

Dienogest-containing Hormonal Contraceptives: Natural Estradiol vs Ethinyl Estradiol.

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In recent years, many birth control pill brands were placed on the market, which created, in many cases, a lot of confusion rather than bringing benefits, both among gynaecologists and among women. The lower cost of generic pills and the higher number of products has shifted the debate from safety and efficacy to cost, as an opportunity for increased use of oral contraceptives (OCs) by Italian women, for whom the use of contraceptive pills has always been the lowest in Europe.

The real debate, however, should always remain focused on safety and the lower risks to women's health, so as to improve compliance by women. Much has changed since oral contraceptives have been placed on the market, more than 50 years ago, with reduced dosage of steroid hormones.

New progestins, in combination with lower doses of Ethinyl Estradiol (EE), the predominant estrogen component, helped reduce the incidence of venous thromboembolism and other negative side effects associated with the use of OCs. In the past, some attempts have been made to replace EE with natural Estradiol (E2), all failed due to poor control of the menstrual cycle. Recently, the debate has focused again on this molecule, with the new pills containing natural estrogens. Despite the fact that EE and OCs are safe, there are some side effects that can affect women, particularly women smokers. Possible negative effects concern coagulation, myocardial infarctions, stroke, weight gain and lack of libido. Other possible effects include spotting, breast tenderness, nausea, headaches and mood changes. As already mentioned, a reduced dosage of EE

has significantly reduced this risk, even though an excessive estrogen production increases the percentages of menstrual irregularities and, consequently, favours the discontinuation of the pill. Switching to natural estrogens was not easy and, only once the E2 valerate/Dienogest was developed in a dynamic regime, the right balance was reached, which allowed a good control of the menstrual cycle and the reduction of side effects related to EE. Dienogest is certainly an important innovation in the field of progestins, thanks to its marked uterotrophic activity, in association with anti-estrogenic activity, able to reduce nuclear estrogen receptors in the endometrium, with important effects on endometrial proliferation. Therefore, after 4-5 years of experience with this formulation (E2V/DNG), we can say that there is a good control of the menstrual cycle in women who use it. As for the antiandrogen action of Dienogest, literature data are controversial, although all women report an improvement in the main hyper-androgenic symptoms, such as acne and hirsutism. As for the metabolic impact, and in particular that on glucose metabolism and on weight gain, scientific studies report an improvement of these parameters in women with a metabolic abnormality, such as women with PCOS.

The market offers some formulations of generic pills containing EE and Dienogest. A "generic" product is a medicinal product, defined as "essentially similar" to another product whose patent has expired and whose formulation is almost the same, while having different excipients that may affect the absorption of the active ingredient, side effects, allergic reactions and intolerances.

As for generic products containing EE and Dienogest, these are preparations similar to other

pills already on the market, in this case OCs sold abroad and never marketed in Italy. For these products, the innovative role of Dienogest as a progestin is emphasized, while the fact that it is associated with EE and not with natural estrogen is often minimized. The fact that antiandrogenic action of EE, exercised through greater liver stimulation to produce higher levels of SHBG levels rather than through increased binding affinity with androgenic steroids, improves symptoms in women with hyperandrogenism, is emphasized as well.

As for the control of the menstrual cycle, better control of uterine bleeding is not guaranteed by 30 mcg of EE, but mainly by the anti-estrogenic action of Dienogest in the endometrium, that is similar for both EE oral contraceptives and for contraceptives containing natural estradiol.

Our clinical experience, paradoxically, has shown a higher incidence of spotting during the first two menstrual cycles in women using the EE/DNG association compared to other pills containing 30 mcg of EE and different progestins, just because of this type of mechanism exercised by Dienogest.

The most important aspect, however, concerns the different incidence of side effects between the two types of dienogest-containing OCs. To understand this difference, it is important to remember how the two types of estrogen behave from a pharmacological point of view. EE is rapidly and completely absorbed following oral administration. For 30 mcg of EE, the peak plasma concentration of EE ranges from 90 to 130 pg/ml, 1-2 hours after ingestion. After repeated administration of EE, there is an increase in blood levels of EE as early as the 5th day of treatment. Numerous studies have shown an increase in plasma levels of EE between 30% and 60% during a cycle of OCs. Also, EE not binding to SHBG, is free to circulate in the plasma and binds to estrogen receptors of the various organs.

E2 is also rapidly and completely absorbed following oral administration of doses ranging from 2 to 3 mg. Circulating levels of natural estrogen are dose dependent. After 2 mg of E2 administered in young women, plasma levels between 30 and 50 pg/ml are detectable after 8-10 hours, similar to those of an early follicular phase. Unlike EE, 38% and 60% of the circulating levels of E2 bind to SHBG and to albumin and, therefore, only 2% of E2 circulates freely. The metabolization of E2 is higher in the liver and in the gastrointestinal tract and about 95% of E2 taken orally is metabolized before entering the general circulation.

E2 and EE exert their biological effects by interacting with estrogen receptors (ER α and ER β). Based on of this mechanism, it is well known that the E2 is much less potent than EE and the difference between these two types of estrogen is due to this different metabolization.

As for the control of the menstrual cycle, this problem becomes less important, since the antiestrogenic action of Dienogest in the endometrium is very strong, regardless of circulating estrogen levels. The situation of side effects for EE/DNG pills and E2/DNG containing pills, on the other hand, is significantly different.

Based on the foregoing considerations, comparing the 2 different formulations is a substantial error. EE/DNG containing pills must be considered as identical to other pills containing 30 mcg of EE and, therefore, only the E2V/DNG association is recommended for all women who had previously discontinued previous the pill due to its side effects.

A well-established clinical experience in recent years on the use of this natural pill ensures its safety and the control of the menstrual cycle and allowed us to prescribe it to women for whom EE-containing pills were not recommended and, in general, to women of any age starting from adolescence, thanks to its peculiar characteristics.