

Consensus

Hormonal contraception in women at risk of vascular and metabolic disorders: Guidelines of the French Society of Endocrinology

Contraception hormonale chez la femme à risque vasculaire et métabolique : recommandations de la Société française d'endocrinologie

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Abstract

Hormonal contraceptive methods are widely used in France, including not only oral estrogen–progestin combinations but also non-oral estrogen–progestin delivery methods (patches, vaginal rings), as well as oral forms, implants and intra-uterine devices that deliver only a progestin. Hormonal contraception has only a modest impact on lipid and carbohydrate metabolism, but estrogen–progestin contraceptives have been linked to a variety of vascular risks. Overall, the risk of venous thrombosis is multiplied by a factor of about 4, depending on age, the compounds used, and other risk factors (including biological thrombophilia and a personal history of thrombosis), whereas the risk of arterial events is only increased in women with risk factors. Available data suggest there is no excess risk with progestin-based contraceptives, but far fewer studies have been conducted. At the initiative of the French Society of Endocrinology, an expert group met in 2010 in order to reach a consensus on the use of hormonal contraceptive methods in women with vascular or metabolic risk factors, based on available data and international guidelines published by WHO in 2009 and subsequently adapted to the United States context. The following text, intentionally limited to hormonal contraception, is intended to serve as a guide when prescribing in specific clinical situations, such as a family or personal history of arterial or venous thromboembolism, or the existence of cardiovascular risk factors (hypertension, smoking, diabetes, dyslipidemia, obesity).

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Résumé

Le recours aux méthodes contraceptives hormonales est très répandu en France, incluant principalement les pilules estroprogestatives, mais également les contraceptions estroprogestatives par voie non orales (patch, anneau vaginal) et les contraceptions progestatives par voie orale, implant ou dispositif intra-utérin. L'influence de la contraception hormonale sur le métabolisme lipidique et glucidique est modeste, mais différents risques vasculaires ont été rattachés à l'utilisation des contraceptions estroprogestatives. Le risque de thrombose veineuse est ainsi globalement multiplié par quatre, plus ou moins marqué en fonction de l'âge, des molécules utilisées et des autres facteurs de risque (notamment les thrombophilies biologiques, les antécédents personnels de thrombose), tandis que le risque d'événement artériel se trouve uniquement majoré chez les femmes présentant des facteurs de risque associés. Concernant les contraceptions progestatives, les données ne montrent pas de sur-risque, mais sont malheureusement nettement moins nombreuses. À l'initiative de la Société française d'endocrinologie, un groupe d'experts s'est réuni en 2010 dans le but d'élaborer un consensus guidant l'utilisation des méthodes contraceptives hormonales dans les situations de risque vasculaire ou métabolique, sur la base des données disponibles et des recommandations internationales publiées par l'OMS en 2009, secondairement adaptées au contexte des États-Unis. Ce texte, volontairement limité à la contraception hormonale, se présente donc comme un outil d'aide à la prescription dans des situations cliniques particulières, telles que les antécédents familiaux ou personnels de maladie thromboembolique veineuse ou artérielle, ou l'existence de facteurs de risque cardiovasculaire (hypertension artérielle, tabagisme, diabète, dyslipidémie, obésité).

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1. Introduction

In France, the latest epidemiological data confirm that a very large proportion of women use medical contraception. According to a large national survey conducted in 2005 [1], three in four women aged from 15 to 49 years use contraception, based on medical methods in 82% of cases. Despite this broad coverage, contraceptive failure is frequent: in France, one-third of pregnancies are unplanned and 40% of women resort to abortion at least once during their reproductive life.

As a result, contraception must be effective and simple to use, meet women's and couples' preferences, and pose a minimal threat to health. The vascular risks potentially associated with the use of hormonal contraception, including both venous thromboembolism and rarer arterial events (especially stroke), are a current focus of attention. The situation is particularly preoccupying, as the prevalence of vascular risk factors among women is growing rapidly.

In 2009 the World Health Organization (WHO) published an international guideline on the prescription of contraception in various situations, taking into account the level of exposure to known risks [2]. The WHO classification comprises four levels: level 1 corresponds to situations with no restrictions, and level 4 to those posing an unacceptable risk. At level 2 the benefits outweigh the risks, whereas at level 3 the risks outweigh the benefits.

At the request of the French Society of Endocrinology, a group of experts was convened to reach a consensus on hormonal contraception for women with metabolic and vascular risk factors. After examining all published studies of the impact of hormonal contraception on the vascular risk, the expert group prepared a consensus statement based largely on the 2009 WHO recommendations [2] and their adaptation to the United States context in 2010 [3], while adapting certain criteria to the specific French situation.

2. Hormonal contraception in France: the present situation

In France, the vast majority of women of childbearing age use contraceptive methods. Who are these women? What are the

most commonly used methods? How is efficacy and safety guaranteed? These and other questions are important when assessing quality of care in the field of family planning. The first part of this document summarizes current trends and remaining issues in the field of contraception, focusing on hormonal methods, the most popular in France.

2.1. Trends in contraception in France over the past three decades

The advent of highly effective contraceptive methods, legalized in France in 1967, marked a turning point for society by allowing French women to control their fertility. These methods, and especially “the pill” [4], have been highly successful, leading to rapid uptake [5].

Over the past three decades the proportion of women using the pill rose from 28% to 45% in the 20- to 44-year age group, while the use of intra-uterine devices grew by 8%, from 9% to 17% of the female population. Conversely, the use of local “barrier” methods fell from 31% to 12% during the same period.

According to the Health Barometer study, a large national survey conducted in 2005, 72.1% of the 14.3 million French women aged from 15 to 49 years used contraception (Table 1) [1]. These figures do not directly reflect unmet contraceptive needs. Indeed, 94.8% of the 4 million non-users did not need contraception, for reasons such as ongoing pregnancy, the desire to conceive, infertility, or a lack of sexual activity [1]. However, it is estimated that 207,000 women potentially at risk of unwanted pregnancy

Table 1
Number of women of child-bearing age in France, and proportion of women who use contraceptive methods [1].

| | Number of women (millions) | % |
|--|----------------------------|------|
| 15–49 years | 14.35 | 100 |
| 15–49 years at risk of unwanted pregnancy | 10.51 | 73.2 |
| Contraceptive users | 10.35 | 72.1 |
| Contraceptive non users | 4.0 | 27.9 |
| Women at risk who do not use contraception | 0.21 | 2.0 |

Table 2
Distribution of contraceptive methods used by women aged 15 to 49 years in France [1].

| Method | Number of users | % of users |
|----------------------|-----------------|------------|
| Pill | 6.1 million | 59.2 |
| IUD (levonorgestrel) | 0.98 million | 9.5 |
| Implant | 134,550 | 1.3 |
| IUD (copper) | 1.48 million | 14.3 |
| Condoms | 1.17 million | 11.3 |
| Withdrawal | 113,850 | 1.1 |
| Periodic abstinence | 41,400 | 0.4 |
| Spermicides | 72,450 | 0.7 |
| Sterilisation | 183,195 | 1.77 |

are not using contraception [1]. These women represent 2% of the population considered “at risk”, as they are sexually active and are not pregnant or do not wish to conceive.

2.2. Current use of hormonal contraception

Hormonal contraception is the most popular method in France (Table 2): more than 7 million French women use hormonal contraception, primarily the pill (6.1 million), or less frequently a subcutaneous implant or intra-uterine device (IUD) based on levonorgestrel (although use of this method is progressing). The choice of contraceptive method varies with age (Fig. 1) [4], following a fairly clear pattern, with condom use in early sexual life, followed by the pill during stable relationships, and ending with an IUD when the desired number of children has been reached [6].

2.3. A high rate of unwanted pregnancies

Despite the widespread use of efficient contraceptive methods, each year there are about 350,000 unwanted pregnancies in France, representing one-third of all pregnancies [7,8]. Of these, 62% end in abortion, representing 21% of the total number of pregnancies in France [8].

Unwanted pregnancies leading to abortion do not only concern young women wishing to postpone parenthood, but also older women who do not wish to have more children or who want to space their births [9]. Thus, 39% of abortions involve women under 25 years of age, but 38% concern women aged 30 years or more.

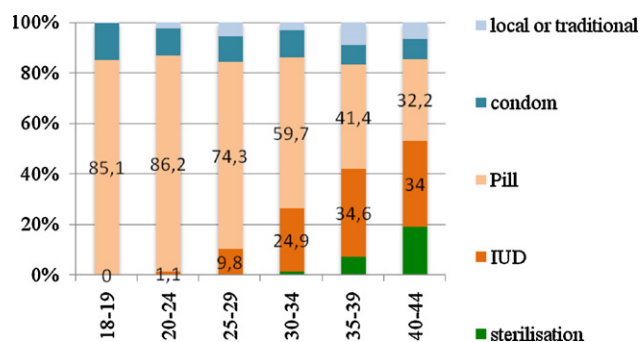


Fig. 1. Contraceptive options according to age in the general population [4].

The three main factors contributing to this large number of unwanted pregnancies are a lack or discontinuation of contraception, a high rate of contraceptive failure, and use of less effective methods [10]. A large survey of women representative of those seeking abortion in France in 2007 showed that only one-third of cases involved the minority of women who were exposed to this risk and were not using contraception (less than 3% of women of childbearing age) [11]. Two-thirds of abortions would therefore be due to contraceptive failure [11]. These pregnancies are not limited to women who use natural or barrier methods, but also those using safer methods, particularly the pill, because of problems with adherence [11].

2.4. Choice of contraceptive method

Effectiveness, convenience and safety are the three factors that physicians should take into account when providing women with the information needed to make an informed choice of contraceptive method.

2.4.1. Contraceptive efficacy

The high rate of unwanted pregnancies associated with contraceptive failure reflects everyday problems in the management of certain contraceptive methods. These difficulties explain the large differences in the failure rates of the different methods in optimal conditions versus real-life use [12,13]. The failure rate during optimal use is defined as the probability of conception during a 1-year period when users follow rules based on clinical studies with close monitoring. The real-life failure rate is estimated from cohort studies in which respect of these rules varies among participants.

The failure rate is typically higher with methods requiring daily adherence, such as oral contraceptives, than with long-acting methods that are easier to use [10]. However, all hormonal contraceptives are more effective than natural and barrier methods. Finally, there is no evidence that the failure rate is influenced by the composition of contraceptive pills, although, theoretically, constraints related to the use of progestin-based contraceptives might lead to greater difficulties.

2.4.2. Acceptance of contraception

The rate of contraceptive discontinuation (including changes in method) among women who remain at risk of unwanted pregnancy can be considered to indicate the acceptability of a method and its ease of use. Transient or prolonged contraceptive discontinuation contributes significantly to the occurrence of unwanted pregnancies [14]. The rate of discontinuation for reasons directly related to the contraceptive method (excluding pregnancy, the desire to conceive, infertility, and lack of sexual activity) is directly dependent on the method used. According to data from the Cocoon cohort, 11% of IUD users, 20% of women on the pill and 30% of women using natural or barrier methods discontinue their chosen method during the first year, although they still need contraception (even though the utility of this contraceptive approach is still justified) [14]. In addition, the discontinuation rate tends to increase as the dose of estrogen in oral combined contraceptives decreases. These results are

Table 3
Oral contraceptive estrogen–progestin combinations available in France.

| Brand name | Dose of EE (µg) | Progestin | Generation | Sequence |
|--|---------------------|-----------------------|------------|------------------------------|
| Triella® | 35 | Norethisterone | 1 | Triphase |
| Stediril® | 50 | Norgestrel | 2 | Monophase |
| Minidril®/Ludeal® Ge/Zikiale® | 30 | Levonorgestrel | 2 | Monophase |
| Adepal®/Pacilia® | 30–40 | Levonorgestrel | 2 | Biphase |
| Trinordiol®/Daily® Ge/Amarance®/Evanecia® | 30–40 | Levonorgestrel | 2 | Triphase |
| Leeloo®/Lovavulo® | 20 | Levonorgestrel | 2 | Monophase |
| Triafemi®/Tricilest® | 35 | Norgestimate | 3 | Triphase |
| Cilest®/Effiprev® | 35 | Norgestimate | 3 | Monophase |
| Melodia®/Minesse® | 15 | Gestodene | 3 | Monophase/continuous |
| Harmonet®/Meliane®/Carlin®/Felixita®/Efezial® | 20 | Gestodene | 3 | Monophase |
| Cycleane 20®/Mercilon®/Desobel G® | 20 | Desogestrel | 3 | Monophase |
| Cycleane 30®/Varnoline®/Desobel G® | 30 | Desogestrel | 3 | Monophase |
| Minulet®/Moneva®/Efezial®/Felixita®/Carlin 30® | 30 | Desogestrel | 3 | Monophase |
| Varnoline continu® | 30 | Desogestrel | 3 | Monophase 21 tabs +7 placebo |
| Phaeva®/Perleane®/Triminulet® | 30–40 | Gestodene | 3 | Triphase |
| Belara® | 30 | Chlormadinone acetate | Other | Monophase |
| Diane 35®/Evepar®/Holgyeme®/Lumalia®/Minerva® | 35 | Cyproterone acetate | | Monophase |
| Jasmine®/Convuline®/Drospibel 30 | 30 | Drospirenone | Other | Monophase |
| Jasminelle®/Belanette®/Drospibel® 20 | 20 | Drospirenone | Other | Monophase |
| Jasminelle® continu | 20 | Drospirenone | Other | Monophase 21/7 placebo |
| Yaz® | 20 | Drospirenone | Other | Monophase 24 tabs/4 placebo |
| Qlaira® | E valerate (1–3 mg) | Dienogest | | Quadriphase |
| Zoely® | E (1.5 mg) | Nomegestrol acetate | | Monophase |

consistent with the findings of a recent analysis of randomized controlled trials, indicating that oral combined contraceptives containing more than 20 µg of estrogen are associated with a lower discontinuation rate than those containing lower amounts [15]. Although the majority of women quickly resume contraception after abandoning a given method [14], these transition periods, even when brief, place them at a significant risk of unwanted pregnancy. This is a major concern, as several studies have emphasized that a significant proportion of women who stop taking the pill opt for a less effective method or discontinue all contraception [16,17].

2.4.3. Safety

It is important to strike a balance between the benefits and risks associated with a given contraceptive method, so that each woman can make an appropriate choice, based on acceptability and long-term efficacy and safety.

Contraceptive use may be deleterious in certain medical situations, either because the contraceptive method exacerbates an underlying condition, or because an underlying condition and/or its treatment reduces its effectiveness. In particular, the rapidly increasing number of women who develop vascular risk factors while still of childbearing age poses serious problems for the choice of contraceptive strategy. Indeed, women with an increased cardiovascular risk need effective contraception in order to avoid potential complications of pregnancy. Moreover, effective methods, especially those based on hormone delivery, may increase the vascular and metabolic risk, and particularly vascular events.

To address these public health issues, WHO, in conjunction with a consortium of healthcare agencies involved in family planning, recently issued guidelines on the choice of

contraception. Based on an exhaustive analysis of the literature, these recommendations examine, among other situations, the potential use of different contraceptive methods according to a woman's risk profile for various conditions, including vascular and metabolic disorders [2].

3. Hormonal contraceptive methods available in France in 2010

The Pill celebrated its 50th anniversary in 2010. Since its initial development by Pincus, the dose of ethinyl estradiol (EE) has declined over the years with the aim of reducing the risk of vascular events, especially thromboembolism. In 2010, hormonal contraceptives were widely used in France, and oral combined contraceptives remained most popular.

3.1. Oral combined contraceptives

Until recently, the estrogen used in all oral combined contraceptives was EE, except for two products. The first (Qlaira®), available since 2009, contains estradiol valerate (EV) and the second (Zoely®), released in late 2011, contains 17β-estradiol (E). The dose of EE varies in the different types of pill, from 50 to 15 µg per day, while the dose of EV is between 1 and 3 mg and the dose of E is 1.5 mg. The discovery of new progestins has led to a gradual reduction in the EE dose (Table 3).

Progestins of the norsteroid family are classified as first-generation (lynestrenol and norethisterone), second-generation (levonorgestrel and norgestrel), or third-generation (gestodene, norgestimate, desogestrel). The generation of progestin determines the generation of the pill. Progestins belonging to other classes are also used in conjunction with EE or E, including

Table 4
Oral macrodose progestin-only contraceptives available in France.

| Class | Drug | Available doses (mg) | Antigonadotropic doses (mg 21d/28) |
|--------------------------------------|-----------------------|----------------------|------------------------------------|
| Pregnanes (progesterone derivatives) | Chlormadinone acetate | 2, 5 and 10 | 10 |
| | Medrogestone | 5 | 10 |
| | Cyproterone acetate | 50 | 50 |
| Norpregnanes | Nomegestrol acetate | 3.75–5 | 5 |
| | Promegestone | 0.25–0.5 | 0.5 |

chlormadinone acetate (Belara[®]; EE), cyproterone acetate (Diane[®]; EE), drospirenone (Jasmine[®], Jasminelle[®], Yaz[®]; EE), dienogest (Qlaira[®]; EV) and nomegestrol acetate (Zoely[®]; E).

Oral combined contraceptives can also be classified according to the monthly sequence of hormone administration. In monophasic products, all the month's tablets contain the same dosage of steroids, while biphasic and triphasic pills contain two or three different hormonal combinations each month. In the latest monthly schedules, the number of active tablets has been increased in order to limit escape phenomena, especially if the patient forgets to start a new pack. Moreover, some products contain four to seven placebo pills to ensure continuous dosing, thus limiting the risk that the patient will forget a daily dose. Estrogen–progestin combinations can also be administered by non-oral routes. Thus, a vaginal ring delivering EE and etonogestrel (NuvaRing[®]) has been available since 2004. This device is inserted for three weeks. Patches containing EE and norelgestromin (Evra[®]) are another alternative; a fresh patch is used each week for three consecutive weeks per month.

3.2. Progestin-based contraception

Two types of oral microdose progestin contraceptives are currently available: levonorgestrel (0.03 mg per tablet, Microval[®]) and desogestrel (0.075 mg per tablet, Cerazette[®]). Macro-dose progestin pills, although widely used in France, are not licensed for contraceptive purposes; however, they have a contraceptive effect when administered 21 days per month. These progestins are divided into two distinct classes: pregnanes and norpregnanes (Table 4). Pregnanes, such as chlormadinone acetate, medrogestone and cyproterone acetate, are progesterone derivatives. Norpregnanes, such as nomegestrol acetate (NOMAC) and promegestone, are 19-norprogesterone derivatives.

Progestins used for contraceptive purposes can also be administered by non-oral routes. An implanted device that delivers etonogestrel for three years (Nexplanon[®]) has been available since 2001, and its new formulation is radiopaque. There is also an intrauterine device, marketed since 1997, that releases levonorgestrel for 5 years (Mirena[®]). Quarterly intramuscular injections of medroxyprogesterone acetate are widely used in many countries but rarely in France.

3.3. Emergency contraception

Although highly valuable, emergency contraception should only be used as a second-line option, never as a regular contraceptive method. Two types of drug are now available for this purpose in France. The first, available since 1999, contains 1.5 mg of levonorgestrel (Norlevo[®] or Vikela[®]). It is now sold as a single tablet to be taken within 72 hours of unprotected intercourse. The second product for emergency contraception (Ellaone[®]), first marketed in 2010, contains 30 mg of ulipristal acetate. This pill contains a new class of contraceptive drug (selective progesterone receptor modulator) and can be administered for up to five days after intercourse.

Thus, over 40 hormone-based contraceptive methods are currently available in France, and it is therefore important to determine the best options for women with known metabolic or vascular risk factors.

4. Hormonal contraception and the vascular risk

4.1. Combined hormonal contraception and the risk of venous thromboembolism

Overall, combined estrogen–progestin oral contraceptives are associated with a 4-fold increase in the risk of venous thromboembolic events [18–21], although the annual incidence remains low (<0.5 per thousand). This risk depends on the estrogen dose: it is higher at daily EE doses of 50 µg than at 30 µg, while more data are needed on pills containing 15 to 20 µg of EE [18–20] (Table 5). The risk also varies with the type of progestin combined with EE: by comparison with second-generation progestins, at identical doses of EE (30 µg), the risk is higher with third-generation progestins and also with specific progestins such as cyproterone acetate and drospirenone [18–24] (Table 6). Clotting factor abnormalities (decreased protein S and antithrombin levels, acquired resistance to activated protein C) are observed in women using oral combined contraception, lending biological plausibility to the increased risk of venous thrombosis [25–30]. Sex hormone binding globulin (SHBG) levels, that reflect the estrogenic climate induced by estrogen–progestin combinations, are higher with third-generation progestins, cyproterone acetate and drospirenone than with second-generation progestins [31–34].

Table 5
Risk of venous thromboembolism according to EE dose. Age-adjusted ORs (95% CI) [18].

| EE dose (μg) | Users (%) | Levonorgestrel | Gestodene | Desogestrel |
|--------------|-----------|----------------|---------------|---------------|
| 20 | 11.2 | 1.1 (0.4–3.1) | 0.3 (0.2–0.7) | 0.7 (0.4–1.2) |
| 30 | 84.4 | 1 | 1 | 1 |
| 50 | 4.4 | 2.2 (1.3–3.7) | | |

Thus, SHBG is also considered a thrombotic risk marker [35].

The risk of venous thromboembolism is higher during the first year of use [18,21]. Several predisposing factors can modulate the thrombogenic effect of hormonal contraception. Indeed, the risk of venous thromboembolism associated with combined hormonal contraception increases significantly with age, particularly beyond 40 years [19] (Table 7), but also in women with a personal history of deep vein thrombosis or pulmonary embolism [36], inherited thrombophilia (risk multiplied by a factor of 5 to 16) [37], or other risk factors for thrombosis (obesity, post-partum, surgery, immobilization, long journeys) [19].

Combined contraceptives delivered by non-oral routes (patches, vaginal rings) also increase the risk of thromboembolism (by a factor of 3 to 4) [38,39], and affect various clotting parameters [34,40–43]. Thus, as with oral administration, these products significantly modify circulating antithrombin and protein S levels, and resistance to activated protein C, and also increase plasma SHBG concentrations [34]. Although the adverse effects of new pills containing estradiol are not yet fully known, it is possible that oral intake of EV or E is associated with some degree of venous risk.

Table 6
Risk of venous thromboembolism observed during the first year of contraception based on EE 30 to 40 μg combined with various progestins [19].

| Progestin | Venous risk OR (95% CI) |
|-----------------------|-------------------------|
| Levonorgestrel | 1.91 (1.31–2.79) |
| Norgestimate | 3.37 (2.38–4.76) |
| Gestodene | 4.38 (3.65–5.24) |
| Desogestrel | 5.58 (4.13–7.55) |
| Cyproterone acetate | 6.68 (4.50–9.94) |
| Drospirenone | 7.90 (5.65–11.0) |
| No oral contraception | 1 |

Table 7
Risk of venous thromboembolism associated with oral combined estrogen–progestin contraception according to age [19].

| Age (years) | Yearly incidence in non users (per 10,000 women) | Relative risk (95% CI) | Yearly incidence in users (per 10,000 women) |
|-------------|--|------------------------|--|
| <30 | 1.2 | 3.1 (2.2–4.6) | 3.7 |
| 30–40 | 2.0 | 5.0 (3.8–6.5) | 10.0 |
| 40–50 | 2.3 | 5.8 (4.6–7.3) | 13.3 |

4.2. Progestin-only contraception and the risk of venous thromboembolism

Six studies, conducted mostly in Europe but including one conducted by WHO on several continents, were published prior to 2002. A first meta-analysis that included only four of these studies evaluated the risk of venous thromboembolism (deep vein thrombosis of lower limbs, pulmonary embolism, or cerebral venous thrombosis) related to progestin-based contraception (OR: 1.45 [95%CI: 0.92–2.26]) [44]. However, this risk varies according to the drug [45]. No excess risk was noted with levonorgestrel 30 μg, norethisterone 350 μg, desogestrel 75 μg, or a levonorgestrel IUD (Table 8) [46]. Initial epidemiological data on microdose progestin-based oral contraceptives containing desogestrel, and on levonorgestrel IUDs, are very reassuring, with no significant increase in the risk of venous thromboembolism relative to women nonusers [18,19]. These results were expected, as these progestins do not affect hemostatic parameters when used in small doses.

Only one study has evaluated the risk of recurrent venous thrombosis associated with the use of chlormadinone acetate at antigonadotropic doses [47]. The data are reassuring, as they showed no significant impact on this risk (OR: 0.8 [0.2–3.9]), even though the women had venous risk factors (history of venous thromboembolic disease and/or biological thrombophilia). However, this was rather a small study and the results need to be confirmed in larger populations. Finally, two studies of the link between medroxyprogesterone acetate and the risk of venous thrombosis call for caution [48,49]. Indeed, a WHO study showed a non-significant trend (OR: 2.19 [0.66–7.26]), while the other showed a significant increase in this risk [49]. The pharmacological properties of this progestin, used at high doses, may explain these results.

Table 8
Risk of venous thromboembolism associated with progestin-only contraceptives [19,49].

| Mode of contraception | Lidegaard et al., 2009 [19] | van Hylckama et al., 2010 [49] |
|---|-----------------------------|--------------------------------|
| Oral route | | |
| Levonorgestrel 30 μg or norethisterone 350 μg | 0.59 (0.33–1.04) | |
| Desogestrel 75 μg | 1.10 (0.35–3.41) | |
| IUD | | |
| Levonorgestrel | 0.89 (0.64–1.26) | 0.30 (0.10–1.10) |

Relative risk (95% CI) during use, compared to non-users.

Table 9

Risk of myocardial infarction in women using combined oral contraception (compared to women not using oral contraception), according to smoking and arterial hypertension (AHT).

| | Odds ratio (95% CI) (Myocardial infarction) |
|------------------------|---|
| Smoker with AHT | 71.4 (16.5–309) |
| Smoker without AHT | 26.6 (7.00–101) |
| Non smoker with AHT | 16.4 (3.10–87.7) |
| Non smoker without AHT | 1.10 (0.12–9.69) |

From the WHO study [55].

4.3. Oral combined contraception and the risk of arterial ischemic events

Data from the Nurses' Health Study, on an initial population of 119,061 women followed for 8 years, showed no increase in the risk of cardiovascular events in users of oral contraceptives (OR: 0.95 [0.81–1.11]) [50]. After adjustment for associated cardiovascular risk factors, the relative risk among women who used oral contraceptives was 0.8 (0.6–1.0) for coronary events, 1.0 (0.7–1.3) for stroke and 0.90 (0.7–1.2) for cardiovascular death [50]. No association was found between the duration of oral contraception and the risk of cardiovascular events [50]. However, in women currently using oral contraception, the relative risk of cardiovascular events was 2.5 (1.3–4.9), and 70% of cardiovascular events occurred among smokers [51]. A post hoc analysis of the Women's Health Initiative showed no increase in the risk of cardiovascular events in women with a history of oral contraceptive use [52].

In the MICA case-control study, involving 2176 women, the relative risk of myocardial infarction (MI) was not significantly increased among women taking oral contraceptives (OR: 1.4 [0.78–2.52]) [53]. After adjustment for cardiovascular risk factors, these RRs were 1.1 (0.52–2.30) for second-generation contraceptives (levonorgestrel or norethisterone + EE) and 1.78 (0.66–4.83) for third-generation contraceptives (gestodene or desogestrel + EE) [53]. In the case-control study published by Tanis et al., in 1173 women, those taking oral contraceptives had an adjusted relative risk of MI of 2.0 (1.5–2.8) [54]. In this study the increased risk was statistically significant only in women using second-generation oral contraceptives (levonorgestrel + EE) (OR: 2.7 [1.6–4.3]), not in those taking third-generation products (desogestrel or gestodene + EE) (OR: 1.3 [0.8–2.3]) [54]. The WHO case-control study of 1309 women living in Europe or in developing countries showed that the relative risk of MI associated with oral contraceptive use was 1.1 (0.12–9.69) among non-smoking women with normal blood pressure [55]. However, this study also showed a strong increase in the risk of MI in women with risk factors who used oral contraception, namely non-smokers with hypertension (OR: 16.4 [3.08–87.7]), smokers with normal blood pressure (OR: 26.6 [7.00–101]), and smokers with hypertension (OR: 71.4 [16.5–309]) (Table 9) [55].

Finally, a large Swedish prospective study of 48,321 women, lasting 11 years, showed no increase in the risk of MI among

women currently using or having used oral contraceptives [56]. After adjustment for age, education, physical activity, alcohol consumption and other risk factors for cardiovascular disease (hypertension, smoking and diabetes), the relative risk of MI was 0.7 (0.4–1.4) among women currently taking oral contraceptives and 1.0 (0.7–1.4) among past users [56]. The duration of oral contraceptive use was not associated with an increased risk of MI.

Thus, in the absence of cardiovascular risk factors, available epidemiological data do not point to a significantly increased risk of ischemic events (MI or stroke) among women who use oral contraceptives. However, the data clearly suggest an increased risk of cardiovascular events in women smokers who use oral contraceptives.

4.4. Progestin-based contraception and the risk of ischemic arterial events

Published data on the risk of vascular disease are much less abundant for progestin-only contraceptives than for estrogen–progestin combinations.

There are no cohort studies of the relationship between the use of a progestin contraceptive and the risk of stroke, and only six case-control studies are available [45,46,48,57–59]. Four of them were conducted in Europe, one in the USA, and one on several continents (the WHO study). In each study, cases of stroke were well documented, along with their nature (ischemic or hemorrhagic). However, some authors combined the two types of stroke for analysis. The women included in these studies were between 15 and 44 years old. Controls were obviously matched for age in all the studies, which involved between 26 and 1828 case patients. The precision of the information provided is thus very different from one study to another. A meta-analysis of the six studies included a total of 3091 cases and 11,385 controls [60]. The nature of the contraceptive progestin also differed according to the study: four of them analyzed microdose progestins, one also included medroxyprogesterone acetate (MPA) injections, and the last focused only on levonorgestrel implants. The combined risk of stroke associated with use of progestin-based contraception, whatever the route of administration, was 0.96 (0.70–1.31), and was consistent across the studies (heterogeneity test non significant: $P=0.989$). The risk associated with MPA was 0.89 (0.53–1.49) [60]. There are no data on the risk associated with the use of microdose progestin-based contraceptives containing desogestrel, or with the use of levonorgestrel IUDs.

Regarding the risk of MI, only six case-control studies are available, three conducted in Europe and two in the United States, and one commissioned by WHO [46,48,53,59,61,62]. The women's ages were similar to those in the above-mentioned studies. Two studies examined the link between the risk of death from MI and the use of progestin-only contraception. The controls differed across the studies: hospital controls in two studies, women recruited from the general population in two studies, and both types of control in the latest study. The meta-analysis included a total of 1817 cases and 6822 age-matched controls [63]. The principal arterial risk factors were taken into account in

the risk calculations in each study. The combined risk of MI associated with the use of progestin-based contraception, whatever the route of administration, was 1.07 (0.62–1.83). Once again, the results were homogeneous (heterogeneity test not significant, $P = 0.55$). The risk associated with DMPA was 0.66 (0.07–6.00) [63]. There are no data on the risk associated with microdose progestin-based contraception containing desogestrel, or on levonorgestrel IUDs.

Finally, a French observational study of about 200 women with systemic lupus erythematosus, with or without antiphospholipid antibodies, showed no unexpected increase in the risk of venous or arterial events in those exposed to chlormadinone acetate or cyproterone [64].

5. Choice of hormonal contraception for women with vascular and/or metabolic risk factors

5.1. Hormonal contraception in women at risk of venous thrombosis

Combined estrogen–progestin contraception is formally contraindicated in women with a personal history of thromboembolic disease. In the acute phase, this type of contraception should be discontinued and replaced by a barrier method, with access to emergency contraception if necessary. Subsequently, women who wish to use hormonal contraception may be prescribed a macrodose or microdose progestin.

In case of documented biological thrombophilia in a woman with no history of clinical events, the approach is the same: combined estrogen–progestin contraception is formally contraindicated, while microdose or macrodose progestin-based contraception may be considered.

A family history of thromboembolic events in a first-degree relative before age 60 years is a relative contraindication to estrogen–progestin contraception. The first-line option for these women is microdose or macrodose progestin-based contraception.

However, a personal history of superficial venous thrombosis does not contraindicate hormonal contraception.

Finally, there is no need for routine screening for thrombophilia when prescribing a hormonal contraceptive; these investigations should be limited to women with a first-degree family history before age 60 [65]. In this case, the tests should include the prothrombin time (PT), activated partial thromboplastin time (aPTT), and antithrombin, protein C, protein S, factor V Leiden and prothrombin (FII) 20210A levels.

5.2. Hormonal contraception in women receiving secondary cardiovascular prevention

Estrogen–progestin contraception is formally contraindicated in women with a personal history of arterial events (coronary heart disease and/or stroke). These women should first be prescribed a nonhormonal method, preferably a copper IUD. If these devices are poorly tolerated, progestin-based contraception (microdose or macrodose) should only be considered after a multidisciplinary consultation. Depending on

age, the possibility of permanent sterilization may be discussed (tubal ligation or an intratubal device).

The same strategy should be adopted for women with a family history of early cardiovascular events (before age 50) or migraine.

5.3. Hormonal contraception and lipid disorders

Hormonal contraceptives can alter the lipid profile, and three different clinical situations should be considered, depending on whether blood lipid disorders (with or without treatment) were present before starting oral contraception or are revealed by the contraception.

5.3.1. Effects of oral contraceptives on lipid metabolism

The influence of oral contraceptives on plasma lipid levels depends on the dose of estrogen and the androgenic potency of the progestin. On the whole, triglyceride levels increase slightly, while there is no significant change in HDL-cholesterol or LDL-cholesterol levels [66,67].

The estrogen component is responsible for the increase in triglycerides and HDL-cholesterol and for the fall in LDL-cholesterol. The impact of the different progestins on lipid parameters is modest and, in most cases, not significant (less than one standard deviation from the mean). However, this depends on the pharmacological properties of the compound in question [68,69]. If the progestin exerts androgenic activity (norgestrel and levonorgestrel), it usually increases LDL-cholesterol and decreases HDL-cholesterol levels. This is also the case of medroxyprogesterone acetate. Contraceptives containing low doses of norethisterone reduce LDL-cholesterol and increase HDL-cholesterol levels through the dominant effect of estrogen and the relatively low androgenicity of this progestin [67]. The latest-generation progestins (desogestrel, norgestimate, gestodene), which are less androgenic, tend to raise HDL-cholesterol levels and to lower LDL-cholesterol levels. Thus, in a meta-analysis of 18 studies, contraceptives containing desogestrel increased HDL-cholesterol by 0.058 g/l and reduced LDL-cholesterol by 0.045 g/l [66].

5.3.2. Hormonal contraception in women with lipid disorders

Lipid disorders are a relative contraindication to combined contraceptives. This means that, in addition to careful consideration of the likely benefits and risks, the prescription should be individually tailored and chosen after thorough discussion with the patient [70]. A plasma LDL cholesterol level of 2.20 g/l may be regarded as an acceptable limit in the absence of other cardiovascular risk factors. Beyond this value, estrogen–progestin oral contraception is contraindicated but progestin-only contraception is feasible, preferably using a compound without significant androgenic activity. Moreover, a baseline LDL-cholesterol value higher than 2.20 g/l raises the possibility of familial hypercholesterolemia, which should be managed appropriately. Plasma levels below 2.20 g/l authorize estrogen–progestin contraception, provided the woman has no additional cardiovascular risk factors, and particularly smoking (Table 10).

Table 10

Tolerable LDL-cholesterol levels during combined oral contraception according to the number of the following risk factors: family history of cardiovascular disease in a first-degree relative before age 55 years (male relative) or 65 years (female relative); current smoking, or cessation less than 3 years previously; AHT or antihypertensive treatment; diabetes (treated or untreated); HDL-cholesterol < 0.40 g/l. Protective factor: HDL-cholesterol > 0.60 g/l.

| | LDL (g/l) |
|----------------------|-----------|
| No risk factor | < 2.20 |
| 1 risk factor | < 1.90 |
| 2 risk factors | < 1.60 |
| 3 risk factors | < 1.30 |
| Secondary prevention | < 1.00 |

The triglyceride threshold can reasonably be set at 2.00 g/l. A higher value contraindicates estrogen–progestin contraception. Contraception should be based on a microdose progestin, and the patient's diet should be analyzed, as 90% of cases of hypertriglyceridemia are due to dietary factors.

5.3.3. Hormonal contraception in women treated with lipid-lowering drugs

In case of hypercholesterolemia characterized by an increase in LDL cholesterol and controlled by treatment in a woman with no associated cardiovascular risk factors, estrogen–progestin contraception is authorized, provided the dose of EE is no more than 35 µg/day. In all other cases, a different method of contraception should be considered, including a progestin-only contraceptive [70].

In case of isolated hypertriglyceridemia, values observed at any given point of treatment should be interpreted with care, as large fluctuations may occur after dietary errors. However, women with triglyceride values that regularly exceed 2.00 g/l should use a progestin-based contraceptive.

5.3.4. Lipid disorders revealed by hormonal contraception

The 2004 ANAES guideline on the choice of female contraceptive methods states (translated from the French) that “in a woman with no personal or familial history of metabolic disease or thromboembolism, who does not smoke, and whose clinical examination is normal, the first lipid profile can be done within 3 to 6 months after starting contraception (including estrogen–progestin combinations)” [71]. At all events, lipid profiling should always be done 3 to 6 months after starting contraception [51].

When hypercholesterolemia occurs in a patient using an estrogen–progestin combination, it should be checked that this is not an isolated increase in HDL-cholesterol, a common situation in women taking EE, which does not imply any change in contraception strategy. However, if the LDL cholesterol level is high, it may be preferable to stop hormonal contraception, depending on the degree of increase and associated risk factors. Hormonal contraception must be stopped if the LDL cholesterol level is higher than 2.20 g/l in a woman with no risk factors (especially smoking). In the presence of risk factors, the tolerated LDL cholesterol threshold should be lowered by 0.30 g/l for each additional risk factor (Table 8) [51]. In case

of hypertriglyceridemia, hormonal contraception should be discontinued if the level exceeds 2.00 g/l.

5.4. Hormonal contraception and arterial hypertension

Among women of childbearing age, 4% of those aged between 18 and 34 years and 8% of those aged from 35 to 44 years are hypertensive [72]. High blood pressure increases the risk of vascular events, including stroke [73], that may result in significant morbidity and mortality. The choice of contraceptive can be particularly tricky in this situation. However, women with systolic blood pressure above 160 mmHg or diastolic pressure above 100 mmHg are also at an increased risk of complications during pregnancy, and it is therefore essential to provide them with effective contraception.

5.4.1. Impact of hormonal contraceptives on blood pressure

Whatever the route of administration (oral, transdermal or vaginal), a minor increase in blood pressure (5 to 7 mmHg) is observed with estrogen–progestin combinations, but frank hypertension occurs in 0.6% to 2.8% of users. This effect is partly explained by the action of EE, which increases the hepatic synthesis of angiotensinogen and stimulates the renin-angiotensin-aldosterone system, whether administered orally, vaginally [68] or transdermally [69]. This reflects the pharmacological potency of this estrogen, due particularly to the lack of hepatic metabolism. The lower doses of estrogen used in recent years have not demonstrated a lesser impact on blood pressure than higher-dose estrogen–progestin formulations. The Nurses' Health Study confirmed the significant increase in the risk of developing hypertension, with no difference according to the dose of EE (lower or higher than 30 µg) [74]. An effect of progestins on blood pressure cannot be ruled out but appears to be minor. EE combination with a progestin with anti-aldosterone properties, such as drospirenone, appears to limit this blood pressure elevation [75]. However, there are no data on the risk of cardiovascular events with such products. There are also very few data on new estrogen–progestin combinations that do not use EE (EV and dienogest, or E and nomegestrol acetate) which, to date, are subject to the same contraindications as pills containing EE [32].

Published results on microdose progestins are reassuring in terms of cardiovascular safety but come from only small studies. Data on the safety of macrodose progestins, including their effect on blood pressure, are also reassuring [76].

As mentioned above, there is a significant increase in the cardiovascular risk when combined hormonal contraceptives are used in hypertensive patients, regardless of the estrogen dose [77,78]. Moreover, according to data from the WHO study, the excess risk of cardiovascular events, and particularly MI, is significant in women with known cardiovascular risk factors, and also in those whose blood pressure is not measured before starting treatment [50]. Blood pressure measurement is therefore the only clinical examination recommended by WHO before prescribing combined oral contraception to a woman with no noteworthy family or personal history.

5.4.2. Hormonal contraception in hypertensive women

The main international guidelines [3,79] are in perfect agreement on the choice of contraceptive methods for women with hypertension.

Estrogen–progestin contraception:

- the theoretical and proven risks outweigh the benefits for women with controlled hypertension or blood pressure values < 160/100 mmHg;
- such combinations are formally contraindicated for women with uncontrolled hypertension ($\geq 160/100$ mmHg);
- the advantages of this contraceptive method, however, outweigh the theoretical or proven risks in women with a history of fully resolved hypertension of pregnancy.

Microdose progestins and levonorgestrel IUDs:

- there are no restrictions on the use of these contraceptives by women with controlled hypertension or blood pressure values < 160/100 mmHg;
- the advantages of these methods outweigh the theoretical or proven risks in women with uncontrolled hypertension ($\geq 160/100$ mmHg) or a history of cardiovascular disease;
- there are no restrictions on the use of these contraceptive methods for women with a history of hypertension during pregnancy.

In summary, combined hormonal contraceptives are not a first-choice option for patients with hypertension, except for those with a history of hypertension in pregnancy. The contraindication is only relative in women under 35 years of age on effective treatment, without complications or other cardiovascular risk factors. There are no contraindications to the use of micro- or macrodose progestins, which therefore constitute the hormonal alternative of choice to estrogen–progestin contraception for women with hypertension.

5.5. Hormonal contraception and smoking

Smoking has increased rapidly among women and is now very common among women seeking contraception. This is worrying because, if mortality due to smoking has started to fall in French men, it is increasing gradually in French women. In addition, interactions between smoking and contraception necessitate greater caution when prescribing contraception to a smoker.

5.5.1. Hormonal contraception and smoking: a risky combination

It is now accepted that the combination of estrogen–progestin contraception and smoking is associated with a risk of stroke and MI that rises exponentially with age. Arterial events, promoted mainly by the pill-tobacco combination, appear to be related to thrombosis rather than accelerated development of atherosclerotic lesions. Thus, the combination of combined oral contraceptives and smoking leads to changes in clotting factors,

including an increase in PAI-1 (a fibrinolysis inhibitor) [80]. In addition, smoking may affect hepatic estrogen metabolism [81].

As noted above, epidemiological data show that the risk of MI increases in proportion to the number of cigarettes smoked daily. Thus, the relative risk of MI reaches 12.5 in women who smoke more than 20 cigarettes per day [53]. The EE content also influences the risk of thrombosis, and dose reduction from 100–150 $\mu\text{g}/\text{d}$ to 30 $\mu\text{g}/\text{d}$ has certainly helped to lower the vascular risk. However, the risk of ischemic events persists even with new pills containing the lowest doses of EE [82]. Concerning stroke, the combination of smoking and combined oral contraception mainly increases the risk of hemorrhagic stroke. As with MI, the risk increases with age, the dose of EE, and the daily number of cigarettes.

Thus, for both MI and stroke, we have an equation with three variables (age, number of cigarettes, and EE content), resulting in a variable level of risk that must be weighed up against the benefits of the different types of hormonal contraception. One should always keep in mind that the incidence of arterial events remains low in absolute terms, but that age is an important risk factor. While the relative risk of stroke and MI is increased at all ages, the vast majority of coronary and cerebral arterial events occur in women over 35 to 40 years old, and especially in smokers. The risk of venous thrombosis appears to be independent of smoking but also increases with age [83,84].

5.5.2. Hormonal contraception in smokers

Estrogen–progestin contraception, regardless of the route of administration (including patches and vaginal rings), is contraindicated in smokers over 35 years old, especially those who smoke more than 15 cigarettes a day (Fig. 2).

Before age 35, and regardless of the daily number of cigarettes, estrogen–progestin contraception may be envisaged in the absence of cardiovascular risk factors or other contraindications, as the benefits of this method outweigh the theoretical or proven risks [3].

Progestin-only contraception (oral or subcutaneous, or a levonorgestrel IUD) can be used regardless of age and the daily number of cigarettes [3]. A copper IUD is an alternative to hormonal contraception

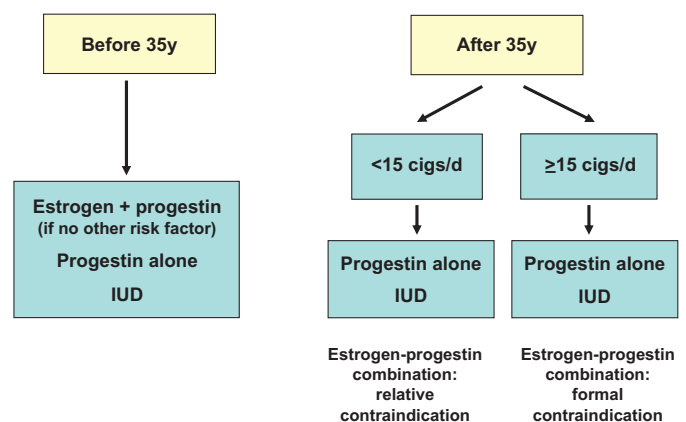


Fig. 2. Contraception for women smokers.

Emergency contraception with levonorgestrel or ulipristal acetate is not contraindicated in smokers.

Finally, it is important to remember that patient visits dedicated to the choice of contraception are a good opportunity to discuss the problem of smoking and to provide assistance to quit; and it should be made clear that it is smoking, not contraception, that must be avoided!

5.6. Hormonal contraception and obesity

Contraception is an important issue in women with obesity. A recent French study showed a four-fold higher risk of unwanted pregnancy in obese women compared with age-matched women of normal body weight [85]. Obese women were eight times more likely to use a suboptimal contraceptive method that did not require intervention by a physician, and much less a gynecologist. It is therefore crucial to improve the contraceptive management of these women. While no forms of contraception are, a priori, contraindicated in women under 35 with isolated obesity, these women often have associated cardiovascular risk factors that may rule out the use of estrogen–progestin contraceptives.

Contraception in obese women should be considered from two perspectives: obesity as a cardiovascular risk factor, and the possibility that hormonal contraception may increase this risk; and obesity as a risk factor for failure of hormonal contraception. Unfortunately, there are still too few data to answer these questions, as obesity is often an exclusion criterion in clinical trials, with the results simply being extrapolated to obese women in most cases.

5.6.1. Vascular tolerability of combined contraception in obese women

Regardless of contraceptive use, obesity is associated with an increased risk of venous thromboembolism. The relative risk of venous thromboembolism increases with the body mass index (BMI), from 2.2 for a BMI between 20 and 25 kg/m², to 3.1 for a BMI above 25 kg/m² [86]. The relative risk is 3.70 for women with a BMI above 30 kg/m² compared to women with a BMI below 21 kg/m² [87]. Several studies have examined the risk of venous thromboembolism according to BMI in women using combined hormonal contraceptives [83,88–90]. Unlike other cardiovascular risk factors, the combination of these two risk factors — obesity and oral contraception — seems to be solely additive [86].

There are few specific studies of arterial events in obese women. Tanis et al. found a relative risk of 3.4 for MI in a population of obese women, rising to 5.1 in those using estrogen–progestin contraceptives [54]. However, these events are rare in women under 35 years of age.

5.6.2. Effectiveness of combined contraceptives in obese women

The metabolic changes observed in obesity, and the larger volume of distribution, can lead to a reduction in the effectiveness of hormonal contraception. The risk of failure of hormonal contraception in obese or overweight women,

however, is highly controversial [91,92]. Two case-control studies showed a significantly increased relative risk of unwanted pregnancy in obese women [93,94]. Conversely, three other retrospective cohort studies and a case/control study showed no association between estrogen–progestin contraceptive failure and obesity [95]. Another clinical study showed that women who were overweight or obese had a moderately increased risk of unintended pregnancy compared to women with a normal BMI, but the difference was of borderline statistical significance [95]. Finally, Zieman et al. found a significant association between bodyweight and the risk of pregnancy in women using estrogen–progestin patches, but not between BMI and the risk of pregnancy [96]. Current data therefore provide no firm evidence that the efficacy of combined hormonal contraception is lower in obese women who use it correctly, even though there are almost no data on women with a BMI above 35 kg/m².

Furthermore, it is important to note that, at the population scale, there is no evidence that estrogen–progestin contraception causes weight gain in obese women [95].

Finally, for women under 35 years of age with no cardiovascular risk factors and a BMI of 30 kg/m² or more, the benefits of combined hormonal contraception outweigh the theoretical risks [2]. However, obesity is still mentioned as a precaution for use in the marketing terms for estrogen–progestin contraceptives.

5.6.3. Tolerability and efficacy of progestin-only contraceptives in obese women

There are no specific studies of the vascular and metabolic tolerability of progestin-only contraceptives in obese women. Moreover, very few studies have examined the effectiveness of these contraceptives in overweight or obese women. In particular, there are no data on the effectiveness of oral microdose or macrodose progestins in this specific population at the usual doses.

Clinical data during the third year of etonogestrel implant use by overweight women are limited. It has been reported that serum etonogestrel concentrations measured after three years of administration are lower in women weighing over 70 kg than in women of normal weight [97]. The contraceptive effect is linked to plasma etonogestrel levels, which correlate negatively with body weight and decrease with time after implantation, and it is therefore advisable to replace these implants after two years in overweight women. However, small series have shown no increase in the rate of unwanted pregnancy among overweight women using this contraceptive. Likewise, no pregnancies were diagnosed in obese women using injectable DMPA during a one-year study, even though circulating levels of this progestin were lower than in normal-weight women.

Microdose progestin-only pills, progestin-only injectables, implants containing etonogestrel and IUDs containing levonorgestrel, can therefore be used without restriction in obese women [2]. Note that injectable DMPA can cause weight gain in obese adolescents, an effect that may undermine its use in this setting [2].

5.6.4. Emergency contraception for obese women

Emergency contraceptives can be prescribed normally to obese women, even though there are currently no specific studies of the effectiveness of these products in obese women at the usual doses. Recently published data suggest that these contraceptives, and especially levonorgestrel, are slightly less effective in obese patients than in non-obese patients [98].

5.7. Contraception after surgical treatment of obesity

Women who receive surgical treatment for obesity are advised not to conceive for the following 12 to 18 months, both to ensure optimal weight loss and a stable weight during pregnancy, and also to begin pregnancy with optimal nutritional and vitamin status. However, rapid weight loss may restore ovulation, and 7% of women who have weight-loss surgery became pregnant during the following year. This issue can be difficult for previously infertile couples, for whom weight loss is a prerequisite to qualify for medically assisted reproduction. The subject must therefore be approached with tact, in order to ensure the woman herself is able to make the difficult decision to postpone conception. Finally, the issue of contraception needs to be raised for very young women and women who are single at the time of surgery, as the ensuing weight loss can rapidly improve these women's body image, femininity, and confidence in their powers of seduction.

Contraception is thus an important issue to address before weight-loss surgery, and the role of the endocrinologist, as part of these patients' multidisciplinary team, is paramount.

5.7.1. Contraception and weight-loss surgery: specific issues

It is first necessary to consider the immediate postoperative period, during which, as after any surgery, all thromboembolic risk factors must be minimized, as the risk associated with severe obesity is already significant. Estrogen–progestin contraception is contraindicated after the operation. The risks inherent in each contraceptive method should be examined according to the context of obesity and associated risk factors. Note that iron deficiency may be prolonged by heavy periods associated with copper IUDs.

Malabsorption following surgery may theoretically affect bioavailability. Data on the surgical techniques currently used in France are still very limited [99]. Some older series showed a higher failure rate of oral contraception in women who underwent biliopancreatic diversion [100,101]. While we have no data on the effects of gastric bypass, it is best to avoid oral contraception in these patients. In contrast, purely restrictive surgeries theoretically pose no problem of malabsorption, although care must be taken in case of severe vomiting [3]. Finally, whatever the type of weight-loss surgery, one must not forget that Pearl's scores for oral contraceptives are established in patients weighing less than 90 kg, which is rarely the case in this population.

It is important to consider the acceptability of the chosen method, which may be influenced by the woman's lifestyle, her

desire for children in the medium term, and her past medical history.

5.7.2. What contraception after weight-loss surgery?

Estrogen–progestin contraceptives should not be started during the first six weeks after surgery, because of the increased thromboembolic risk.

After purely restrictive surgery, oral combined contraceptives or progestins can be used, but the restrictions imposed by risk factors must be taken into account.

After surgeries leading to malabsorption (gastric bypass or biliopancreatic diversion), oral contraceptives should be avoided in favor of combined hormonal contraception with a patch or vaginal ring, a progestin-only implant, or an intrauterine device.

Contraception should be prescribed before weight-loss surgery, after consultation with the patient's gynecologist, as part of the endocrine work-up for all such women of childbearing age. Indeed, the resulting weight loss will affect the patient's fertility, her self-image, her confidence, and often her sex life. It may be necessary to place an implant or IUD before surgery, or to provide alternative contraception during the postoperative period if combined oral contraception is being considered in the long-term.

5.8. Hormonal contraception and diabetes

5.8.1. Influence of estrogen and progestins on carbohydrate metabolism

Most studies showed no significant change in fasting glucose in women taking oral contraceptives [102–104]. After beginning oral contraception, the post-load glucose level is unchanged [105], or moderately increased [103,106,107], depending on the study. Thus, Oeklers et al. found an increase in the area under the curve after a glucose load, reaching 10% with EE 15 µg + drospirenone 3 mg, 14% with EE 20 µg + drospirenone 3 mg or EE 30 µg + levonorgestrel, and 19% with EE 30 µg + drospirenone 3 mg [106].

Fasting insulin is reported to be unaffected [108,109] or increased [103,110] by oral contraception, depending on the study. In a cross-sectional study of 559 Finnish women, this parameter was not altered in women on EE + levonorgestrel or EE + desogestrel, by comparison with those not receiving oral contraceptives [109]. In the CARDIA prospective study, conducted in 1940 American women, there was a significant increase in fasting insulin (+0.12 mU/L) after adjustment for potential confounders in women using oral contraceptives compared with women not using oral contraceptives [110]. Note that a decrease in insulin sensitivity was observed with oral combined contraception in some studies [111,112]. However, in general, the data indicate that changes in carbohydrate metabolism are limited in women without diabetes who use oral contraception [104].

The vast majority of epidemiological data suggest that oral contraceptives do not increase the risk of diabetes. In the Nurses' Health Study there was no significant increase in the incidence of diabetes among women who were taking or who had taken oral contraceptives [113,114]. Thus, among 98,590 women followed

for four years from 1989, the relative risk of diabetes was 1.6 (0.9–3.1) in women taking oral contraceptives and 1.2 (0.8–1.8) in those with a history of oral contraception, after adjusting for age, the body mass index, family history of diabetes, smoking, physical activity, alcohol consumption, hypertension, parity, and hypercholesterolemia [113]. Likewise, a case-control study of 57,180 Chinese women (the Shanghai Women's Health Study) showed no increase in the risk of diabetes associated with combined oral contraceptives [115].

5.8.2. What contraception after gestational diabetes?

The choice of contraception for women with gestational diabetes (GD) is regularly discussed, given the subsequent risk of type 2 diabetes (T2D) in this population. Indeed, many studies agree that the risk of T2D after GD is generally multiplied by a factor of about 7 [116]. However, a recent article shows that a history of GD does not influence the choice of contraceptive method, with a few exceptions [117]. It is crucial, at all events, to check that glucose tolerance normalizes after delivery of a woman with GD.

Studies of the effects of hormonal contraception in patients with history of GD are rare. Some show no short-term change in glucose tolerance but a slight decrease in insulin sensitivity after prescription of hormonal contraception to patients having had GD [118]. In a longer study (7 years), there was no evidence of an increased risk of T2D in a cohort of Hispanic women with a history of GD who used combined hormonal contraception [119]. Baptiste-Roberts et al. examined data from 14 studies and confirmed that estrogen–progestin contraception is not a risk factor for T2D in patients with a history of GD [120]. The only exception is a retrospective study of 590 Hispanic women in whom glucose metabolism at 2 years deteriorated more strongly in women on estrogen–progestin contraception than in those using non-hormonal methods [121]. There is only one published study on the risk of T2D in women receiving microdose progestin-only contraceptives [119]. It showed an excess postpartum risk of T2D among breastfeeding Latin American women using microdose progestins and who had a history of GD: the relative risk was 2.87 overall (1.57–5.27), 2.96 (1.35–6.52) after exposure for 4 to 8 months, and 4.92 (1.76–13.73) after exposure for more than 8 months [119]. These data have not so far been confirmed. Moreover, it is important to note that this study included only breastfeeding women, and that this excess risk may not concern non-breastfeeding women.

In the current state of knowledge, the risk of precipitating T2D by prescribing an estrogen–progestin contraceptive to a woman with a history of GD seems to be extremely low, and possibly nil. There are no data on possible metabolic changes associated with levonorgestrel implants or IUDs in this population of women with a history of GD.

Contraception based on estrogen–progestin combinations, a progestin alone, a levonorgestrel implant, or an IUD (whether or not it delivers a progestin) may thus be used normally in patients with a history of GD. In the absence of contraindications due to a significant venous or arterial risk, an estrogen–progestin combination remains an excellent choice for women who prefer hormonal contraception.

However, given the risk of postpartum thromboembolism, combined hormonal contraceptives are prohibited during the six weeks following childbirth, as in the general population. A microdose progestin is the only acceptable hormonal contraceptive in this situation.

5.8.3. Influence of hormonal contraception in patients with type 1 diabetes (T1D) or type 2 diabetes (T2D)

In terms of glycemic control, no significant effect of low-dose combined contraceptives was found in a Cochrane review published in 2006 [122]. Even if there are no studies comparing different doses of EE, studies of T1D patients have shown no increase in insulin requirements during estrogen–progestin contraceptive use. Likewise, no change in carbohydrate metabolism was found in T1D patients who used a vaginal ring releasing estrogen and progestin [123].

One important issue is the fear that hormonal contraception might aggravate diabetic complications, including microvascular disorders. However, microvascular complications are neither more frequent nor more severe in patients with T1D who use a combined oral contraceptive: several studies have shown no deleterious effect in terms of the frequency or severity of retinopathy or nephropathy (microalbuminuria). The progression of microvascular complications was studied prospectively in 86 patients with T1D (mean diabetes duration 14 years, HbA1c close to 12%), in whom no effect of combined estrogen–progestin contraception was found after one year of follow-up [124]. No worsening of retinopathy and no increase in the incidence of macular edema was seen after 10 years in 400 women with T1D using combined oral contraception [125]. Only one small observational study of T1D patients showed a significant increase in proteinuria among women on combined oral contraception [126]. It is therefore essential to keep in mind that prescription of a combined contraceptive should be considered with care in case of severe ischemic or proliferative retinopathy, macular edema, or glomerulonephritis with proteinuria, given the potentially deleterious effects of these drugs on microcirculatory phenomena on the one hand, and, on the other hand, the lack of prospective data on the safety of this contraceptive method in this context.

Beyond glycemic control and microvascular complications, the safety profiles of the different hormonal contraceptive methods should be considered according to the degree of cardiovascular risk, especially in women with T2D who frequently have other vascular risk factors. There are no specific studies in diabetic patients, but simply the results of subgroup analyses. For example, in the WHO study, the risk of stroke was higher (OR 2.6) in diabetic patients [127]. Another study also showed a higher relative risk of stroke (OR: 7.1 [3.5–16.1]) in women treated for diabetes and using oral contraceptives [128]. Only one case-control study has analyzed the risk of MI associated with estrogen–progestin contraception according to the presence or absence of diabetes. Estrogen–progestin exposure was associated with a significantly increased risk of MI in diabetic patients (OR: 17.4 [3.1–98.1]) compared to exposed non-diabetic patients (OR: 4.2 [1.6–10.9]) [54].

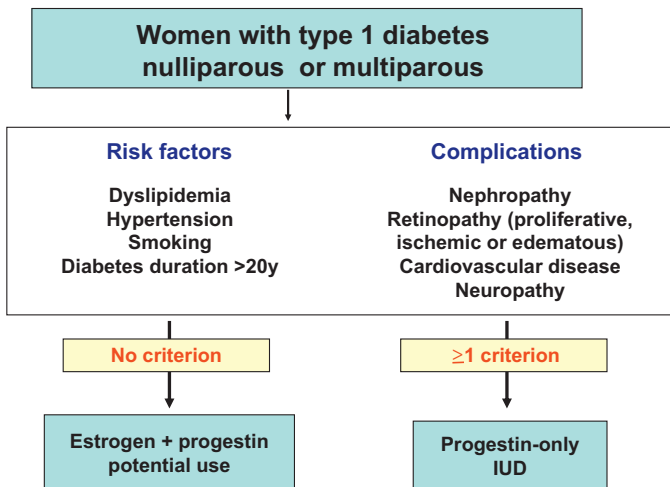


Fig. 3. Choice of contraceptive method in women with type 1 diabetes.

Estrogen–progestin contraceptives were not found to affect insulin sensitivity, lipid metabolism or coagulation status in a population of women with T1D compared to a non-diabetic population [129]. In contrast, there are no specific studies of the effect of combined oral contraceptives on blood pressure in diabetic patients. However, the presence of one or more risk factors associated with diabetes may contraindicate combined oral contraception, and the contraindication is formal in women with poorly controlled hypertension or nephropathy with proteinuria. While transdermal (patch) or vaginal (ring) delivery of estrogen–progestin combinations can limit the effect of first-pass metabolism, their cardiovascular safety has not been demonstrated and their contraindications are therefore the same as those of oral combined contraceptives in diabetic women.

Finally, it is important to note that the thromboembolic risk is globally elevated in diabetic patients, largely because of the obesity associated with T2D; hyperglycemia has no significant impact on this risk of venous thromboembolism.

5.8.4. What contraception for patients with type 1 diabetes?

Risk factors should be taken into account in nulliparous and multiparous patients (dyslipidemia, hypertension, smoking, diabetes lasting more than 20 years), along with complications of diabetes (Fig. 3).

If there are no risk factors and no microangiopathic or macroangiopathic complications, combined oral contraception can be proposed.

In case of complications — nephropathy, advanced retinopathy (edematous, ischemic or proliferative), cardiovascular disease or neuropathy — the use of progestin-only contraceptives, especially microdose progestins and IUD, is recommended.

Uncomplicated mild to moderate retinopathy does not contraindicate combined oral contraception.

5.8.5. What contraception for patients with type 2 diabetes?

For both nulliparous and multiparous women, the contraceptive of choice is an oral progestin, a levonorgestrel implant, or an IUD (with or without progestin delivery) (Fig. 4). It is important

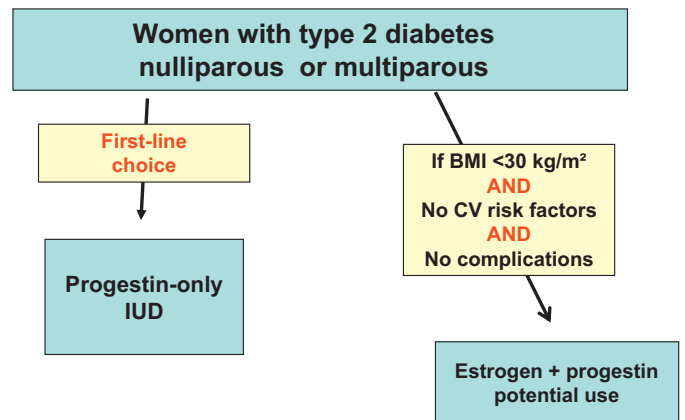


Fig. 4. Choice of contraceptive method in women with type 2 diabetes.

to note that T2D is occurring in increasingly young and mostly nulliparous women, in a context of overweight and obesity.

Use of estrogen–progestin contraception should be extremely limited in women with T2D. Combined oral contraceptives can only be used in such patients in the following conditions: absence of obesity (BMI < 30 kg/m²), no associated cardiovascular risk factors, and no microangiopathic or macroangiopathic complications. Prescription of a combined contraceptive necessitates regular bodyweight monitoring, glycemic control, and blood pressure monitoring.

5.9. Alternatives to hormonal contraception in women at risk

A copper IUD can be used by all women with vascular or metabolic risk factors. This method may also be proposed, if necessary, to nulliparous women, as stated in the recent WHO guidelines [2,79]. Because of their low Pearl index, barrier methods, and particularly condoms (other than for prevention of STDs), should be avoided in hypertensive, obese or diabetic women, who need to plan their pregnancies in order to minimize the associated maternal and fetal risks.

Finally, sterilization may be an option for some women who no longer wish to have children and for whom no other acceptable contraceptive method is available. The permanent nature of sterilization must be underlined, and relevant regulations must be respected, including a 4-month period of reflection. Approaches include tubal ligation by laparoscopy and hysteroscopy-controlled insertion in the tubal ostia of a device that induces fibrosis (Essure method).

6. Conclusion

Despite the growing variety of contraceptive methods, and particularly new pills, management of the venous and arterial risks related to the use of hormonal contraceptives remains a complex but crucial issue. This SFE 2010 consensus statement does not claim to deal with all contraceptive difficulties in women at risk of vascular or metabolic disorders. It does, however, place quantitative limits on the use of combined oral contraceptives. It is important to note that vascular risk factors

are rarely present in isolation, and that the existence of several risk factors imposes even greater caution when prescribing this type of hormone combination. Finally, this document is limited to hormonal contraception, and it should be kept in mind that alternative methods are often an attractive option for women with multiple risk factors.

Disclosure of interest

N. Chabbert-Buffet has been an investigator in clinical research protocols conducted by Theramex laboratories (Merck Serono), Organon (Schering Plough) and HRA. S. Christin-Maitre and G. Plu-Bureau have provided expertise/consultancy for Theramex laboratories, and N. Chabbert-Buffet and C. Moreau for HRA. The other members of the expert group declare that they have no conflict of interest relating to the theme of this consensus statement.

Appendix 1. SFE 2010 Consensus Statement Hormonal contraception for women with vascular and metabolic risk factors. Key points for clinical practice.

Risk of venous thromboembolic disease:

- estrogen–progestin combinations, delivered orally or non-orally, are formally contraindicated in women with a personal history of thromboembolic disease or with documented biological thrombophilia but no relevant clinical history;
- in these situations, at a distance from the acute episode, it is possible to use a microdose or macrodose progestin;
- a family history of thromboembolic events in a first-degree relative before age 60 is a relative contraindication to estrogen–progestin contraception;
- a personal history of superficial venous thrombosis does not contraindicate hormonal contraception;
- testing for thrombophilia before prescribing hormonal contraception is only justified when there is a family history of thromboembolic disease in a first-degree relative before age 60.

History of cardiovascular disease:

- combined contraception is formally contraindicated in patients with a personal history of arterial events (coronary heart disease and/or stroke). Non-hormonal contraceptive methods should be preferred. The possible use of progestin-only contraception (microdose or macrodose) must be discussed by a multidisciplinary panel;
- the decision tree is identical for women with migraine or a family history of premature cardiovascular events (before age 50).

Cardiovascular risk factors - dyslipidemia:

- in the absence of a personal or family history of metabolic or thromboembolic disease and cardiovascular risk factors, lipid

profiling is not necessary before starting hormonal contraception but must be performed routinely after 3 to 6 months;

- combined contraception must be discontinued in women with a high plasma level of LDL cholesterol (>2.20 g/l in the absence of risk factors) or triglycerides (>2.00 g/l). The tolerated LDL cholesterol threshold must be reduced by 0.30 g/l for each additional risk factor;
- documented dyslipidemia (untreated, or uncontrolled by treatment) contraindicates estrogen–progestin contraception if the plasma LDL-cholesterol level exceeds 2.20 g/l and/or the triglyceride level exceeds 2.00 g/l (the LDL cholesterol threshold is lower in women with associated cardiovascular risk factors);
- women with dyslipidemia may be proposed progestin-only contraception, preferably based on a compound lacking significant androgenic activity.

Cardiovascular risk factors - hypertension:

- blood pressure measurement is the only clinical investigation recommended before prescribing combined oral contraception for every women, even for women without noteworthy personal or family history of hypertension;
- first-line combined oral contraception is contraindicated in women with hypertension, except for those with only a history of hypertension of pregnancy;
- the contraindication is relative for women under 35 years who are on effective antihypertensive treatment and have no complications or other cardiovascular risk factors;
- microdose or macrodose progestin-only contraception is the alternative of choice for hypertensive women who prefer hormonal contraception.

Cardiovascular risk factors - smoking:

- combined contraception is contraindicated, regardless of the route of administration, in smokers over 35 years of age, especially when consumption exceeds 15 cigarettes a day;
- before age 35 years, and regardless of the number of cigarettes smoked, combined hormonal contraception may be envisaged in the absence of associated cardiovascular risk factors;
- progestin-only contraception, in any form, can be used regardless of age and the number of cigarettes smoked.

Cardiovascular risk factors - obesity:

- in obese women (BMI >30 kg/m²) under 35 years of age with no associated cardiovascular risk factors, the benefits of combined hormonal contraception outweigh the theoretical risks and may therefore be proposed;
- there are no restrictions on the use of progestin-only contraceptives in obese women;
- after weight-loss surgery leading to malabsorption (gastric bypass or biliopancreatic diversion), all oral contraceptives should be avoided, in favor of combined hormonal contraception delivered via a patch or vaginal ring, or a progestin implant, or an intrauterine device;

- oral contraceptives can be used following purely restrictive surgery, after taking associated risk factors into account.

Cardiovascular risk factors: diabetes:

- all forms of hormonal contraception may be considered, without restriction, in patients with history of gestational diabetes and no venous or arterial risk factors;
- in women with type 1 diabetes:
 - estrogen–progestin contraception may be proposed if there are no vascular risk factors and no microangiopathic or macroangiopathic complications,
 - progestin-only contraception, especially microdose progestins and IUD, are alternatives in case of documented complications (proteinuric nephropathy or renal failure, advanced retinopathy, neuropathy, or cardiovascular disease);
- in women with type 2 diabetes:
 - prescription of estrogen–progestin contraceptives should be restricted to the following circumstances: no obesity (BMI < 30 kg/m²), no cardiovascular risk factors, and no microangiopathic or macroangiopathic complications,
 - in all other cases, hormonal contraception, if preferred, should be based on a progestin alone, regardless of the mode of administration.

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