



# IF THE AIM IS OVARIAN CANCER PREVENTION AND ESTROGEN MEDIATED BENEFITS, NOT ONLY ENDOMETRIOSIS SUPPRESSION, ARE CONTRACEPTIVES WITH ETHINILESTRADIOL BETTER THAN PROGESTOGENS ALONE?

L. DEL PUP

Gynecological Oncology, National Cancer Institute, Aviano (PN), Italy

**Abstract:** *The estrogen contained in combined oral contraceptives (OCs) could theoretically stimulate endometriosis growth, but some new in vitro data have postulated the opposite: ethinilestradiol (EE) could not significantly stimulate the growth and helps the progestogen action in the endometriotic tissue which is progesterone resistant. The balance between the stimulating and indirectly inhibiting effects of estrogen is critical to the clinical outcome of OCs-based treatment of endometriosis. Dienogest (DNG) is the best progestogen treatment for endometriosis, but what happens if is combined with EE? Only randomized clinical data can confirm it as beneficial or detrimental. While waiting, prescribers must rely on in vitro data and the theoretical considerations hereby reviewed.*

*Endometriotic tissue self-produces estradiol, while the EE/DNG pill maintains stably low E2 levels, which could not significantly stimulate endometriosis growth. Endometriotic tissue is progesterone resistant. The EE in OCs may support the beneficial action of progestins, like DNG, up-regulating progesterone receptors and thereby enhancing responsiveness to progestin. There is a long lasting experience with OCs to suppress endometriosis, reduce recurrence and control endometriotic pain. The link between OCs use and endometriosis, found by some studies, is not a causal one, but it could be better explained by the preferential OCs use by endometriosis symptomatic patients. Therefore there should be no reason to avoid OCs in these patients and, as endometriosis increases the risk of endometriosis-associated ovarian cancer, OCs could reduce this risk better than DNG only. While waiting for adequate clinical data, the effect of EE/DNG versus DNG alone in endometriosis patients will remain controversial. If endometriosis suppression is the only need DNG is still the first choice. When the aim of the treatment is ovarian cancer prevention and estrogen mediated benefits, like contraception and non contraceptive OCs benefits, the EE plus DNG pill seems better than DNG alone or at least not contraindicated in endometriosis patients.*

**KEY WORDS:** *Endometriosis, Dienogest, Ethinilestradiol, Ovarian cancer.*



## BACKGROUND

Endometriosis is defined as an estrogen-dependent disease, consequently, medical therapies have focused on lowering estrogen levels, but nowadays it is known that the pathogenetic mechanism is much more complicated and not only estrogen mediated<sup>1</sup>.

Surgery is the only cytoreductive treatment, but progestins are an effective suppressive therapy<sup>2</sup>. They have been extensively used to relieve endometriotic pain by suppressing ovarian estrogen biosynthesis, in turn, suppressing growth and inflammation. Unfortunately, the relief of pain appears to be relatively short-term and approximately 9% of females with endometriosis simply do not respond to progestin therapy. Among progestogens, dienogest (DNG) seems the most effective, approved for endometriosis and well documented. It remains the first choice being as effective as Gn RH analogue for the relief of pain symptoms associated with endometriosis, but with a better clinical profile: more tolerated and less expensive<sup>3,4</sup>.

Oral contraceptives (OCs) have been widely used for endometriosis suppression being safe, effective, and appropriate for long-term use<sup>5,6</sup>.

Low-dose OCs inhibit the growth of ovarian endometrioma as confirmed in placebo-controlled double-blind randomized trials<sup>7</sup> and postoperative use of OCs reduces the risk of ovarian endometrioma recurrence after laparoscopic cystectomy, as confirmed by many studies<sup>8-10</sup>.

DNG is also combined with estradiol valerate in OCs necessitating more stringent dosing guidelines for maximum contraceptive efficacy: backup contraception is usually required for any pill taken more than 12 hours later than scheduled<sup>11</sup>. Irregular timing of use is frequent in ordinary practice. This could allow some follicular development with consequent increased estradiol production which could affect endometriosis if compared with other OCs that have a better follicular inhibition.

An OC that combines DNG with 30 mcg of ethinilestradiol (EE) seems a particularly interesting option as it is well tolerated, safe, metabolically neutral and has a good follicular inhibitory effect<sup>12</sup>.

In spite of this no OCs have been specifically approved for the treatment of endometriosis; furthermore, the estrogen contained in OCs, which is EE for almost all formulations, is also theoretically suspected to stimulate endometriosis growth.

Fortunately recent *in vitro* data<sup>13</sup> have demonstrated the opposite: the estrogen in OCs can enhance the inhibitory effect of progestin on the growth of ovarian endometrioma cells.

The best treatment, only DNG or EE and DNG, remains thus controversial and a recent study<sup>13</sup> must be considered and discussed, together with other

data, when choosing the right contraceptive and /or the medical endometriosis treatment. Only adequate clinical randomized studies will resolve the question. While waiting, the clinical decision must rely on the considerations hereby reviewed and discussed.

## METHODS

Review of the literature in pubmed searched with the following strategy: (( "Endometriosis/diet therapy" [Mesh] OR "Endometriosis/drug therapy"[Mesh] OR "Endometriosis/enzymology" [Mesh] OR "Endometriosis/etiology" [Mesh] OR "Endometriosis/physiology" [Mesh] OR "Endometriosis/physiopathology" [Mesh] OR "Endometriosis/prevention and control" [Mesh] OR "Endometriosis/therapy" [Mesh] )) AND "Estrogens"[Mesh]

## RESULTS

### *Endometriotic tissue autoproducts estradiol while the impact of ethinilestradiol is less*

The results of the review are summarized in Table 1 and discussed below.

Prescribe and take estrogen containing drugs for and estrogen sensitive diseases like endometriosis could concern physicians and patients, but the following considerations must be done. There is an increased local self-production of estradiol (E2) in

**Table 1.** Reasons not to contraindicate EE/DNG, if the endometriosis patient has other needs like a more reliable ovarian cancer prevention or contraception.

- Endometriotic tissue autoproducts estradiol while the impact of ethinilestradiol is less
- The EE/DNG pill maintains constant low estradiol levels which could not significantly stimulate endometriosis growth.
- Endometriotic tissue has a particular receptor status that makes it progesterone resistant.
- The EE could help the endometriosis suppressive effects of dienogest.
- There is a long lasting experience with pills to suppress endometriosis, reduce recurrence and control endometriotic pain.
- Endometriosis patients could have more used the pill because they were symptomatic, but the past pill use does not cause endometriosis
- The choice of medical treatment must rely not only on endometriosis suppression, but on the overall benefits, compliance and safety.
- Endometriosis patients have a higher ovarian cancer risk and combined estrogen-progestin pills reduce that more than the only progestin does.

the endometriotic lesions, from inactive adrenal precursors<sup>14</sup>, that further promotes proliferation and disease progression through autocrine and paracrine effects, resulting in more inflammation and localised prostaglandin (sigla?) production, thus further enhancing estrogen synthesis<sup>15</sup>.

Endogenous, and not only exogenous, estrogen promotes growth of endometriotic lesions<sup>16</sup>.

Estradiol can be increasingly synthesized locally in endometriotic lesions via the aromatase pathway, which catalyzes conversion of ovarian or adrenal testosterone (sigla?) to E2 and conversion of androstenedione to estrone (E1)<sup>17,18</sup>.

E1 formed via the aromatase pathway is converted into E2 by the action of reductive 17 beta hydroxysteroid dehydrogenase type 1 (HSD17B1), but this E2 can be inactivated by the action of the oxidative 17 beta hydroxysteroid dehydrogenases type 2 (HSD17B2). Expression of HSD17B1 increases in endometriotic lesions, and expression of HSD17B2 decreases<sup>14,19,20</sup>. There is therefore an abnormal intracellular accumulation of E2 which prolongs the activity and proliferative effects. The EE is not metabolized by 17 $\beta$  HSD, it is catabolized by oxidation. So even in the endometriotic lesions, there is no buildup of estrogen and the impact of EE is less than that of estradiol<sup>21</sup>.

### ***The EE/DNG pill maintains constant low estradiol levels which could not stimulate endometriosis growth***

Clinicians are concerned about the undesirable action of estrogen because it antagonizes progestin in the eutopic endometrium, but the mitogenic effect of estrogen contained in OCs (EE) could be negligible or limited in endometriotic patients. The levels of E2 in the presence of 30 mcg EE plus 2 mg of DNG are much lower than in non OCs users<sup>22</sup>, and similar to those produced in the presence of only DNG ( $\leq 50$  pg/ml like in the early follicular phase). In the already mentioned recent study<sup>13</sup> by Bono et al, the concentration of EE used assay (0.6 nmol/L) is within blood concentration range based on in vivo data from patients treated with OCs. Those doses are insufficient for endometriosis growth activation in vitro. A significant endometriosis cells growth stimulation occurs at 100 nmol/L, but not till 10 nmol/L of EE.

Dienogest alone does not suppress FSH and LH as the addition of 30 mcg of EE does in the OCs and it has a high incidence of abnormal menstrual bleeding patterns<sup>23</sup>.

Furthermore estrogen alone fails to promote cell growth of ovarian endometrioma in vitro<sup>24</sup>, despite the accumulating etiologic evidence that es-

trogen is key to growth of endometriosis. It is not due to insufficient expression of ERa, that is over-expressed in these cells. A possible explanation is that estrogen requires additional humoral factors to promote growth of endometriotic cells in vivo which may be lacking in the in vitro culture system. Again this are in vitro data and must be considered with caution, but they challenge the common view of the absolute contraindication of estrogens in endometriosis or the detrimental effect of EE combined with DNG.

### ***Endometriotic tissue has a particular receptor status that makes it progesterone resistant***

Endometriotic cells are progesterone resistant because they are severely deficient in progesterone receptor B (PR-B) and estrogen receptor alpha (ER $\alpha$ )<sup>25,26</sup>.

PR-B is stronger activator of progesterone target genes, whereas progesterone receptor A (PR-A) is a dominant repressor of PR-B and is increased in the endometriotic tissue.

There is also a strikingly lower estrogen receptor alpha to beta (ER $\alpha$ /ER $\beta$ ) ratio in endometriotic stromal cells that may cause a shift from estradiol stimulation to inhibition of PR expression. ER $\alpha$  deficiency in endometriosis may be responsible for failure of E2 to induce PR expression, thus contributing to secondary PR deficiency and progesterone resistance in women with this disease<sup>27</sup>. ER $\beta$  simulates prostaglandin via inducing COX2 expression.

DNG may improve progesterone resistance in endometriotic tissue by increasing the relative expressions of PR-B and PR-A, and decreasing the relative expressions of ER $\beta$  and ER $\alpha$ <sup>28</sup>.

To summarise, the peculiar endometriotic tissue sex steroid receptor status, a high ER Beta/Alpha and PR-A/ B ratio, results in progesterone resistance<sup>29</sup>. This in vitro data can help understanding the supposed beneficial exogenous estrogen effects, even though they have to be taken with caution before inferring clinical considerations based on observational basic research findings.

### ***The EE could help the endometriosis suppressive effects of the dienogest***

The addition of EE to DNG seems to significantly enhance endometriosis progestin growth suppression, instead of harming. An in vitro finding<sup>13</sup> supports the concept that estrogen in OCs does not interfere with progestin. Paradoxically estrogen may support the action of progestins on ovarian endometrioma epithelial cells, while in the absence of estrogen priming the



only progestin inhibits its receptor. In the above mentioned study telomerase-immortalized epithelial cells derived from ovarian endometrioma have been treated with progestogens with or without EE (0.6 nmol/L) for 96 hours, and the cell growth has been monitored. Estrogen receptor (ER)  $\alpha$ , PR-A, and PR-B expressions in clinical samples of ovarian endometrioma epithelial cells have been analyzed with the use of immunohistochemistry.

Progestations have effectively suppressed cell growth, and the addition of EE has significantly enhanced the growth suppression. This EE mediated enhancement of cell growth suppression has been observed only in cells expressing ER $\alpha$  and therefore it was ER $\alpha$  dependent. The expression of PR-B has been significantly induced by the addition of EE. The ER $\alpha$  expression and PR-B expression are significantly correlated, indicating that progestin-sensitive cells with PRB expression are predisposed to react with estrogen stimulation.

Thus, progestins in a OCs act more if their receptors are primed by the estrogen, like EE and they could more strongly reduce cellular growth, prevent implantation, induce cellular differentiation, decidualization and apoptosis of endometriotic cells<sup>30,31</sup>.

### ***There is a long lasting experience with pills to suppress endometriosis, reduce recurrence and control endometriotic pain***

Medical therapy constitutes an important alternative or complement to surgery that could not always give a complete relief of pelvic pain or its recurrence and has some risks like oocyte depletion. However, pharmacological intervention suppresses instead of eliminating the endometriotic implants. Because this implies prolonged periods of medical treatments, therapy for endometriosis is inevitably a compromise: the one with the best safety, tolerability, efficacy and cost profile is the first choice. Progestins seem the best first choice, but the other benefits and the supposed no harming effect of OCs, makes the combined pill a good treatment for most patients with symptomatic or recurring endometriosis.

Low-dose OCs inhibits the growth of ovarian endometriomas as confirmed in placebo-controlled double-blind randomized trials<sup>7</sup>. Pills (OCs) also effectively prevent recurrence<sup>32</sup>.

Furthermore, there is no difference in outcomes between the OCs and GnRH analogue in treating for endometriosis-associated painful symptoms<sup>33</sup>.

OCs used continuously are a worthy option in women with peritoneal and ovarian lesions. Pills are extremely effective in prevention of endometrioma recurrence, whether used continuously or cyclically, as the main mechanism of action seems to be ovulation inhibition.

OCs are therefore widely used to treat the symptoms of endometriosis, although they are not approved for this indication in the majority of countries due to the lack of supportive trial evidences.

### ***Endometriosis patients could have more used the pill because they were symptomatic, but the past pill use does not cause endometriosis***

A meta-analysis claims that the incidence of endometriosis is decreased in current OC users but increased in past users<sup>34</sup>.

The history of OC use for severe primary dysmenorrhea is associated with surgical diagnosis of endometriosis, especially deep infiltrating endometriosis (DIE) later in life, but this association would not constitute a proof of cause and effect. The past use of OC for primary dysmenorrhea may serve as a marker for women with endometriosis and DIE<sup>35</sup>. It is more likely that women who receive OC for dysmenorrhea may already have developed endometriosis, but it is still undiagnosed. In fact, dysmenorrhea as a reason to initiate OCs use is more frequent among endometriotic patients<sup>36</sup>. The link between endometriosis and OCs use remains unclear, and further research is needed to fully evaluate the role of OCs in the management of endometriosis, but the harming effect seems unlikely.

### ***The choice of medical treatment must rely not only on endometriosis suppression, but on the overall benefits, compliance and safety***

Endometriosis medical treatment is based on suppression of ovarian function and induction of a steady hormonal condition, anovulation and, eventually, amenorrhoea. The steroidal environment should be modulated to avoid excessive hypo-estrogenism as well as hyper-androgenism. In both cases, subjective and metabolic untoward effects would considerably undermine safety and tolerability.

OCs, used cyclically or continuously, may constitute an adequate first-line option for peritoneal and ovarian endometriosis. Low-dose oral norethisterone acetate (NETA) could be a choice for rectovaginal lesions but with a worse benefit/side effects profile than OCs. The extensive epidemiologic information available demonstrate that OCs are a safe medical alternative for long-term treatments of endometriosis, well tolerated, with many added benefits beside contraception and relatively cheap<sup>37-42</sup>.

To date, the first-line treatment for endometriosis associated pain or a valid, safe, and economical therapeutic coverage for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis<sup>43,44</sup> is still represented by COs used continuously<sup>45</sup>.

Dienogest is significantly more effective than placebo in reducing endometriosis-associated pelvic pain<sup>46</sup>, but there are no clinical trials that have proven its contraceptive efficacy and a recent Cochrane review has shown that the use of progestogens does not seem to be more effective than low-dose COs in controlling symptoms<sup>47</sup>.

### ***Endometriosis patients have a higher risk for ovarian cancer and combined estrogen-progestin pills reduce that more than the only progestin***

A current topic in the field of endometriosis research is the malignant progression of benign ovarian endometrioma to ovarian cancer<sup>48</sup>.

A woman's lifetime risk of developing any invasive ovarian cancer is 1.2% (0.47-1.8%)<sup>49</sup> or about 1 in 72 and the overall 5 year survival is around 44%. Ovarian cancer risk is 27-80% higher in women with endometriosis compared with the general population, especially for some tumor morphologies: the relative risk of clear cell carcinoma is 3.05 (95% CI 2.43-3.84,  $p < 0.0001$ ), of low-grade serous is 2.11 (1.39-3.20,  $p < 0.0001$ ) and the OR of endometrioid ovarian adenocarcinoma is 2.04 (95% CI, 1.67-2.48,  $p < 0.0001$ )<sup>50,51</sup>.

According to a recent meta-analysis<sup>52</sup> the risk of ovarian cancer in women with endometriosis has a standardized incidence ratio of 1.43-8.95, a rate ratio of 1.6-2.88, an odds ratio of 1.34, with a prevalence of ovarian cancer in 2.0-17.0% of women with endometriosis. Conversely, the prevalence of endometriosis in women with ovarian cancer ranges from 3.4 to 52.6%. A regimen of relatively frequent examinations, including transvaginal ultrasound, in endometriosis patients with a "high risk" of developing ovarian cancer seems therefore reasonable.

Endometriosis-associated ovarian cancer (EAOC) risk is increased in another recent meta-analysis<sup>53</sup> in case-control or two-arm cohort studies (RR, 1.265; 95% CI, 1.214-1.318) and even more in single-arm cohort studies (SIR, 1.797; 95% CI, 1.276-2.531).

EAOC shows favourable characteristics including early-stage and low-grade disease. Although progression-free survival is not different between EAOC and non-EAOC (HR, 1.023; 95% CI, 0.712-1.470), EAOC is associated with better

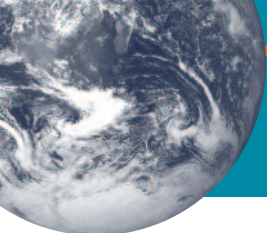
overall survival than non-EAOC in crude analyses (HR, 0.778; 95% CI, 0.655-0.925). In spite of favorable characteristics of EAOC, there is no difference in prognosis between EAOC and non-EAOC when adjusted with stage and a specific histology that suggests that endometriosis may not affect the progression after the onset of ovarian cancer.

Ovarian cancer and endometriosis have some causal factors in common, such as immune imbalance, inflammation and an association with retrograde menstruation<sup>54</sup>.

Endometriosis shares common characteristics of ovarian cancer such as tissue invasion, unrestrained growth, angiogenesis and a decrease in the number of cells undergoing apoptosis. Atypical endometriosis seems to represent a transition from benign endometriosis to carcinoma. It is characterized by genetic instability, it is monoclonal in origin, several studies have documented loss of heterozygosity and mutation of genes like PTEN, TP53, ARID1A. Endometriosis, like cancer, can be both locally and distantly metastatic and it can attach to other tissues, invade, and damage them<sup>55</sup>. Both progestogens, like DNG, or OCs may be used as first-line therapy for endometriosis. Ovarian cancer incidence is significantly reduced in OCs users (OR [odds ratio], 0.73; 95% CI 0.66 to 0.81), with greater reductions seen with longer duration of use<sup>56,57</sup>.

The protective effect of OCs against ovarian cancer may be mainly explained by duration of anovulation. The use of combined OCs only and the mixed use of COs and progestin-only pills decreased the risk of ovarian cancer, while no reduction was found with exclusive use of progestin-only pills, in a recent study<sup>58</sup>. No major differences in risk were found for users of COs with high- and low-potency estrogen and progestin. There was no effect of cumulative progestin intake, but decreased risks of ovarian cancer with increasing cumulative intake of estrogen (OR = 0.82; 95% CI 0.67-0.99, per 100 mg estrogen) and increasing duration of oral contraceptive use (OR = 0.95; 95% CI 0.92-0.98, per year of use). No effect of cumulative estrogen intake was found, however, after adjustment for duration of oral contraceptive use.

Using oral contraceptives, bearing children, and having a tubal ligation or hysterectomy reduced ovarian cancer among women with and without endometriosis, but only the use of oral contraceptives for >10 years was associated with the greatest reduction in risk among women with endometriosis (odds ratio, 0.21; 95% CI, 0.08-0.58)<sup>59</sup>. In that study the odds ratio of ovarian cancer in the endometriotic patients is 1.32 (95% CI, 1.06-1.65). Generally women with endometriosis are treated initially with OCs, but then move on to



other medical treatments for the condition, potentially reducing the protection against ovarian cancer afforded by OCs use (analogues) or maybe increasing that risk (danazol)<sup>60</sup>.

So far, no study sufficiently investigated the potential of contraceptive effect of DNG alone and therefore, it should be recommended with other methods of contraception (e.g., barrier methods) and its ovulation inhibiting effect is likely not as much as that of EE/DNG<sup>61</sup>.

To summarize, the high case-fatality rate that is associated with ovarian cancer makes risk reduction critical especially in women at an identifiably increased risk, such as women with a history of endometriosis. Clinicians should thus be aware of the highly increased risk of specific subtypes of ovarian cancer in women with endometriosis and that, to date, only OCs have emerged as its chemopreventive agents.

## CONCLUSIONS

Dienogest alone is the first choice, as it is a good medical treatment of endometriotic patients, safe, well tolerated and specifically approved for that indication. The adding of EE in a COs prescribed to patients with an estrogen sensitive disease, that affects approximately 10% of women in reproductive age, seems counter-productive but, some new *in vitro* data indicate it could be no detrimental or maybe, paradoxically, beneficial. The balance between estrogen's endometriosis stimulating and indirectly inhibiting effects is critical to the final outcome of OCs based treatment of endometriosis. Endometriotic tissue autoproducts estradiol, while the EE/DNG pill maintains a low stable E2 levels, which seem not significantly stimulate endometriosis growth. Endometriotic tissue is progesterone resistant, so that the presence of EE in OCs does not interfere with progestin. It may instead support the beneficial action of progestins, like DNG, on ovarian endometrioma epithelial cells, up-regulating PR and thereby enhancing responsiveness to progestin. There is a long lasting experience with pills to suppress endometriosis, reduce recurrence and control endometriotic pain. The link between OC use and endometriosis is not a causal one, but it could be explained by the preferential OCs use by endometriosis symptomatic patients. So it should not be a reason to avoid COs in these patients.

OCs reduce the rate of post-operative endometrioma recurrence and they limit further endometriotic and surgical damage to future fertility. They have contraceptive and other added benefits that should be considered upon prescription. Fi-

nally, endometriosis is strongly associated with the increased risk of ovarian cancer and OCs reduce the risk of ovarian neoplasms, which is also important in the choice. Endometriosis therapy and ovarian cancer prevention need a very long term treatment. Only adequate clinical studies will resolve the controversy about EE/DNG versus DNG effects on endometriosis.

Many patients have other desires, beside endometriosis suppression. The prescriber should choose the treatment that can resolve, at the same time, controversial and sometimes opposite needs. If the aim of the treatment is not endometriosis suppression, but ovarian cancer prevention and estrogen mediated benefits, like contraception, non contraceptive OCs benefits, compliance and/or long term affordability of the treatment, the EE plus DNG pill seems better than DNG alone or at least not contraindicated in endometriosis patients.

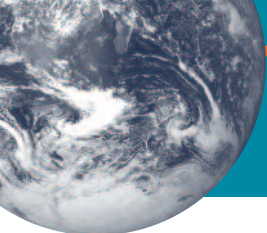
## Conflict of Interests:

The Authors declare that they have no conflict of interests.

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