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Original article

Contraception and diabetes: Which modalities should we consider in 2021?

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ABSTRACT

Diabetes affects many women of reproductive age. Choice of contraceptive method is essential in order to combine efficacy and the patient's wishes, while taking into account the potential side effects. In this review, we will discuss the different methods available for women with diabetes, focusing the discussion on their metabolic and general effects. We will not discuss the side effects and contraindications common to all women, whether they have diabetes or not. The objective is to try to identify an algorithm to help in the decision to choose the most suitable contraceptive method for women with type 1 or type 2 diabetes.

1. Introduction

Prevalence of diabetes is increasing strongly worldwide. More and more women of childbearing age present type-1 or type-2 diabetes. Managing contraception is particularly important given the risks related to unplanned pregnancy, for both mother and child, and the potential consequences of the various contraceptive methods in case of diabetes.

Pregnancy incurs greater risk in case of diabetes. For the mother, closer surveillance is required due to metabolic instability, the impact of diabetes on chronic complications and on the pregnancy itself. For the child, the risks are related to metabolic and vascular factors and concern organogenesis, growth and fetal vitality. Fortunately, the risks are limited when glycemic balance can be optimized as of conception and throughout pregnancy. It is thus essential for diabetic women to be able to plan pregnancy and envisage conception only with the agreement of their diabetologist or gynecologist. The American Diabetes Association (ADA) recommends achieving $HbA_{1c} < 6.5\%$ without significant hypoglycemia, notably to reduce risk of congenital malformation, pre-eclampsia and macrosomia [1].

Even so, two-thirds of pregnancies in diabetic women are unplanned. A population-based study in the UK reported $HbA_{1c} < 6.5\%$ in the 1st trimester in only 14.3% (IQR: 7.7–22.2) of women with type-1 diabetes and 37.0% (IQR: 27.3–46.2) with type 2 [2].

It is therefore crucial to discuss the risks of unplanned pregnancy with diabetic patients, and the various means of contraception available so as to agree on the best-adapted method. Contraception is not something that can be imposed, as compliance is essential to efficacy. This is especially important as studies showed that, among 18–45 year-olds, diabetic women received less advice and prescriptions for contraception than non-diabetic women (47.8% vs. 62.0%) [3]. Hormonal contraception is less widely use by women with type-1 (OR: 0.83 [0.59–0.93]) or type-2 diabetes (OR: 0.60 [0.42–0.83]) than by controls [4]. Interestingly, a recent large-scale study found a decrease in contraception use in the year following diagnosis of diabetes, in all age-groups [5].

Several parameters are involved in choosing a means of contraception: age, type of diabetes, cardiovascular risk factors, gynecologic situation, psychosocial context, risk of sexually transmitted disease, and the woman's idea of contraception. It is also important to take account of efficacy and the rigor and regularity of implementation.

Efficacy is assessed on Pearl index (PI): number of pregnancies over total number of cycles per 1000 women per year. PI of 0.1% or 1 per thousand indicates 1 pregnancy among 1000 users per year.

The present review covers the various means of contraception available and discusses their specific effects on glucose metabolism and vascular risk, with the aim of drawing up a decision-aid algorithm for contraception in diabetic women.

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2. Combined oral contraceptives

This is the best-known method.

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Pills differ in ethinylestradiol dose and type of progestin:

- 1st generation: 50 μg ethinylestradiol and levonorgestrel; these are almost never used now;
- 2nd generation: 20–30 μg ethinylestradiol and levonorgestrel;
- 3rd generation: 15–30 μg ethinylestradiol and desogestrel or gestodene;
- 4th generation: 20–30 μg ethinylestradiol and drospirenone, dienogest or nomegestrol.

Another change has been from synthetic to natural estrogen, associated with a better safety profile.

Different combinations of estrogen and progestin distinguish 3 types of pill according to component distribution over the cycle:

- monophase: estrogen and progestin at fixed dose in all pills throughout the cycle;
- biphase: estrogen and/or progestin at higher dose in the second part of the cycle;
- triphase: estrogen and/or progestin at variable dose for 3 phases during the cycle.

Combined oral contraceptives block ovulation by inhibiting GnRH pulsatility in the hypothalamus, inhibiting secretion of both LH and FSH and preventing the pre-ovulation LH peak. They also make the endometrium less susceptible to implantation and increase the viscosity of cervical mucus, hindering the progression of spermatozoids in the cervix.

They all show broadly comparable efficacy, but this can be diminished by forgetting to take a pill, by vomiting, severe diarrhea or associated enzyme induction treatment.

The WHO reports a PI of 0.1 per 100 women per year of optimal use, or 6–8 per 1000 for usual use, with no difference between does of 20 μg or more than 20 μg ethinylestradiol [6].

2.1. Metabolic effects of combined oral contraceptives

2.1.1. Effects on glycemia

Ethinylestradiol at < 35 μg has no effect on glucose tolerance or insulin secretion. Progestin effects vary according to type and dose but are moderate at the doses actually used in combinations [7–10]. After each oral glucose load, there is a rise in the area under the insulinemia curve, without impact on fasting glycemia and thus no clinical consequences in non-diabetic women [7,10,11]. Most studies of long-term use of these contraceptives reported no change in fasting glucose in non-diabetic women [10,12] or women with history of gestational diabetes [13]. The risk of secondary diabetes is comparable to that observed in the general population [7,8,10,11].

Studies of hormonal contraceptives based on natural estrogen reported no changes in the various parameters of glucose metabolism, including HOMA index [14].

There are no differences in HbA_{1c}, fasting glycemia or insulin level in type-1 diabetics according to use of combined oral contraceptives [7,15].

2.1.2. Effects on lipids

The estrogen and progestin components of combined contraceptives are both associated with changes in lipid metabolism. Estrogens have a generally positive impact, reducing LDL-cholesterol and increasing HDL-cholesterol concentrations. The effect of the progestin depends on its androgen activity. Levonorgestrel increases LDL-cholesterol and reduces HDL-cholesterol, whereas drospirenone has more favorable impact, reducing LDL-cholesterol by around 18% and increasing LDL-cholesterol by around 16% [14]. These changes are, however, slight, as shown in a meta-analysis of 23 studies of combined contraception using desogestrel [16]. Berenson et al. found that, after 36 months' use of a pill containing a 2nd or 3rd generation progestin, LDL-cholesterol levels improved from 113 to 100 mg/dl ($P = 0.002$), with a consequent slight improvement in LDL/HDL ratio [16,17]. Thus, these changes have no impact on atherosclerosis risk.

The main change in lipid profile is hypertriglyceridemia induced by estrogen. Studies reported 30% triglyceride elevation at 6 months [7,10,11,16,17]. Berenson et al. reported 43% elevation at 3 years [16]. This elevation was rather less in case of natural estrogen: 24% at 6 months [14].

This effect, slight in women with normal lipid profile, can be major in case of dyslipidemia, and this type of contraception is contraindicated in severe hyperlipidemia, triglycerides > 200 mg/dL and/or LDL > 220 mg/dL. LDL-cholesterol > 160 mg/dL contraindicates combined oral contraception in smokers, and also in diabetics [7,10,18,19].

Lipid assessment should imperatively be implemented at 3 and 6 months after starting combined oral contraception and continued regularly during follow-up.

2.2. Vascular effects

2.2.1. Blood pressure

Systolic blood pressure may increase by 4–8 mmHg under combined oral contraception [20], increasing the risk of high blood pressure (RR 1.8 [95% CI: 1.5–2.3]) [21], thought to affect up to 3% of users [10]. The risk is lower with a lower estrogen dose, and with recent progestins such as drospirenone (which has an antimineralocorticoid effect) [10]. A study using drospirenone even found a 2-mmHg drop in systolic blood pressure with stable diastolic pressure after 1 year's use [22].

Women with high blood pressure using combined contraception show high risk of stroke [23]. Myocardial infarction risk is increased 12-fold compared to non-users with high blood pressure [19].

Therefore, history of blood pressure elevation, even when controlled, is a contraindication, in under-35 year-old non-diabetic non-smokers [18,19]. Poorly controlled elevation (systolic > 160 mmHg or diastolic > 100 mmHg) is an absolute contraindication [7,10,19].

Blood pressure monitoring is essential with this type of pill.

2.2.2. Myocardial infarction and stroke

Myocardial infarction (MI) and stroke risk also increases slightly with use of combined oral contraception, even without high blood pressure. A large-scale Danish cohort study found increased risk of MI and stoke in combined oral contraceptive users, with RR ranging from 0.9–1.7 for an ethinylestradiol dose of 20 μg to 1.3–2.3 for 30–40 μg, with slight variations according to type of progestin. The risk was even higher in the diabetic subgroup, with RR 4.66 after adjustment [24,25]. A case-control study published in the New England Journal of Medicine in 2001 confirmed increased MI risk in diabetic (RR: 17.4 [3.1–98.5]) compared to non-diabetic users (RR: 2.1 [1.5–3.0]) or diabetic non-users (RR: 4.2 [1.6–10.9]) [26]. The risk depends on estrogen dose, independently of the progestin, and exists even at low doses [27]. It is greater in case of high blood pressure. However, it may be lower when natural estrogens are used [14].

The extra risk is, however, low in absolute terms, as this kind of event is, fortunately, rare in women of childbearing age [23]. In a population of almost 3000 diabetic women, no correlation was found between oral contraceptive use and cardiovascular mortality [11,28]. According to a Cochrane review, a formulation with 30 μg ethinylestradiol and levonorgestrel is the safest [27].

Ischemic stroke risk is also higher in combined oral contraceptive users, with 7-fold higher risk for diabetic users [7]. Recognized stroke risk factors include age, smoking, high blood pressure, dyslipidemia, obesity, family history of early arterial disease, and history of migraine with aura.

2.2.3. Thromboembolic events

Combined oral contraceptives also incur a risk of venous thromboembolism, proportional to the ethinylestradiol dose [28,29]: at < 50 μg, the risk is 3–4-fold higher than for non-users [25], but is lower when recent natural estrogens are used [10,28,30].

Risk also depends on the type of progestin. In a case-control study, 3rd-generation pills were associated with twice as many non-fatal thromboembolic events as 2nd-generation pills [10,20,25,31].

Recognized risk factors include age, obesity, surgery, prolonged breast-feeding, postpartum period and acquired or hereditary thrombophilia [19]. Personal history of thromboembolism is an absolute contraindication, as are predisposing coagulation abnormalities such as Leiden factor V mutation. Even so, coagulation screening is unnecessary ahead of contraceptive prescription in the absence of family history of thromboembolism.

Diabetes does not seem to increase the risk of thromboembolism under combined oral contraception [11].

2.3. Impact on the microvascular complications of diabetes

The literature reports no increase in retinopathy or diabetic nephropathy [7,11,18]. Most studies also report no aggravation of chronic complications in case of low-dose pills even after prolonged use [10,11,18]. Women using oral contraception for more than 10 years showed prevalence of retinopathy and maculopathy comparable to that of women who had never used this type of contraception [7,10,11]. Reports for nephropathy were more contradictory. One study of some hundred women with type-1 diabetes reported increased incidence of microalbuminuria and macroalbuminuria after 20 years' use of combined oral contraception [32]. A 2006 study found a nephroprotective effect in a population of 216 women with type-1 diabetes [11].

Guidelines, however, contraindicate combined oral contraception in case of proliferating retinopathy or maculopathy and in case of nephropathy, due to potential microcirculatory effects [10,18,19].

2.4. Other effects of combined oral contraceptives

The classic adverse effects and contraindications of combined oral contraception obviously also apply in case of diabetes, and will not be dealt with here. A review of the literature found no weight change following use of the various combinations [14,15].

3. Non-oral combined contraception

Efficacy is comparable to that of oral contraceptives, and adherence is better. The contraindications are the same as for combined oral contraceptives, and use by diabetic women is governed by the same precautions.

3.1. Transdermal patch (Evra®)

This is a 20-cm^2 contraceptive patch applied to the skin. It delivers a mean 20 μg ethinylestradiol and 150 μg norelgestromin for 1 week, is applied weekly for 3 weeks followed by 1 week's pause. Tolerance is poorer, with more frequent breast tension (19% vs. 6% for oral route), dysmenorrhea and local reactions [33].

Impact on glucose metabolism is the same as with oral formulations [11]. Thromboembolic risk is greater due to higher bioavailability of estrogen [34].

3.2. Vaginal ring (Nuvaring®)

The 54 mm ring delivers a mean daily dose of 15 μg ethinylestradiol and 120 μg etonorgestrel for 3 weeks. It is positioned by the woman for 3 weeks, followed by 1 week's pause. The main side effect is vaginal discomfort. It shows no metabolic consequences [35].

4. Progestin-only contraception

Progestin-only contraception modifies the cervical mucus and inhibits implantation. Ovulatory blocking depends on the type of progestin.

There are different administration modalities.

4.1. Microgestin contraception

This consists in uninterrupted daily low-dose administration of desorgestrel, levonorgestrel or drospirenone. Administration has to be highly rigorous to ensure efficacy: same time each day. In optimal use, PI is 0.7–0.8. In real life, pregnancy rates are 1.8% [36]. These are the only pills that can be prescribed during breast-feeding due to the absence of estrogens or passage into breast-milk.

Tolerance may be impaired by poorer control of the cycle, with intermittent bleeding.

Microgestins do not affect blood pressure, as shown in a 2004 meta-analysis [37]. Due to its antimineralocorticoid action, a drospirenone-only pill could induce a median decrease of 8 mmHg in systolic blood pressure and 5 mmHg in diastolic blood pressure in women with basal values higher than 130/85 mmHg [38]. Nor do they cause weight-gain. One study, however, found increased fatty mass after 1 year's use [39]. Lipid profile shows a slight decrease in HDL-cholesterol and no effect on LDL-cholesterol [11]. There is no impact on glucose tolerance [11]. A 1998 study of Latin American patients with gestational diabetes, however, found a 3-fold increased risk of diabetes after microgestin use during breast-feeding [13]. These date have not so far been confirmed. Microgestins have no impact on coagulation factors [10,38,40] and are not associated with any increase risk of venous thromboembolism [10,28].

A systematic review found no associated increased risk of stroke, MI or venous thromboembolism [11,41].

Microgestins are thus a useful alternative in case of high vascular risk, notably in diabetics [7,10,12,19,20].

4.2. Etonorgestrel implant (Nexplanon®)

The implant is inserted subcutaneously and releases progestin continuously over a 3-year period. Efficacy is excellent, with a PI of 0.38 pregnancies per 100 women-years [42]. Classically, it induces weight-gain [11,42]. After 3 years' use, Villa-Boas et al. reported 3 kg weight-gain and 1 kg/m^2 increase in body mass index in 213 26 year-olds [43]. A 2016 study found around 12% increase in glycemia with increased insulinemia and insulin resistance on HOMA modeling after oral glucose challenge in implant bearers [43]. Oderich et al., however, concluded that there was no implant effect on glucose metabolism after 1 year's use [44]. In reality, changes seem to be slight, without clinical impact [11,45]. In diabetic women, diabetes balance was unaffected, with no aggravation of microvascular complications at 2 years [35]. There was also no negative impact on lipid profile [35,45].

Insertion may cause local irritation, pain, ecchymosis and itching. The implants induce a slightly hypo-estrogenic state and could impair bone mineral density after prolonged use [45].

4.3. Injectable progestin-only contraception (Depo-provera®)

Deep intramuscular injections are made every 3 months. Efficacy is good, with a 0.7% pregnancy rate when scheduling is well planned (exactly every 3 months) [46].

Weight-gain reports are contradictory. In a study in adolescents, fatty mass increased by 11% and lean mass decreased by 4%, without overall weight change at 1 year [47]. In contrast, a systematic review in 2013 found more than 5% weight-gain in an at-risk population [46]. Certain data suggest increased weight-gain in overweight or obese subjects [47].

This method is also associated with fasting glycemia elevation in the general population, insulin resistance and increased risk of diabetes in at-risk subjects (obese or with history of gestational diabetes) [48]. It also impairs lipid profile, increasing total cholesterol and LDL-cholesterol [12,16].

However, there is no impact on blood pressure. But risk of thromboembolism [10,38,40], MI and stroke may be increased [25,37].

This type of contraception is thus not indicated for diabetics [25].

5. Intrauterine devices

IUDs are widely used in Europe, by about 20% of women. There are 2 types.

5.1. Copper IUDs

Copper IUDs induce a sterile inflammatory reaction in the endometrium that is toxic for gametes, preventing spermatozoids from entering the Fallopian tube. Efficacy is excellent: the WHO reported 0.8% PI at 1 year's optimal use [49].

5.2. Levonorgestrel IUDs

Levonorgestrel IUDs release 20 μg progestin per 24 hours in utero for 5 years. The action mechanism combines that of an IUD and that of progestin-only contraception. They induce uterine mucosal atrophy. PI is 0.2% at 1 year [49]. They do not affect glucose metabolism, lipid profile or blood pressure [11].

5.3. Comments

The most frequent complications are inflammatory pelvic diseases, extrauterine pregnancies (in case of pregnancy despite an IUD), uterus perforation and insertion-related problems of pain, bleeding, and spotting, notably with levonorgestrel IUDs.

The main contraindications to IUDs are congenital or acquired uterine abnormalities, unexplained genital bleeding, uterine fibroma deforming the uterine cavity, severe genital infection, and cervical or endometrial cancer. Contraindications to levonorgestrel IUDs are the above plus those for progestin-only contraception.

IUDs are the method of choice for diabetic women. There is no extra risk of pelvic infection associated with diabetes except in case of severe imbalance, whether of type 1 [50] or type 2 [51]. Levonorgestrel IUDs have no impact on glycemia, and are not contraindicated in case of diabetes [44].

6. Other contraceptive methods

Other methods (condoms, sterilization, diaphragms, spermicides, etc.) are not covered here. Condoms or spermicides, however, seem insufficient to ensure against pregnancy in diabetic women [8,10].

7. Emergency contraception

The various forms of emergency contraception can be used by diabetic women.

8. Contraception after gestational diabetes

In practice, there are no specific contraindications to oral contraceptives in case of history of gestational diabetes [52]. However, it is obviously important to take account of the contraindications applying to all women, given the frequently associated vascular risk factors [52,53].

There is no change in incidence of diabetes after combined oral contraception in case of history of gestational diabetes [13]. There are no data on possible metabolic changes associated with levonorgestrel implants or IUDs in this population [10,47,53].

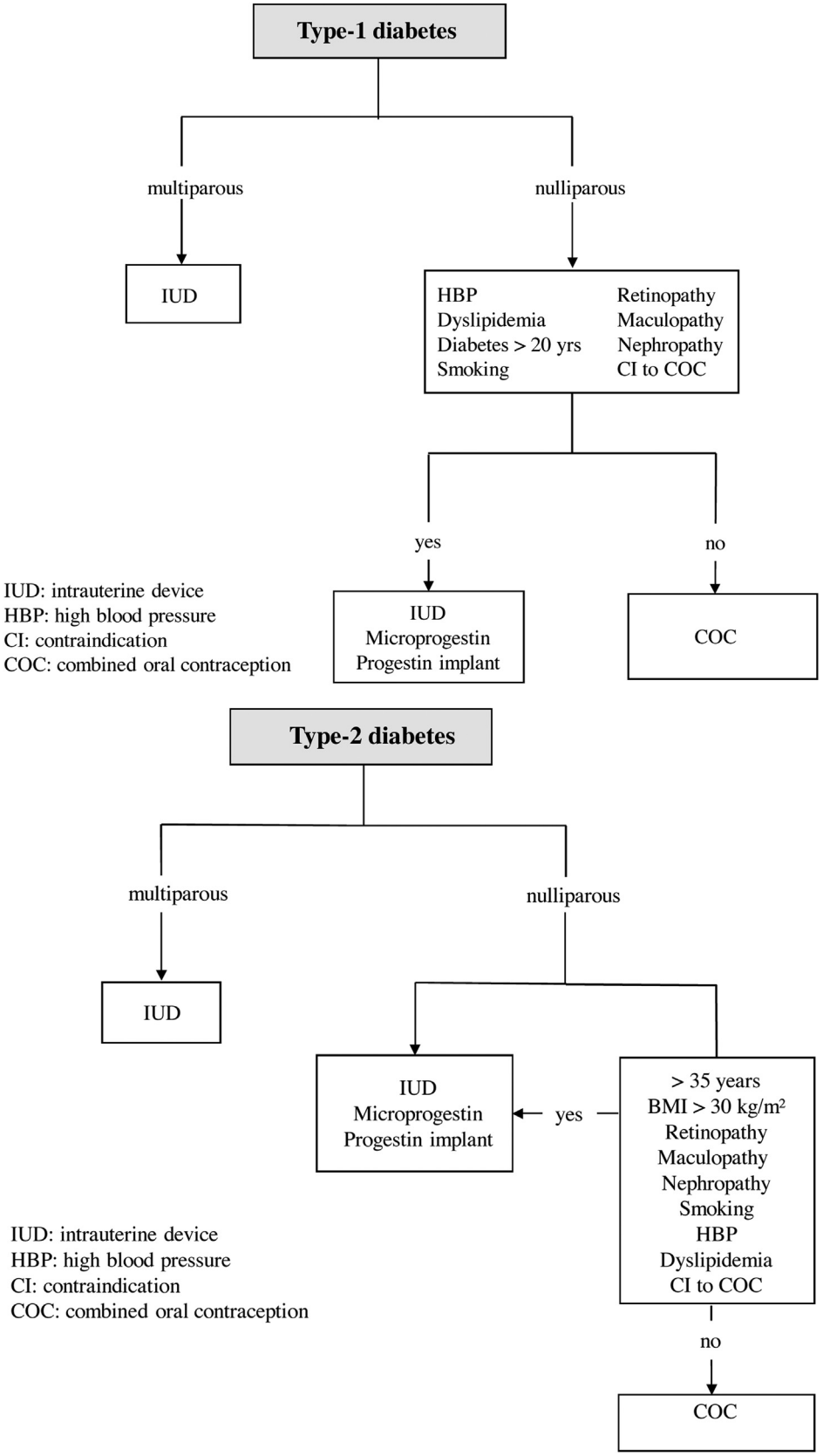
9. To sum up, what contraception for diabetic women?

For multiparous women with type-1 diabetes, IUDs are the solution of choice.

For nulliparous women, combined oral contraception is the method of choice, given its efficacy, acceptability and tolerance. However, it is contraindicated in case of dyslipidemia and of hypertriglyceridemia in particular, high blood pressure, smoking, nephropathy, proliferating retinopathy or maculopathy or diabetes of > 20 years' progression [7,10,19]. Simple retinopathy is not a contraindication and nor is microalbuminuria. Poor control of diabetes is not a contraindication.

As well as these cardiovascular risk factors and chronic complications of diabetes, the specific contraindications to combined contraception obviously also apply.

When combined contraception is contraindicated, microgestins are the solution of choice. Progestin implants are also an alternative in the absence of gynecologic contraindications. Macrogestins are generally not recommended, due to adverse impact on control of glycemia. IUDs are another alternative.



Figs. 1 and 2. Algorithm for selecting a contraceptive method for women with type-1 diabetes.

An algorithm is shown in Fig. 1.

In type-2 diabetes, choice of contraception is more difficult. These women tend to be older, with multiple cardiovascular risk factors.

IUDs are the solution of choice for multiparous women.

For nulliparous women, as well as microgestins, implants and IUDs, there is a limited role for combined oral contraception in the absence of cardiovascular risk factors. Monitoring glycemia, blood pressure and lipid profile is mandatory. The WHO advises against combined contraception in women older than 35 years and when BMI exceeds 30 kg/m^2 [10].

Fig. 2 presents an algorithm for these cases.

Disclosure of interest

The authors declare that they have no competing interest.

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