

Contraception and Hormonal Therapy in Women with Diabetes Mellitus

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Abstract

The administration of hormone steroids in women with Diabetes Mellitus (DM), either via suppressive doses as contraceptives administered in order to prevent pregnancy, or by using substitutive doses as hormonal therapy (HT) in periods of peri or postmenopause, represents a therapeutic decision-making challenge for both health care providers, the endocrinologist and the gynecologist. The World Health Organization (WHO) has stipulated regulations on the prescription of contraceptive methods for women with DM in a safety guideline document of consensus, whose recommendations on this matter, for the purpose of facilitating its prescription, will be the object of analysis in this manuscript. Our analysis of such valuable proposals will not only consist in carrying out a critically review of the existing studies regarding hormonal therapy in diabetic postmenopausal women, but also by establishing the parameters that physicians should take into consideration before prescribing any hormonal regimen, to make the right risk/benefit balance and to establish the ideal time of use, accordingly to each patient needs and concerns.

Keywords: Hormonal contraceptives; Menopausal hormonal therapy; Diabetes Mellitus

Introduction

Before prescribing steroid hormones in women with Diabetes Mellitus (DM), the physician must take into account, which the actual risks for each patient are. That according to a wide range of factors: reproductive age in which the patient is, clinical history of gestational diabetes, the time of evolution and the type of DM, the presence or not of vascular disease (nephropathy, retinopathy, neuropathy), and other preexisting risk factors (cardiovascular, thrombotic or neoplastic). An adverse event is less likely to occur in a healthy woman in reproductive age that is usually younger, even though the doses administrated with combined contraceptives are larger. On the other hand, for a healthy woman with menopause these risks can be increased due to the age, even though the doses of exogenous hormones in a hormonal therapy (HT) regimen are smaller than those administrated for contraception purposes. In the case of a patient with DM this probability can change depending on each particular stage of the disease process at the moment in which hormonal treatment is required. Nevertheless, an appropriate balance among the actual risks and benefits of each patient must be always individually made, that is to emphasize the huge importance of the gynecological and the endocrine background and current state of each woman, so that the greatest benefits with minimal risks can be offered to them. In the current review, a more suitable way to perform this critical risk/benefit balance in women with DM who ask for contraception or HT will be explored.

Contraception in Women with Diabetes

As in any other decision-making process in Medicine, the prescription of a contraceptive method given to a female patient with diabetes must be based on scientific evidence. The World Health Organization (WHO) has regulated the prescription of contraceptive methods for women with DM in a safety guideline document elaborated by different actors: international agencies, scientists, and policies makers of health programs in family planning.

Prescription criteria of contraceptive methods, from the first administration to the continuation of the treatment, has been established by the WHO basing its arguments on existing medical literature and updating the information every four years. In that document 1,700

recommendations on the best options of contraception for healthy women and for women with medical issues or other special conditions have been established.

Prescription needs of women with DM are included in this deep medical literature review taking into account not only the disease process of each woman, but also their gynecologic and obstetric medical background along with the medication that has been given to them at the moment in which contraception is required [1]. This document utilizes several categories to establish the indications or contraindications of different contraceptive methods. These categories go from 1 to 4, in which 1 indicates that the woman is allowed to use the contraceptive method in question without restriction. Category 4 indicates that the woman cannot use, under any circumstance, that method. Category 2 correspond to the case in which benefits of the administration of the contraceptive methods exceed the potential risks, contrary to the third category in which benefits of administrating a particular contraceptive method are exceeded by the risks, in this case the prescription of such method must be meticulously considered. Table 1 shows the different categories assigned to women with diabetes for every single contraceptive method.

The correct risk/benefit balance for contraception prescribing in every type of DM

The risk of developing non-insulin dependent diabetes in women with medical history of gestational diabetes is not increased by the use of combined oral contraceptives (COC) [2-4]. In women with insulin-dependent or non-insulin dependent DM, the COC have little effect on

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CONDITION: Diabetes Mellitus	COC	CIC	P/R	POP	DMPA/NET-EN	LNG/ETG Implants	Cu-DIU	DIU-LNG
a) <i>History of gestational disease</i>	1	1	1	1	1	1	1	1
b) <i>Non-vascular disease</i>	2	2	2	2	2	2	1	2
(i) <i>non-insulin dependent</i>	2	2	2	2	2	2	1	2
(ii) <i>insulin-dependent</i>								
c) <i>Nephropathy, retinopathy, neuropathy</i>	3/4	3/4	3/4	2	3	2	1	2
d) <i>Other vascular disease or diabetes of > 20 years' duration</i>	3/4	3/4	3/4	2	3	2	1	2

Modified from reference [1]
 1: A condition for which there is no restriction for the use of the contraceptive method.
 2: A condition where the advantages of using the method generally outweighs the theoretical or proven risks.
 3: A condition where the theoretical or proven risks usually outweigh the advantages of using the method.
 4: A condition that represents an unacceptable health risk if the contraceptive method is used.
 Combined oral contraceptives (COC), Combined injectable contraceptives (CIC), Combined contraceptive patch (P), Combined contraceptive ring (R), Progestogen-only pills (POP), Progestogen-only injectables (DMPA/NET-EN), Progestogen-only subdermal implants (LNG/ETG implants), Copper-bearing intrauterine device (Cu-IUD) and Levonorgestrel-releasing intrauterine device (LNG-IUD)

Table 1: World Health Organization Guidelines: Medical Eligibility Criteria for Contraceptive Use in Diabetes Mellitus.

daily insulin requirements and no impact on the control effects of the disease in a long term evaluated through the glycosylated-hemoglobin concentrations (HbA1c) or the progression of the retinopathy. The studies that explore both, lipid serum concentrations and haemostatic marker levels with combined contraceptive methods use; have been shown no relevant increase, whose variations fluctuate within previous established normal concentrations ranges [5-8]. In the case of the diabetic patient who already shows signs of vascular damage or has a considerable time of evolution with the disease, the category for using combined methods has to be established depending on the grade of severity of the condition and preferably another contraceptive alternative should be taken into consideration before prescribing COC. In the case of progestogen-only contraceptives, the use of progestogen-only pills (POP) did not show significant clinical changes on lipid concentrations of woman with medical history of gestational diabetes [9]. Different from combined methods, there is not enough evidence to establish the risk of developing non-insulin dependent diabetes in progestin contraceptive method users with antecedent of gestational diabetes [2,10]. For women with insulin or non-insulin dependent diabetes, limited evidence with progestogen-only methods (including the Levonorgestrel-releasing intrauterine device) suggests the absence of an effect for the good control of the disease at short and long term, since no change has been seen in fasting glucose, HbA1c, lipids and hemostatic parameters [6,11,12]. Non-hormonal contraceptives are safe for women with diabetes. To use a contraceptive method by making the correct balance between risk and benefits of contraceptive use in diabetic women of reproductive age in high risk of pregnancy will always be safer before facing an unintended pregnancy assuming all the medical consequences for both, the woman and the neonate.

Additionally to DM, the coexisting high prevalence of hypertension, obesity, and dyslipidaemia, is another important situation that must be considered to make the correct contraceptive choice in the case of type 2 diabetic women. The complexity of health risks within this association gives an additional challenge to define which the correct contraceptive prescription is. However, these pathological situations are well explained in the WHO consensus document [1]. Therefore, all of them should be taken into account, at the same time, before prescribing any option.

In the situation where DM is associated with all these conditions, which frequently occurs, the use of combined contraceptives must be, in most cases, avoided. And other options as progestin-only or non-hormonal contraceptives should be systematically considered.

Does the decision-making process for contraceptive prescription change depending on the type of DM?

The type of DM is a fundamental aspect that physicians must take into consideration in the decision-making process to prescribe hormone-based contraceptive methods. The female population who has DM type I, is composed of a younger group of women, who don't usually have multiple risk cardiovascular factors (hypertension, obesity, and dyslipidaemia) as in DM type 2. However, their prevalence of menstrual cycle alterations is higher. The majority of endocrinologist and gynecologist tend to be more concern about diabetes complications than in menstrual cycle irregularities (oligomenorrhea, amenorrhea, or polymenorrhea) or in the contraceptive choice. For this reason, physicians are more likely to assume that adolescents with diabetes have a low pregnancy risk. Codner et al. [13] found out that young diabetic women had longer menstrual cycles, along with a greater variability cycle compared to the control group. They also discovered a direct relationship between cycle irregularities and metabolic control, where higher HbA1c serum concentrations are more related with menstrual problems. Besides, in this elegantly systematized review, the authors describe a significant delay in menarche age (one year later) than in the control group or in girls with a proper metabolic control. Willis et al. [14], and Poretsky et al. [15] have suggested that higher insulin doses, required in decontrolled patients, affect ovarian steroidogenesis or folliculogenesis, which explains the ovarian cycle clinical manifestations. More prevalence of hypogonadotropic hypogonadism, hyperandrogenism and polycystic ovaries have been reported in type I diabetic girls. It has been demonstrated that hyperglycemia affects both, the ovarian reserve and the reproductive function, by two mechanisms, insulin resistance and the presence of advanced glycation receptors and products [16-18]. These conditions have important repercussions, not only in fertility but also in mineral bone density and theoretical cardiovascular future complications. Women, in general, don't have their maximal mineral bone density until the age of 30 years old. That means that neither adolescent nor young adult women have reached their maximum peak bone mass.

Although, the WHO medical eligibility criteria for contraceptive use [1] does not distinguish between the type of DM and contraceptive choice (Table 1), the physician should take into account the clinical differences observed in both types of DM, in order to make the best possible and individualized decision for every woman's contraceptive prescription. Also, it is very important to consider, that ovulatory function is not totally impaired in type I diabetic girls, who present higher incidence of adverse pregnancy outcomes, as it has been

described in epidemiological studies [13]. Options like progestin-only or non-hormonal contraceptives are good alternatives to prevent pregnancy in this group of women. It is always important to put into practice a thinking process to carry out the correct risk-benefit balance, this process must be specifically made according on each patient's medical background and needs; some girls can be in high risk of bone loss and future osteoporosis. Therefore, a combined estrogen-progestin contraceptive may be more benefit than any other option in this particular case. That is why the prescription of contraceptives in diabetic women can be an important challenge for clinicians.

Hormonal therapy in women with diabetes

In an electronic fact sheet bulletin published by the World Health Organization in May 2009 [19], it is estimated that within the next 25 years the number of individuals with DM will be duplicated from 130 to 300 millions. Due to the increase in the current life expectancy, menopause is now considered as an event at a middle point of women's life. DM is the most common chronic disease present in postmenopause and it is considered as the main risk factor for developing cardiovascular disease, the first cause of death in occidental women [20]. Despite the physiological nature of menopause, the quality of life of women can be seriously affected by the different symptoms attached to this event, such as: vasomotor, urogenital and psychological symptoms, sexual dysfunction, skin changes, loose of bone mass density with risk of fracture. Menopause symptoms can be potentially mitigated by HT; however, the risks of developing cancer (breast and endometrial) and cardiovascular disease (coronary heart disease, stroke and deep venous thrombosis) in healthy woman or in woman with a chronic disease can be also increased, pending on the type of HT administrated. Especially in the case of women with DM, the risk of developing cardiovascular disease increases, even before the arrival of the postmenopausal period. Once a diabetic woman presents the menopause, the risks of developing coronary disease are significantly increased.

Clinical and epidemiological studies on HT use in DM

The decision to start the administration of HT in the diabetic patient must be made by taking into consideration the existent clinical and epidemiological studies along with the individual characteristics of each patient. In a meta-analysis of 107 clinical trials, Salpeter et al. [21] concluded that HT reduces insulin resistance, DM incidence, serum lipid concentrations, abdominal obesity, blood pressure, cell adhesion molecules and procoagulant factors on women without DM; in contrast to the patient with DM in which HT only reduces the resistance to insulin and fasting glucose. Following the results of combined therapy study (progestogen plus estrogen) developed by the Women's Health Initiative (WHI) [22], the DM incidence per year in the treated group reported an important reduction of 21% (hazard ratio [HR], 0.79; 95% CI, 0.67-0.93) versus the placebo group; this is translated in 15 fewer cases of DM per 10,000 women per year of use of HT. In the so-called *Heart and estrogen/progestin replacement study (HERS)* [23], it was observed a similar reduction on DM risk (HR, 0.65; 95% CI, 0.48-0.89). In the WHI's study (HT branch only with estrogen) [24], there was a 12% reduction (HR, 0.88; 95% CI, 0.77-1.01); meaning 14 fewer cases of DM per 10,000 women per year of HT use. The hypothetical idea about HT reduce the abdominal perimeter as a mechanism through insulin resistance is reduced, is still unclear.

In the branch of dietary modification mentioned in the WHI's study [25], it was found that weight loss, and not the composition of the macronutrients, can be the main predictor on diabetes risk reduction in postmenopausal women.

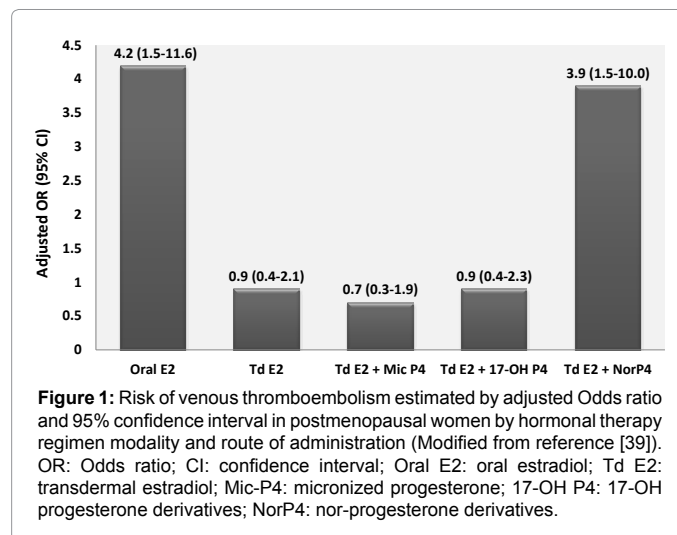
In spite of these findings, there is still not enough evidence to recommend the use of HT to prevent DM in women with peri or postmenopause [26].

Choosing the correct HT modality

In the case of the patient who starts experiencing menopause with DM non-insulin dependent already preexistent, besides the mitigation of the climacteric symptoms, the main goal of prescribing HT, is not only to keep an optimal control of the concentrations of surrounding glucose, but also to reduce the risk of coronary disease. Some data suggest that women with diabetes who receive oral estrogen HT require a smaller dose of hypoglycemic agents. When HT is prescribed to a patient with diabetes, it is important to choose the correct type of HT (combined or estrogenic-only), doses, route of administration and the type of progestin component, in view of the fact that some progestogens can increase insulin resistance [27-32].

In a small-randomized clinical trial [33], it was proved that short doses of continue combined HT are capable to reduce fasting glucose, but not to improve its depuration. Other trials agree that low doses of oral, transdermal or subcutaneous HT improve insulin sensibility [34,35], but this beneficial effect is lost at higher doses [36,37]. It seems that in the recent trials carried out in patients with diabetes, what has been observed is that the benefits of transdermal treatment with estrogen combined or estrogen alone with natural progesterone can be higher than those administrated via oral therapy [38]. Both, DM and HT are associated with an increase of deep venous thrombosis risk; however, Canónico et al., through a systematic review of the literature with a meta-analysis of data, have proved that transdermal therapy and micronized natural progesterone reduce this risk (Figure 1) [39]. Serum concentrations of different lipids as well as prothrombotic factors present increased levels on patients with DM, while transdermal HT has no further increase on these metabolic parameters [40,41]. Sporadically and in an idiosyncratic way, alterations on blood pressure of women, who use HT, with hypertension or hypertension free, have been reported [42,43].

With a view to mitigate severe vasomotor symptoms without any other more cardiovascular risk in the patient with diabetes, in the present review we suggested estrogen transdermal therapy administration for women with hysterectomy, or combined with micronized natural progesterone or with 17-OH progesterogen



derivatives (medroxyprogesterone acetate) in the diabetic patient with uterus.

It has not yet been defined in recent analysis how long hormone therapy should be administered neither on healthy woman nor on a patient with a chronic disease. According to the results of the first WHI's study on hormone therapy unadjusted risk during postmenopause, the Food and Drug Administration (FDA) restricted the recommendation of the treatment administration only for the less amount of time needed to achieve the desired benefit for each case. This benefit is usually looks for the mitigation of the menopause symptoms and the maximum length recommended for treatment is around 5 years. This observation was made due to the risk/benefit analysis of the WHI, which did not shows a reduction on the incidence of coronary disease. In fact, when the analysis was adjusted by age and time since menopause, it was proved higher risk of coronary disease on those women whose time of evolution with the HT since menopause was larger and also in older women or with higher cardiovascular risk as in the case of the diabetic patient, while in younger women a significant change towards a beneficial tendency was not observed..

In are evaluation on outcomes of the WHI's study in the combined therapy branch, it has been suggested that a risk reduction in cardiovascular outcomes does not appear until after 5 upto 6 years of treatment. In the estrogens-only branch the relative risk for coronary disease was 1.08 (IC 95% 0.86-1.36) from the first to 6th year of treatment, and of 0.46 (IC 95% 0.28-0.78) from the 7th to 8th year of treatment. The FDA has suggested, as a consequence of the findings obtained by reviewing previous studies, which also prove a benefit on cardiovascular risk in a prolonged length of use, along with a lack of evidence to support a real benefit in a short term of use, to make a new evaluation of its previous recommendation in order to adjust the indication based on an individualized risk/benefit analysis. It is clear the urgent need and relevance of carrying out new trials and studies that establish the important role of HT adjusted to the time since menopause, length of use, dose and route of administration, type of progestin not only in healthy women with menopause, but also in woman with chronic disease, whose risk of developing cardiovascular disease is even higher [44].

Does the decision of prescribing a menopausal hormonal therapy change with the type of DM?

In the case of HT, the decision about the prescription is independent of the type of DM. There are few studies that evaluate a risk-benefit balance of HT in type I DM patients. In the case of HT, decisions are almost the same in both types of DM due to similar socio-demographic characteristics among women and high cardiovascular risk in both situations. In the case of type I DM, there is a trend to present menopause earlier than general population and type 2 DM. An epidemiological study showed that Latino American type I diabetic women have menopause at 40.06 ± 4.68 years old, and 49.32 ± 3.22 years old in non-diabetic women, $p < 0,003$ [45]. This situation increases the risk of osteoporosis; theoretically the benefit in these patients is higher. Additionally, in this study authors showed no difference in the prevalence of hypertension, body mass index or climacteric symptoms, assuming the same risk-benefit than in general population and type 2 DM patients.

Conclusion

In consonance with was previously said and considering the perinatal risks in uncontrolled patient with diabetes (premature

delivery, fetal macrosomia, fetal death, hypoglycemia and neonatal jaundice); it is suggested that the patient with DM, with no signs of vascular disease, is allowed to use any contraceptive method. In the case of a patient with a current nephropathy, retinopathy, neuropathy or any other vascular disease, it is suggested the use of any estrogen free contraceptive method, and in the case where a combined method is chosen, two factors must be considered by the physician: the grade of vascular damage or the time of evolution of the diabetes at the moment of the contraception first use.

In the case of HT for postmenopausal women that has been diagnosed with DM, it would seem that the clinical benefit of the HT administration in them is significantly lower in comparison with the benefice obtained by a healthy woman. It is for this reason that in this type of patients a well-done and individualized analysis of the potential risks and benefits of hormone administration must be made. Having taken all the previously said into consideration and given the increase of the risk of developing cardiovascular disease on women with menopause generated by DM, it can be concluded that prescription of HT in the peri or postmenopause on women with DM is not an easy decision to make and it should be analytically taken and individualized for each case, paying special attention to the type and route of administration in order to avoid a mayor risk to the patient.

Conflict of Interest

The authors declare no conflict of interest.

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