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# Contraception today and family planning: a comprehensive review and position statement on the ethical, medical, and social dimensions of modern contraception

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## ABSTRACT

In a society whose needs are constantly changing, family planning plays a central role for women, men, and sustainable development. This comprehensive review and position statement summarises the proceedings of a meeting on contraception held in Rome in March 2024, supported by major scientific societies in the field. The aim is to inform the medical community about current medical and ethical issues of contraception use. First, the review addresses the complex ethical, religious, and social dimensions of contraceptive use and access; second, it provides a comprehensive analysis of traditional and modern contraceptive methods, discussing their safety and effectiveness; third, it examines current knowledge about male hormonal contraception. When prescribing a contraceptive method, medical indications or contraindications must be integrated to women's religious beliefs, the geopolitical context in which they live, the risk of violence, their need for self-determination and their right to make decisions for themselves. If a partner is involved, the couple's dynamics and shared needs must be considered. Healthcare providers are responsible for providing them with all the information they need to make informed choices, while ensuring individual autonomy. This position statement provides recommendations on how to guide contraceptive choice and identifies knowledge gaps about contraception today.

### SUMMARY BOX

- Safe contraception and family planning access are a fundamental human right and are part of the 2030 Agenda for Sustainable Development of the World of the United Nations.
- This review focuses on the multifaceted issue of contraception, addressing the ethical, medical, religious, and social dimensions of contraceptive use. Fertility awareness-based methods, which are compatible with the teachings of most world religions, are usually compared with hormonal methods in terms of safety, efficacy, and ethics. Side effects and non-contraceptive benefits of hormonal contraception (HC) are discussed in detail.
- In general, current guidelines for HC often lag behind technological advances. New therapies with increasingly safe estrogens and progestins have been developed, and further safety studies should be conducted that could eventually open the door for their use in at-risk populations.

## Introduction

The freedom to decide when and how many children to have, is a fundamental right of women, men, and couples. This right goes hand in hand with the importance of controlling the world's growing population. Nowadays, population growth varies from country to country, worryingly slowing in developed countries but continuing to grow in low- and middle-income ones [1]. Contraception helps to control rapid growth where fertility rates are still very high, and to prevent the practice of voluntary abortion in all countries, in favor of conscious planning of pregnancy.

The Department of Economic and Social Affairs of the United Nations (UN) Secretariat consider contraceptive prevalence and unmet needs for family planning as fundamental indicators of development and progress of individual countries and regions. Its Population Division has published data on global contraceptive method use since 2003, and in 2015 Target 3.7 was included in the 2030 Agenda for Sustainable Development. This Target 3.7 says: '*By 2030, ensure universal access to sexual and reproductive health-care services, including family planning, information and education, and the integration of reproductive health into national strategies and programmes*' [2]. This Target is articulated in Sustainable Development Goal indicator 3.7.1: '*Proportion of women of reproductive age (aged 15–49 years) who have their need for family planning satisfied with modern method.*' The Population Division of the UN distinguishes between traditional methods (i.e. fertility awareness-based methods [FABMs], withdrawal, and periodic abstinence methods) which have been in existence for millennia, and modern methods (i.e. male and female sterilization, hormonal, intrauterine, barrier, emergency contraception [EC] and lactational amenorrhea method [LAM]), which mostly use technological advances to modulate biology and allow for sexual freedom [3]. However, this classification is not unique, and different organizations have various definitions of this dualism. For example, some definitions include the LAM in the traditional methods [4], while other include two periodic abstinence methods, the TwoDay and the Standard Days Method, as modern ones [5].

According to the UN World Family Planning 2022 report, there are 1.9 billion women of reproductive age worldwide. Of these, 874 million women use a modern method of contraception (a doubling since 1990) and 92 million use a traditional method. 164 million women still do not have access to any method of contraception even if they want to delay or avoid pregnancy [6]. As a result, nearly half of all pregnancies are unintended (121 million per year), with more than half of them ending in an induced abortion, often under unsafe conditions [7]. The UN data on the unmet need for family planning, updated to the year 2023, is presented in Figures 1 and 2.

There are many disparities between rich and poor regions in terms of access to contraception and family planning programs, with sub-Saharan Africa being the region with the lowest proportion of women meeting their needs with modern methods (56%). In addition, young women and adolescents represent challenges with respect to access to family planning methods compared to other age groups [6].

FABMs have usually been compared to the ever-evolving hormonal methods in terms of safety, efficacy, and ethics, while barrier methods remain the only effective for preventing sexually transmitted infections (STIs). Another important method that is used around the world to avoid fertility is male or female sterilization. This represents a permanent birth control method (which is out of the scope of this work), frequently used in couples who have already exhausted their desire for pregnancy. Even if today the procedures are very safe and of rapid performance, the potential advantages and disadvantages of the method should always be discussed during the counseling, in a world where many reversible, safe and long-acting contraceptive methods exist [8,9].

The complex intersections of religious, cultural, and scientific spheres must contend with the evolving needs of reproductive health practices, the individual rights to sexual freedom (i.e. the freedom to define, explore, and experience one's sexuality as one chooses, without fear of oppression or violence) and family planning, and the societal need to control rapid and sometimes uncontrolled
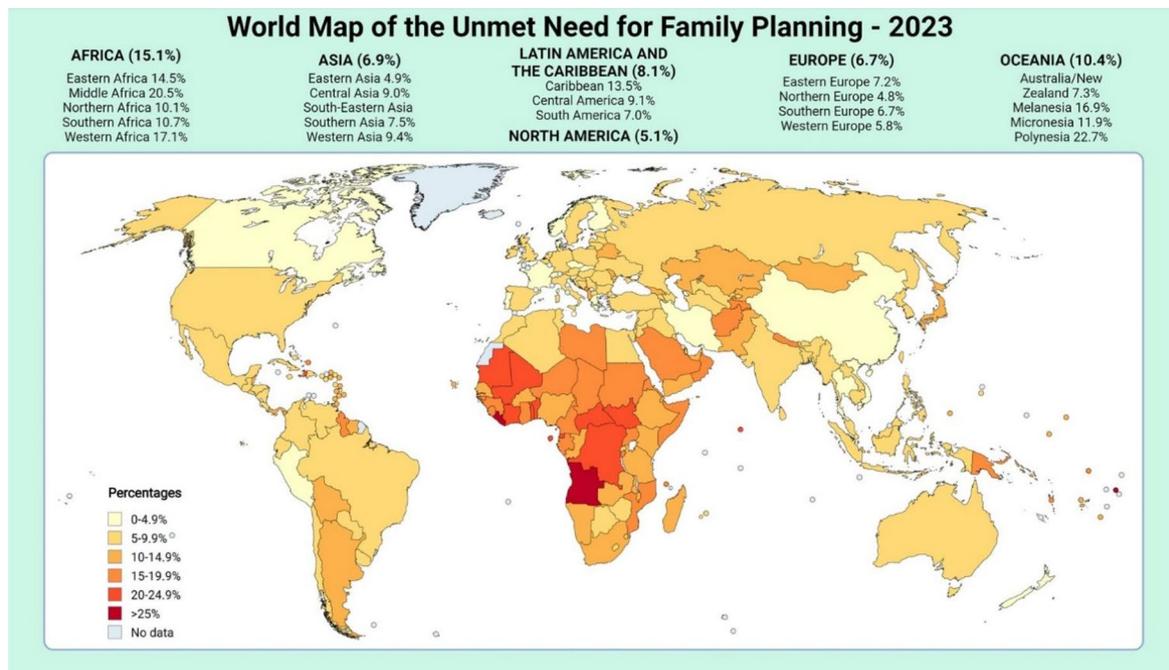


**Figure 1.** Unmet need for family planning in the world in 2023. Data refer to the percentage of women of reproductive age (15-49 years) who want to stop or delay childbearing, regardless of marital status, but are not using any method of contraception (traditional or modern as defined by the United Nations) in 2023. The unmet need for family planning is presented as a color scale for different countries in the map and as percentages by region, inter-region and/or Sub-region according to the United Nations geo-scheme. Aggregated data for the South-east asia sub-region and individual data for some countries (indicated as 'no data' in the color scale legend) are missing.
Source of the data: United Nations, Department of Economic and Social Affairs, Population Division (2024). *Model-based Estimates and Projections of Family Planning Indicators 2024*, custom data acquired via website with the permission of the United Nations (https://population.un.org/dataportal/home?df=56bbbdfd-3e7d-4b25-aa72-ac7b533cf5b7; downloaded on 4th Aug. 2024). Map created with mapchart.net; figure created with BioRender.com.

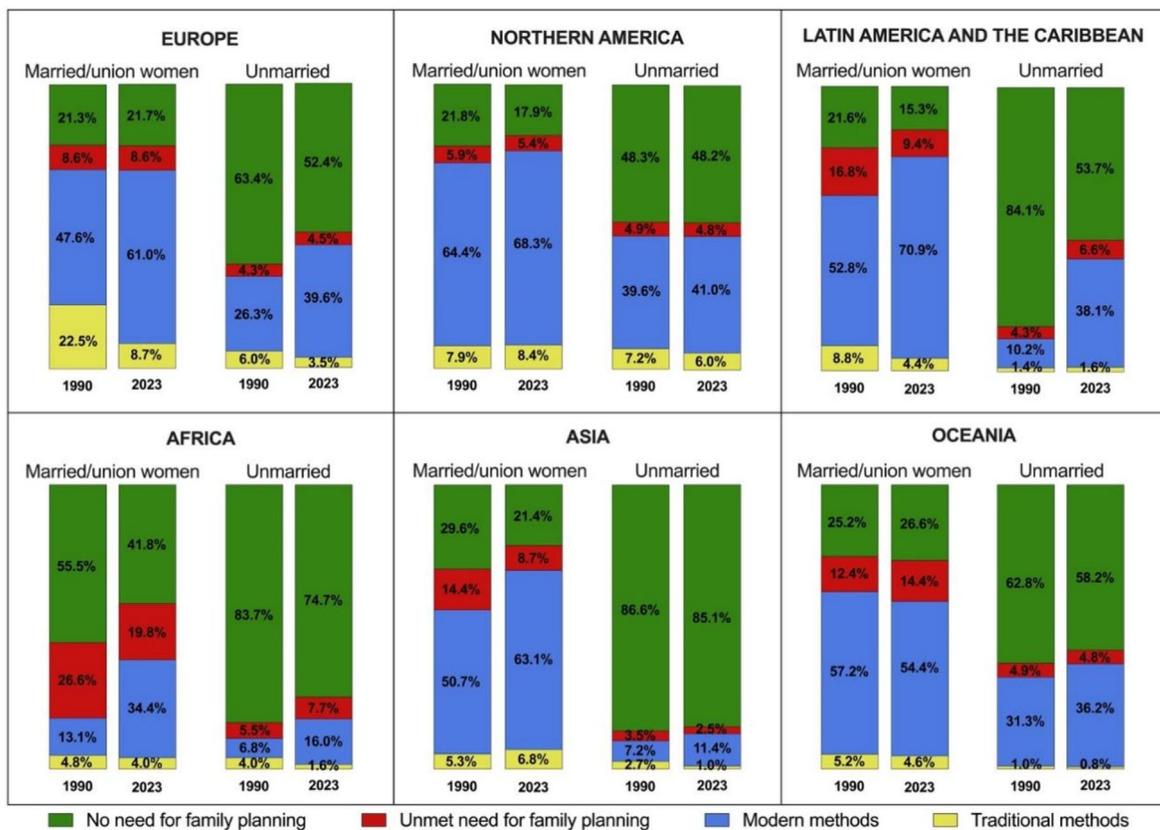**Figure 2.** Changes in global family planning need and method use by marital status from 1990 to 2023. Unmet need for family planning (red): percentage of women of reproductive age (15-49 years) who want to stop or delay childbearing but are not using any method of contraception (traditional or modern). Modern methods (blue): percentage of women of reproductive age who are currently using any modern method of contraception (i.e. male and female sterilization, hormonal, intrauterine, barrier, emergency contraception and lactational amenorrhea method). Traditional methods (yellow): percentage of women of reproductive age who are currently using any traditional method of contraception (i.e. fertility awareness-based methods, withdrawal, and periodic abstinence methods). No need for family planning (green): percentage of women of reproductive age who do not want to stop or delay childbearing (data obtained as: 100% – % unmet needs – % modern methods – % traditional methods). Data are divided according to the marital status in married women/women in a union (married/union women), and unmarried women.

Source of the data: United Nations, Department of Economic and Social Affairs, Population Division (2024). *Model-based Estimates and Projections of Family Planning Indicators 2024*, custom data acquired via website with the permission of the United Nations (https://population.un.org/dataportal/home?df=56bbbdfd-3e7d-4b25-aa72-ac7b533cf5b7; downloaded on 4th Aug. 2024).

population growth. The issue of violence against women, particularly intimate partner violence and sexual violence, is a significant and unacceptable obstacle to accessing and exercising sexual freedom and family planning rights.

This paper summarizes the proceedings of a workshop held in Rome in March 2024, organized by the International Academy of Human Reproduction, supported by the International Federation of Gynecology and Obstetrics and endorsed by: European Society of Gynecology; European Society of Contraception and Reproductive Health; International Society of Gynaecological Endocrinology; the Population Council; Società Italiana di Ginecologia e Ostetricia; Associazione Italiana Ginecologia Endocrinologica; Associazione Ginecologi Universitari Italiani; Associazione Ostetrici Ginecologi Ospedalieri Italiani; Associazione Ginecologi Consultoriali; Federación Latinoamericana de Sociedades de Obstetricia y Ginecología.

It aims to address the ethical debate that surrounds contraception use and access and intersects with debates about the efficacy and safety of today's reversible contraceptive technologies. The ethical considerations will echo the principles of the monotheistic religions that originated in the Middle East and subsequently spread throughout the world. This dialogue emphasizes the need for informed, shared decision-making with the woman and/or the couple.

## The ethical debate on contraception

Contraception has been a central point of debate for decades. Since the ancient times, the dual nature of the sexual act as a means of procreation and an instinct to foster relational intimacy between partners was recognized being part of ethical and religious debates.

In the twentieth Century, the world witnessed two revolutions in reproductive technology, namely the development of HC and of assisted reproductive technology [10]. These raised an intense ethical and religious debate globally. Fortunately, there was also a parallel evolution of the field of bioethics which increased the protection of human welfare, dignity, and future generations. The contraception debate strictly intersects with family planning and should consider many factors: the principles of biomedical ethics; the different ideas of marriage, sex, and the family; 'procreative liberty' and a woman's right to control her own body; the environmental and resource problems caused by over-population; and different cultural and religious beliefs, among others. The first human rights treaty to mention family planning as one of its goals was the 'Convention on the Elimination of All Forms of Discrimination against Women', adopted by the UN in 1979 [11].

The guiding principles of biomedical ethics that were adopted in the late 70's and early 80's were: the principle of autonomy or individual liberty, the utilitarian principle (which can be subdivided into beneficence and non-maleficence), and the principle of justice [12].

In the field of reproductive health, these principles can be translated as: the right to make reproductive choices based on adequate and thorough information about all available methods; the right of the individual to have a method that is safe, effective, and acceptable to that person; the right to have access to health and family planning, with no economic or social differences [12].

With the evolution of technologies, in 2005 the United Nations Educational, Scientific and Cultural Organization (UNESCO) updated the principles of bioethics in the 'Universal Declaration on Bioethics and Human Rights' [13], a fundamental document that linked bioethics to human rights.

The World Medical Association revised and adopted its Code of Ethics at its 73rd General Assembly in Berlin, Germany, in October 2022. It stated that the primary duty of the physician is to promote the health and well-being of the individual patient by providing competent, timely and compassionate care in accordance with good medical practice and professionalism. In human reproduction, meeting the unmet need for contraception would prevent one-third of maternal, neonatal and child mortality and contribute to safe motherhood. Moreover, physicians must not allow their professional judgment to be influenced by the possibility of benefit to themselves or their institution [14]. Good medical care should be based on the principle of patient-centred care, with the values and beliefs of the physician not interfering with patient information and service delivery.

### *The main monotheistic religions, contraception, and family planning*

Globally, more than eight out of ten people identify with a religious group [15] that shapes their values and attitudes and influences their conduct. Religious figures are key actors in their own communities as well as in the international community, and they play an important and influential role as advocates to promote positive behaviors, such as contraceptive use, and to counter harmful practices, such as unsafe abortion and denial of family planning. The question remains whether different religious sentiments can represent all the needs of the world's population, which includes many minority cultures whose voices are often less heard. It is crucial to consider diverse perspectives and ensure that family planning policies reflect the needs and rights of all individuals.

In the development of the monotheistic religions of the Middle East (i.e. Judaism, Islam, non-Catholic Christians, and the Roman Catholic Church), a significant difference in their views on contraception and family planning has emerged over time. There are some more liberal interpretations of the sacred texts, often based on an acceptance of modern historical hermeneutics and of the principle of the autonomy of the (religious) individual. Nevertheless, in all these religions there are groups and individuals who reject or ignore such modern hermeneutics.

Judaism, Islam, and non-Catholic Christians emphasize a deep reading and interpretation of the sacred texts, inextricably linked to the development of knowledge, with a plurality of institutions or

individuals claiming authority to interpret the sacred texts. In contrast, the Roman Catholic Church has maintained the unique authority of one institution, the official Magisterium, which refers to the Church's authority to give definitive interpretations of Scripture and Tradition. The Magisterium is entrusted to the Pope and the bishops, who are considered the official teachers of the faith. According to Catholic teaching, the interpretations of the Magisterium are binding and must be followed by all members of the Church. These interpretations cannot be reconsidered or changed unless a future Magisterium issues a new interpretation. This hierarchical approach to interpretation adds a layer of complexity to the Catholic faith by centralizing doctrinal authority and limiting the scope for individual or communal reinterpretation of Scripture and Tradition. It provides authoritative teachings to guide believers in their moral and spiritual lives and addresses contemporary issues [16]. While this approach aims to preserve the integrity of the faith, it can also lead to tensions when official Church positions are perceived as out of step with modern scientific understanding or societal changes.

This concept of the Magisterium of the Catholic Church is unique within Christianity. In most Protestant churches of today, for example, the authority and the actual influence of institutions or leading individuals which define the 'truth of faith' and ethical obligations derived from it is limited. This general limitation derives from the reformatory principle that each Protestant Christian is personally responsible for all his or her actions, including his or her ethical behavior [17].

All the monotheistic churches have faced the issue of contraception in their history. In Islamic religion, a thorough examination of the Quran reveals no text (*nuss*) prohibiting the prevention of pregnancy. To provide quality contraceptive services based on ethical principles and Islamic teachings, women should have the ability to reproduce and the freedom to decide if, when and how often to do so. Women have the right to information, consent, and access to safe, effective, affordable, and acceptable methods of contraception of their choice, with the agreement between husband and wife [18]. Islam encourages breastfeeding for two years [19]. This may be considered a natural method of contraception. Islam has also indicated that no mother shall suffer because of her pregnancy [20]. Several traditions of the Prophet Mohamed indicate the permissibility of coitus interruptus based on Fatwas issued in 1970 and 1980. By analogy, which is one of the sources driving rulings in Islam, temporary methods of contraception such as breastfeeding, FABMs, HCs, intrauterine devices (IUDs), barrier methods, or other temporary methods of contraception are permitted [21]. However, contraceptive use is still low among Muslim women, which is mainly related to misinterpretation of Islamic Sharia on family planning and fear of side effects [22].

Judaism places great emphasis on Talmudic study and rabbinic tradition, and ongoing discussion and interpretation of the Torah and other sacred texts are central to religious practice. This approach keeps Jewish law and ethics relevant and applicable to modern life. There is no central authority in Judaism. Jews believe that there is a single God who not only created the universe, but with whom every Jew can have an individual and personal relationship. Different communities and individuals pick and choose a different Rabbinic authority. The Jewish faith is greatly concerned with the problem of reproduction and sexual relations.

The duty of procreation, i.e. '*Be fertile, multiply, and fill the earth*' (Genesis 1:28) [23], is the first commandment in the Bible, a mitzvah. According to Halakha ('*to go*'; i.e. the collective body of Jewish religious law, including the Torah biblical law [the 613 mitzvot, or commandments] and the later Talmudic and rabbinic law as customs and tradition ['The Responsa']), the commandment to procreate is obligatory for the male, but not for the female. He must beget at least two children, a male and a female, according to the Genesis verse 'male and female He created them' (Genesis 1:27) [23]. The commandment '*a man must not withhold from his wife her food, her clothing, or her conjugal rights*' (Exodus 21:10) [24] means that a man's duty to have sexual relations with his wife is independent of his duty to procreate, and consequently the duty to satisfy the woman's sexual needs continued even after the man had fulfilled his duty to procreate (after he had fathered two children).

The practice of contraception during the Talmudic period is documented by a passage called '*The Beraita of the Three Women*', which is the basis of Jewish teaching on contraception. It states that a woman may drink the *kos shel ikkarin* (cup of roots - abortifacient) in three circumstances where pregnancy would seriously harm the woman: the woman is a minor, the woman is already pregnant (in those times they thought that another pregnancy would endanger her health and that of the

previous fetus, even though we now know that a new pregnancy cannot begin if one has already begun), or the woman is breastfeeding (Yevamot 12b) [25]. Another documented contraceptive method, the 'moch', is a tampon that can be inserted before intercourse to act as a mechanical barrier to sperm, or after intercourse to absorb sperm.

Today, according to Judaism, any method of contraception used by the man is forbidden: abstinence, since it does not fulfill the conjugal rights of the woman; coitus interruptus because of the prohibition of improper emission of sperm (Genesis 38) [23]. Condoms are opposed in Talmudic and rabbinic literature since the prohibition of destruction of semen and its improper emission. Male hormonal methods are also prohibited.

In contrast, all rabbinical rulings permit the use of female contraceptives to prevent conception for medical indications, as discussed in the Talmud. Economic hardship and other problems are not considered indications by Orthodox rabbinical authorities, although modern Reform and Conservative rabbinical authorities may be more lenient in allowing the use of contraception for non-medical reasons. If there is an indication for contraception, the order of contraceptive methods to be preferred is as follows: oral contraceptives, IUD, diaphragm, spermicides.

Within the Christian religion, there is a great deal of diversity in how contraception is viewed according to specific beliefs. Since about the 40s, most Western Protestant mainline churches (most Lutheran, all Reformed churches, also the Anglican Church) have given up former (particularly harsh) official restrictions on contraception. In the view of these churches, the Bible is seen as '*God's Word in the mouth of human beings*' [26] and must be interpreted with the help of all the advanced instruments of modern historical (and, in part, scientific) research. The problems associated with contraception have mostly been shifted from the realm of normative (prescriptive and prohibitive) ethical theory to the realm of individual practice and responsibility. This is especially true for contemporary academic and church theology in the German-speaking world. Nevertheless, there are still Protestant groups and churches where the debate about the permissibility of contraception (and specific methods of contraception) is ongoing. This is the case for some of the 'fundamentalist' evangelical churches in the USA, for some (very) conservative Protestant groups such as the 'Amish' or the Laestadian Lutheran Church, and for many of the rapidly growing Pentecostal churches in Latin America and Africa. However, according to a recent study of an African Pentecostal church, the actual influence of such conservative readings of the biblical command to 'be fruitful and multiply' as a binding divine command on young church members and their sexual behavior is limited by the degree of their personal agency and education [27].

According to the teachings of the Roman Catholic Church, it is the responsibility of the couple to decide the number and timing of their children. This decision should consider the well-being of the children, the family, the community, as well as social, environmental, and financial conditions [28]. In the encyclical *Humanae Vitae*, Pope Paul VI spoke of responsible parenthood, which also includes the possibility of deciding, for serious reasons and in accordance with the moral law, to refrain temporarily or permanently from having more children. At the same time, however, this encyclical also stated the moral rejection of any form of so-called 'artificial' contraception [29]. This has caused much controversy within the Catholic community, but in general the Magisterium has ultimately condemned the morality of the use of artificial modern methods of contraception.

To be precise, the Catholic Church did not forbid conception regulation within the marital relationship. This can only be achieved by choosing natural methods (i.e. FABMs). The importance of knowing the female body and its rhythms is also emphasized as part of the couple's relationship. Over the years, there has been a gradual opening to the possibility of delaying pregnancy for economic or personal reasons [30], although the question of the method used has not been addressed, leaving only the possibility of using natural methods. A recent document from the Pontifical Academy for Life argues for a rethinking of the permissibility of HCs, overcoming the duality between natural and artificial methods: '*[...] The wise choice will be made by an appropriate evaluation of all the possible techniques in relation to the specific situation, obviously excluding abortion. [...] In the perspective we have outlined, the alternative between 'natural' and 'artificial' methods should be transcended: the radical question is played out in the concretely possible forms of a generous and no less demanding responsibility for the gift of procreation*' [31]. This has opened the discussion within the Catholic

community because, in fact, the position of the Magisterium has still not changed: only natural methods are universally accepted by the Catholic Church, even if a more open part of the Catholic community may begin to consider some artificial methods in some specific situations. A final consideration is that the scientific community has now concluded that the biological statement in Humanae Vitae that the two meanings of sexuality (unitive and reproductive) are indissolubly linked does not correspond to biological reality as we know it today.

### Contemporary society: a need for family planning

As we can see, contraception is shrouded by ethical polarity with different viewpoints related to morality, religion, politics, culture, and economic standpoints [32]. For centuries, sexuality has been seen as strictly reproductive, but principles of sexual pleasure are increasingly being articulated, opening new problems related to family planning and a different definition of unplanned pregnancies in extramarital relationships. Common misconceptions about HC include: it prevents gametes from contacting each other in an unnatural way; it prevents the blastocyst from implanting in a primed endometrium; it acts as an abortifacient; it leads to promiscuity and breaks the core of family units; sex should not be for pleasure but limited to procreation and there is no room for premarital engagement or safe abortion for unplanned pregnancies. These common misconceptions clearly illustrate how much work clinicians and organizations still need to do to disseminate proper knowledge for informed choice.

Population demographics and dynamics are influenced by policies, climate change mitigation and adaptation, food systems, peace and security, disease eradication, poverty reduction, technology, and the quality of the next generation [33]. Family planning becomes the most integral nidus with an impact on population and public health.

Easy access to contraception and family planning should be a universal human right, even though it can be influenced by socio-economic factors. About 1.2 billion people in 11 developing countries live in multidimensional poverty (19% of the world's population) [34].

Contraception is crucial for the success of two recent initiatives of the World Health Organization (WHO), the Ending Preventable Maternal Mortality [35] and the Every Newborn Action Plan act [36], which is now renamed Every Woman, Every Newborn, Everywhere. Increasing child spacing provides an opportunity for offspring to grow up in an optimal environment of good nutrition, health, and education, recognizing that it is also a multisectoral agenda and an opportunity for mothers to be economically productive and empowered, contributing to national development.

Additionally, contraception has a central role in gender and intimate partner violence. The UN defines violence against women as '*any act of gender-based violence that results in, or is likely to result in, physical, sexual, or mental harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or in private life*' [37]. According to the WHO, one out of three women in the world will experience physical and/or sexual violence in her lifetime, most often at the hands of a partner, with significant consequences for physical, mental, sexual, and reproductive health [38]. Efforts to promote family planning and contraception use must be accompanied by robust measures to prevent and respond to violence against women. This includes ensuring access to support services, legal protection, and educational campaigns aimed at challenging harmful gender norms and promoting gender equality.

Contraception can also reduce the so-called maternal depletion syndrome, fetal programming (i.e. the theory that environmental cues experienced during fetal development play a seminal role in determining health trajectories across the lifespan) with risks of non-communicable diseases in the offspring, and child malnutrition, and can promote adolescent growth and development [39–41].

The family planning roadmap should focus primarily on awareness raising, education, effective communication, and the provision of ethical and professional services, emphasizing its importance for sustainable development [42]. We should all work together to ensure that there is an inclusive and equitable normative environment, financing and resource allocation, procurement and supply chain, resilient health system, marketing and promotion of products and services. Training of health professionals is essential to disseminate appropriate information to the population [43].

## Fertility-awareness based methods (FABMs): a fertility or a contraceptive method?

FABMs are a group of natural contraceptive methods that allow users to track one or more biomarkers to predict days when intercourse is more likely to result in pregnancy. As contraceptive methods, they can also be used to identify days of potential fecundity and avoid unprotected intercourse on these days [44,45], even though they are characterized by high rates of pregnancy if rules are not precisely followed. FABMs are very unforgiving of incorrect use (i.e. unprotected intercourse during highly fertile days) compared to other family planning methods [45,46].

Cervical mucus methods like the Billing Ovulation Method are based on the user recognizing changes in the cervical mucus pattern as an indicator of the fertile and infertile phases of the cycle. Sympto-thermal methods combine the observation of the mucus changes, calendar calculations, and the basal body temperature shift which occurs after ovulation. New FABMs incorporate rapid home urine hormone monitoring for the recognition of ovulation [47]. Internet applications with predictive algorithms have also been developed, which may increase the dissemination of FABMs to a broader population.

Moderate-quality contraceptive efficacy data exists for several FABMs, including the Standard Days Method, the Two-Day Method, the Billings Ovulation Method, the Sensiplan symptothermal method, the Marquette Model sympto-hormonal method, and Natural Cycles, a United States Food and Drug Administration (US-FDA) approved Internet application. Effectiveness estimates for FABMs vary by method, with multiple marker methods such as Sensiplan and Marquette having typical and perfect use effectiveness estimates like combined HCs, while other FABMs (i.e. Standard Days Method, Two Day Method and Billings Method) having typical use effectiveness estimates like barrier methods [44,45]. There is limited data on the effectiveness of FABMs in special populations such as lactating amenorrhoeic women, perimenopausal women, and women with long cycles and polycystic ovary syndrome (PCOS). More high-quality efficacy trials of FABMs for pregnancy prevention are needed, especially in populations with unpredictable ovulation [44,48]. Fertility apps and FemTech may make FABMs more accessible, but only one of the many available fertility apps, Natural Cycles, has undergone effectiveness testing and been US-FDA approved as a contraceptive [44,49,50].

FABMs are not consistently offered or accessible to all people who might want to use them due to lack of provider knowledge, provider bias, and lack of insurance coverage for training and supplies [51–53]. There is a need for healthcare providers to improve their training and knowledge of FABMs so that they can help people make informed choices and use them effectively. This increased education is needed at all levels, from medical school, nursing school, residency, and continuing education [44,50–52]. Advantages of FABM use include: compatibility with the teachings of most of the world's religions [44], lack of side effects, education for people about their fertility and health, fertility tracking information that can be used to manage health conditions, and use of the methods for both avoiding pregnancy and trying to conceive. Educating people about their fertility early in life can help them to understand their health and ovulatory function and empower them to make reproductive decisions across the life course [50,54]. However, FABMs may not be the right method of contraception for all women. Potential users should understand that, if incorrectly used, the chance of pregnancy is very high, and that FABMs should preferentially be used to prevent pregnancy in a stable relationship without reproductive coercion. These methods encourage shared responsibility between partners [44].

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Box 1. Take-home messages and recommendations

1. FABMs can only be used to avoid pregnancy in a relationship without reproductive coercion; these methods encourage shared responsibility between partners.
2. There is a need for more high-quality effectiveness studies for FABMs to prevent pregnancy, especially in populations with unpredictable ovulation.
3. Teaching people about their fertility starting early in life may empower their reproductive decision-making across the life course.
4. FABMs are compatible with the teachings of most world religions.

## The copper intrauterine device: a long-acting non-hormonal contraceptive method

The copper intrauterine device (Cu-IUD) is an important non-hormonal contraceptive method. The contraceptive efficacy of the Cu-IUD is primarily due to the toxic effects of copper on sperm and the subsequent development of a sterile inflammatory process in the uterus [55]. Many devices have been developed over the years with variations in shape and copper content. However, the first commercialized device, the TCu380A (a T-shaped device with a 380-mm copper surface in its two arms) is still considered the most effective [55,56].

Cu-IUDs are highly effective and last at least 10 years. The efficacy rate varies slightly among models depending on the size of the copper surface area. Higher contraceptive efficacy is achieved with IUDs containing more than 300 mm$^2$ of copper surface area (Pearl Index of 0.1–1.0 vs. 0.5–2.2 for those with less than 300 mm$^2$) [56–58]. Additionally, their efficacy may vary slightly according to the patient's age. [59]. After ten years of use, contraceptive efficacy may still be present, particularly in women over 35 years of age, whose fertility decreases with age. Ideally, the device can remain unchanged after this age until menopause [55].

Uterine perforation during insertion is rare with all IUDs (levonorgestrel or copper) and is slightly more common during the immediate postpartum period and while breastfeeding. Heavy menstrual bleeding may increase the risk of expulsion, though it is generally low [60,61]. This contraceptive method is generally preferred for women who have already given birth. However, nulliparous women can also safely use it, though they may experience slightly higher rates of expulsion [62].

The main side effects of the Cu-IUD are increased menstrual bleeding and pain during the menstrual cycle. These side effects usually decrease over time. However, long-term use may be associated with an increased number of days with intermenstrual bleeding and pain. This may result in premature removal [63].

The main contraindications to its use are endometrial cavity distortion, Wilson disease, a current pelvic infection, or a high risk of pelvic infection [64]. It can safely be used as a contraceptive method for women who cannot use hormonal methods, such as those who have survived breast or gynaecological cancer [65].

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Box 2. Take-home messages and recommendations

1. Cu-IUDs are very effective and safe contraceptive methods that can potentially be used in all women.
2. Irregular bleedings and pain may be cause of premature removal, and proper counseling about this possible effect is needed.
3. They can be used also in hormone-sensitive cancer survivors, if no other contraindications exist.

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## Hormonal contraceptive methods: recommendations

More than a century ago, Sigmund Freud predicted: '*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 behavior in order to separate it from the imperative to satisfy a natural urge*' [66].

When Freud wrote these words, the series of scientific discoveries that led to the development of HC had already begun. Progesterone was tested to block fertility, but due to the low activity and irregular bleedings at therapeutic doses, it could not be orally administered [67]. Orally active progestins were then synthesized to achieve ovulation inhibition (through the inhibition of the luteinizing hormone – LH – release and alteration of the cervical mucus permeability) [68], and an estrogen was added to increase contraceptive efficacy, improve endometrial control, and compensate for the estrogen deficiency potentially induced by progestins [69]. The first combined oral contraceptive (COC) was introduced in the United States in 1960. In 2011, 50 years later, more than 100 million women worldwide used COCs, and the number continues to grow [70]. Combined hormonal contraceptives (CHCs), which include oral (COCs) and non-oral methods, are still the most widely used form of contraception in the developed world.

Today, the side effects of modern contraceptives have decreased dramatically compared to the early days, and new progestins has further broadened the range of non-contraceptive benefits. Moreover, progestin-only contraceptives, such as new progestin-only pills (POPs) and IUDs, have become available [71].

## Molecules, combinations, and routes of administration

### History of contraception and combined hormonal contraceptives

The first two orally active progestins used for contraception were 19-nortestosterone derivatives: norethynodrel and norethisterone. Norethynodrel combined with mestranol, a prodrug of ethinyl-estradiol (EE), formed the first COC [72]. EE quickly replaced mestranol, and its doses were gradually reduced to 'low-dose' CHCs (by classic definition ≤ 50 μg) [73], even though contraceptives containing >35 μg of EE are no longer available and today 'low-dose' CHCs may refer just to those with <35 μg of EE. Thus, a decreased incidence of side effects has been achieved [70].

The history of progestins used in CHCs is more complex. Each synthetic progestin has its specific pharmacodynamic profile and a progestogenic effect on the endometrium, with a specific dose required to inhibit ovulation. Because of the need to balance all these effects and ensure the safety of the molecule, only some progestins can be used for contraception [68,74]. They are traditionally divided into 'generations' according to their structural origin and time of first synthesis. First generation progestins (pregnanes and oestranes) have been partially abandoned due to their androgenic properties that can cause troublesome symptoms [74]. Second generation (gonanes) retain some androgenic properties and include levonorgestrel (LNG). Third and fourth generations have favorable partial activities (anti-androgenic and/or anti-mineralocorticoid) whose intensity varies from molecule to molecule and that reduce some of the troublesome side effects of earlier CHCs, such as weight gain and acne [71,74]. However, the classification of progestins into 'generations' should be replaced by the traditional classification based on pharmacological properties.

The metabolic effects of the estrogenic component can be modulated and counteracted by progestins with androgenic properties. For this reason, the combination of EE and LNG has traditionally been considered the gold standard for thromboembolic and metabolic risk, and newer combinations are usually compared against it [75].

Non-oral CHCs, such as patches and vaginal rings, provide stable steroid blood levels and do not require daily administration. They remain an underutilized contraceptive option. However, due to the long half-life of EE and its second liver pass, the increased risk of venous thromboembolism (VTE) is not eliminated [76].

Recently, a new prolonged-release COC was released with the aim of reducing the dose of EE while maintaining stable plasma concentrations. This new pharmaceutical technology may help to reduce the risk of side effects on hemostatic parameters using EE, even if more studies are needed to draw definitive conclusions [77]. Moreover, a first randomized controlled study showed that this formulation may help to reduce unscheduled bleeding compared with classic COCs [78].

EE, due to its pronounced hepatic impact, is progressively being reconsidered in favor of natural estrogens such as estradiol (E2) and estetrol (E4), which exhibit a more favorable impact on hemostatic parameters and show a lower thrombotic signal in both clinical and pharmacovigilance studies [79–87].

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**Box 3. Take-home messages and recommendations**

1. The classification of progestins into so-called 'generations' should be replaced by the traditional classification according to pharmacological properties.
2. Given the evolving evidence base, the recommendation to favor EE-LNG as a first-line option may require reevaluation in light of the favorable biological, clinical, and pharmacovigilance profiles of COCs containing natural estrogens.

## Progestin-only contraceptives

Progestin-only contraceptives are available as POPs, implants, LNG-releasing IUDs (LNG-IUDs), and depot-medroxyprogesterone acetate (DMPA) injections (Figure 3).

The POPs (formerly known as 'minipills') are a suitable HC alternative. Newer POPs containing desogestrel or drospirenone combine the classic progestin action on the endometrium with ovulation inhibition: about 97% of women have a constant ovulation inhibition with high contraceptive efficacy, in contrast to previously used progestins [88]. Moreover, they have a longer half-life: for drospirenone, a window of 24 h for taking the pill is possible, like for some COCs [89]. The effectiveness of both COCs and newer POPs is the same [58].

The risk of side effects with modern POPs is considered to be so low by the US-FDA that a POP is available over-the-counter in the United States [90]. Also, the risk of VTE, one of the main limitations in the use of CHCs, is not present with the use of POPs [91].

Progestin containing long-acting reversible contraceptives (LARCs), in the form of progestin-only implants, injections and LNG-IUDs, are particularly well-suited for women who cannot meet the compliance requirements for daily administration of contraception, and they may also present some non-contraceptive benefits that make them a good option for many women [92].

IUDs are widely used worldwide, with more than 160 million women using them. The LNG-IUD acts by making the cervical mucus impermeable to sperm and by suppressing the endometrium and reaches a very high contraceptive efficacy [59]. The LNG-IUD is slightly more effective than the Cu-IUD [59,93]. The approved duration of use varies from 3 to 8 years for different LNG-IUDs. The 52 mg LNG-IUD was first approved for a 5-year duration with a failure rate <0.5% [59,93], but an extended use up to 8 years has recently been approved, with a cumulative failure rate of 0.68% in years 6 to 8 [93]. Other lower doses LNG-IUD (13.5 and 19.5 mg) have similar failure rates, but their contraceptive efficacy lasts after 3 to 5 years depending on the type [94,95]. The continuation rate of IUD use is high [96]. The contraceptive benefits of IUDs are important for everyone but may be most impactful for young women with high fecundity [97]. IUDs are also very safe. Perforation on insertion is a rare event [61]. Expulsion predisposing to unplanned pregnancy occurs at an overall rate of 5%/5-years [60]. Risk of ectopic pregnancy is mistakenly raised as a concern with IUDs, when in fact all IUDs (including Cu-IUDs) reduce the incidence of ectopic pregnancy compared to women who do not use contraception [98]. However, if pregnancy occurs due to rare method failure, there is a higher chance it could be an ectopic one. Their efficacy in obese women is maintained [99]. The 52 mg LNG-IUD has also some therapeutic indications that should be considered. It is approved for the treatment of heavy menstrual bleedings [100,101]. Moreover, it is also recommended as first-line treatment in women with typical endometrial hyperplasia [102–104] and can be used in endometrial hyperplasia with atypia or early stage endometrial carcinoma when fertility preservation is needed, weighing benefits and risks [104,105].

Other contraceptive options include subcutaneous implants, typically two capsules (LNG) or a rod (etonogestrel), which provide contraceptive protection for 3 to 5 years, and injectables (DMPA), which should be administered every three months. Both options have very low failure rates (0.4-0.6/100 women/year) [106–108]. Common side effects include abnormal uterine bleeding (AUB), weight changes, and mood changes [106–108]. DMPA's actions do not dissipate until at least three months after injection and it may cause delayed return of fertility after discontinuation of the method, unlike other reversible hormonal methods [109].

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**Box 4. Take-home messages and recommendations**

1. Progestin-only contraceptives represent a good contraceptive option for all women thanks to their safety and efficacy profile. They can also be used as an alternative for women at risk of estrogen-related cardiovascular or thromboembolic complications, expanding the number of women that can benefit from the use of HCs.
2. DMPA should not be recommended to women seeking pregnancy immediately after stopping the method. If all hormonal therapies are contraindicated, non-hormonal alternatives such as the Cu-IUD may be recommended. DMPA should not be recommended to women seeking pregnancy immediately after stopping the method.
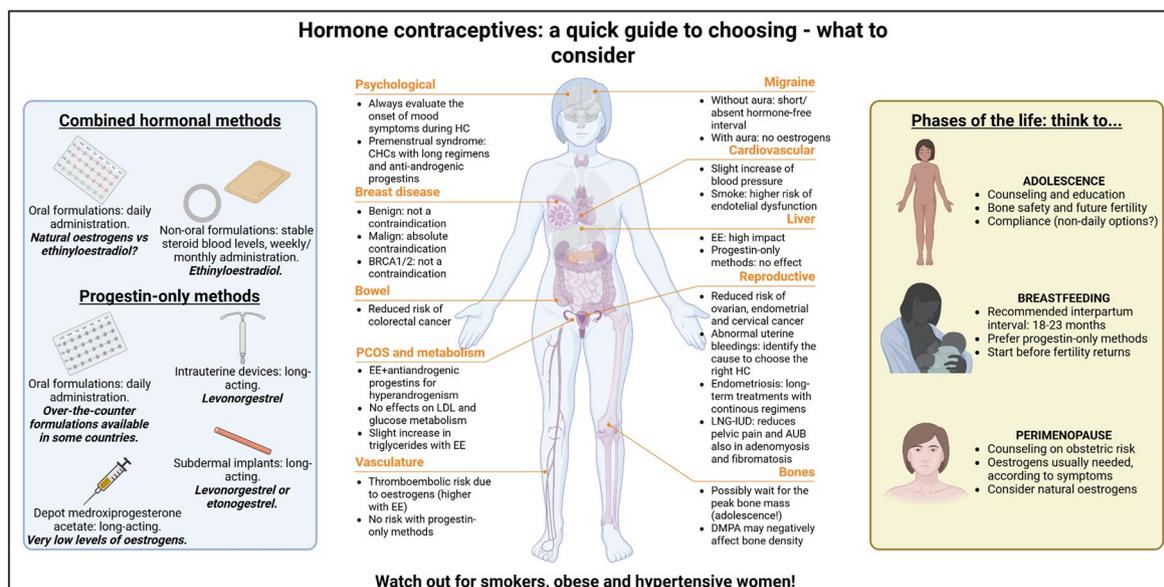
**Figure 3.** A quick guide on what to consider when choosing a hormonal contraceptive. When a clinician faces a woman who needs a hormonal contraceptive, there are several factors to consider. First, he or she must be aware that there are different formulations and routes of administration, and that each carries different risks and benefits. Second, an accurate personal history is essential to assess whether there are any risk factors or contraindications to certain hormonal methods, always considering the effect of exogenous steroid hormone administration on the various systems of the body. Thirdly, some stages of life may require specific recommendations. It is essential that the patient is properly counseled and informed. Illustration created with BioRender.com.
BRCA1/2, BReast CAncer 1/2; CHCs, combined hormonal contraceptives; DMPA, depot medroxyprogesterone acetate; EE, ethinylestradiol; HC, hormonal contraception; LNG-IUD, levonorgestrel-intrauterine device; PCOS, polycystic ovary syndrome.

## Secondary effects of hormonal contraceptives

HCs have many secondary non-contraceptive benefits. However, they can also interact with the body's physiological mechanisms. Here, we summarize the most important positive and potential negative side effects of HCs which can guide selection of the right contraceptive for specific clinical situations or life stages (Figure 3).

## Effects of hormonal contraceptives on the liver and haemostasis

*Liver effects.* In addition to controlling the reproductive system, contraception with estrogens and progestins influence the liver, particularly when administered orally because of the hepatic first pass [110]. These effects may vary depending on the specific types of estrogen and progestin used in the combination. An estrogen-related increase in levels of sex hormone-binding globulin (SHBG), corticosteroid-binding globulin, angiotensinogen, and apolipoprotein A1, as well as changes in various coagulation and fibrinolytic factors, is usually observed with CHC use [110,111]. Non-oral formulations partially reduce this effect, but EE still retains a strong effect on liver after a second hepatic pass [76,112]. Progestins do not affect liver function in any progestin-only contraception formulation [75], but in combined formulations they can reduce (androgenic progestins) or not (antiandrogenic progestins) the effects of EE [113]. Thus, the effect of CHC on the liver depends on the overall 'oestrogenicity' of the formulation. New prolonged-release formulations of COCs may potentially reduce the effect of EE on liver [77], but more studies are needed.

EE also causes an increase in high-density lipoproteins (HDL), very low-density lipoproteins, and a slight decrease in low-density lipoproteins (LDL), an overall effect that is lost when combined with androgenic progestins [113].

Over the past decades, interest has grown in replacing synthetic EE with natural estrogens, such as E2 or E4, in CHCs. These molecules differ in their metabolism, receptor binding, and pharmacodynamic impact on hepatic and coagulation markers [86]. E4, in particular, displays tissue-selective receptor modulation and induces a distinct biomarker profile compared to EE, including lower effects

on SHBG and APC resistance [87]. Although these findings are promising, regulatory authorities such as the FDA have emphasized that such differences do not currently support conclusive claims of reduced hepatic or thrombotic risk in humans. Nevertheless, the consistent directionality of biological and observational data suggests that a systematic reevaluation of thrombotic risk stratification across estrogen types may be warranted [79–81,84,87,114,115].

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**Box 5. Take-home messages and recommendations**

1. EE exerts well-established hepatic and hemostatic effects, which contribute to the thrombotic risk profile of CHCs.
2. E2 and E4 show a differentiated impact on surrogate markers of thrombosis, but no conclusive clinical superiority has been established to date.
3. Ongoing surveillance and real-world data collection remain essential, especially for newer formulations under additional monitoring (black triangle ▼).
   Progestin-only contraceptives (excluding DMPA) remain an option when estrogens are contraindicated, given their absence of increased thrombotic risk.

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*Hemostatic effects of hormonal contraceptives.* The increase in thromboembolic risk remains the main concern of CHC. Thrombosis is described as a multifactorial disease. Indeed, while CHCs can increase the risk of VTE, they are only one of many factors contributing to thrombosis. A proper anamnesis is essential, considering that a positive family or personal history for VTE, known thrombophilia, smoke and obesity represent common important risk factors for thromboembolic events [116].

The increased risk of VTE caused by CHCs is due to the estrogen's effect on the liver: they alter the synthesis of coagulation and fibrinolytic factors in a prothrombotic direction [117]. EE is the main responsible for this effect [110]. Antiandrogenic progestins do not counteract either the beneficial effects (i.e. increased HDL levels) or the negative effects (i.e. prothrombotic state) of EE [118]. Therefore, the choice of estrogen and progestin components can significantly influence this risk [119]. Non-oral CHCs containing EE maintain the VTE risk due to the 'potency' of EE on the liver second pass [76]. As previously stated, E2 and E4 may potentially show a more favorable hemostatic profile than EE thanks to a lower impact on liver, and future studies should focus on validating these differences.

The European Medicines Agency's guidelines for investigating haemostasis during the development of steroid contraceptives [112] suggest that haemostasis testing is critical to identifying risk of VTE of steroids used in contraception at an early stage of development [120]. Some of these tests, such as the normalized activated protein C sensitivity ratio, can also be used to assess risk at the individual level, allowing for safer and more personalized contraceptive prescribing [121].

POPs, LNG-IUDs, and implants are considered safe with respect to VTE risk [91]. Therefore, they can be recommended also when a woman's personal risk factors contraindicate CHCs [122]. On the contrary, evidence suggests that DMPA injections are associated with a small increase in the risk of VTE, particularly in high-risk populations [91].

In addition to VTE risk, CHCs have also been associated with increased cardiovascular risk, particularly in women who smoke, have hypertension, dyslipidaemia, or are obese [122]. Smoking, hypertension, and obesity are known cardiovascular risk factors that may synergistically increase the risks associated with COC use, particularly thromboembolism, myocardial infarction, and stroke [123].

In women who smoke, CHCs may increase the risk of endothelial dysfunction, inflammation, and altered coagulation [124]. Low-dose CHCs reduce this risk [123]. Similarly, women with preexisting hypertension or those who develop hypertension while using CHCs are at an increased risk of cardiovascular events. Regular blood pressure monitoring and consideration of alternative contraceptive methods are essential for these women [125].

Obese women who use CHCs have a higher risk of thromboembolism and cardiovascular events compared to non-obese women. The altered pharmacokinetics of CHCs in obese women, along with

the underlying metabolic and inflammatory changes associated with obesity, may contribute to this increased risk [122,126].

Healthcare providers should assess the cardiovascular risk profile of women before prescribing contraception and regularly monitor them for the development of adverse cardiovascular effects. Alternative contraceptive methods with lower cardiovascular risks should be considered in the presence of multiple risk factors, as progestin-only contraceptives.

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**Box 6. Take-home messages and recommendations**

1. VTE risk and cardiovascular health should be carefully evaluated during the prescription of contraception to balance benefits and risks.
2. Progestin-only contraceptives, except for DMPA, do not increase the risk of VTE and cardiovascular risk and should be used when estrogens are contraindicated.

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### Positive and negative oncological effects

Communicating cancer risk information is an important part of contraceptive counseling. Reliable epidemiologic assessment of any association between hormone therapy use and cancer may be difficult because it requires large numbers and careful control for all potential sources of bias. If incorrect information is spread without accurate, controlled data, it is difficult to counteract any misconceptions and myths that may arise, both in the general population and among providers who prescribe the therapy.

*Breast diseases.* Benign breast diseases can be divided into fibroadenoma and fibrocystic disease, the latter consisting of cysts, proliferation, or hyperplasia without atypia. Proliferative disease without atypia is associated with a mild increased risk of breast cancer [127].

CHC use is associated with less benign breast disease [128,129], and benign breast diseases are not usually a contraindication for use of CHCs [129]. Mastalgia can be a symptom of fibrocystic disease and should be monitored, often representing a reason to change contraceptive method. A switch to a progestin-only treatment can help relieve the pain, reduce the cysts and possibly the risk of breast cancer; and will ensure contraception. Percutaneous progesterone may help control mastalgia [130]. Progestin treatment may also help reduce the size of fibroadenomas in polyadenomatosis [131]. However, there are limited data on benign breast disease and contraception.

HCs are generally associated with an increased risk of breast cancer in current users with long duration of use, an effect that decreases after cessation of treatment, suggesting a promoter effect [132,133]. For this putative promoter effect, hyperplasia with atypia (associated with a high risk of breast cancer) is a contraindication to any HC because of the increased risk of developing breast cancer, although no data are available [127]. Contraception is mandatory in women with breast cancer. However, any breast cancer type is a contraindication to the use of any HC [65]. The Cu-IUD is recommended in this context [122].

In the general population, according to a very recent study, LNG-IUDs are associated with a small increase in the risk of breast cancer, regardless of the duration of use [134]. Thus, the LNG-IUD is contraindicated in women with breast cancer and should be used only for specific gynaecological indications after discussion/approval by the woman's oncologist [65]. The increase in the risk of breast cancer in women using POPs is similar to that of CHC use [135], and POPs are, therefore, contraindicated in women with breast cancer.

Given the magnitude of protective effect of HC on ovarian and endometrial cancer (see below), the benefits of use in individuals without preexisting cancer exceeds the risk, even in women at high risk of breast and ovarian cancer, as BReast CAncer (BRCA) 1 or 2 pathogenic variant carriers [136].

> **Box 7. Take-home messages and recommendations**
>
> 1.  Benign breast diseases are not usually a contraindication to HC.
> 2.  HCs are contraindicated in women who have breast hyperplasia with atypia due to the risk of developing breast cancer.
> 3.  The use of any HC is absolutely contraindicated in women with breast cancer; Cu-IUD may be used for safe contraception.
> 4.  In BRCA1/2 mutation carriers CHC can be used because benefits (ovary and endometrial cancer prevention) outweigh the risks (breast cancer).

*Gynaecological and intestinal tumors.* Data derived from independent international trials show that the risk of any cancer as a whole and their related mortality is not increased in CHC users, while that of gynaecological cancers seem to be reduced [137].

The use of CHCs has consistently shown a significant protective effect on the risk of ovarian cancer, with a 50% risk reduction after 15 years of use with a remnant effect of up to 30 years [138]. This is true for various histotypes, not just epithelial cancers, especially for perimenopausal use [139], and it greatly influences the potential risk-benefit ratio of use by BRCA mutation carriers [136]. The risk of endometrial cancer is reduced by about 50% in ever users of CHCs, a benefit which is greater with increasing duration of use and remnant [138].

A positive association has been found between increased risk of uterine cervical cancer and long-term CHCs use, but this risk is influenced by different human papilloma virus (HPV) exposures in users and non-users, and it will be affected by primary prevention policies (vaccination) [140].

As for extra-gynaecological cancers, CHC use seems to reduce colorectal cancer risk [141]. The use of CHCs should be avoided in breast cancer, stromal ovarian cancer (granulosa cells) and follicular lymphoma survivors [142].

The effect of progestin-only methods over the risk of developing tumors has not been studied much. However, the protective effects appear to be more limited than that of combined formulations on some organs (i.e. ovary, colon-rectum). LNG-IUD was found to have a protective effect on endometrial cancer [143] and, in general, IUD use is associated with reduced risk of cervical cancer [144].

> **Box 8. Take-home messages and recommendations**
>
> 1.  CHC reduces the risk of ovarian, endometrial, cervical, and colorectal cancers.
> 2.  The use of CHCs should be avoided in women with breast cancer, stromal ovarian cancer (granulosa cells) and follicular lymphoma survivors.
> 3.  Few data are available regarding cancer risk and progestin only contraceptives.

### Non-contraceptive benefits of hormonal contraceptives

*Polycystic ovary syndrome and metabolism.* PCOS is a systemic disorder whose manifestations affect different organs and systems. The reason for patients to consult a doctor is often related to androgenic manifestations like acne, seborrhea, hirsutism, accompanied by oligo/amenorrhea and infertility [145]. Women with PCOS often have metabolic abnormalities (i.e. obesity, insulin resistance, and metabolic syndrome) that should be evaluated and treated to prevent cardiometabolic consequences later in life [145,146].

The rationale behind the use of HCs in PCOS is to improve clinical hyperandrogenism while providing menstrual regularity in women who are not seeking pregnancy [145,147]. Estrogens play an important role by increasing SHBG. This is true particularly for EE, which has a greater impact on the liver [75,110]. Progestins, especially antiandrogenic ones (cyproterone acetate, dienogest,

drospirenone, and chlormadinone acetate), inhibit 5-alpha reductase and thus prevent the conversion of testosterone to dihydrotestosterone, its biologically active metabolite [148]. Therefore, to obtain optimal therapeutic results, CHCs containing EE and antiandrogenic progestins are best suited for treating women with PCOS [149,150]. However, if not tolerated by the patient or contraindicated, other formulations may be used, such as those containing natural estrogens or POPs. Obesity, smoking, and cardiovascular or metabolic disorders should be considered when choosing a contraceptive in this population, as these comorbidities are highly prevalent and, if severe, may sometimes limit the prescription of CHCs [151].

From a metabolic perspective, obesity and insulin resistance always require treatment and metformin and inositols are currently indicated for use in PCOS patients [152]. The use of CHCs remains a first-line treatment in women with PCOS who do not want to conceive [145]. Their use is not associated with significant changes in insulin, glucose, total cholesterol, or LDL levels, but they do help with weight loss, especially when combined with metformin or myo-inositol [153]. Lifestyle modifications, a hypocaloric diet and physical activity remain the first choice in the treatment of obesity, also contributing to the improvement of clinical hyperandrogenism and menstrual irregularities [154]. Whatever treatment is chosen, ongoing support and advice from the treating gynecologist is necessary.

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**Box 9. Take-home messages and recommendations**

1. Treat PCOS as a systemic disease with a large metabolic component.
2. Consider CHCs as an important therapeutic tool, especially for women who do not want to have children. EE combined with an antiandrogenic progestin should be a first-line treatment for hyperandrogenism, when no specific risk factors exist.
3. Metformin and myo-inositol are important therapeutic tools and may be combined with CHCs. Body weight control through a healthy lifestyle is essential.

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*Abnormal uterine bleeding and menstrual cycle disorders.* AUB is a common disorder affecting 30% of women of reproductive age. It has a significant impact on quality of life (QoL), causing physical, social, emotional, sexual, and financial problems [101]. AUB in women of reproductive age is defined as bleeding from the uterine body which is abnormal in terms of duration, volume, frequency, and/or regularity [155]. The FIGO published two classification systems for AUB in the reproductive years: one for nomenclature of symptoms and one for classification of causes (PALM-COEIN system) [156].

AUB from ovulatory disorders (AUB-O) [157] can be managed by a range of options, which include HCs, progesterone/progestins and estrogens, surgical management, and treatment of underlying disease such as thyroid disorder. The appropriateness of various treatments should be determined based on each patient's medical history, discussion of risks and benefits, reproductive goals, and patient acceptance of a particular therapy.

When amenorrhea occurs, it is sometimes accompanied by severe hypoestrogenism, like in functional hypothalamic amenorrhea, and CHCs can help to reintegrate an appropriate balance of hormones to avoid long-term consequences, like osteoporosis [158]. A similar situation may occur with premature ovarian insufficiency (POI) [159].

Restoring normal bleeding in terms of frequency with HC is just a secondary end point since the primary end point is the restoration of normal QoL. When AUB-O is caused by a known entity (i.e. POI, adenomyosis/endometriosis, PCOS) [157], HC choice should be selected according to the symptoms and the characteristics of the specific disorder.

For other causes of AUB in terms of duration or volume, once organic causes that may require a surgical approach are ruled out, HCs continue to represent an option [160]. E2 valerate and dienogest in combination can improve heavy menstrual bleeding [161]. For idiopathic AUB, the LNG-IUD is effective at reducing menstrual blood loss [162].

Box 10. Take-home messages and recommendations

1.  AUB should be classified according to the FIGO classification system.
2.  Once the cause is identified, HCs can be used to treat the symptoms when there is also a contraceptive need to address.
3.  The choice of the right HCs should be guided by the specific cause of the AUB.

*Endometriosis, adenomyosis and uterine fibromatosis.* Endometriosis, adenomyosis, and fibroids are benign gynaecological conditions that affect women of different ages with various symptoms. HCs play a fundamental role in medical treatment of these conditions. The rationale behind this is based on the pathogenetic mechanisms of these disorders (i.e. sex steroid hormone abnormalities, impaired apoptosis, and increased inflammation) [163–165] and in the antiproliferative and anti-inflammatory effect of progestins such as dienogest [166], which help to control pain.

Endometriosis is an estrogen-dependent disease. The goal is to inhibit ovulation and menstruation to achieve a stable steroid hormonal environment and thus relieve endometriosis-associated pain. For this reason, long-term treatments with continuous regimens of HCs are the preferred therapeutic choice for chronic treatment [167]. Among progestins, norethisterone acetate and dienogest showed the highest efficacy [165] and dienogest was efficacious in preventing recurrences after surgery [168].

There are no specific medical therapies for adenomyosis approved by the US-FDA. Therefore, current management involves the use of contraceptive approaches and management of symptoms [169]. First-line treatment is usually the LNG-IUD with nonsteroidal anti-inflammatory drugs for pain control. POPs or CHCs can be used as alternatives. If symptom relief is inadequate, gonadotropin-releasing hormone (GnRH) agonists or antagonists can be used [169].

Treatment of fibroids depends strictly on the symptoms, with pelvic pain and AUB being the most troublesome [170]. Medical treatment is becoming more and more important. The LNG-IUD is effective in improving AUB when fibroids do not distort the endometrial cavity, but there is a higher risk of device expulsion than in the general population [171]. Other LARCs may also be effective for symptom control, as may CHCs [172]. However, the effectiveness in reducing the size of fibroids is debated.

Today, new GnRH antagonist, namely Relugolix, Elagolix and Linzagolix, are available for symptomatic uterine fibroids and endometriosis, which can be combined to an add-back combined estro-progestin therapy to improve the induced bone loss and hot flashes [173–176].

Box 11. Take-home messages and recommendations

1.  Long-term treatments with continuous regimens of HCs should be recommended for endometriosis.
2.  The LNG-IUD is effective in reducing pelvic pain and AUB in women with endometriosis, adenomyosis and uterine fibroids that do not distort the endometrial cavity.
3.  In women of reproductive age with moderate to severe symptomatic fibroids, treatment with GnRH antagonists with an add-back therapy is indicated.

*Bone metabolism.* Effects of HCs on connective tissues, especially bone development, have not been given adequate consideration, and in many cases still need to be studied to better understand the long-term side effects of some HC preparations and the more appropriate use of others. Additionally, many factors that are completely independent from sexual steroids, and thus from HCs, highly impact the bone acquisition and resorption, as genetics, physical exercise and diet [177]. In females, age at menarche is a factor that influences the time of reaching peak bone mass attainment, as studies show that bone mass increment falls after 16 years of age and/or 2 years after menarche [178].

Some studies show that CHCs with very low doses of EE may prevent the acquisition of peak bone mass in young women, without compromising already acquired bone mineral density [179]. On the other hand, they do not seem to affect the bone density of older premenopausal women [180,181]. Indeed, in the perimenopausal period, positive results on bone density were observed with the use of CHCs [180,181]. EE was responsible for these positive findings [182]. However, it must be remembered that bone density is just a surrogate marker of bone health, and fracture risk cannot be determined solely considering it. Data on fracture risk during HC are scarce, and the effect of CHCs on fracture risk cannot be determined from the existing literature [183,184].

The choice of CHC should include a consideration of the patient's age. As peak bone mass is generally reached by the age of 16 years [178], it may be prudent to use higher estrogen doses before this age, even though systematic reviews do not currently provide definitive evidence that 0.03 mg EE doses reduce the risk of bone fractures compared to lower doses at any age [183,184]. After this age, every CHC can be used as no difference is known in the effect on bone mass density [183,184]. In perimenopausal women, no detrimental effect on bone health of any formulation of CHC has been demonstrated [180,181], thus the choice should be primarily based on other risk factors (i.e. VTE or cardiovascular risk). The effects of E4-containing contraceptives on bone metabolism remain to be established, as E4 may have a similar effect on bone turnover to EE [185].

There is no apparent mechanism by which the LNG-IUD would impact bone health. Studies on progestin-only implants are scarce, but they seem not to negatively affect bone mineral density [186]. Conversely, DMPA has been shown to induce hypoestrogenism, significantly increasing bone resorption markers and decreasing bone mineral density, particularly in very young girls [187]. POPs can be used safely. The WHO stated that there should be no restriction on the use of POPs and on duration of use [188]. In general, it has been postulated that plasma E2 levels of 30-50 pg/mL with progestin-only contraceptives are sufficient to prevent bone loss [189], and studies on POPs and implants all report E2 levels in this range [187].

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**Box 12. Take-home messages and recommendations**

1. Low-dose CHC in very young women (<16 years) may prevent the acquisition of peak bone mass and higher doses of EE should be used. However, more studies should address this issue as results are still not conclusive and bone mass density do not accurately reflect the risk of fracture.
2. During menopausal transition, every CHC has the same neutral effect on the bones, thus the choice of the method and molecules should be based on risk factors.
3. Except for DMPA, other progestin-only contraceptives do not cause changes in bone mass density.
4. Plasma E2 levels of 30-50 pg/mL should be maintained to protect bone.

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### *Brain, mood, and migraine*

CHC do not have uniform effects on the brain because type and dose of estrogens and progestogens may have a diverse impact on the complex balance affecting brain plasticity. Indeed, both human and rodent studies have shown that brain structure and function vary with naturally cycling ovarian hormones [190,191] and HC may be considered an endocrine disruptor of mood, pain, and other brain-mediated functions in vulnerable women. Most women adapt quite well to the new neuroendocrine balance induced by using CHCs, and negative mood effects are infrequent (4-10%) [192]. Depressive symptoms in adolescent CHC-users should be considered [193]. CHC may lead to side effects, including deterioration of mood, especially in vulnerable women (i.e. those with a previous diagnosis of mood, anxiety or eating disorders) [194].

On the other hand, CHC may represent an option for the treatment of premenstrual syndrome/premenstrual dysphoric disorder, given the blockade of the ovulatory surge of sex steroids. Longer regimens or shorter hormone-free interval (HFI) and anti-androgenic progestins such as drospirenone appear to yield better results in premenstrual disorders [195].

The most common way of administration of CHC is the 21/7 regimen (i.e. 7 days of HFI). Migraine headaches frequently occur during the HFI and are more intense and less responsive to treatment, especially in women who suffered from migraines before CHC use [196]. However, the availability of oral regimens with a shorter (6, 4 or 2 days) or absent HFI can prevent migraine worsening in the HFI, modulating pain threshold and leading to decreases in frequency, intensity, and duration [197]. The main concern for CHC in subjects with migraine is their vascular risk and, specifically, stroke risk. CHC is not contraindicated for women with migraines without aura and menstrual migraine. Conversely, migraine with aura carries a 2-fold increased risk of stroke [198]; thus, it constitutes a contraindication to CHC use (progestin-only contraceptives can be safely used) [122]. CHC containing E2 or E4, thanks to the potential lower cardiovascular and thromboembolic risk and to the short HFI, may potentially become an alternative for women suffering from migraines, but studies are lacking on this field. Future research should investigate the impact of CHC containing natural estrogens on migraines, especially on migraine with aura [199].

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**Box 13. Take-home messages and recommendations**

1. Providers should carefully evaluate the onset of mood disorders during CHC use, which, although not common, may occur in vulnerable women.
2. CHCs with long regimens and anti-androgenic progestins should be chosen for women suffering from premenstrual syndrome or premenstrual dysphoric disorder.
3. In case of migraine without aura, a short or absent hormone-free interval should be preferred.

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## *Effects on women's sexuality and quality of life*

As described in previous sections, HCs are known to have non-contraceptive benefits that potentially enhance a woman's QoL. However, issues like breakthrough bleeding and changes in sexual function may be troublesome [200].

Efficacy and health risks are the two medical characteristics of importance to the user. Tolerability and health benefits are the properties of a method having an influence on the QoL of a user and on method compliance. Impairment of the QoL can have indirect effects on efficacy and should be evaluated when considering the choice of contraceptive [201].

Effects on female sexuality is even more difficult to assess and standardize. Some women report alterations in sexual function, including changes in overall sexual response, desire, lubrication, orgasm, and relationship satisfaction, but the data are insufficient to draw clear conclusions [202]. Moreover, no definitive information is available on the pathophysiology leading to reduced libido and vulvo-vaginal atrophy, which may strongly affect sexual function [202].

Users need individualized follow-up care to assess symptoms, explore contributing factors, and identify solutions for changes in QoL, which may include changing the type, dosage, and regimen of the used hormones. Education and supportive counseling for sexual health issues are essential.

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**Box 14. Take-home messages and recommendations**

1. The impact of contraceptive choice on QoL should always be assessed, as it affects contraceptive effectiveness and method adherence.
2. Individualized contraceptive choice, considering the woman's previous experience, impact on QoL and sexuality, is essential.

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## *Contraception in different stages of life*

During adolescence and perimenopause, the beginning and end of the fertile years, women may be particularly susceptible to hormonal fluctuations, as well as during the postpartum and lactation

periods (Figure 3). Therefore, the provider who wishes to prescribe an HC to women in these phases should consider their unique features and specific needs.

### Adolescence

It is very important to discuss sexual health, especially during adolescence and before becoming sexually active. The age of first sexual intercourse varies worldwide from 12 to 18 years [203–205]. Sexual activity, lower genital tract infections and EC are the main topics of discussion related to adolescent sexual health, and it is a provider's duty to instruct both adolescents and their families to approach sexual life safely.

HCs in adolescents should combine efficacy (failure can be a significant psychological threat at this age) and safety. In general, young girls have few clinical problems and can safely use any type of contraceptive. However, high estrogen doses may be preferred until peak bone mass is reached [179]. Compliance may be an issue for these girls, and counseling should include strategies to promote daily oral contraceptive use. A useful option may be the use of non-daily contraceptives (non-oral CHCs and LARCs) [206]. If there are medical conditions that require HCs as a treatment for their non-contraceptive benefits, these should guide the choice.

Future fertility must be kept in mind, as well as the psychology of the young girl and the crosstalk with the parents and the partner. In addition, the importance of protecting against STIs should always be discussed before sexual activity begins [207].

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**Box 15. Take-home messages and recommendations**

1. Counseling and education about contraception is essential during adolescence, both for young people and their families.
2. During adolescence, bone safety and future fertility, as well as added health benefits, should be kept in mind when choosing the contraceptive.
3. Non-daily options may be useful to increase compliance when HCs is used only for contraceptive reasons.

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### Post-partum and breastfeeding

The occurrence of a new pregnancy within a short period of time after childbirth can lead to an increase in maternal and fetal complications, as well as social and economic consequences. An inter-partum interval of 18-23 months is generally recommended [208]. Contraceptive counseling in the postpartum period is essential.

Fertility return is highly dependent on breastfeeding, and if the woman does not breastfeed, ovulation may resume 40-45 days after delivery [209]. Contraception should be started before fertility returns, about 4 weeks after delivery. The LAM is considered a natural family planning method with an efficacy of more than 98% in the first 6 months when used perfectly (i.e. the presence of three simultaneous conditions: the baby is under 6 months; the mother is still amenorrhoeic; and she practises exclusive or quasi-exclusive breastfeeding on demand, day and night) [210]. However, many women are unable to breastfeed regularly during this period, which can cause a return to fertility in a shorter period [210]. Therefore, other contraception methods should be used to avoid pregnancy.

The use of CHCs is contraindicated during the first 6 weeks of postpartum, as they increase the risk of VTE. They should generally be avoided during breastfeeding, if there is a possibility of using another method [208,211]. Progestogen-only methods, apart from DMPA, have no contraindications, they do not alter milk quantity and quality, and can be started soon after birth. DMPA should be delayed until 6 weeks after birth [208,211]. The Cu-IUD is safe and does not interfere with lactation. It can be inserted vaginally immediately after delivery or up to 48 h after birth, or abdominally during a cesarean section [212]. Some postpartum users may prefer to use FABMs. Unfortunately, these methods have not been well-studied in breastfeeding population.

Women who are breastfeeding can use EC without restriction, but there is no indication to use it if the sexual intercourse occurs before 21 days postpartum. Barrier methods of contraception may be offered, as well as female or male permanent contraception [208,211].

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**Box 16. Take-home messages and recommendations**

1. An interpartum interval of 18-23 months is recommended to reduce the risks of maternal and fetal complications.
2. Contraception should be started before the return of fertility.
3. Progestin-only methods are preferred for breastfeeding women.

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### Menopausal transition and premature ovarian insufficiency

Contraceptive counseling during the menopausal transition is essential because of the possibility of unwanted pregnancies that carry a high risk of obstetric and fetal abnormalities due to advanced age [213]. Moreover, clinicians should consider the potential relief of perimenopausal symptoms [214]. This transition can occur very early in women with POI, exposing them to a prolonged period of estrogen deprivation and potentially more serious long-term consequences [159].

Estrogen supplementation in perimenopause, regardless of age, is useful to manage mood, sleep disorders and vasomotor symptoms. Menopause hormone therapy (MHT) is not contraceptive, so individuals desiring treatment and contraception should consider use of CHCs. E2 and E4 should be considered in perimenopause for the optimal benefit and potentially lower risk ratio [215], even if no contraceptive method or molecule is contraindicated based solely on age. The non-contraceptive benefits of HCs are important, as age increases the risk of bone demineralization [216], endometrial hyperplasia [217], ovarian and colorectal cancer [218], all of which can be reduced with HCs. However, special attention should be paid also to cardiovascular risk factors, the prevalence of which increases with age [219]. When the only bothersome symptom is AUB, progestin only contraceptives can be used, specifically the LNG-IUDs or POPs [215]. The 52 mg LNG-IUD can also be used for endometrial protection and contraception combined to estrogens for MHT [220,221].

Women with POI may have fluctuating ovarian hormones, causing ovulation to occur unexpectedly. Thus, the choice between HC and MHT during POI is often not evidence-based and should be individualized, considering a woman's age, desire to become pregnant, psychological needs, and cardiometabolic and bone health [159].

The timing of the transition from HC to MHT should be evaluated considering the woman's risk factors and comorbidities and the control of symptoms. In general, an assessment of the onset of spontaneous menopause with reevaluation of symptoms should be performed when the average age of menopause is reached [215].

When the desire for pregnancy is concluded, salpingectomy can be considered as a permanent contraceptive method, useful also to reduce the risk of ovarian cancer [222].

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**Box 17. Take-home messages and recommendations**

1. The choice of HC method in the perimenopause should consider: symptoms, osteoporosis risk, oncological risk, cardiovascular comorbidities, obstetric risk.
2. Estrogens are usually needed, and natural estrogens should be preferred if no contraindication exists.
3. Progestin-only contraceptives may be chosen when AUB is the only symptom.
4. Risk of pregnancy in patients with POI should be considered when choosing between HCs and MHT.

## Other contraceptive methods

### Emergency contraception (EC)

EC is defined as any method used after unprotected intercourse to prevent an unwanted pregnancy. It is a backup option when contraception fails or is not used and reduces rates of voluntary abortions [223]. Early methods were based on existing CHCs, but later LNG alone proved being more effective with fewer side effects [224].

Ulipristal acetate (UPA), a more recent EC, offers even better efficacy due to a wider time window for use. Cu-IUDs also provide highly effective EC. Controversy and barriers to EC use still exist and it remains underutilized globally [225].

The contraceptive effect of LNG 1.5 mg or UPA 30 mg used for EC is due to impaired ovarian function: they delay or inhibit follicular development and ovulation during the follicular phase [224–226]. LNG-EC is effective until LH increases, while UPA-EC is also effective after LH has started to rise and until LH peaks [224,226]. If used beyond these time points, LNG or UPA in the doses used for EC have no significant effects on the endometrium and are not effective in preventing pregnancy [224–226]. When CHCs or POPs are already being used, UPA-EC should be preferred because of interactions between LNG and progestins [225]. The Cu-IUD is the most effective EC method. However, it requires a trained health care provider for insertion [227].

LNG-EC and UPA-EC in doses used for EC do not inhibit embryo implantation *in vitro* [228]. EC pills have no adverse effect on pregnancy if conception has already occurred [224,226].

Caution should be used with LNG-EC in obese women due to the possibility of method failure; UPA or Cu-IUD should be preferred [229].

New studies are investigating how to improve the efficacy of available EC. For example, there are data suggesting that the addition of piroxicam, a reversible nonselective cyclo-oxygenase inhibitor, to LNG may increase efficacy in preventing pregnancy after high-risk sexual intercourse [230].

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Box 18. Take-home messages and recommendations

1. ECs should be used after unprotected sex to prevent pregnancies.
2. They do not work if used after the rise of LH for LNG or LH peak for UPA, or if pregnancy has already started.
3. Caution should be used with obese patients due to the higher risk of method failure. UPA or Cu-IUD should be preferred in this case.

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### Barrier methods and sexually transmitted diseases

Barrier methods include male and female condoms, as well as diaphragms, cervical caps, spermicides, and vaginal sponges. Male condoms are the most used method, but have a high failure rate, especially if used incorrectly: the Pearl Index for correct use ranges from 2.5 to 5.9 [58]. This underscores the importance of proper use for optimal efficacy. To improve effectiveness, condoms can be combined with spermicides.

Because condoms do not cover all exposed areas, they are more effective at preventing infections transmitted by fluids from mucosal surfaces than those transmitted by skin-to-skin contact.

Male condoms protect against human immunodeficiency virus (HIV) infection. In heterosexual relationships, HIV-negative partners who used condoms were 80% less likely to acquire HIV than non-users [231]. Condoms are slightly, but not significantly, less effective in preventing HIV infection in male homosexual couples (60-70% of effectiveness in always users) [232]. The efficacy is lost in sometimes users. Condoms can reduce the risk of gonorrhea and chlamydia [233,234] and the risk of acquiring genital herpes if correctly used every time [235]. The male condom is known to have a protective effect against cervical cancer, which has been linked to the HPV [236].

The female condom is an effective mechanical barrier to viruses, including HIV. However, few clinical data are available on their efficacy in providing protection from STIs [237].

Among spermicides, most research has been performed using nonoxynol-9 (N-9): the most frequently used. Vaginal spermicides containing N-9 are not effective in preventing cervical gonorrhea, chlamydia, or HIV infection. Frequent use of spermicides containing N-9 has been associated with genital lesions, which may be associated with an increased risk of HIV transmission. Thus, spermicides alone are not recommended for STI/HIV prevention [238].

Barrier methods are more likely to be successful when users receive effective counseling. Partner communication and cooperation are required for effective use. Clear and practical information on how to correctly use the method and how to avoid common usage mistakes is also essential [207].

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**Box 19. Take-home messages and recommendations**

1. The use of male condoms must always be recommended to prevent STIs; there is less data on female condoms.
2. Spermicides and other barrier methods alone are not recommended for STI prevention.
3. The provider must counsel couples on proper condom use and the importance of communication and cooperation between partners. However, the provider must avoid giving a sense of security. Condoms are an effective tool against STI transmission, but they do not eliminate the risk of infection.

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### *Male hormonal contraceptives*

The search for male contraceptive started more than 50 years ago, but the results have been less impactful than for female contraception. However, there is a demand for male contraception. Indeed, an international survey indicated that >50% of men would opt to use a reversible method [239], and in another international survey, 90% of women confirmed that they would rely on their partner to use a contraceptive [240].

The use of contraceptives by men will likely not decrease female contraception use. Increasing access and choices for men and women may reduce the burden of unintended pregnancies. In addition, male contraception may bring other societal benefits as it will expand access to male sexual healthcare and provide sexual education opportunities for young men.

Advanced methods of male hormonal contraception include combinations of progestin and modified androgens to ensure both sperm suppression and androgenic actions [241]. Hormonal methods given *via* various delivery systems show full reversibility within a few months. Novel non-hormonal contraception products target a decrease in sperm motility, or acrosome reaction acceleration, to prevent fertilization. In addition, non-surgical, reversible vas occlusive methods are in development [241]. The search for novel methods must continue, in order to offer several options to men.

New guidelines have been published that are intended to review the status of male contraception, the current state of the art supporting clinical practice, and to recommend the minimal requirements for new male contraceptive development, that provides evidence-based recommendations from the European Academy of Andrology and the American Society of Andrology [242].

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**Box 20. Take-home messages and recommendations**

1. There is an urgent need for male contraceptive methods that will assure the right to family planning of all individuals and couples.
2. It is recommended that sexual education opportunities be provided to young men.
3. Increasing access and choices for men and women will reduce the burden of unintended pregnancies.

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## Conclusions

It is essential to strike a balance between efficacy and safety of contraceptive methods. When a contraceptive method is effective but carries potential risks, the health care provider has the responsibility to guide the choice and to fully inform women and their partners. Equally, when safe, but low-effectiveness methods are chosen, women need to be informed and prepared for the consequences of method failure.

The principle that one size does not fit all, applies particularly to contraception. The need of each woman, health profile and personal circumstances, including marital status and couple's preferences, must guide the choice of a contraceptive method. The provider should recommend the most appropriate option based on the woman's individual characteristics. This decision-making process must be couple-centred and well-informed.

First, the physician must understand if hormonal methods may be acceptable for the couple or if they would prefer a natural one. Then, if HCs are chosen, the choice must be made between CHCs and estrogen-free methods, and finally which type of estrogen is to be used. EE remains a viable and valid option, particularly in cases where its anti-androgenic properties are beneficial. However, if there is no specific need, the healthcare provider should evaluate whether natural estrogens (E2 or E4) combined with the appropriate progestin could be a better choice, as evidence is progressively showing that these molecules may have a more favorable liver and thromboembolic profile. In the world of estrogen-containing contraceptives, some issues should be addressed by future research. One of the main limitations of current international guidelines [122], included the WHO Medical Eligibility Criteria for Contraceptive Use of 2014, is that they do not make differentiations between the various molecules. Recently, the US Center for Disease Control and Prevention has published new US Medical Eligibility Criteria for Contraceptive Use [243]. Despite this, a specific differentiation between the risks of various estrogens has not been added, even if knowledge in the field is progressively increasing. This issue should be addressed in future research and guidelines. Moreover, the US Medical Eligibility Criteria for Contraceptive Use do not meet the need for international guidelines because they reflect the experience of a single country.

There is also a need for a new definition of 'low dose' HCs. Today, the dose range of EE can be 15 and 35 μg and the classic definition does not differentiate between these doses, which may have various effects on the physiology of the human body. Furthermore, natural estrogens are excluded from this classification.

If estrogen is contraindicated, careful individual assessment is essential. This assessment should consider factors such as bone mass, endogenous estrogen levels and the woman's stage of life, particularly adolescence and the menopausal transition.

Contraception goes beyond its primary role of preventing pregnancy in the context of a relationship. Especially in difficult environments, it is a critical element of women's health and autonomy. In workplaces with occupational hazards or where menstrual side-effects can limit a woman's performance, in regions affected by conflict and war, and in situations where women are vulnerable to violence, contraception becomes an essential protective measure that protects and empowers women.

Further research should focus on widening the range of people who can benefit from contraception, evaluating how new safer hormonal options can potentially be used in women at high health risk for whom any method is now contraindicated, and spreading knowledge about the existence and function of natural methods that may perfectly be suited to some specific situations.

## Knowledge gaps

1. Considering that evidence on E2 and E4 supports the hypothesis that natural estrogens have a more favorable impact on hemostatic and liver parameters, research should focus on increasing the range of estrogen/progestin combinations that contain natural estrogens.
2. More research should be performed on new progestin and estrogen/progestin combinations with a neutral effect on the central nervous system (i.e. with fewer side effects on mental health).

3. There are many subpopulations of women with relative or absolute contraindications to some HCs. However, research on them is often scarce. Future research should focus on selecting the best choice for each category of women, also considering the new available molecules and pharmaceutical technologies. Examples of cohorts of women for which research should be increased include: women who are obese, with coagulopathies, arterial hypertension, dyslipidaemia, renal failure, hepatic insufficiency, mood disorders, and/or migraine.

4. New guidelines that differentiate the current available choices are recommended, considering that changing the molecules contained in HC can greatly affect the potential side effects. Non-hormonal methods should also be strengthened and made available to people with contraindications to hormones.

5. More accurate data should be collected on the effectiveness and prevalence of different contraceptive methods in the real world, both FABMs and HCs, and in different countries with different cultures.

6. New studies suggest that the effectiveness of EC pills can be increased. More data are needed to allow combined treatment to be made available over the counter and on demand.

## Author's contributions

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