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Guidelines for clinical practice

Clinical practice guidelines for contraception of the French National College of Gynecologists and Obstetricians (CNGOF)

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ABSTRACT

The French College of Obstetrics and Gynecology (CNGOF) has released its first comprehensive recommendations for clinical practices in contraception, to provide physicians with an updated synthesis of the available data as a basis for their practice.

The organizing committee and the working group adopted the objective methodological principles defined by the French Authority for Health (HAS) and selected 12 themes relevant to medical professionals' clinical practices concerning contraception. The available literature was screened through December 2017 and served as the basis of 12 texts, reviewed by experts and physicians from public and private practices, with experience in this field. These texts enabled us to develop evidence based, graded recommendations. Male and female sterilization, as well as the use of hormonal treatments not authorized for contraception ("off-label") were excluded from the scope of our review.

Specific practical recommendations are provided for the management of contraception prescription, patient information concerning effectiveness, risks, and benefits of the different methods, patient follow-up, intrauterine contraception, emergency contraception, local and natural methods, contraception in teenagers, in women after 40, for women at high thromboembolism or cardiovascular risk, and for those at of primary cancer or relapse.

The short- and mid-term future of contraception depends mainly on improving the use of currently available methods. This includes reinforced information for users and increased access to contraception for women, regardless of their social and clinical contexts. The objective of these guidelines is to aid in enabling this improvement.

1. Introduction

French guidelines for the prescription of contraceptives were updated in 2010 by the French Society of Endocrinology (SFE), specifically for hormonal contraception in women with vascular risk factors, then in 2013 by the French National Authority for Health (HAS) to recommend a comprehensive strategy for choosing contraception, and finally in 2015 by the French National College of Gynecology and Obstetrics (CNGOF) and the HAS for the postpartum period.

Until now, CNGOF has never issued comprehensive guidelines for contraception.

This working group selected 12 themes relevant to physicians' clinical practices concerning contraception: epidemiology; drug interactions with contraceptives; consultation for contraception/family planning; emergency contraception; good practices concerning intrauterine devices (IUDs); contraceptives and vascular risk; contraceptives, cancer risk, and after cancer; good practices for hormonal contraception (excluding the LNG-IUD); contraception for adolescents; contraception for women after 40; utility of other contraceptives (local and natural methods); additional benefits and the future of contraceptives.

These guidelines do not, on the other hand, concern permanent contraception, that is, sterilization, for which specific legal regulations exist; nor do they cover off-label contraception by macrodose progestins, which will be considered for specific guidelines in 2019–2020 by the CNGOF "off-label" committee.

2. Methodology

The aim of the CNGOF clinical practice guidelines is to assist physicians in making medical decisions by providing them with a synthesis of the current scientific data on specific subjects. These recommendations are not criteria for determining the relevance of medical practices, or standards of practice quality, or measures of their performance.

Abbreviations: ANSM, national Agency of Drug Safety (Agence nationale de sécurité du médicament); BMI, body mass index; CHC, combined hormonal (estrogen–progestin) contraceptives; CIN, cervical intraepithelial neoplasm; CNGOF, French National College of Gynecologists and Obstetricians (Collège National des Gynécologues Obstétriciens Français); DMPA, depomedroxyprogesterone acetate; EC, emergency contraception; EE, ethinyl estradiol; HAS, National authority for health (Haute Autorité de Santé); IUD, intrauterine device; LARC, long-acting reversible contraception; LE, level of evidence; LNG, levonorgestrel; MI, myocardial infarction; PC, professional consensus; SFE, French society for endocrinology (Société française de l'endocrinologie); STD, sexually-transmitted disease; VTD, venous thromboembolic disease.

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A very important methodological point is the use of levels of scientific evidence (LE) (Fig. 1). These texts do not and are not intended to reflect the personal opinion of the expert authors, but must instead be drawn from the scientific literature with a level of evidence assigned for each important statement.

To develop these particular clinical practice guidelines, we have adopted the objective methodological principles defined by HAS to ensure the validity of such guidelines in general. CNGOF is the sponsor of these clinical practice guidelines. This rigorous methodological procedure can appear constraining but is essential for a clear definition of health interventions that are appropriate as well as those that are inappropriate and those for which supporting evidence is currently equivocal or unknown. In the latter situation, where the data are sparse or unreliable, the opinion of the members of the working group is reported, or that of another professional society that has reached an opinion; these are qualified as professional consensus (PC). In the absence of data, no recommendation is possible. These clinical practice guidelines are not a consensus conference in which a group of experts gives their opinion. The selection of the working group attempted to reduce any authors' conflicts of interest, and any potential conflicts and links with industry are reported.

Let us review schematically the five stages that precede the development of clinical practice guidelines:

1 1 Designation by the sponsor (CNGOF) of the members of the organizing committee (with a scientific president, a coordinator, and a methodologist):
2 Development of the precise questions for each specified topic, and the designation by the organizing committee of the authors (experienced or expert physicians) to answer these questions. Each senior author may choose a younger colleague to write the section with him or her.
3 Analysis of the literature by the authors and the proposal of provisional conclusions based on their report, with a level of evidence (LE) (Fig. 1) assigned to each important statement.
4 The conclusions and the texts are then sent to a large number of reviewers expert on the subject or physicians experienced in providing care related to the topic, in either the private or public sector.
5 Elaboration and drafting of the final guidelines by the organizing committee, including the assignment of a grade to the recommendation, after taking into account the authors' opinions and the reviewers' comments.

The distinction between the levels of evidence, strictly speaking, and the grades must be underlined. The levels of evidence apply to the factual data from the literature (conclusion and interpretation of data). For example, "*Decision support has shown its utility when a therapeutic choice exists (LE1). The use of computerized modules or audiovisual presentations in the waiting room before consultation may enable women to choose more effective contraception more easily (LE2)*" is a *conclusion* from the data in the literature, based on the results of consistent published trials. The grades apply to the *recommendations,* which are proposals for management. They come from the working group, which took into account, not only these factual data and their interpretation, but also factors such as the safety of the treatment or diagnostic procedure, the net benefit attributable to it, and its reproducibility or reliability. We used two different basic formulations to state recommendation, as follows: "*It is recommended that decision support tools be used (Grade A)" or 'Decision support tools should be used." Both "recommend" and "should" are intended to mean that decision support is strongly suggested, or even must be used, in the absence of a specific reason not to (which may include the physician's professional experience, the woman's specific clinical or other situation, and so on).*

The long texts for each section have been published in French by their authors, who are responsible for them. The short text, which includes the principal guidelines and their justification, has been published by the entire writing group in French for dissemination in France and in French-speaking countries and is now being presented in English for an international public. They were presented for the first time at the CNGOF conference in December 2018. The references in both the long and short texts are limited to around 50; that is, they are the most convincing of the much larger selection of articles we assessed.

3. Epidemiology of contraception in France

Although the effectiveness of oral contraception is theoretically 99.7%, its practical effectiveness in France does not exceed 97.6%. Moreover, a year after starting, 30% of women have discontinued its use (LE2). Regardless of the method used (pills, condom, IUD, withdrawal, or a method based on knowledge of fertility), its practical effectiveness diminishes over time (LE2) (1). Accordingly, it is recommended that women and couples be informed that there is a difference between theoretical and practical effectiveness (grade B), that the risk of failure increases over time, and that failure is associated mainly with inadequate consistency of the method (grade C). Contraceptive failure due to imperfect adherence is one of the principal causes of elective abortions in France (LE3) (2). Since 2000, although the rate of emergency contraception use has increased, no simultaneous changes have been observed in contraceptive practices nor has the elective abortion rate fallen in France, as it has in the United Kingdom.

LEVEL of EVIDENCE	STUDY TYPE	RECOMMENDATION GRADE
LEVEL 1	High power Randomized Controlled Trials (RCT) Meta analyses of RCTs Decision analyses based on well conducted studies	Grade A (established scientific proof)
LEVEL 2	Low level Randomized controlled trials (RCT) High quality comparative non randomized studies Cohort studies	Grade B (scientific presumption)
LEVEL 3	Case control studies	Grade C (low level of evidence)
LEVEL 4	Comparative studies with bias Retropsective studies Epidemiological studies Case series	

Fig. 1. Level of scientific evidence (LE) and grade of guidelines.

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Contraceptive use is high in France. In 2013, 97% of the women aged 15–49 years and at risk of unplanned pregnancy used a method of contraception, most of them medical methods (72%) (3,4). Although the "pill scare" of 2013 called into question the use of combined oral contraceptives and the information physicians were providing to their patients, the "pill" remains the leading method of contraception in France, ahead of the IUD, the condom, sterilization, and the methods referred to as "traditional" or "natural".

Contraceptive use changes with age and pregnancies, according to a defined norm: condoms at the beginning of sexual activity, replaced by the pill in stable relationships, and the IUD once the desired family size has been reached. Sterilization (permanent contraception) is very rare in France (Baromètre Santé 2016) and very rarely proposed by healthcare professionals [5]. Contraception in France remains principally the woman's responsibility, as it essentially cannot be shared within the couple or assigned to men.

The mortality associated with contraception is very low. Neither large-scale registry studies nor prospective cohorts comparing women using contraception to controls not using contraception have shown any increase in mortality specifically associated with either contraception or hormonal contraception (LE2). The last large US cohort study showed a higher rate of violent or accidental deaths among users than non-users (LE2). Mortality studies consistently conclude contraception reduces mortality from ovarian cancer and from cancer in general. The increase in breast cancer mortality remains controversial, with different results from different studies (6–10).

It is recommended that women/couples be informed that there is a difference between the theoretical and the practical effectiveness of contraceptives (grade B) and that the risk of failure increases over time (grade C).

Further, they should be informed that the risk of contraceptive failure is due first of all to poor use of the method (grade C) or to the prescription of a method inappropriate to their living conditions, life style and sexual activity. They should also be informed about adherence to and accessibility of contraception in general and especially of emergency contraception and its availability at no cost (grade C).

It is also justified and appropriate to inform them (grade B) that all-cause mortality is not associated with contraceptive use (HR: 0.94; 95% CI 0.87–1.02) and that the benefit-risk balance must be assessed at each life stage (grade B) to help them to make an appropriate, personalized choice.

Obese women are a population at risk of unplanned pregnancy because of their limited access to contraception. Nonetheless, despite the relatively few studies on this point, the effectiveness of contraceptives for them is equal to that of women of normal weight (LE3). For cardiovascular and thromboembolic risks, the risk of use of any contraceptive method is lower than the risk associated with pregnancy.

It is recommended that women with obesity and no other risk factors be offered the full range of contraceptive choices (grade B) and that their access to contraception be facilitated (grade C).

Women in socially and economically precarious situations are at risk of lower contraceptive use (LE4). Their access to consultation for contraceptives should be facilitated, and they should be offered the entire range of contraceptive options (PC).

It is recommended that clinicians provide information about all contraceptive possibilities to women using drugs. Long-acting reversible contraception (LARC) appear to be the most appropriate type for women at risk of poor adherence, if they want it (grade C).

4. Pharmacology and drugs interactions with contraceptives

The risk of drug interactions with hormonal contraceptives must be anticipated, because these can lead to unplanned pregnancies, in particular with some methods, such as implants, which are not always perceived as hormonal (7).

It is essential for clinicians to use the National agency of drug safety's (ANSM) official thesaurus to assess the risk of drug interactions with contraceptives (8).

Most of the time, it is the combined hormonal (estrogen–progestin) contraceptives (CHCs) that are subjected to the effects of other drugs the woman is taking. That is, most of the interactions reduce the effectiveness of CHCs, due to hepatic enzyme induction. It is thus essential to take into account the risk that drug interactions will reduce the effectiveness of all hormonal contraceptives, whether they are administered orally, transdermally (patches), subcutaneously (an implant), vaginally (a ring) or by injection of.

Clinicians should take into account the risk of reduced contraceptive effectiveness due to drug interactions for women using CHC, regardless of its route of administration, in the prescription of any new drug, even for a short period (PC) and should ensure that women are aware of this risk of interaction with medication, in particular for self-medication, but also with consumption of some other products (e.g., phytotherapy and dietary supplements) (PC). This risk rises as the contraceptive dose decreases (PC).

In the case of the prescription of enzyme inducers, such as Saint John's wort and some antiepileptic agents (carbamazepine, fosphenytoin, phenobarbital, phenytoin, and primidone), some antituberculosis agents, rifampicin, rifabutin, some antiretrovirals, griseofulvin, modafinil, vemurafenib, dabrafenib, bosentan, and aprepitant in women using hormonal contraception, an additional mechanical contraceptive (barrier method) should be used throughout any short treatment period and through the cycle after it is stopped; if the treatment is long, a non-hormonal contraceptive method should be chosen (ANSM recommendation 2018). If an enzyme-inducing drug has been administered in the preceding months, a non-hormonal emergency contraception method (copper IUD) is recommended. If that is not possible, the ANSM recommends that the dose of levonorgestrel be doubled (8).

Women using oral contraception should be informed of how to manage strong vomiting or diarrhea, regardless of its origin (medication-related or not), in accordance with the recommendations of the HAS, the ANSM, and the pharmacological data (HAS). It is recommended that medications containing coal be taken more than two hours, if possible, before or after administration of an oral contraceptive.

If any woman using a CHC with a high dose of ethinyl estradiol (EE) is prescribed etoricoxib, atorvastatin, azole antifungal agents (ketoconazole, itraconazole, voriconazole, or posaconazole) or boceprevir, the prescriber should take into account the risk of an increase in the EE concentration.

It is recommended that a CHC not be started during the dose-adjustment period for lamotrigine. Any modification (introduction, change, or cessation) of hormonal contraception requires a simultaneous adaptation of the lamotrigine dosage, in collaboration with the neurologist (PC).

Because Saint John's wort (a potentially effective antidepressant) induces a substantial reduction in the concentrations of CHC estrogen, it is contraindicated with hormonal contraception. Grapefruit juice consumed in large quantities has the inverse effect, increasing estrogen concentrations (PC).

The association of the copper IUD with non-steroidal anti-inflammatory drugs (NSAIDs) has not been shown to reduce its contraceptive effectiveness (LE3) (9,10).

Contraception by a copper IUD is not contraindicated by either chronic or ad hoc NSAID treatment (grade C). The data concerning the association of glucocorticoids with a long-term copper IUD are too limited to enable any conclusion. Levonorgestrel rather than

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ulipristal should be used as emergency contraception for a women using hormonal contraception, or for whom hormonal contraception is envisioned after the emergency contraception (PC).

If the administration or resumption of a hormonal contraceptive is envisioned after ulipristal acetate is used for emergency contraception, additional mechanical contraception is recommended during the 12 days after the ulipristal intake (ANSM 2018).

5. Consultation for contraception

The physician's clear statement of contraceptive preference during the visit reduces the woman's satisfaction (LE1) and may reduce contraceptive continuation (LE4) (11). A structured consultation, however, enables women to change their contraceptive choice and reduces unplanned pregnancies (LE1) compared with traditional, non-personalized consultation. The principal themes to cover in this consultation are effectiveness, risks, cost, duration of activity, and practical aspects (LE2). Good interpersonal communication appears to result in a higher contraceptive continuation rate (LE2) (12,13) and better contraceptive satisfaction at 2 years (LE4).

It is recommended that contraceptive/family planning consultations be structured (with complete information and patient choice) and evidence-based (grade A) to enable them to conclude with a personalized prescription. In fact, personalization of contraceptive advice is recommended (PC).

The potential adverse effects of the contraception chosen by the woman should be explained to her (grade B), as these explanations appear to improve contraceptive continuation rates (PC).

Decision support, for example, by audiovisual presentations, has shown its utility when a therapeutic choice exists (LE1). The use of computerized modules or audiovisual presentations in the waiting room before consultation appears to facilitate the choice of more effective contraception (LE2). At consultations, the presentation of contraceptives by category of effectiveness enables women to understand differences in effectiveness better than presentations of the pregnancy numbers (LE1) (14).

The audiovisual tools associated with improved contraceptive continuation rates are educational (LE1) (14). The use of an information form describing combination oral contraception was associated with better knowledge of this method (LE2). Nonetheless, after the visit, a large proportion of women do not know what action to take if they become pregnant while using such contraception, even after ongoing advice (LE2) (15).

Decision support tools should be used.

Sufficient comparative data do not currently exist to recommend a particular method of decision support (PC).

6. Emergency contraception (EC)

Two methods of emergency contraception (EC) are used in France: the hormonal method (emergency oral contraceptives), by either levonorgestrel (LNG) or ulipristal and the mechanical method with postcoïtal insertion of a copper IUD. Hormonal emergency contraception is not 100% effectivè, and its effectiveness' decreases as time between the unprotected intercourse 'and its intake increases' (LE1).

It is recommended that women be informed that emergency contraception is not 100% effective (grade A).

A pregnancy test is recommended if menstruation appeared delayed after this emergency contraception (PC).

Levonorgestrel (LNG) is a progestin that must be used within 72 h after unprotected intercourse or the failure of a contraceptive method (LE1) (16).

The closer in time to the unprotected intercourse, the more effective it is in preventing pregnancy (LE1).

It is also more effective when taken as early as possible before ovulation (LE2).

Early menstruation is more likely to result after LNG for emergency contraception (LE1).

Ulipristal delays the rupture of the follicle by 5 days when it is given just before the LH surge (LE2).

Ulipristal delays ovulation more effectively than LNG when it is given in the late follicular phase (LE1).

Its adverse effect profile is similar to that of LNG (LE1).

Periods are more likely to be delayed with ulipristal (LE1).

The two non-inferiority trials comparing ulipristal with LNG in the first 72 h after sexual relations did not show significant differences in pregnancy rates. Two meta-analyses of these studies show that ulipristal is superior (17,18), especially in the immediate preovulatory phase (17). After 72 h, the data show that ulipristal is more effective than LNG (LE1) (17,18). In the absence of long-term contraception, ulipristal and LNG can be offered in the first 72 h after unprotected intercourse (Grade A). Because of its better effectiveness in the periovulatory period, and given the difficulty of determining exactly when that period is, the prescription of ulipristal can be recommended (PC). After 72 h, ulipristal must be preferred (Grade A).

The effectiveness of emergency contraception by ulipristal may be diminished by taking a progestin-only contraceptive beginning the next day, but on the other hand, ulipristal intake has not been shown to affect progestin-only or combined contraceptives begun immediately after the ulipristal. These data remain limited, based on assessment of the follicular rupture (LE3).

It is recommended that ulipristal not be used for emergency contraception for women using long-term hormonal contraception (Grade C).

The copper IUD is the most effective means of emergency contraception (LE1) (18,19). The copper IUD can be used as emergency contraception in the 5 days (120 h) after unprotected sexual intercourse or in the case of a risk that the contraceptive method used failed (LE2).

The copper IUD also has the advantage of providing more long-term contraception after its insertion (LP2).

The copper IUD is usable as first-line treatment (Grade A), and its use should be encouraged.

Data about the use of the LNG-IUD are currently too limited to allow it to be recommended as emergency contraception.

Impact of obesity

A body mass index (BMI) $\geq$ 25 decreases the effectiveness of LNG as emergency contraception (LE1) (20).

The risk of the failure of emergency contraception for obese women (BMI $\geq$ 30) is multiplied by 4.4 for LNG and by 2.6 for ulipristal (LE1).

A copper IUD or ulipristal is recommended for emergency contraception for women with BMI > 30 (grade A).

7. Intrauterine contraception

Intrauterine contraception can be offered to adolescents and nulliparas (grade B) because it is accompanied by excellent effectiveness and a high continuation rate with a low risk of complications (no higher than that observed in other age groups or among women who have already given birth) (LE2) (21).

The available data do not show a higher risk of infection among women living with HIV before the AIDS stage (LE3). Intrauterine contraception does not increase the risk of either virus progression or transmission to a partner (LE2).

The IUD is not contraindicated in women living with HIV before the AIDS stage (grade B).

The several studies of women with heart disease have failed to find a contraindication to intrauterine contraception (LE2). In the

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case of severe heart disease, the benefit-risk balance of IUD placement appears more favorable than that of pregnancy (PC). Antibiotic prophylaxis to prevent the risk of infectious endocarditis is necessary in women with severe valve disease (PC).

Only digital cervical examination with a bimanual examination and cervical inspection are formally recommended (grade B) before IUD placement.

The standard regimen for cervical cancer screening should not be modified for IUD users (Grade B) (22).

Routine screening for STDs is not recommended before IUD placement (Grade B). Practitioners should, however, screen for STDs, especially *Chlamydia trachomatis* and *Neisseria gonorrheae*, when STD risk factors are present: age less than 25 years, with partner for less than three months, multiple partners in the last year, history of STD, or unprotected intercourse (grade B). Ideally this screening is performed the day that the IUD is prescribed (with vaginal and endocervical samples or self-samples), but it can be performed the day of IUD placement without delaying it, if the woman is asymptomatic (grade B) (23).

The IUD can be placed at any point during the cycle (grade B) as long as it is certain that no pregnancy is underway (LE2); neither antibiotic prophylaxis nor routine premedication is indicated for IUD placement (grade A).

It is advisable to cut the strings at 2–3 cm from their projection from the external os immediately after insertion (PC). They can be shortened at a subsequent visit in the event of discomfort, especially during sexual intercourse (PC).

After IUD insertion, women must be informed of the symptoms for which they should consult the clinician (PC). A follow-up visit can be proposed in the weeks after IUD placement (PC). Women must be informed of the date at which the IUD should be removed (PC).

Systematic ultrasound verification is not recommended (grade B) if the woman is asymptomatic, the IUD insertion took place without difficulty, and on examination the strings are visible and the length as expected (LE2).

Uterine perforation is a rare complication of intrauterine contraception (LE2). It most often occurs during placement (LE4). It is frequently diagnosed some time later, however (LE2). The risk factors include: ongoing breast feeding, placement less than 6 months after delivery, operator inexperience, and extreme uterine (ante- or retro-) version (LE2). Should any suspicion of perforation exist, pelvic ultrasound scans and plain abdominal radiography must be performed to locate the IUD (PC). The laparoscopic approach is preferred for removing an IUD that has migrated into the abdomen (PC).

Expulsion most often occurs during the first year after placement (LE1). Risk factors for expulsion include: age<20 years, menorrhagia, dysmenorrhea, myomas, adenomyosis, history of expulsion, and large transverse diameter of the endometrial cavity (LE2). The presence of the threads should be verified during the gynecologic examination during the follow-up visit in the weeks after IUD placement, and then annually (PC).

The copper IUD causes an increase in menstrual flow (LE1); the 52-mg LNG-IUD is accompanied by a reduction in menstrual flow or even amenorrhea (LE1).

It is necessary to inform women about the modifications in menstrual flow before IUD placement (grade A).

Regardless of the type of IUD, vaginal bleeding that is persistent or associated with pelvic pain requires supplementary exploration to identify the complication (PC) (24).

Intrauterine contraception is not a risk factor for an ectopic pregnancy (LE2). Nonetheless, should a pregnancy occur despite the IUD, it is appropriate to rule out an ectopic pregnancy (Grade B). A history of ectopic pregnancy is not a contraindication to IUD placement (Grade C).

A viable and wanted intrauterine pregnancy is a more important complication in the presence of an IUD (LE3); if the threads are accessible, the IUD should be removed (grade C).

Functional ovarian cysts are frequent during the use of a 52-mg LNG-IUD, but most often regress spontaneously (LE1). In asymptomatic patients, it is unnecessary to remove the device. A history of functional cysts is not a contraindication for LNG-IUD placement.

The presence of *Actinomyces-like* organisms on the PAP smear in an asymptomatic woman must not motivate supplementary exploration, early removal, or antibiotic treatment (grade B).

Intrauterine contraception does not appear to be a risk factor for upper genital tract infection (LE2) (25) except early (3 weeks to 4 months) after insertion. It is not recommended that the IUD be removed immediately after diagnosis of a sexually transmitted infection or an upper genital tract infection (grade B). If treatment does not produce a favorable outcome within 48–72 hours, removal of the device must be discussed (Grade B). A history of STIs or upper genital tract infection does not contraindicate the placement of an IUD at a time reasonably distant from the episode (PC).

8. Contraceptives for women with venous and arterial risk

Although the benefit-risk balance is most often favorable for contraceptives, the use of CHC is associated with harmful effects, principally vascular, which appeared quite rapidly after the use of the first combined oral contraceptive, developed by Jordan in 1960. These diseases are rare: the prevalence of venous thrombosis in France is estimated at 120,000 cases/year, divided between 78,000 deep vein thromboses and 42,000 pulmonary embolisms; 57% of them are in women. The incidence of hospitalization of women younger than 65 years with ischemic strokes in France is 21.9/100,000 and the incidence of their hospitalization with myocardial infarction (MI) is 16.9/100,000.

8.1. Venous thromboembolic risk

It is now clearly established that CHC use increases the risk of venous thromboembolism (VTE) by a factor of 3–6 compared with that of non-users (LE1) (26). A starter effect exists, since this risk is highest during the first year of use. Globally, this increase depends on the hormonal balance of the combination, related simultaneously to the type of estrogen (EE or 17 beta estradiol), the EE dose, and the specific progestin used (27). The results of studies comparing the risks of VTE associated with combination oral contraceptives containing 30 compared with 20 μg of EE are discordant. There is no evidence that these two doses induce different risks of VTE (LE2). The VTE risk of oral contraception combining estradiol and dienogest appears equivalent to that containing LVG/EE 150/30 (LE2). This risk has not been evaluated clinically for the oral contraceptives combining estradiol and nomegestrol acetate. Those containing third-generation progestins (gestodene or desogestrel), drospirenone, or cyproterone acetate are associated with a higher risk of VTD than those containing LVG (LE2), while those containing norgestimate are associated with a VTD risk similar to that of those containing LVG (LE2). The risk of VTD through non-oral administration routes of CHC is probably equivalent to the risk of the oral CHC containing third-generation progestins (LE2).

Family histories, especially of first-degree relatives (parents and siblings) or with a high number of relatives, regardless of the degree, and known thrombophilia are all risk factors for VTD, especially when the history occurred in a hormone-related context (estrogen–progestin treatment or pregnancy) (28).

Progestin-only contraceptives, orally or as implants or LNG-IUDs, are not associated with any increase in the risk of VTD,

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contrary to progestin-only contraception by intramuscular (IM) medroxyprogesterone acetate (RR 2.6, 95% CI 1.8–3.8) (LE1) (29).

It is recommended that physicians assess by history and clinical examination all vascular risk factors of VTD, including family history, before any prescription for combined hormonal contraception (PC).

Unless a family history of vascular disease exists, a work-up for thrombophilia is not recommended before the prescription of CHC.

A first-degree family history of VTD (from either the paternal or maternal side) with an onset before the age of 50 years is a contraindication to the use of CHC (grade B). CHC, regardless of the type or route of administration, is contraindicated for women with congenital laboratory-confirmed thrombophilia (grade B).

The first-line CHC prescribed for women without contraindications should contain either LVG or norgestimate (grade B).

A progestin-only contraceptive is recommended for women at high risk of VTD desiring hormonal contraception (grade B). Injectable depot medroxyprogesterone acetate (DMPA) contraception should not be prescribed for women at high risk of VTD (grade B).

Should a deep vein thrombosis or pulmonary embolism occur, combined hormonal contraception must be discontinued, in the absence of a risk of pregnancy during the current cycle. DMPA must not be renewed (PC). The available data are insufficient to justify a recommendation about the maintenance of progestin-only contraception at the acute phase of a venous thromboembolism.

8.2. Arterial disease risk and hormonal contraceptives

Numerous epidemiologic studies have assessed the association between the use of oral CHC and the risk of MI (30,31), for a pooled risk associated with the use of a CHC, regardless of its particular components, of 1.7 (95% CI 1.2–2.3 (30). When the type of progestin is taken into account, the risk of MI is higher among users of first-generation combined oral contraception compared with non-users (pooled OR 2.9, 95% CI 2.1–4.1) than with second- or third-generation users (respectively, pooled OR 2.1, 95% CI 1.7–2.4 and 1.8, 95% CI 1.6–2.1). These results are similar to those for ischemic stroke.

The most recent Cochrane review on this topic analyzed 24 epidemiologic studies, including the older ones (31); it showed that only combined oral contraception containing at least 50 mcg of EE is associated with the risk of arterial events (MI or ischemic stroke) (OR 2.0, 95% CI 1.3–2.9). This meta-analysis found no difference in risk between the generations of oral CHC. No risk difference appears between oral CHC containing 30 or 20 μg EE.

Only sparse data are available about CHC containing drospirenone, but they suggest that the risks of ischemic stroke and MI associated with their use are significantly higher than those for non-users (RR 1.64, 95% CI 1.24–2.18 and 1.65, 95% CI 1.03–2.63, respectively) (32).

In conclusion, there is no significant difference in the risk of arterial thrombosis between the generations of oral CHCs currently used in France (LE2). Data concerning the non-oral routes of administration — ring or patch — are insufficient for a valid conclusion. No epidemiologic study has assessed the arterial risk of contraceptives containing estradiol.

There is a dose-dependent synergistic effect of smoking (more than 15 cigarettes/day) in users of CHC vis-à-vis the risk of MI and probably that of ischemic stroke (LE2).

Oral CHC is contraindicated in women at high risk of arterial disease (grade B).

Among smokers, individual risk should be assessed according to the associated cardiovascular risk factors (Table 1) (grade B).

No significant increase in the risk of MI or ischemic stroke has been reported in the literature associated with the use of progestin-only contraception, whether oral (minipill) or as an implant or an LNG-IUD (32). In conclusion, progestin-only contraceptives, regardless of type, do not appear to be associated with arterial risk (ischemic stroke or MI) (LE2). The data concerning DMPA are quite sparse (LE3)

Contrary to the other methods of progestin-only contraception, DMPI, for injection quarterly, must not be prescribed to women with at least two cardiovascular risk factors or a history of arterial ischemic events (PC).

When an arterial event (MI or ischemic stroke) occurs, CHC must be discontinued, in the absence of a risk of pregnancy during the current cycle. Non-hormonal contraception must be preferred as a first-line treatment (PC).

8.3. Migraine and contraceptives

The absolute risk of ischemic stroke among women aged 20–44 years was assessed by a European consensus group, which found

Table 1
Arterial or venous vascular risk factors (VRFs) and use of combined hormonal (estrogen-progestin) contraception (CHC).

Risk factors	Use of CHC
Age > 35 years	Possible, if no other VRFs
Overweight – obesity	Possible, if no other VRFs
Smokes > 15 cig/day	Possible, if no other VRFs
1 st degree family history of MI or stroke before the age of 55 years (men) or 65 years (women)	Contraindication
Hypertension	Contraindication
Dyslipidemia	Contraindication
Uncontrolled	Possible, if no other VRFs
Controlled	Relative contraindication, if dyslipidemia began with CHC
Insulin-dependent (Type I) diabetes	Contraindication if diabetes > 20 years or if vascular complications
Type 2 diabetes	Possible, if no other VRFs but in second line (1 st choice: progestin-only contraception or copper IUD).
Migraine with aura	Contraindication
Migraine simple	Possible if no other VRFs

Venous risk factors	Use of CHC
Age > 35 years	Possible, if no other VRFs
Overweight – obesity	Possible, if no other VRFs
Laboratory-diagnosed thrombophilia	Contraindication
1 st degree family history of VTD (venous thromboembolic disease) before the age of 50 years	Contraindication

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that migraines with aura are associated with a stroke incidence of 5.9/100,000 vs 4.0/100,000 without aura, and 2.5/100,000 without migraines. The use of CHC increased these figures quite notably, especially for women with migraines, with respective increases to 36.9, 25.4, and 6.3/100,000 (LE1) (33).

These risks are still higher among women with other risk factors, smoking in particular.

Before a prescription of CHC, woman should be asked about any history of migraine and to distinguish between migraines with and without aura (grade A).

It is recommended that CHC not be prescribed to women who have migraines with aura (grade A) or to those with migraines without aura and with another vascular risk factor (grade A).

Non-hormonal contraception or progestin-only hormonal contraception should be recommended to women who have migraines with aura (grade B).

9. Contraception and cancer

9.1. Contraception and cancer risk

Globally, no increase in cancer incidence or mortality (all types) has been found in women using contraception (34).

A moderate increase in the risk of breast cancer is associated with ongoing use of CHC (LE1). This increased risk diminishes after cessation of its use (LE1). A moderate increase in this risk has also been reported with progestin-only contraceptives (LE2), including the LNG-IUD, albeit with contradictory data (LE2) (35). The data about the risk associated with DMPA and with progestins implants are scarce and do not allow any conclusions to be reached.

An increased risk of invasive cervical cancer (36) has been described in users of oral contraception, especially for prolonged periods of use, with an impact that appears to fade after cessation (LE2). Many biases make this analysis difficult, as HPV exposure and oral contraception use are not independent factors.

On the other hand, CHC is associated with a reduced risk of endometrial cancer, ovarian cancer (LE1), and malignant blood diseases (LE2), all reductions that persist after cessation; it is linked as well to a reduction in the risk of colorectal cancer (LE1) (34,36). A reduction in the risk of endometrial and ovarian cancer is also associated with LNG-IUD (LE3).

No increase has been found in the global risk of melanoma (LE2), hepatocellular carcinoma (LE2), thyroid cancer (LE2), bronchial cancer in nonsmokers (LE2), or CNS tumors (LE2) (34,36).

Data about the risks of cancer are an important part of the information provided to women who have neither cancer nor any particular risk factors. They do not, however, modify the prescription of contraception, as its benefits remain greater than its risks. The choice of contraceptive continues to depend on the individual benefit-risk balance, taking into account the increase in the absolute risk, which is variable and rises with age, as well as with individual and family history (PC).

There is no reason to modify the usual follow-up (Grade B).

9.2. Contraception during cancer treatment

A minimum interval of six months to one year after the end of treatment — and often more, depending on the oncologic context — is advised before envisioning a pregnancy.

Contraception is necessary during cancer treatment for all non-menopausal sexually active woman (PC).

The oncologic context sometimes limits the contraceptive choices, in relation to the immune situation, the thrombotic risk, and gastrointestinal tolerance of treatments.

In cases of immunosuppression (hemopathies, myélo-ablative treatment), condom use is recommended to limit the risks of STDs (grade A). In immunodepressed women, any IUD placement must be very prudent, because of the high risk of genital infection especially during the weeks after insertion. To minimize these risks, PCR testing for *Chlamydiae* and gonococci by PCR can be proposed before IUD insertion (PC).

The effectiveness of IUDs in this context has not been evaluated. An LNG-IUD, which has a mode of action independent of the inflammatory response, may be preferred (PC).

All prescriptions for CHC must consider all medication co-prescriptions and the risks of drug interactions (grade A).

Because treatments that induce vomiting can reduce the effectiveness of oral contraceptives, the use of hormonal contraceptive by implants, patches, or ring or non-hormonal contraceptives should be preferred.

Non-oral contraceptives must be preferred during treatments that induce vomiting (grade A).

Thromboembolic risk frequently increases during cancer treatment because of the disease itself, the chemotherapy, surgery, and immobilization. Because thromboembolic risks are increased by CHC, it is preferable to avoid their use throughout the treatment period, to avoid multiplying risks.

Macrodose progestins, that is, at an antigonadotropic dose, might be an interesting alternative for nonhormone-dependent cancers, for they could cause amenorrhea and thus avoid menorrhagia while limiting the risk of thromboembolism (37). GnRH agonists are also sometimes an (off-label) contraceptive solution during treatment.

It is preferable to avoid CHC throughout cancer treatment, to avoid multiplying the risks of thromboembolism (PC).

Reassessment of contraceptive choice is necessary in women diagnosed with cancer (PC).

9.3. Male antitumor treatment: are condoms necessary?

Two studies conducted before the turn of the century suggested that chemotherapy agents might be transmitted in seminal fluid (LE4).

The data are too limited to justify a recommendation for the routine use of condoms by men being treated for cancer, except when new antitumor agents are being evaluated in research protocols.

9.4. Contraception after cancer

Women who have previously been treated for cancer report receiving poor information and having inadequate contraceptive use (LE3). Late resumption of ovarian activity is possible (LE3).

Contraception must be routinely considered for all women who have undergone treatment for cancer who were not menopausal at diagnosis, including women with chemotherapy-induced amenorrhea (PC).

Because of the potential risk of relapse and the limited data available, hormonal contraceptives are contraindicated after breast cancer (LE4).

For women with a history of breast cancer, non-hormonal contraception must be preferred. Among these, the copper IUD must be considered to be the first-line contraceptive method due to its reversibility, its long duration of action, and it's very good effectiveness (PC). All hormonal contraceptives are contraindicated after breast cancer, regardless of the time since treatment, hormone receptor status, and the histologic type of cancer (ductal/lobular/invasive/in situ) (PC).

In cases of endometrial cancer, there are very few indications for conservative treatment that do not induce sterility, and they are reserved for very early stage tumors in young women who want to preserve their fertility (stage IA and grade 1 endometrioid tumors).

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The use of CHC, injectable DMPA, progestin-only contraception, and either a copper IUD or an LNG-IUD, is possible while awaiting treatment for endometrial cancer (LE4). The 52-mg LNG-IUD can be proposed as conservative treatment for atypical hyperplasia (LE1) or grade 1 endometrial adenocarcinoma (LE4).

CHC, DMPA, and progestin-only contraception can be used while awaiting treatment for endometrial cancer (PC).

Guidelines for contraception after rare malignant ovarian tumors were issued in 2017 by the national network for rare gynecologic cancers (TMRG/GINECO) (38).

After conservative treatment of borderline or germ-cell tumors, hormonal contraception, regardless of the type, is not contraindicated. After conservative treatment of an adult granulosa cell tumor, only contraceptives containing estrogens are contraindicated. After conservative treatment of a mucinous, high-grade serous or high-grade endometrioid adenocarcinoma, hormonal contraceptives, regardless of type, are not contraindicated. It is advised not to use hormonal contraceptives after treatment of low-grade serous or endometrioid adenocarcinomas (PC).

Guidelines for the management of malignant epithelial neoplasms of the ovary were published by CNGOF and approved by the national institute for cancer (INCA) at the end of 2018.

Interruption of any type of contraception on diagnosis of cervical intraepithelial neoplasms (CIN) or cervical cancer, while awaiting treatment is not recommended, in view of the positive benefit-risk balance in this situation (PC).

There is no evidence that contraceptive use, regardless of whether it is hormonal, combined, progestin-only, or by IUD, is contraindicated after conservative treatment of CIN or cervical cancer (PC).

For invasive cervical cancer, the data currently available do not justify guidelines concerning the use of hormonal contraception.

The literature contains no data about contraception after colorectal cancer. A reduction in the risk of colorectal cancer has been observed in users of oral contraception.

No evidence justifies limiting the use of hormonal or nonhormonal contraception after colorectal cancer (PC).

The data currently available do not justify the issuance of recommendations concerning hormonal contraception after a melanoma.

Although no data in the literature report an association between hormonal contraception and the risk of hepatocellular carcinoma, non-hormonal contraception should be preferred because of its potential impact on liver function (PC).

No evidence justifies limitation of the use of hormonal or non-hormonal contraception after thyroid cancer (PC).

The data currently available do not justify the issuance of recommendations concerning hormonal contraception after lung cancer (multidisciplinary decision) (PC).

The data are inadequate to contraindicate hormonal contraception for women who have had malignant central nervous system tumors (multidisciplinary decision, adapted by histologic subtypes) (PC).

Women who have received strong thoracic irradiation (especially for Hodgkin disease) have an excess risk of breast cancer. The impact of hormonal contraception on this risk has not been evaluated.

The data currently available do not justify the issuance of recommendations concerning hormonal contraception after thoracic irradiation.

9.5. Emergency contraception after hormone-dependent cancer (in particular, breast cancer)

Given the impact of pregnancy occurring during cancer treatment, all emergency contraceptives, including oral contraception, can be used after diagnosis of a hormone-dependent cancer (PC). Nonetheless, when possible, prudence requires preferring use of a copper IUD because it is non-hormonal (PC).

9.6. Contraception and family predisposition to cancer

1 Hereditary breast and ovary cancer syndrome (BRCA1/2) In 2017, INCa issued guidelines for the follow-up and management of women carrying the *BRCA1/2* gene mutation. These guidelines conclude that the' 'use of hormonal contraception, whether combined or progestin-only, and regardless of its route of administration, can be offered to women with the *BRCA1 or 2* mutation who do not have breast cancer" (grade A).
2 Lynch syndrome Lynch syndrome, also known as HNPCC syndrome (hereditary non-polyposis colon cancer), is a syndrome of susceptibility to cancers, transmitted as an autosomal dominant trait conferring a high risk of colorectal and endometrial cancers, but also of cancers of the ovaries, small intestines, upper urinary tract, hepatobiliary tract, and the stomach. There are currently no data that enable an assessment of the effectiveness of CHC, progestin-only contraception, or the LNG-IUD in preventing the risk of colorectal cancers in Lynch syndrome. A reduction of the risk of endometrial cancer in this syndrome has been described (LE4). Nonetheless, these data remain insufficient, and prophylactic surgery is currently considered the only effective method of prevention.

There is currently no specific contraindication to the use of hormonal or non-hormonal contraception in Lynch syndrome (grade B).

10. Hormonal contraception in practice (except LNG-IUD)

CHC can be administered orally, vaginally, or transdermally. Administration can also be continuous or discontinuous. All combined contraceptives have identical contraceptive effectiveness, regardless of their route of administration (LE1). The venous thromboembolic risk is greater for some estrogen–progestin combinations (LE1), especially when not administered orally.

The first-line combined contraceptives recommended for women preferring oral forms are those containing either LNG or norgestimate (grade A).

It is possible to offer extended or continuous administration of CHC for some medical situations (39) (e.g., menstrual symptoms, functional menorrhagia, and endometriosis), but also for personal convenience (grade B).

Progestin-only contraceptives are available for oral use, as a minipill, to be taken continuously, or as a subcutaneous implant, or as a macrodose by quarterly intramuscular injections.

The etonogestrel implant is a very effective means of contraception (LE2), including among obese women (maximum BMI assessed in these studies: 56 kg/m^2 (LE2) (40).

As a long-acting reversible contraceptive (LARC) method, the implant can — like IUDs — be proposed to women who want effective medical contraception with few constraints that impede adherence (grade B).

There is no reason to propose changing the etonogestrel contraceptive implant before 3 years for obese women using this method (grade B).

Generally, hormonal contraceptives are started the first day of a period. Quick start involves beginning a hormonal contraceptive at another moment of the cycle.

Quick start initiation of a hormonal contraceptive can be offered to all women who want it, after clear information about the precautions required (verify the absence of pregnancy, combine

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with a supplemental barrier method of contraception for 7 days and inform the woman about the risks of vaginal bleeding during the first month of administration) (grade A).

The most frequent side effects of hormonal contraceptives, especially progestins, are vaginal bleeding, acne, weight gain, and reduced libido; they create a risk of unplanned cessation. Vaginal bleeding while taking contraceptives is often associated with mediocre adherence, but can also be associated with an infection, endometrial pathology, or a functional cause (41).

A history should be taken and a complete examination performed for women with vaginal bleeding while using hormonal contraception. Other examinations (pelvic ultrasound, cytobacterial examination of leukorrhea) may be appropriate. An hCG assay must be performed when adherence appears poor or there is clinical suspicion of pregnancy (PC).

There is no solid evidence that any one combined oral contraceptive is better tolerated than any other.

In the case of poorly tolerated vaginal bleeding developing for at least 3 months and with no identified organic cause, changing the contraceptive is recommended. An increase in the estrogen dose, a modification of the type of progestin, or use of a non-oral form of CHC (patches or vaginal ring) can be envisioned. Neither modification of the progestin nor moving toward multiphasic formulations is recommended (grade C).

Given the absence of demonstrated effectiveness, it is not recommended to add an estrogen treatment or another medication for any vaginal bleeding developing for at least three months, with no identified organic cause, while taking a progestin-only oral contraceptive (PC) (42).

Should acne develop while taking a second-generation CHC, it seems reasonable to propose either a change of contraceptive or the association of a combination triphasic contraceptive containing 35 μg of EE and norgestimate (PC). Should that fail, a dermatologist's opinion to initiate a specific treatment for acne, and/or use of a CHC containing a different, anti-androgenic progestin, will also be discussed with the woman (PC).

Any reduction in libido while using hormonal contraception must be explored by questioning, in particular by assessing other psychological aspects of this complaint. A change of contraceptive can be discussed at the same time (LE3) (PC) (43).

Hormonal contraceptives are not associated with weight gain (LE2) (44).

The use of the subcutaneous etonogestrel implant or injectable DMPA may moderately increase the risk of weight gain, which is not, however, routine (LE2).

In the case of substantial weight gain, a complete work-up should be performed to search for another cause if appropriate (PC).

Headaches occurring with hormonal contraceptives may be a marker of vascular risk and require appropriate management.

The onset of *de novo* migraines or the aggravation of preexisting migraines while using CHC requires its permanent discontinuation (grade C).

Should menstrual migraines occur during the treatment-free interval while taking CHC, it is possible to suggest a continuous course of treatment (grade A). The percutaneous administration of fairly high-dose estrogen (minimum: 1.5 mg gel/day or patches dosed at 100 μg/24 h) during the treatment-free interval is an alternative to continuous CHC administration (grade C).

The other contraceptives do not appear to influence the natural history of migraines significantly (LE3).

Mood disorders have been described by women using hormonal contraception.

Data about the link between hormonal contraception and mood disorders are varied and contradictory. No solid evidence establishes that the use of hormonal contraception is a risk factor for mood disorders (LE2) (45,46).

Any change in mood while using hormonal contraception must be explored by questioning and assess in particular other psychological aspects of this complaint. A change in contraceptive can be discussed at the same time (LE3) (PC) (43).

11. Contraceptives for adolescents

The follow-up of adolescents taking contraceptives must integrate more specifically their general equilibrium with the stability of their weight and adequate calcium intake, at the same time that it does not forget STD prevention or vaccination against HPV. The use of condoms combined with the regular use of contraception is essential for their role as a barrier against STDs (LE1) (47).

The first visit for contraceptives is an essential moment with adolescents for providing sex education and advice on contraceptives to help them avoid unplanned pregnancy.

The patient is seen alone for at least a part of the visit to protect her confidentiality (LE2) (grade B) (48).

The clinical examination comprises: a general examination, height, body mass index, blood pressure, as well as looking for signs of hyperandrogenemia (acne, hirsutism). A gynecologic examination is not necessary at the first visit, unless a history or symptoms justify it (grade C) (49).

Women who use contraceptive methods other than condoms should be advised about condom use and the risk of STDs (grade A).

The abundant literature on preventive activities (groups, educational sessions, etc.) demonstrates their positive impact on STD prevention but also their lack of effect on unplanned pregnancy rates.

It appears important to give teens a real choice of contraception and to inform them objectively about the different methods of contraception (LE2). The very high effectiveness of LARC (LE1) is an important element of this information.

In the absence of any contraindications, if the first prescription is for a CHC, the progestin must be either LNG or norgestimate. It is not desirable to use the vaginal (ring) or percutaneous (patch) routes of administration as first-line contraception because both use third-generation progestins. Nonetheless, depending on the situation, the latter may be prescribed after a benefit-risk assessment. Adolescence is the age group in which vascular risk is lowest (LE1). For some experts, the benefit of a prescription of a pill with 30 mcg of EE may be more important, to ensure better protection in case of forgotten pills, especially for very young women, and also to maintain bone mineralization (LE4).

There is no evidence in the literature to justify proposing more specifically, except for specific contraindications, a more particular type of contraceptive to an adolescent. It is recommended that all of the modalities of contraception be presented together and then to proceed according to these guidelines (grade A). LARCs, such as IUDs and implants, are not contraindicated and have very favorable effectiveness profiles.

12. Contraceptives after the age of 40 years

The data in the literature and the levels of evidence for this age group, especially women older than 50 years, are limited. Different recent consensus statements and guidelines are available (50–52).

Despite the reduction in fertility with age, effective contraception remains necessary if pregnancy is not desired; pregnancies are at higher risk in this age group, and elective abortions for unwanted pregnancies more frequent.

The international literature agrees that CHC can be used by women 40 years and older, in the absence of a specific contraindication, because it can provide non-contraceptive benefits (possible prevention of bone demineralization, and diminution

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of menorrhagia, dysmenorrhea, and symptoms of the onset of estrogen deficiency) during this period of women's lives (LE3). No study provides evidence justifying strict contraindication of any particular contraceptive on the basis of age (50,51,53).

All progestin only contraceptives except DMPA can be proposed because of their neutrality vis-à-vis vascular risk factors. Nonetheless, quality of life can be impaired in this population because of spotting, potential aggravation of signs of hyper-estrogenism, and the failure to manage signs of hypo-estrogenism (LE3). DMPA in women older than 40 years has a harmful effect on vascular (54,55) (LE2 and 3), blood glucose, and bone (LE3) status.

The IUD is effective and well tolerated, especially after the age of 40 years (LE4).

Clinicians should inform women aged 40 years and older about fertility, the risks of pregnancy, and the vascular, metabolic, and carcinogenic risks (PC) to help them assess the benefit-risk balance of types of contraception.

The risks and benefits of oral contraception must be reassessed in women aged 40 years or older (PC).

Progesterone-only oral contraception can be offered as a first-line treatment for women after the age of 40 because of its lack of effect on vascular, metabolic, and bone indicators (PC), after information about the side effects.

DMPA is not recommended as first-line contraception in women older than 40 years, given its negative effect on vascular, glycemic, and bone indicators, especially for women with vascular risk factors, for whom it may be a contraindication (grade C) or a relative contraindication (for osteoporosis).

A copper IUD placed after the woman has turned 40 can be left in place until menopause (grade C).

The LNG-IUD is particularly appropriate for the treatment of menorrhagia, after exploration, or of the dysmenorrhea of peri-menopause (grade A).

An LNG-IUD placed after the age of 45 years can be left in place until menopause. Its benefits may extend to the menopausal period, combined with percutaneous estrogen (grade C).

Women must also be informed of the different barriers methods available to them. On the other hand, natural methods based on fertility awareness and knowledge of the period of ovulation, which becomes random over the years, are particularly unreliable among women older than 40 (grade C).

Emergency contraception (by progestins or a selective progesterone receptor modulator, SPRM) presents no specificities in this age group.

Permanent contraception, that is, sterilization, for the man or woman, can be interesting after the age of 40 years.

Above 50 years, the principal question is when contraception can be ceased (56).

Women using non-hormonal contraception should be advised to continue it until a full year of amenorrhea after they turn 50 (PC).

Cessation is essential for women still using CHC (PC).

Hormone assays are not recommended for women using hormonal contraception. A treatment window must be proposed while maintaining contraception by a barrier method (PC). In the absence of menopause, non-hormonal or progestin-only contraception (excluding DMPA) must be established (grade C).

Among women using progestin-only contraception (oral, subcutaneous, or intrauterine), a window can be proposed by maintaining contraception by the barrier method to confirm the persistence of ovarian activity.

13. Natural and barrier methods

Overall, 4.6% of women report using natural methods based on determination of their fertile period. The identification of these periods is based either on the observation of symptoms (Billings' cervical mucus method, the Two Day method, the Temperature method or the Symptothermal method) or by calendar methods, by calculating fertile days (Ogino-Knaus method, or the Standard Day method®) (LE3). The evidence of effectiveness for these methods is limited, with the quality of studies ranging from moderate to low (57).

Women should be informed of the lower effectiveness rates of these methods compared to hormonal contraception and IUDs (PC).

Women wishing to use these methods should be informed precisely how to use them, including that abstinence (no vaginal penetration) increases its effectiveness and that the use of a barrier method, which can be used incorrectly, reduces its effectiveness (grade B). Data about the reliability and effectiveness of LH peak monitors and detection kits are too limited.

The MAMA method is based on lactational amenorrhea, which corresponds to the anovulation induced by breast feeding in specific conditions (58).

Women using the MAMA method for contraception should be advised that its effectiveness is 98% until 6 month after birth if amenorrhea continues and if the breast feeding is exclusive (grade B).

They must be informed that the risks of pregnancy increase if they reduce the number of feedings (stop night feedings or introduce other food or a pacifier), after 6 months, or if they menstruate (Grade B).

The withdrawal method (coitus interruptus) requires that the man withdraw from the vagina and the genital area before ejaculation occurs. The sperm must not be in contact with the vagina or the vulva. Its effectiveness is low.

The withdrawal method is not recommended as a contraceptive method by itself or even as an alternative or back-up to barrier methods (PC).

Barrier methods are either physical (male and female condoms, cervical caps, and diaphragms), or chemical (spermicides), sometimes combined.

Condoms offer double protection — preventing unplanned pregnancy but also most STDs, including HIV. Their effectiveness is high compared with other barrier methods on condition of adherence to the strict rules for its use (LE2) (59,60).

Cervical caps and diaphragms must be left in place for at least 6 h after the last intercourse. They do not protect against STDs and HIV.

The effectiveness of spermicides used alone is low. Products made of nonoxynol-9 are not recommended because they can cause vaginal lesions that can increase the risk of HIV transmission (LE1) (61).

Healthcare professionals must provide patients with detailed information about how to use male and female condoms. For best effectiveness, it is recommended that cervical caps and diaphragms be used with spermicidal creams. The spermicidal gel must be applied for each instance of successive intercourse (grade B). Products based on nonoxynol-9 are not recommended (grade A).

Natural and barrier methods can be used as simultaneous or alternative back-up methods, especially when adherence to other methods is low. Their use is in any case preferable to the total absence of contraception. Only condoms (male and female) protect against most STDs and HIV.

Women should be performed of the existence and availability of emergency contraception.

14. Non-contraceptive benefits of contraceptives

14.1. Non-contraceptive benefits of CHC

These additional effects are similar regardless of whether the CHC is administered orally, vaginally, or transdermally. All induce

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anovulation and thus reduce exposure of the ovaries and endometrium to naturally occurring female hormones.

- Prevention of some cancers: CHC is associated with a protective effect against cancers of the endometrium (RR 0.76, 95% CI 0.73-0.78, $P < 0.0001$) (LE1) and the ovaries (RR 0.73, 95% CI 0.7-0.76, $P < 0.0001$)) (LE1) (34,36). This protection is positively correlated with duration of use and persists for more than 30 years after cessation of CHC. CHC is also associated with a reduction in the risk of colon cancer (RR 0.81, 95% CI 0.72-0.92) (LE1). It is recommended that physicians provide women with information about protective effects vis-à-vis endometrial, ovarian, and colon cancer as part of their responses to women's questions about the cancer risk associated with CHC (grade A).
- Menstrual cycle disorders CHC reduces the volume of functional menorrhagia (LE1) (41) and improves dysmenorrhea (LE1) (62) and premenstrual syndrome (LE1). It is recommended that CHC be offered to women who want contraception and report menorrhagia, dysmenorrhea, or premenstrual syndrome, after clinical evaluation of these disorders and in the absence of any contraindications to CHC (grade A).
- Endometriosis The role of CHC in the management of painful endometriosis and in the prevention of postoperative recurrence was discussed again during drafting of the recent CNGOF guidelines (approved by the HAS (63); this class is a first-line treatment among the hormone therapies. Its effects are observed under treatment and disappear when it stops. The literature is insufficient to specify the benefits of its continuous administration in women with painful endometriosis, except in situations involving surgery or intense dysmenorrhea. CHC is recommended as a first-line treatment in the medical management of painful endometriosis (grade B). Unless pregnancy is desired, prescription of a postoperative hormonal therapy is recommended to reduce the risk of painful recurrence and to improve the woman's quality of life (grade B). CHC is indicated to reduce the risk of recurrence of surgically resected endometriomas (grade B). Continuation of CHC is recommended for as long as tolerance is good and the woman does not want to become pregnant (grade B). In women with dysmenorrhea, continuous CHC prescription must be preferred (grade B). In view of the thromboembolic risk, the good practice rules for CHC must be followed (grade B)
- Benign diseases of the breast and the uterus A reduction in the incidence of fibrocystic breast changes without atypia and of breast fibroadenoma (RR 0.64, 95% CI 0.47-0.87) has been associated with CHC use and is correlated with its duration (LE3). Similarly the incidence of myomas has diminished in CHC users (OR 0.3, 95% CI 0.2-0.6), a reduction proportional to duration of use (LE3). Benign breast and uterine lesions are not per se indications for CHC, nor is it automatically contraindicated (in the absence of atypia). The individual benefit-risk balance must be assessed (grade C).
- Rheumatoid arthritis The use of CHC for at least 7 years is associated with a reduction of around 20% in the incidence of rheumatoid arthritis (OR 0.84, 95% CI 0.74-0.96). The longer the use of CHC, the greater the risk reduction (LE3).
- Acne CHC is clinically effective against acne, although its effectiveness compared with that of other treatments is controversial (LE1) (64). Its effect stops with the cessation of CHC treatment. In 2015, the French Society of Dermatology issued guidelines specific for acne that do not take a position on CHC as a first-line treatment in view of the benefit-risk balance (65).

In the absence of contraceptive needs, the first-line prescription of CHC for acne treatment is not recommended (grade A).

14.2. Non-contraceptive benefits of progestin-only contraceptives

This section on progestin-only contraception considers only those authorized for marketing as contraceptives: minipills of LNG or desogestrel, etonogestrel implants, and DMPA.

Intrauterine systems with LNG (52-mg LNG-IUD) are considered with IUDs.

Generally very few studies have evaluated the potential noncontraceptive benefits of progestin-only contraception, and their level of evidence is low.

The CNGOF 2017 clinical practice guidelines (63) specified the role of progestins in women with endometriosis.

Progestin-only contraceptives can be proposed in second-line for the management of painful endometriosis for women who do not want to become pregnant for whom CHC is contraindicated (grade B/C).

No study has assessed the action of progestin-only contraceptives in the medical treatment of myomas. The only study of the risk of myomas in users of progestin-only contraceptives (LE4) suggests that risk is lower in present or past users of DMPA.

No study has assessed the action of minipills or of the etonogestrel implant on the reduction of menorrhagia, all causes combined. Two randomized studies (LE3 and LE4) suggest that the effect of the 52-mg LNG-IUD is superior to that of DMPA or of the usual medical treatments.

No study has examined the preventive or treatment activity that microprogestin contraceptives might possibly have on functional uterine bleeding.

Several small prospective studies show a modest increase in hemoglobin among users of the etonogestrel implant.

14.2.1. Dysmenorrhea

The etonogestrel implant and continuous desogestrel contraceptives may diminish dysmenorrheic pelvic pain (LE2) or chronic pelvic pain for venous congestion (implant only) (LE3/4).

The non-contraceptive beneficial effects of progestin-only contraception, either oral or implants, are not evident. The studies are sparse and their level of evidence is low. It is especially difficult to determine in advance which women might possibly benefit, as the reaction, especially of hemorrhage, can be contrary to that sought.

14.3. Non-contraceptive benefits of the LNG-IUD

These benefits have been well demonstrated for many diseases, so that the LNG-IUD must be considered simultaneously as contraception but also as a true therapeutic agent. Its marketing authorization takes this particularity into account and the 52-mg LNG-IUD is already included in some recommended treatment regimens (41,63).

Most studies have assessed the LNG-IUD for its therapeutic activity. Fewer studies have assessed its beneficial effects during use for contraception. They confirm its interest for women with some symptoms of pain or excessive bleeding.

14.3.1. Menorrhagia

For women with menorrhagia, the LNG-IUD is the treatment with the most benefits in terms of quality of life and leads to the fewest complications. The risk of complication is twice as high in women treated by endometrectomy, which is also less effective (LE1) (66).

The LNG-IUD is thus notably effective in the treatment of menorrhagia and in the prevention of anemia.

- Dysmenorrhea: The use of a 52-mg LNG-IUD is associated with a significant reduction in the severity of dysmenorrhea, compared

with the use of non-hormonal contraceptives (LE3). The 52-mg LNG-IUD is recommended for its contraceptive activity as well as its beneficial effects on menorrhagia and dysmenorrhea, which should nonetheless be explored before this prescription. Any prescription requires the woman's informed choice (grade B).
- Endometriosis The LNG-IUD reduces pain scores in women with endometriosis that has not been treated surgically (LE2) and diminishes the risk of painful recurrence and improves quality of life in women after surgery (LE2), with an effect similar to that of GnRH analogs (GnRHa) (LE1) (63).

For women who do not want to become pregnant, the contraceptive use of LNG-IUD is recommended as first-line treatment, equally with CHC, after surgery for painful endometriosis (grade B).

14.4. Beneficial non-contraceptive effects of copper intrauterine devices

The beneficial noncontraceptive effects of copper IUDs reported in several publications have focused on two effects:

- reduction in the risk of endometrial cancer (67), although the mechanism of action has not been elucidated (LE2);
- cofactor in protection against epidermoid or adenomatous cervical cancer (LE2) (68), an effect that may be greater in the population at risk (LE2) (69).

IUDs may play a role in the natural history of cervical cancer, by inhibiting the development of precancerous cervical lesions in women infected by Papillomavirus or by improving their clearance.

The use of the copper IUD is associated with a significant reduction in the risk of endometrial and cervical cancers (LE2). This action is nonetheless not sufficient to justify a recommendation for its use for prophylactic purposes alone (PC).

15. Conclusion

Research related to contraceptives is developing in many directions to improve their tolerability for as many women as possible and to improve their continuity. This research involves new methods of administration, new compounds, and new combinations. Some are already in use in some countries. Let us note (but this list is not exhaustive and continues to change):

- decrease in the dose of ethinyl estradiol to 10 micrograms
- introduction of a new "natural" estrogen (estetrol)
- shortening, or even elimination, of the treatment-free interval, with or without placebo
- injectable CHC (estradiol cypionate + medroxyprogesterone acetate)
- new transdermal systems with a progestin such as LNG or gestodene
- vaginal ring, with a one-year duration of activity.
- over-the-counter availability of progestin-only contraception.

The search for contraceptive vaccines appears stalled today, as is that for male contraceptives, which in practice remain limited to barrier contraception (condom) or permanent sterilization (vasectomy). The future of contraception, to the extent we can anticipate it today, lies above all else in the good use of the means that are already available. The objective of these CNGOF clinical practice guidelines is to aid in enabling this good use.

Declarations of interests

NCB reports consultant activities for TEVA, Gedeon Richter, and HRA Pharma. AA reports relationships with Gedeon Richter, Bayer, and MSD. TL reports relationships with CCD, MSD, Gedeon-Richter, HRA Pharma The other authors report no relationships.

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