World Journal of Obstetrics and Gynecology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5317/wjog.v3.i2.28

World J Obstet Gynecol 2014 May 10; 3(2): 28-34
ISSN 2218-6220 (online)

TOPIC HIGHLIGHT

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Pathological conditions predisposing to infertility and gynaecological neoplasia

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Received: January 6, 2013 Revised: March 4, 2013
Accepted: April 10, 2013
Published online: May 10, 2014

Abstract

Some of the conditions long blamed for female factor infertility are now acknowledged as well established risk factors of gynecological neoplasia. This realization has lead to the proposition that infertility might be a risk factor for the development of several types of gynecological neoplasms. This review addresses different conditions that play a role in both infertility and gynaecological neoplasia. An intricate interplay between growth factors and hormonal factors (estrogens and progestins, androgens and gonadotropins) is said to link the state of infertility to some gynecological tumors. The relation between endometriosis -as one of the well established causes of female infertility - and ovarian cancer is well known. Endometriosis has been particularly related to endometrioid and clear-cell ovarian carcinomas. Another evidence for this association is embodied in finding endometriotic lesions adjacent to ovarian cancers. The polycystic ovary syndrome (PCOS), one of the most prevalent endocrine disorders and a long studied cause of female infertility increases the risk of endometrial carcinoma. The link between PCOS and endometrial carcinoma seems to be endometrial hyperplasia. PCOS-associated endometrial carcinoma tends to present at a younger age and early stage, with lower grade and lower risk of metastasis. Turner's syndrome and other types of ovarian dysgenesis constitute a rare cause of infertility and are known to confer a definite risk of germ cell tumors. There seems to be a link between infertility and an increased risk of gynecological neoplasia. Hence, it is important to assess the risk of malignancy in each category of infertile patients so as to provide optimal and timely intervention.

Key words: Infertility-gynecological cancer; Endometriosis; Polycystic ovary syndrome; Ovarian dysgenesis; Endometrioid carcinoma; Clear cell carcinoma; Turner's syndrome; Gonadoblastoma; Hyperestrogenemia

Core tip: Female infertility is now acknowledged as a risk factor of gynecological neoplasia. In this mini-review we conduct a comprehensive literature review to verify this prospect. The principal pathogenetic mechanisms linking infertility to gynecological neoplasia are pointed out. The relationship between each of endometriosis and polycystic ovary syndrome and gynecological neoplasia is explored in depth. We discuss the relation of Turner's syndrome (the prototype of ovarian dysgenesis) to gynecological cancer. Is there a relation between increased risk of ovarian cancer and ovulation-stimulation drugs? We will attempt to answer this question.

El Sabaa BM. Pathological conditions predisposing to infertility and gynaecological neoplasia. *World J Obstet Gynecol* 2014; 3(2): 28-34 Available from: URL: http://www.wjgnet.com/2218-6220/full/v3/i2/28.htm DOI: http://dx.doi.org/10.5317/wjog.v3.i2.28

INTRODUCTION

In a World Health Organization 1992[1] study of 8500 infertile couples, the female factor was responsible for infertility in 37% of cases *vs* the male factor which was responsible in 8% of cases, while both factors were jointly

responsible for infertility in 35% of cases[1]. Ovulatory disorders, genetic factors, endometriosis, pelvic adhesions, tubal obstruction and hyperprolactinemia together constitute the principal causes of female factor infertility[1].

IS THERE A RELATION BETWEEN INFERTILITY AND GYNECOLOGICAL NEOPLASIA?

Some of the conditions responsible for female factor infertility are known risk factors of gynecological neoplasia. Ovarian and endometrial cancers are associated with several risk factors such as low parity, early age of menarche and late age of menopause[2].

It is a well known fact that infertile females are more at risk of endometrial cancer[2].

Compared with fertile ones, infertile women had an adjusted odds ratio for endometrial cancer of 1.7 (95%CI: 1.1-2.6). On the other hand, infertile women due to ovarian factors had an adjusted odds ratio of 4.2 (95%CI: 1.7-10.4) suggesting that much of the increased risk of endometrial carcinoma seen in some infertile women might be ascribed to anovulation[3]. In the same context, there is some evidence to suggest that infertility increases risk of ovarian cancer as well[4,5].

Numerous studies have endeavored to explain the observed increased risk of ovarian cancer in infertile females. Most have inferred that factors operative in that setting include the pathogenesis of infertility itself, the effects of ovulation inducing drugs, a "putative" shared genetic susceptibility to infertility and ovarian cancer, or an as yet unrecognized factor[6].

The etiology of ovarian cancer is poorly understood. Many hypotheses point to the cumulative insults of repeated ovulation "theory of incessant ovulation[7]" coupled with exposure of the ovary to high gonadotropin levels. These factors are believed to be the proximate players that can stimulate cell proliferation and malignant transformation of the ovarian surface epithelium. Factors interrupting ovulation and empowering progesterone stimulation or androgen reduction were found to decrease the risk of ovarian cancer. Such factors include pregnancy, breastfeeding and the use of oral contraceptives. On the other hand, factors that prolong exposure to ovulation as infertility were found to augment the risk[8-12] by as much as 36%-46%[4,5].

In fact the number of lifetime ovulatory cycles (LOC) relative to age was found to be a significant predictive factor for survival in ovarian cancer patients, where patients with higher LOC had worse overall survival (HR = 1.67; 95%CI: 1.20-2.33)[13]. Years before that research was conducted; the role of ovarian surface epithelium in ovulation had been demonstrated. Ovarian surface epithelial cells in the vicinity of the apical portion of preovulatory graafian follicles produce a urokinase which augments the production of tumour necrosis factor-α. The latter induces matrix metalloproteinase gene expression, apoptosis and inflammatory necrosis leading to follicle rupture. Afterwards, the disrupted ovarian epithelium is reconstituted by stem cell multiplication. The damaging effects of the liberated reactive oxygen species and the reparative/regenerative events that occur due to the repeated bouts of ovulation[14] have been linked to surface epithelial ovarian cancer. During the ovulatory process, DNA integrity of surface epithelial cells surrounding the rupture point is deranged. Replication of such cells will perpetuate the putative DNA error which might play a role in ovarian carcinogenesis[15].

In the same context, vitamin E and progesterone have been experimentally proven, recently, to confer protection against ovarian neoplastic transformation by abrogating ovulation associated oxidative bursts and by improving the repair capacity of surface epithelium[16].

Different phases of a woman's reproductive life display varying sensitivities of ovarian cells to hormone stimulation. Loss of ovarian function taking place during transition to menopause results in follicular depletion and hence fluctuation in estrogen and a corresponding surge in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. However, menopause is also associated with a remarkable attenuation of the negative feedback exerted by gonadal steroids on the hypothalamo-pituitary axis. Based on these facts, Tung *et al*[17] came to the conclusion that the risk reducing effects of anovulatory states as pregnancy and intake of oral contraceptives were more pronounced in pre-menopausal compared to postmenopausal women.

Evidence is now accumulating about the existence of stem cells in postnatal and adult mammalian (including human) ovaries. This has great potential for initiating major developments in understanding and managing ovarian infertility as well as ovarian carcinogenesis[18].

Pathogenetic link between infertility and gynecological "malignancy"

Abnormalities in growth factors and hormonal status seem to be the pivotal players in this link.

Growth factors: Adipose tissue and stromal cells of the ovary generate growth factors, *e.g.*, insulin-like growth factor 1 (IGF-1), transforming growth factor and tumor necrosis factor after hormonal stimulation. A complex interplay of growth factors in polycystic ovary syndrome (PCOS) patients is believed to be the main cause of subfertility/infertility in these patients[19,20]. One such example is the elevated serum IGF-I concentrations in obese PCOS patients[21-25]. On the other hand, growth factors can enhance cellular autonomy and are stimulatory to neoangiogenesis, which are key factors in tumor development and progression[26-28]. In the endometrium, estrogen exerts its trophic effect *via* driving the local expression of the *IGF-1* gene[24]. Genetic variation in strategic genes in the IGF pathway may have impact on the rate of endometrial cell proliferation/differentiation and hence on the risk of malignant transformation[25].

Steroid hormones have been implicated in the etiopathogenesis of epithelial ovarian cancer[26].

Androgens: Hyperandrogenemia during the reproductive years is known to interfere with the normal ovulatory cycle and may result in infertility[27-31]. Several lines of evidence point to a possible role for androgens in ovarian carcinogenesis. There is increased incidence of ovarian cancer after menopause when there is relative predominance of androgens over estrogens. Androgen receptor positivity is expressed in 90% of ovarian cancers with favorable outcomes and chemotherapy induced reduction in androgen elaboration by cancer cells[26].

Gonadotrophins: Pituitary gonadotrophins are considered indirect tumor promoters for ovarian cancer. Furthermore, there is increasing evidence that ovarian and uterine carcinomas express gonadotrophin receptors, indicating the possibility of a direct tumorigenic role for FSH and LH[29-32].

Estrogens: It is a well established fact since 1947, that prolonged endometrial stimulation by unopposed estrogen is a risk factor for the development of endometrial cancer[33]. Anovulatory females recorded higher serum levels of estrogen and higher incidence of endometrial carcinoma especially in PCOS[34].

ENDOMETRIOSIS AND CANCER

Multiple factors seem to be involved in the etio-pathogenesis of both endometriosis and ovarian cancer including hormonal, genetic and immunologic factors. Endometriosis confers a twofold increased risk of developing ovarian cancer rising to fourfold in high risk endometriosis patients with infertility[2].

Several studies confirm endometriosis as an independent risk factor for ovarian cancer[35]. In fact, these two conditions share common predisposing factors, comparable patterns of local invasion and distal spread, similar response to estrogen-induced growth signaling, resistance to apoptosis and genomic instability[35].

The incidence of endometriosis in epithelial ovarian cancer has been calculated to be 4.5%, 1.4%, 35.9% and 19% for serous, mucinous, clear-cell and endometrioid ovarian carcinoma, respectively[35]. It is common knowledge now that the latter two types (endometrioid[36] and clear-cell ovarian[37] carcinomas) are the types most frequently associated with endometriosis[37].

Another evidence for this association is finding endometriotic lesions adjacent to ovarian cancers. Common genetic alterations[38] as *PTEN, p53*[39-41], *HNF-1* activation[42], *K-ras*[42,43], and *bcl* gene mutations[39,44] present further evidence to a possible sequence of genetic changes resulting in transition from endometriosis to ovarian cancer[40]. Furthermore, analogous to neoplastic proliferations, endometriosis has been shown to be monoclonal with several studies documenting loss of heterozygosity[39,42,45,46].

Recently, mutation of *ARID1A*, a tumor-suppressor gene[39,47], and loss of BAF250a[48], both detected in tumor tissue and contiguous foci of atypical endometriosis (but not in distant endometriotic lesions)[48] have been considered important early events in the malignant transformation of endometriosis to endometrioid and clear cell carcinomas[39,48,49].

Another phenomenon linking endometriosis to ovarian cancer is the state of heme and iron induced oxidative stress and chronic inflammation[39,50,51] associated with endometriosis. This state entails cytokine release that through a series of complex steps can eventually culminate in unregulated mitosis, growth, apoptosis and migration; all of which represent key events in tumour development and progression[40,42].

Endometriosis-associated ovarian cancer has been shown to have a more favorable biological behavior as compared to non-endometriosis-associated ovarian cancer, with presentation at a lower stage and a better survival[35].

PCOS AND GYNECOLOGICAL NEOPLASIA

The PCOS is one of the most prevalent endocrine disorders, affecting around 5%-10%[52] of women in the reproductive age group. PCOS is characterized by signs of hyperandrogenism[53], obesity[54], hirsutism[55,56], anovulation, infertility, menstrual irregularities[57] and insulin resistance[58,59]. On sonographic examination the ovaries are usually enlarged with multiple small cysts (2-8 mm)[60,61].

PCOS patients have long-term, higher risk for endometrial hyperplasia and endometrial cancer[62-65], (three[34] to fourfold[66]) due to chronic anovulation which results in continuous estrogen stimulation of the endometrium, unopposed by progesterone[60,67].

Most of the factors known to increase the risk of developing endometrial cancer as obesity, long term unopposed hyperestrogenaemia, nulliparity, infertility and diabetes[68-70] are also known to be associated with PCOS.

The link between PCOS and endometrial carcinoma seems to be endometrial hyperplasia. Forty-eight point eight percent of PCOS cases have endometrial hyperplasia[34]. The estimated rate of progression from hyperplasia to carcinoma within 2 to 10 years seems to be 0.4% for simple hyperplasia[60] and approaches 18% for cases of atypical complex hyperplasia[60,71].

PCOS-associated endometrial carcinoma tends to present at a younger age and early stage, with lower grade and lower risk of metastasis. These factors have practically invited some authors[72,73] to advocate conservative management of carcinoma in these patients.

PCOS has also been reported to be associated with low-grade endometrial stromal sarcoma and uterine carcinosarcoma[74].

Other sex hormone dependent cancers as breast and ovarian cancers have also been linked to PCOS[61]. Recent evidence about association between PCOS and ovarian malignancy are still conflicting[71,74]. According to Danish

studies, the implied state of infertility *per se* increases the risk of borderline and malignant ovarian tumors[75]. High local steroid and growth factor concentrations - frequently observed in PCOS - are considered risk factors for ovarian carcinoma[61]. However, a large scale British study confirms that the standardized mortality rate for ovarian cancer in these patients does not exceed 0.39 (95%CI: 0.01-2.17)[76]. There is insufficient evidence to implicate PCOS in the development of vaginal, vulval and cervical cancers[34].

OVARIAN DYSGENESIS, GENETIC INFERTILITY AND CANCER

Sex chromosome abnormalities compose the largest category of chromosome aberrations and the most common genetic cause of infertility among humans[77-80]. Dysgenetic gonads are at risk for development of germ cell tumors[81-84] which may stem from genetic and/or hormonal factors[85,86].

Dysgenetic gonads are reported to progress to invasive germ cell neoplasms namely; dysgerminoma and less commonly embryonal carcinoma, teratoma, yolk sac tumor and choriocarcinoma[87]. Accordingly some authors[81,88] advocated prophylactic gonadectomy once the diagnosis of gonadal dysgenesis is established.

Turner syndrome is one of the most common conditions resulting from cytogenetic abnormalities where there is complete or partial monosomy of the X-chromosome. These patients have a significantly increased risk of ovarian gonadoblastoma[81,85], dysgerminoma[84] and cancer of the corpus uteri in addition to a constellation of somatic tumors including central nervous system, ocular and urinary bladder tumors[85,89,90]. Paradoxically, risk for breast cancer is decreased among patients with Turner syndrome[85,91,92].

FERTILITY DRUGS AND GYNECOLOGICAL CANCER

Generally, data concerning the possible association of exposure to ovulation induction medications and developing invasive ovarian cancer show no increased risk[6,93-95]. A group exploring the long-term (over 20 years) health effects of ovarian-stimulation drugs showed no relationship between ovarian cancer risk and ovulation-stimulation drugs[91]. However they stressed the importance of continuous monitoring to verify whether such risks were higher among particular user cohorts[96-98]. According to some studies, women who failed to conceive after infertility treatment were found to be at a higher risk for ovarian malignancy compared to women who responded successfully[6,91,99].

The relationship of these agents with risk of breast and endometrial cancer is still controversial[95,100].

CONCLUSION

Infertility seems to confer an increased risk of gynecological neoplasia. It is important to assess the risk of malignancy in each category of infertile patients so as to provide optimal timely intervention. To date, no solid relation has been declared between fertility drugs and causation of gynecological malignancy.

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