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PHYSIOLOGIC (FUNCTIONAL) OVARIAN CYSTS IN REPRODUCTIVE AGE WOMEN: WHO IS AT RISK

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ABSTRACT

Functional or physiologic ovarian cysts are common gynecological problems among women of reproductive age worldwide. Cyst may discover incidentally during routine gynecologic examination or during ultrsounography. Ultrasound characterization is currently considered the most accurate method for predicting the histological diagnosis of ovarian tumors. Most of those cysts are physiological, consisting of either follicular cysts or corpus luteum cysts. Several risk factors have been studied in the literature, some of these are well understood, while the others are poorly understood. Among those risk factors; cigarette smoking, obesity, ovulation induction treatment, progesterone-only pills, levonorgestrel intrauterine system, nutrition, diet, tamoxifen, immune suppressive therapy and tubal sterilization. Surgical intervention is rarely required since most of those cysts resolve spontaneously with observation alone without any medical treatment. When dealing with women of reproductive age with suspected physiologic or functional ovarian cyst; patient should be reassured about the nature of those cysts as the majority will resolve spontaneously.

Introduction:
During the process of normal ovulation, a follicle develops to maturity and then ruptures to release an ovum; this is followed by formation and subsequent involution of the corpus luteum. Follicular cysts arise when rupture does not occur, and the follicle continues to grow. Corpus luteum cysts occur when the corpus luteum fails to involute and continues to enlarge after ovulation (1). Those cysts are therefore called physiologic or functional. Functional ovarian cysts are common gynecological problems among women of reproductive age worldwide. Most patients during reproductive age group with ovarian cyst are asymptomatic. Cyst may discover incidentally during routine gynecologic examination or during ultrsounography. Many patients with functional ovarian cysts found through ultrasonographic examination do not require treatment because most of those cysts are physiological, consisting of either follicular cysts or corpus luteum cysts. The major concern of a cyst is occurrence of possible complications, like rupture or adnexal torsion. The purpose of this review is to highlight the risk factors for the physiologic or functional ovarian cysts.

Material and Methods:
A review of the literature using the keywords: functional ovarian cyst, follicular cysts, corpus luteum cysts and risk factors and conducted the search in Medline, EMBASE, and Cochrane Database of systematic reviews.

Prevalence:
The reported prevalence varies widely depending upon the population studied and the criteria employed. Functional ovarian cysts are a common cause of hospital admission in the USA and the UK (2). The rate of hospitalization for functional ovarian cysts has been estimated to be as high as 500 admissions per 100 000 women in the United States (3). The prevalence of benign ovarian cysts in women of reproductive age is reported as 7% (4). There are nearly 200,000 hospitalizations annually among US women with this gynecologic condition (5).

Risk factors: Several risk factors have been studied in the literature, some of these are well understood, while the others are poorly understood.

a. Cigarette smoking:
It has been suggested that altered serum gonadotropin levels can lead to development of functional ovarian cyst (6). Cigarette smoking is known to affect gonadotropins, ovarian hormones, and ovarian function (7). Generally, smokers tend to have lower follicular-phase serum luteinizing hormone (LH) and higher follicle stimulating hormone level (FSH) (8, 9). This leads to altered production and metabolism of estrogen and progesterone, with shorter, more irregular cycles, increased anovulation and short luteal phase (10-12). The case is like women who smoke marijuana: substantial suppression of plasma levels of LH during the luteal phase of the menstrual cycle, shortened luteal phase and overall cycle length, and anovulation (11).

There is conflicting evidence from several studies regarding this issue; smoking was found to significantly increase ovarian cyst risk by Holt et al. (13). A hospital-based case-control study in Italy, the authors found no significant associations of smoking with cyst formation (14). Wyshak et al. found that the relation between smoking and cyst risk was stronger for women who had been athletes in college than for nonathletic women (RR: 1.90 vs. RR: 1.25) (15). The risk of ovarian cyst in women using marijuana was like cigarette smoking risks (13).

b. Obesity:
It is well known that Increased BMI has hormonal effects in women during their reproductive age. Leptin level is closely correlated with degree of amount of adipose tissue, it counteracts the inhibitory effect of fasting on secretion of LH. Leptin may counteract the LH-suppressive effects of smoking as well (16). Holt et al. found that cigarette smoking, and diagnosis of functional ovarian cyst varied significantly according to women's BMI. The risk of cyst was elevated with current smoking for underweight and normal-weight women but not for overweight women. They also found significant elevations in risk of a functional ovarian cyst with current smoking among women whose BMI was <20.0 (OR= 2.48, 95 percent confidence interval (CI: 1.32, 4.64) or 20.0–25.0 (OR = 1.60, 95 percent CI: 1.04, 2.46). Among women whose BMI was >25.0, smoking was not associated with ovarian cyst risk (OR= 0.85, 95 percent CI: 0.53, 1.37). They also found an increased ovarian cyst risk associated with marijuana use for underweight and normal-weight women as well (13). Parazzini et al. found higher risks for current smoking than for former smoking; they concluded that results indicate that increased BMI may attenuate the adverse impact of smoking on the risk of functional ovarian cyst (14).

c. Ovulation induction:
During induction of ovulation with clomiphene citrate (CC), several women may develop ovarian cysts (17). Functional or persistent ovarian cysts occur more frequently with CC. In a retrospective cohort study evaluating the incidence and factors associated with ovarian cysts in infertile patients receiving CC found that cysts were more likely to persist if a patient had received CC in the preceding cycle (18). Altinkaya et al. found that persistence of ovarian cysts was significantly higher in women with a longer duration of CC treatment than in women with a shorter duration (19). McNatty suggested that early follicular development is caused primarily by FSH, and therefore, the surge of FSH, rather than LH, is probably responsible for functional cyst formation (20). Therefore, to prevent the formation of functional ovarian cysts in the follicular phase of the cycle, the initial FSH surge should be

attenuated. Meldrum et al. found that pituitary suppression by GnRH agonists if begun in the early follicular phase, it results in formation of functional ovarian cysts in up to 40% of patients (21). In patients who have ovarian cysts develop the administration of GnRH agonists generally must be continued for a prolonged time before serum estradiol concentrations decrease to a basal level. The administration of oral contraceptives (OCs) significantly suppresses the levels of FSH and LH (22). The administration of the OC pill could, therefore, reduce the incidence of cyst formation. One of the disadvantages of early follicular over midluteal initiation of GnRH agonist is the generally increased incidence of ovarian cyst formation when GnRH agonist is started in the early follicular phase (23). Biljan et al. found that pretreatment with OCs prior to pituitary suppression in the early follicular phase decreases ovarian cyst formation, without an apparent effect on subsequent follicular recruitment or pregnancy rates, they concluded that pretreatment with an OCs, probably because of its estrogen component, results in a significant decrease in functional ovarian cyst formation during pituitary suppression by GnRH agonists initiated in the early follicular phase of the menstrual cycle (24).

d. Oral Contraceptive Pills (OCP)

It is well known that one of the advantages of using OCP is less risk of functional ovarian cysts. From recent epidemiologic studies the relative risks associated with current monophasic or triphasic OC use ranging from 0.2 to 1.3 (25). It has been hypothesized that the lower dose pills currently prescribed may have a diminished protective effect on cyst formation (26). The potential for increased cyst formation with current multiphasic OC use was first described in the 1980s (27). Holt et al. found a nonsignificant 20% decrease in functional ovarian cyst risk associated with current prescription of monophasic OCs of all ethinyl estradiol doses combined (RR 0.8; 95% CI 0.4, 1.8) (13). Holt et al. investigated 400 cases and 600 controls users of multiphasic OCs, they found that women using 35µg ethinyl estradiol monophasic OCs had a slightly lower OR than less than 35 µg ethinyl estradiol monophasic or multiphasic OC users, among whom current OC use had no effect on functional ovarian cyst likelihood. compared with use of nonsurgical, nonhormonal contraception, or no contraception, the functional ovarian cyst risk associated with use of 35 µg ethinyl estradiol OCs (OR 0.69; 95% CI 0.44, 1.10) was slightly lower than that associated with use of less than 35 µg ethinyl estradiol monophasic (OR 0.79; 95% CI 0.43, 1.47) or multiphasic (OR 0.76; 95% CI 0.49, 1.19) OCP. They concluded that the results of this study suggest that current use of low-dose monophasic OCs does not substantially decrease a woman's risk of functional ovarian cyst formation (28).

Lanes et al. found large, although nonsignificant, decreases in functional ovarian cyst risk among women currently prescribed greater than 35 µg ethinyl estradiol (RR 0.2; 95% CI 0.01, 1.3) or 35 µg or less ethinyl estradiol OCs (RR 0.5; 95% CI 0.2, 1.3), compared with former OC users who had not filled an OC prescription for at least 3 months (25).

e. Progesterone –only pills and levonorgestrel-releasing intrauterine system (LNG-IUS):

Several studies have shown an increased incidence of ovarian cysts associated with LNG-IUS use (29, 30). Progestin-only oral contraceptives and LNG-IUS have both been associated with increased occurrence of ovarian cysts. The incidence of ovarian cysts has been in the range of 8%–31% in some studies (30, 31). Inki et al. found that ovarian cysts occurred in 17.5% of women using LNG-IUS, compared with 3.0% in women subjected to hysterectomy at 6 months (32). There is no known mechanism by which the ovarian cysts are formed by LNG-IUS, several studies have shown disturbances in the normal growth and rupture of follicles during LNG-IUS use (33). Most of the menstrual cycles seem to be ovulatory according to normal progesterone levels observed in the luteal phase (34). Inki et al. found a weak positive correlation between the occurrence of ovarian cysts and irregular bleeding; they concluded that use of LNG-IUS in the treatment of menorrhagia was associated with a relatively high rate of ovarian cysts. The vast majorities of the ovarian cysts were functional showing a high rate of spontaneous resolution and were symptom-free (32). Järvelä et al. found that 31% of patients develop ovarian cyst 3 months after LNG-IUS application. They observed high level of serum levonorgestrel in patients with ovarian cyst compared to patient without cyst. Cyst range between 34 to 65mm in diameter, all cysts disappeared spontaneously with 3-4 months of follow up (30). Pakarinen et al. found 6.5% of their subjects develop ovarian cyst 3 months after insertion of LNG-IUS, all cyst resolved within 8 weeks expect one case required laparoscopic removal and final pathology was endometrioma. (31)

f. Nutrition and diet:

It seems that diet is associated with ovarian cysts. Diet plays a role in the regulation level of testosterone in women with polycystic ovary syndrome (PCOs). Comparison of hormonal and metabolic markers in women with PCOs showed that high-fat, Western meal affects testosterone, insulin, blood glucose, and cortisol level in this female (35). Nutrition and diet affect sexual hormones and their binding proteins as well (36). Fat can affect the metabolism of prostaglandins, thereby having an impact on ovarian function. 37 In addition to this; plasma levels of Insulin like growth factor 1(IGF1) are directly linked with the energy situation and IGF1 is also one of the factors affecting the production of estrogen from the dominant follicle and plasma estradiol level. Thereby, it also affects the ovulation and development of follicles (38). It has been shown on animal study that mice with high fat and high energy diet were insulin resistant, glucose tolerant, and had dyslipidemia; these factors can be due to oxidative stress, cytokines inflammatory effect, and other factors which may affect the function of the ovaries (37, 38). Other studies performed on animals have shown that the Dietary Unsaturated Fatty Acids are effective on the quality of the oocyte and follicular development (39). High levels of dietary fat are associated with insulin signaling on ovarian function, and insulin resistance also affects the ovarian function. Tafazoli et al. investigated 264 female patients (132 with cyst in the case group and 132 in the control group) aged 13 to 49. They found that the amount of fat consumption was higher in women with ovarian cysts; however, this difference was not statistically significant. They recommended that women of reproductive age should reduce their fat intake (40). However, some studies showed that there was a relationship between the consumption of milk and dairy products with ovarian cancer, and they hypothesized that the association may be due to the presence of lactose in milk. A high galactose diet is toxic for the oocytes, and evidence showed that ovarian cancer may arise due to the premature depletion of the oocyte, the intake of dairy products is associated with a modest increase in the risk of ovarian cancer (41, 42).

g.Tamoxifen :

Among the risk factor for cysts formation studied, is tamoxifen. It was found that tamoxifen increases the incidence of ovarian cysts in premenopausal patients. Tamoxifen is selective estrogen receptor modulators (SERMs), it binds to estrogen receptors (ERs) and elicits estrogen agonist or antagonist responses, depending on the target tissue (43). Its estrogen antagonist properties have made tamoxifen an important treatment modality for patients with breast cancer, especially those whose tumors are positive for ERs. It also exerts a weak estrogenic effect resulting in a variety of lesions in the female genital tract. Tamoxifen works by blocks ERs in the hypothalamus, leading to the inhibition of estrogen feedback, which leads to increases in the production of GnRH, FSH, and LH. Consequently, the ovaries may become hyperstimulated, form cysts, and produce more estrogen leading to hypoestrogenism (44, 45). However, the mechanism by which tamoxifen stimulates the development of ovarian cysts has not well understood. In the ovaries of premenopausal patients, tamoxifen stimulates estrogen production by affecting the hypothalamic-pituitary-ovarian feedback mechanism (46). It was suggested that the mechanism by which tamoxifen induces ovarian cysts in premenopausal women could be by a direct action on the ovaries to stimulate excessive growth of ovarian follicles, resulting in elevated estradiol levels (up to 3,700 pg/ml), throughout all phases of the menstrual cycle (47). An additional mechanism involved in the increased estrogen production by tamoxifen is its direct effect on granulosa

cells (48). Tamoxifen-induced ovarian cysts commonly occur after three months of tamoxifen treatment, with the highest incidence in the interval between three to 11 months after treatment initiation. Majority of these ovarian cysts are functional, such as follicular or luteinized cysts (44, 47). Several studies have described ovarian cyst formation during prolonged tamoxifen treatment (45, 46, 49). It was also described in series of tamoxifen-treated breast cancer patients (44, 49).

Interestingly, these cysts regress if tamoxifen is withdrawn or if premenopausal patients are treated with GnRH agonists during tamoxifen treatment (44).44 These lesions, although benign, may be complicated by torsion or cystic necrosis and may pose a diagnostic dilemma in patients at risk of ovarian metastases from breast cancer or of primary ovarian cancer (49, 50). Mourits et al. performed a prospective study using transvaginal ultrasound with hormonal assessment and reported ovarian cysts in 40% of premenopausal women during tamoxifen treatment, whereas none of the postmenopausal patients developed cystic ovaries. In patients with regular menstrual cycles during tamoxifen treatment, 81% developed ovarian cysts. In these premenopausal women with cystic ovaries, the serum estrogen levels were markedly elevated, with gonadotropin concentrations either unchanged or slightly increased (51). Sadan et al. reported that 7 of 10 (70%) women with tamoxifen administration developed ultrasonographically benign ovarian cysts ranging from 1.5 to 6.0 cm in diameter. One woman underwent surgery to remove an enlarging cyst. In all of the other patients, ovarian cysts disappeared within three months after the cessation of therapy (52). Mourits et al. showed that in patients who remained premenopausal after standard dose chemotherapy, tamoxifen use was associated, despite amenorrhea, with the development of ovarian cysts associated with the high estradiol levels that were indicative of overactive ovaries (54). Ovarian hyperstimulation, with increasing circulating estrogens, induced by tamoxifen in premenopausal patients was reported by Madeddu et al (55).

h. Immune suppression therapy

Immunosuppressive treatments are associated with a high prevalence of benign ovarian cysts. Steroid-free immunosuppressive regimens can maintain insulin independence in the majority of soft organ transplant (56). It is possible that glucocorticoids may be protective against the development of ovarian cysts by its anti-proliferative effects and by suppressing adrenal androgen production. This could further explain the low prevalence of ovarian cysts following solid organ transplants. Although ovarian cysts are not common (1–7%) following renal transplantation (57). A recent small series from the University of Miami reported finding ovarian cysts in eight out of 13 (61%) female islet transplant recipients (58). It is clear that ovarian cysts are a common complication (70%) in premenopausal women undergoing clinical islet transplantation and receiving the combination of sirolimus and tacrolimus for maintenance immunosuppression. The longer duration of follow-up in women who developed ovarian cysts suggests that the risk of developing cysts increased with increasing exposure to immunosuppression. For larger, persistent or symptomatic cysts, alternate immunosuppression regimens could be considered. Avoidance of the long-term use of sirolimus may also be considered as there are myriad other adverse effects associated with it (59). Ovarian cysts were found in 31 out of 44 (70.5%) premenopausal and two out of 13 (15.4%) postmenopausal women receiving sirolimus and tacrolimus following islet transplantation (60).

Recent studies have emphasized a potential impact of with new immunosuppressive drugs are still poorly documented and probably underestimated on female reproductive tract. There is a high prevalence of ovarian cysts in chronically immunosuppressed women undergoing islet transplantation and receiving tacrolimus and sirolimus (61). Formation of ovarian cysts were observed islet transplantation and the posttransplant after initiation of immunosuppression. The cysts were either unilateral or bilateral cysts (56%). Five of the patients with on sirolimus and history of ovarian cysts presented frequently throughout the follow-up. All the cysts were benign, but eight of them were considered complex because of size (>6 cm) (62). Another study including 13 female recipients of allogeneic islets for type I diabetes, under immunosuppression therapy based on daclizumab induction and tacrolimus/sirolimus maintenance. Chronic immunosuppression remains a necessity to prevent organ rejection, despite increased risks of infection, organ toxicity, and malignancies. Abnormalities of female gonadal function in patients of reproductive age are recognized, clinically significant ovarian cysts were frequently observed in patients, some requiring medical or surgical intervention. All ovarian cysts appeared of benign nature.

i . Tubal sterilization

Tubal sterilization was found to be associated with a functional ovarian cyst formation, but the exact mechanism is not well understood. Holt et al. found a substantially increased risk of diagnosis of functional ovarian cyst (OR 1.70; 95% CI 1.05, 2.75), the risk elevation was higher among women who had undergone postpartum tubal sterilization (OR 2.55; 95% CI 1.04, 6.28), and higher for those with postpartum sterilization; age< 30 (OR 3.54; 95% CI 1.24'|, 10.11) (28). A Mexican cohort study reported that twice as many sterilized women developed cysts as did women who had not been sterilized (24.1% versus 12.4%) (63).

Conclusion: When dealing with women of reproductive age with suspected physiologic or functional ovarian cyst, several risk factors should be excluded; patient should be reassured about the nature of those cysts as the majority will resolve spontaneously.

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