



AS DIENOGEST EFFECTIVELY SUPPRESSES ENDOMETRIOSIS, COULD IT ALSO REDUCE ENDOMETRIOSIS-ASSOCIATED OVARIAN CANCERS? A FURTHER MOTIVATION FOR LONG-TERM MEDICAL TREATMENT

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Abstract – Endometriosis increases the risk of endometriosis-associated ovarian cancer (EAOC). Although the issue is still controversial, the malignant transformation of endometriotic lesions seems more plausible than a mere risk factor sharing between endometriosis and ovarian cancer. As a consequence, an effective endometriosis suppressive medical treatment, like dienogest, could reduce at least some subtypes of estrogen sensitive ovarian cancer, like the endometrioid one. Endometriosis medical treatment aim is to control pain and to reduce surgery. The potential and still speculative ovarian cancer preventive effect could be a further suggestion to increase compliance to a long lasting treatment, while adequate clinical trials are necessary to confirm this hypothesis.

KEY WORDS: Endometriosis, Dienogest, Ovarian cancer, Endometriotic cancer, Clear cells cancer, Ovulation inhibition, Progestogens, Inflammation, Apoptosis, Angiogenesis.

BACKGROUND

Endometriosis is an estrogen-dependent inflammatory disease characterized by the presence and proliferation of endometrium-like cells outside of the uterine cavity. Progestogens can help suppress endometriosis pain¹.

Dienogest (DNG) is a safe, effective and well tolerated progestogen treatment specifically studied for endometriosis management^{2,3}.

DNG is as effective as Gn RH analogues for the relief of pain symptoms associated with endometriosis, but with a better clinical profile: is more tolerated and less expensive^{4,5}.

Endometriosis patients are at higher risk of ovarian and breast cancers, cutaneous melanoma, asthma, and some autoimmune, cardiovascular and atopic diseases⁶. In women suffering from endometriosis, the risk of ovarian cancer is doubled: it increases from about 1 in 100 to 2 in 100. Some ovarian malignancies, particularly endometrioid and clear cell subtypes, arise in the

context of concomitant endometriosis. There is still controversy whether endometriosis transforms into cancer or there are only shared risk factors. DNG has not only progestin effects, but it also suppresses endometriotic tissue growth, angiogenesis and inflammation and promotes apoptosis⁷. These are mechanisms that could also reduce ovarian cancer growth. So we can speculate that DNG could help to reduce endometriosis-associated ovarian cancer. The aim of this article is to discuss this hypothesis in order to consider the feasibility of testing it in adequate clinical trials.

METHODS

A literature search in Pubmed using the keywords “dienogest”, “endometriosis” and “ovarian neoplasms”. Other important databases were searched: Medline, Trip Database and The Cochrane Library up to June 2015.



RESULTS

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

Endometriosis patients have higher risk of some ovarian cancer subtypes.

A woman's lifetime risk of developing any invasive ovarian cancer is 1.2% (0.47-1.8%)⁸, 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 odds ratio of endometrioid ovarian adenocarcinoma is 2.04 (95% CI, 1.67-2.48, $p < 0.0001$)^{9,10}.

Endometriosis-associated ovarian cancer (EAOC) risk has been reported increased in another recent meta-analysis¹¹ 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).

When compared with population-based controls, the risk of endometrioid/clear cell ovarian cancer for women with endometriosis is three times greater¹².

Approximately 9% of the ovarian malignancies, particularly endometrioid and clear cell subtypes, arises in the context of concomitant endometriosis. In the ovary most are endometrioid adenocarcinomas. In contrast, clear cell carcinomas are most commonly observed in extraovarian endometriosis¹³.

In a review of 64492 women with endometriosis¹⁴, the standardized incidence ratio of ovarian cancer has been found to be 1.43 and in women with long standing history of endometriosis it is 2.23.

EAOCs, as nonserous carcinomas of the ovary, present with pelvic pain, abnormal vaginal bleed-

ing, with or without a pelvic mass and are usually detected early in contrast to serous papillary carcinomas, which present with asymptomatic masses and are usually late diagnosed¹⁵.

EAOC shows favorable 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), in crude analyses EAOC is associated with better overall survival than non-EAOC (HR, 0.778; 95% CI, 0.655-0.925)¹⁶.

EOAC have lower preoperative serum CA 125 level (mean 122.9 vs 1377.5 U/ mL) and are more likely to display normal CA 125 levels¹⁷.

In spite of the favorable characteristics of EAOC, there is no difference in prognosis between EAOC and non-EAOC when adjusted with stage and specific histology, suggesting that endometriosis may not affect the progression after the onset of ovarian cancer.

It is likely that endometriosis could transform into malignancy, rather than being only associated with it

Endometriosis might transform into ovarian cancer or they may only share similar risk factors and/or antecedent mechanisms¹⁸.

Histologic transition from benign endometriosis to ovarian malignancy, including malignant transformation of extraovarian endometriosis has been confirmed¹⁹.

According to a recent case series and review, endometriosis can transform into malignancy in about 1% of lesions, with ovary being the primary site in 79%²⁰.

This is biologically plausible and coherent with the new unifying theory that could explain the origins and pathogenesis of epithelial ovarian cancer²¹⁻²⁴.

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 them²⁵.

Ovarian carcinogenesis from endometriosis could be related to oxidative stress, inflammation and estrogenic effect or a combination of this mechanisms common to both endometriosis and ovarian cancer²⁶.

Repetitive hemorrhage and the accumulation of heme and free iron within endometriotic lesions

Table 1. Dienogest, endometriosis and ovarian cancers.

- Endometriosis patients have a higher risk of some ovarian cancer subtypes.
- It is more likely that endometriosis could transform into malignancy, rather than being only associated.
- Some endometriosis presentations have a higher risk of malignant transformation and need to be more closely monitored.
- There is no consensus on whether surgery effectively prevents endometriosis neoplastic transformation.
- As dienogest reduces endometriosis proliferation it could theoretically also reduce its neoplastic transformation.

lead to the formation of reactive oxygen species that cause oxidative stress. Inflammatory mediators and increased number of activated macrophages, cytokines, and chemokines in the peritoneal fluid in endometriosis, along with prostaglandin PGE 2, promote the development and progression of endometriosis-associated ovarian cancer.

The microenvironment provided by endometriosis facilitates the accumulation of excess estrogen by increased aromatase and absent 17- β -hydroxy-steroid-dehydrogenase activity, which in turn results in cellular proliferation through stimulation of cytokine and PGE 2 production.

The question of whether endometriosis causes cancer or it is merely associated remains speculative because, while monoclonal growth has been demonstrated, the other aspects, such as epigenetic alterations, and telomerase activity, are not known and controversy exists regarding the chromosomal gains/losses. Data pertaining to mutations of tumor suppressor genes and oncogenes are limited, discordant, and inconclusive. A loss of estrogen receptor (ER) expression may be pivotal in the carcinogenic pathway separating the development of estrogen-dependent carcinoma (i.e., endometrioid carcinoma) from estrogen-independent carcinoma (i.e., clear cell carcinoma)²⁷.

Endometrioid carcinoma accounts for 10% to 15% of ovarian carcinomas, it is most common in the fifth and sixth decade and is the subtype more likely correlated with endometriosis. Up to 42% of the tumors are associated with endometriosis in the same ovary or elsewhere in the pelvis. Patients whose tumors occur in association with endometriosis are averagely 5 to 10 years younger than patients without associated ovarian endometriosis²⁸. The presence of shared molecular genetic changes in endometriosis, endometrioid borderline/atypical proliferative tumors and low-grade endometrioid carcinoma, supports endometriosis as a precursor lesion. Endometriotic deposits are monoclonal and demonstrate loss of heterozygosity (LOH) on chromosomes 9p, 11q, and 22q. Atypical endometriosis and endometrioid carcinoma of the ovary share these genetic alterations and in particular, the patterns of genetic alteration are related to the proximity between endometriosis and endometrioid carcinoma, indicative of the spectrum of tumor progression²⁹.

The patterns of LOH in endometriotic-associated carcinoma are similar to those found in endometriosis but the rates of LOH are significantly higher (20% to 60% in endometriotic-associated carcinoma vs. 10% to 20% in endometriosis)³⁰.

Nevertheless the biological evidence supporting the idea of endometriosis as a preneoplastic condition is still controversial³¹.

Ovarian cancer and endometriosis have some risk factors in common, such as immune imbalance, inflammation and an association with retrograde menstruation. They also share features such as tissue invasion, unrestrained growth, angiogenesis and a decrease in the number of cells undergoing apoptosis³², thus the association could also be non ethiological. Causal mechanism and common unrelated risk factors could also coexist.

Some endometriosis presentations have a higher risk of malignant transformation and need to be more closely monitored

Some women with endometriosis and ovarian endometriomas must be followed up more carefully and they theoretically need to be treated more aggressively and/or with a longer medical suppressive treatment in order to prevent endometriosis associated ovarian cancer.

The risk factors for malignant transformation that could substantiate a causal relationship include long-standing endometriosis, endometriosis diagnosed at an early age, infertility and/or history of infertility treatment, and ovarian endometriomas³³.

The features suspicious for malignant transformation of endometriosis are a rapidly enlarging mass with solid regions or abundant blood supply on sonography³⁴.

Contrast material-enhanced mural nodules within a cystic mass or enlargement of the endometrioma and the disappearance of shading within the mass are typical T2-weighted images on MRI³⁵.

A high level and/or rapid increase of serum CA-125 level can raise suspicion too³⁶.

Severe endometriosis and ovarian endometriomas >9 cm in size in women \geq 45 years increase the risk³⁷.

Atypical endometriotic foci are histologically characterized by large hyperchromatic or pale pleomorphic nuclei, an increased nuclearto-cytoplasmic ratio cellular crowding, stratification, or tufting, atypical glandular structures and absence of ER and progesterone receptor (PR) protein expression³⁸.

There is no consensus on whether surgery effectively prevents endometriosis neoplastic transformation

Complete excision of ovarian endometriomas, which may harbor occult malignancies, is preferable to cyst aspiration since the latter fails to provide definitive tissue diagnosis.



There is no consensus on whether a systematic and serial surgery in women with endometriosis to eradicate visible lesions is justifiable, for the only purpose to eliminate risk of malignancy, as there could be major operative morbidity due to adhesions and other anatomical distortions.

Until now, no definitive data confirm that early surgical treatment of limited implants is associated with a reduced risk of disease progression and malignancy³⁹.

As dienogest reduces endometriosis proliferation it could theoretically also reduce its neoplastic transformation

Some medical treatments reduce the risk of ovarian cancer. Oral contraceptives inhibit ovulation and this is a reason of their confirmed ovarian cancer preventive effect⁴⁰.

Women with endometriosis who are using oral contraceptive for more than 10 years have a 80% lower occurrence of ovarian cancer⁴¹.

We do not have yet such data for progestogens, like DNG, as its use is more recent. Therefore, the question whether to use an oral contraceptive or only DNG for ovarian cancer preventions, remains controversial. Each women have to personalize the choice according to their specific needs and priorities⁴².

DNG is a first-line drug for endometriosis-associated pain. As endometriosis is potential ovarian cancer precursor, the suppressive DNG effects makes this drug a further good ovarian cancer preventive strategy candidate.

DNG also in monotherapy possesses potent ovulation-inhibiting effects at doses equal or higher than 2 mg⁴³. During ovulation the ovary can attract extra-ovarian malignant cells and provide a fertile soil to support the adhesion of malignant cells, that in most cases seems to have an extra ovarian origin. Therefore, ovulation inhibition, that is one of the main anticancer effects of pills, could also be one of the DNG ovarian cancer preventive mechanisms.

DNG has also a potent progestogenic effect. At least a subset of low-grade endometrioid adenocarcinomas arise from ovarian endometriosis with mutations of CTNNB1 and PTEN, probably progressing through endometrial-like hyperplasia as an intermediate step³⁰. Progesterone and its derivatives can prevent endometrial cancer and they can even reverse some kinds of early well differentiated endometrial cancers better than combined oral contraceptives⁴⁴. Fourth generation progestins also inhibit endometrial cancer. DNG antitumor activity is specifically attracting close attention following a report that this drug suppressed the proliferation in vitro of endometrial cancer-de-

rived cell lines which failed to respond to other progestins such as medroxyprogesterone acetate (MPA). The mechanism for antitumor activity of DNG is considered to be different than the mechanism of conventional progestin preparations used for treatment of endometrial cancer. This drug is expected to be clinically applicable as a new drug for the treatment of endometrial cancer⁴⁵.

Adiposity is implicated in carcinogenesis especially for estrogen sensitive diseases⁴⁶ and a progestogen, like DNG, can help to counteract the higher endogenous estrogen levels.

Inflammation, apoptosis inhibition and angiogenesis are among the pathogenetic mechanisms of ovarian cancer. DNG is not only a safe, well tolerated and specifically approved medical treatment for endometriosis, it has a stronger growth inhibiting and endometrial secretory transforming potency, compared with other progestogens. DNG has also anti-inflammatory, proapoptotic and antiangiogenic properties⁴⁷⁻⁴⁹.

We can speculate that these further anti-cancer mechanisms of DNG⁵⁰ can help to reduce endometriosis transformation. These putative anti-ovarian cancer effects of DNG, summarized in Table 2, will need adequate studies to be confirmed.

CONCLUSIONS

When compared with population-based controls, the risk of endometrioid and clear cell ovarian cancer for women with endometriosis is about three times greater. Endometriosis and ovarian cancer could share common risk factors and not be etiologically related. Alternatively, it seems more biologically plausible that endometriosis could cause ovarian carcinogenesis because of oxidative stress, inflammation and estrogenic effect, or a combination of these mechanisms. Endometrioid ovarian cancer is particularly estrogen sensitive and a progestogenic effect can be suppressive.

DNG is a safe, well tolerated and specifically approved medical treatment of endometriosis. At a 2 mg dose, it suppresses ovulation. Compared with other progestogens DNG has a stronger endometrial secretory transforming potency. It also

Table 2. Possible mechanisms by which dienogest could reduce endometriosis associated ovarian cancer.

- Inhibition of ovulation
- Progestogenic effects
- Reduction of inflammation
- Increase of apoptosis
- Reduction of angiogenesis

have growth inhibiting, anti-inflammatory, proapoptotic and antiangiogenic proprieties. All the mentioned actions could potentially counteract ovarian cancer pathogenetic mechanisms.

Clinicians should not only inform endometriotic patients of their higher ovarian cancer risk, but, while waiting for clinical confirmation, they could also use the likely ovarian cancer prevention effect as a further motivation to use DNG as a long term treatment.

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