-preferred method by men living in Latin America and Indonesia, but were rated as more acceptable by men living in Europe [64]. Such surveys demonstrate geographic differences in acceptability that might be due to social determinants such as culture, religion, age, and education. Cultural attitudes may change over time; work utilizing more modern survey techniques to explore current cultural preferences in male contraceptive acceptance and preferences is needed.

25.7.1 Method of Delivery Acceptability

A critical aspect of MHC development is ensuring that products appeal to potential users. In surveys comparing modes of hypothetical MHC delivery, men rank oral pills highest, followed by injections and transdermal formulations [64]. There have been challenges with developing safe, effective, oral delivery of androgens, but recent studies of oral dimethandrolone and 11-βMNTDC are encouraging [21, 71]. Long-acting injectable or implantable regimens (e.g., annual administration) are more acceptable than short-acting regimens (e.g., monthly administration) [64]. In preliminary data from these studies, a majority of subjects report satisfaction and high acceptability with these novel oral MHC despite the requirement to ingest with fatty food. Similarly, over one-third of men who participated in a transdermal gel study reported they would use the gel as their primary contraceptive method if available, and 51% reported they would recommend the method to others [67]. In another study on a transdermal T plus progestin gel formulation, over 80% of participants reported overall satisfaction with the daily gel as a potential method for male contraception [29]. In the third WHO study, despite being made aware of safety concerns regarding the product and the early termination of the study, 88% of the men and a majority of couples reported that they would use a method of contraception similar to the study's injection regimen [14].

MHC regimen using transdermal patches have not been extensively studied, but they might have the advantage of regarding secondary transference of drug to other individuals that might occur with a transdermal gel product [72, 73]. The patch is also uniquely visible to others. A recent study of male college students found that use of a male contraceptive by peer role models and leaders can influence men's

willingness to use male contraception – a concept only possible with methods that are visible to the eye [74]. Visible methods of delivery such as a patch could also spread awareness of male contraception and normalize the notion of men assuming a more active role in contraception.

25.7.2 Acceptability Related to Suppression Time and Reversibility

Male hormonal contraceptive methods require 1–6 months for effective suppression of spermatogenesis; this delay in onset of effectiveness is similar to vasectomy [6]. However, in contrast to vasectomy, MHC is readily reversible [16]. An integrated multivariate time-to-event analysis of spermatogenic recovery after MHC use assessed 1549 men enrolled in 30 studies [16]. The median time to recovery to normal sperm concentrations was 3.4 months, with longer recovery periods expected for longer treatment times and longer-acting drug regimens. This comprehensive analysis also found small effects of age, baseline sperm concentration, and LH serum concentrations on the time to recovery of spermatogenesis after MHC cessation.

25.8 Ethics of Male Contraception

The risk-benefit analysis of MHC is unusual (Fig. 25.3). Unlike most medications, MHC would be taken by healthy individuals who may not perceive a direct health benefit. MHC, however, has important potential societal, as well as individual, health

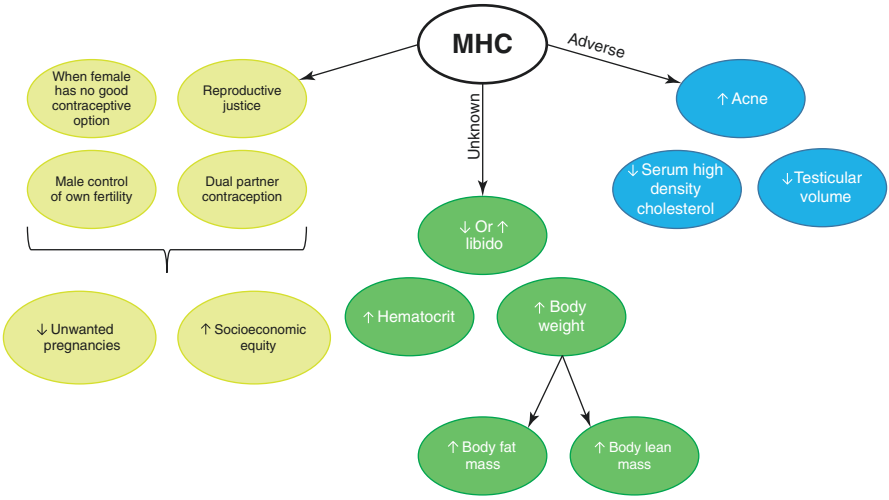

Fig. 25.3 Possible outcomes of male hormonal contraception (MHC). Benefits of MHC, such as dual partner contraception for increased contraceptive effectiveness, are depicted in yellow. Outcomes that are adverse, or might be perceived as adverse, are depicted in blue. Outcomes that users might perceive as positive, adverse, or neutral are depicted in green

benefits that have been under-explored. MHC would give men additional choices to control their own fertility. The ability to control one's family planning might help prevent psychological and financial risks associated with unintended pregnancy.

Male contraception must also be understood from a reproductive justice framework. Access to MHC would give men and couples greater agency and autonomy in their reproductive choices. This is particularly relevant for at-risk and marginalized populations, who might have greater socioeconomic consequences from unplanned pregnancy. Using reproductive justice as a guiding principle, many men in heterosexual relationships want to share the risk and responsibilities of contraception. There are various examples where individuals want to contribute meaningfully (sometimes at personal risk) to the health of their family members. Organ donation is one example. Similarly, men could utilize MHC to facilitate optimization of the health of their female partners. Many men want additional effective male-based contraceptive options in order to contribute meaningfully in reproductive justice and family planning.

25.9 Barriers to MHC Development

Despite various studies affirming men's interest in using a MHC, there has been little support or interest shown by pharmaceutical companies in the last decade. The withdrawal of initial support from pharmaceutical sponsors has introduced logistical and financial challenges in the progression of MHC development. Reasons for this market withdrawal are not publicly available. It is likely that the lack of a clear pathway regarding safety and efficacy benchmarks from regulatory agencies for this new class of medications contributes to the view that investment in MHC is high risk.

How big an impact might introduction of an MHC have? Many factors influence contraceptive availability and use, and these are largely untested among men due to the paucity of male methods currently available. Work in this area is just beginning. A 2018 study modeling the potential impact of novel male contraceptives suggests that the introduction of MHC could meaningfully reduce unintended pregnancies [75]. The study estimated reductions in unintended pregnancies in Nigeria, South Africa, and the United States, with the highest reduction of 30% to 38% in Nigeria. The authors concluded that the effect of introducing MHC would likely be greatest in settings where current contraception use is low and where MHC would attract new contraceptive users.

As development of MHC progresses, the manner in which it is branded might be integral for its success among investors and the pharmaceutical industry. A 2013 multinational survey identified distinct target groups for male contraception, suggesting that market segmentation may be a beneficial framework for branding and promotion [76]. For example, when targeting a group, the study identified that promoting effects such as increased libido and muscle mass (if substantiated) would be more effective for increasing uptake with some men, whereas highlighting control over fertility would be more effective for others [76]. Data also suggests it might be important to include female partners and potential female partners in marketing

campaigns for developing MHC and other novel male-based contraceptives. In one multinational survey, the majority of respondents expressed that both partners participate in deciding which method of contraception to use [64]. Women have been found to have a strong influence on a man's decision to use (or potentially use) contraception [63]. Thus involving both partners in method choice and adherence is likely to be important for both contraceptive effectiveness and marketing.

25.9.1 Male-Based Contraceptive Accessibility

While women have frequent opportunities to discuss family planning at recommended, regularly scheduled clinic visits with their healthcare providers, there is no equivalent expectation for younger men to have regularly scheduled healthcare visits. There is a gap in healthcare engagement in this sector, such that male-related health issues including prevention and treatment of sexually transmitted diseases and issues surrounding sexual function, fertility, or family planning are not addressed [77]. Two-thirds of young women report receiving counseling on condoms and contraceptive use [78]; in one study of men, only 12% received counseling on condoms, and only 12% received counseling on STD/HIV testing during a 12-month space of healthcare services [77]. A survey of 346 men in the United States found that almost all men were willing to discuss sexual and reproductive health, but the majority preferred that their physician initiate the discussion [79]. Discussions like these could not only make the concept of male contraception more accessible, but could improve contraceptive uptake and lead to overall improved reproductive health for men and women.

25.10 Conclusion

There is an unmet need for male contraception [80]. A greater array of male contraceptive options, particularly user-friendly, reversible methods, are needed to meet this need. Development of novel, male-based methods has made slow progress, but efficacy trials have proven that male hormonal contraceptive methods are effective, reversible, and acceptable to men and their female partners. Androgen-progestin or single agents with androgenic and progestogenic properties currently show the most promise as MHC. In these efficacy trials, MHC appears to be more efficacious than condoms and comparable to many female hormonal methods. Larger, longer-term studies are needed to assess real-world effectiveness. Introduction of novel MHC may decrease unintended pregnancies, bolster reproductive justice, and provide men with greater agency in their reproductive futures, resulting in improved health for both men and women.

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