

Benign ovarian cysts in reproductive-age women undergoing assisted reproductive technology treatment

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ABSTRACT

The scope of this review is to focus on the management of benign ovarian cyst in the reproductive-age group of women undergoing ART. Ovarian cysts are a common occurrence in this patient population. The differential diagnosis includes functional cysts, dermoid cysts, endometrioma. The appropriate evaluation includes medical history and physical examination, laboratory tests and imaging. The treatment options include conservative follow-up, medical treatment and surgery. This review will explore the differential diagnosis, appropriate work-up and treatment options to the various cyst types encountered.

Keywords: Ovarian Cyst; Assisted Reproductive Technology; Reproductive Age

1. INTRODUCTION

The scope of this review is to focus on the management of benign ovarian cyst in the reproductive-age group of women undergoing ART.

In relative frequency, functional cysts account for about 24% of all ovarian cysts, benign cysts 70% and malignant 6% [1]. The great majority of ovarian cysts occur in reproductive-age patients and most of them are benign [2]. Up to 4% of reproductive-age women will have an ovarian cyst in the luteal phase [3]. Cyst formation may appear during GnRH agonist treatment [4]. Therefore, it is common to encounter patient undergoing assisted reproductive technology (ART) with a concomitant ovarian cyst. The question arises as to the adequate diagnosis and management.

Although an ovarian mass may represent a variety of Ultrasonographic and pathological findings, there are three main and common types of benign ovarian cysts encountered in the reproductive-age patients: functional

cysts, benign cystic teratoma (dermoid) cysts and endometrioma [5,6]. Each type has unique characteristics that usually enable achieving the correct diagnosis and management.

An ovarian cyst diagnosed during the reproductive age is rarely malignant. Nevertheless, as a rule, a finding of an ovarian cyst >5 cm, should be followed up and if persistent, a workup should include a medical history and physical examination. Imaging tests include ovarian echography. A computed tomography scan (CT scan) is usually performed if the cyst is not clear and/or shows invaginations and solid areas. Laboratory test and markers should be performed if findings are suspicious to rule out malignancy.

We note that a possible relationship between prolonged use of clomiphene citrate and borderline or invasive ovarian cancer was reported in patients with an ovarian mass and a history of prolonged exposure (above 12 cycles) [7]. Further studies are requested to confirm these findings.

When evaluating a patient with an ovarian cyst undergoing ART treatment, in addition to the routine work-up of any woman with a similar finding, the physician should assess her ovarian reserve. After completing the appropriate work-up and reaching a diagnosis and after assessing the ovarian reserve, the physician should be able to tailor the best treatment option for the specific patient.

2. DIFFERENTIAL DIAGNOSIS

Differential diagnosis of any adnexal mass should include gynecologic and non-gynecologic sources. When evaluating an ovarian cyst the differential diagnosis includes both benign and malignant lesions [8]. At this age group, the vast majority of ovarian masses are benign however if a suspicion of malignancy arises, management should continue appropriately.

Benign ovarian cysts include:

- functional cysts,
 - follicular cysts;
 - cysts following GnRH agonist treatment;
 - corpus luteum cysts;
 - theca lutein cysts.
- benign cystic teratoma (Dermoid),
- endometrioma,
- serous cystadenoma,
- mucinous cystadenoma.

Functional cysts are benign and usually asymptomatic and therefore do not require any treatment. Follow-up and repeated scans will usually confirm spontaneous resolution of the cysts. This is not the case when the cyst is large and may interfere with fertility treatments and *in vitro* fertilization (IVF).

The formation of cysts during IVF treatment may be of no clinical significance or may negatively influence its outcome [4]. Transvaginal Ultrasonographic-guided cyst aspiration is often performed in cases with cysts appearing during GnRH agonist treatment before starting ovarian stimulation.

Benign cystic teratoma (dermoid) cyst is the most common ovarian tumor in women in the second and third decade of life [9] and as a rule is benign. Since torsion is not uncommon, surgical management was often advised with a view of making a definitive diagnosis during the de-torsion procedure and remove the cyst while preserving ovarian healthy tissue.

Recently, a more conservative approach has been suggested regarding dermoid cysts. Evidence suggests that a dermoid cyst, especially smaller than 6 cm, can be followed conservatively with little risk of complications [10-12]. If cysts are not growing, removal of a dermoid cyst can be deferred after family planning is resumed.

Endometrioma is usually a sign for more advanced endometriosis which is a cause of infertility. According to the new (European Society of Human Reproduction and Embryology) ESHRE guidelines [13,14], surgery should not be performed before ART only in the aim of improving pregnancy rate. Surgery should be considered before ART for tissue diagnosis, reducing the risk of infection after oocyte retrieval and improve accessibility of follicles.

It is important to notice these two recent reviews that explored the relationship between endometriosis and infertility. In the first, the authors found no adverse effect of endometrioma on IVF cycle outcome [15,16]. In the second, the authors concluded that the presence of severe endometriosis (stage III/IV) is associated with poor implantation and clinical pregnancy rates in women undergoing IVF treatment. This coincides with the new ESHRE guidelines regarding the management of endometrioma before ART treatments as will be discussed

later.

3. DIAGNOSIS

3.1. Medical History & Physical Examination

Any evaluation of a patient with an ovarian cyst should include a thorough medical history and a complete physical examination in the search of warning signs of malignancy. The medical history should focus on risk factors and red flags for malignancy. Symptoms such as abdominal bloating, abdominal and pelvic pain, and early satiety and appetite changes should alert the physician to the presence of malignancy and the appropriate steps should be taken [17,18]. It is also important to search for symptoms suggesting endometriosis, especially in this cohort of patients—reproductive-age women with infertility [19].

The physical examination should include an abdominal and pelvic examination including a bimanual pelvic examination. One should look for alerting signs such as an irregular, solid, fixed and nodular mass or a bilateral finding. The presence of ascites should warn us about the possibility of malignancy.

The physician should remember that physical examination has poor sensitivity for detecting ovarian masses (15% - 51%) [18,20]. In addition, one should remember that in this age group it is not uncommon to find the above warning sign with benign conditions such as endometriosis which can present with bilateral findings and irregularity on pelvic examination and ascites.

3.2. Laboratory Tests

In the settings of a benign ovarian mass in a reproductive-age group, there is no added value in measuring CA-125 [21-23]. CA-125 in the reproductive-age group rises in numerous conditions such as fibroids, endometriosis, adenomyosis and pelvic infections and during normal menstrual cycle. This makes CA-125 an unreliable marker for differentiating benign from malignant masses and not helpful at all in the differential diagnosis of benign cysts [21-23].

Serum levels of CA-125 are not necessary when the Sonographic appearance of the cyst is simple-thin walled, clear fluid, no intracystic structures and less than 50 mm in diameter [23-26].

Anti-mullerian hormone (AMH) is a relatively new marker of ovarian reserve and considered the most accurate one available today. A serum AMH level above 0.5 ng/mL is consistent with good ovarian reserve, while lower levels suggest the presence of a depleted ovarian follicle pool. Levels of serum AMH may provide guidance as to the appropriate management of the patient with an ovarian cyst [27-31].

Reduced ovarian reserve as measure by serum levels of AMH may contraindicate surgical management in the specific patient.

Pre-operative and post-operative AMH levels may be used as a tool for evaluating ovarian damage after surgery [27-31].

3.3. Ultrasonography

The most widely used imaging modality is gray-scale, high frequency transvaginal ultrasonography. In asymptomatic and reproductive age group, this is the imaging modality of choice [32].

Ultrasonographic examination will provide us with the size, consistency, laterality and intracystic structures (septations, nodules, papillary extensions) of the cyst. These findings, in correlations with the physical examination will provide us with a deeper insight as to correct diagnosis.

Benign cystic teratoma (Dermoid) is characterized by fat-fluid level and intracystic floating balls, shadowing echogenicity, diffuse or regional high amplitude echoes, dermoid mesh and tip of the iceberg sign [33]. When two or more characteristic sign are present, the diagnosis of dermoid cyst can be made with a high positive predictive value [33].

Endometrioma is sonographically characterized by ground glass echogenicity and one to four compartments and no papillary structures with detectable blood flow [34].

Color Doppler alone does not improve diagnostic evaluation [35-37], but the combination of color flow mapping with 3D imaging may improve sensitivity in complex masses [38,39].

3.4. Other Imaging Modalities

The role of computed tomography (CT) scan and magnetic resonance imaging (MRI) in the evaluation of a suspected mass in reproductive-age women is reserved for cases in which suspicion for malignancy arises.

4. TREATMENT OPTIONS

The treatment option includes conservative follow up, medical treatment and surgical management.

4.1. Conservative Management

Conservative management can be undertaken with women with small and simple ovarian cysts (less than 50 mm in diameter, thin walled, clear fluid, no intracystic structures). This group of women need no follow up, since the cysts are almost invariably physiological and will regress spontaneously within 3 menstrual cycles [40].

A consensus statement published by the Society of Radiologists in Ultrasound concluded that asymptomatic simple cysts with a diameter of 30 - 50 mm in diameter do not require any follow-up, cysts with a diameter of 50 - 70 mm require follow-up, and cysts more than 70 mm in diameter should be considered for either further imaging or surgical intervention due to difficulties in examining the entire cyst [41].

The course of pregnancy of patients with dermoid and other benign ovarian cysts, including perinatal outcomes, is favorable. The cysts should be managed conservatively if possible with routine ultrasound follow-up during the pregnancy since complications are extremely rare [42].

4.2. Medical Management

The use of combined oral contraceptives has been proposed for the treatment of functional ovarian cysts. According to the Cochrane review of the effects of the oral contraceptive pill in the treatment of functional ovarian cysts, there was no earlier resolution in the treatment group compared to the control group [43]. However, these trials were small with significant heterogeneity. It has been shown that the use of combined oral contraceptives may reduce the risk of cyst occurrence [43-45]. Therefore, combined oral contraceptives are still a possible treatment option for already existing functional cyst.

There is no medical treatment for benign cystic teratoma (dermoid) except for expectant follow up.

Medical treatment for endometriosis includes oral contraceptives, progesterone, GnRH agonists or antagonists. The problem with this treatment options is that they impair fertility and though are counter-effective in patients seeking fertility treatments [46]. Some of the treatments are useful prior to starting stimulation for IVF, increase in the implantation rate in stages III and IV endometriosis [15, 46-49].

4.3. Surgical Management

Surgical management should be offered when tissue diagnosis is necessary or when the ovarian cyst interferes with oocyte retrieval or ovarian stimulation. When considering surgery in reproductive-age patient, the ovarian reserve should be assessed prior to the procedure and if severely reduced surgery may be deferred in order to further explore other treatment options.

Before performing surgery, we should discuss with the patient the issue of ovarian reserve compromise after surgery and its implication on future fertility.

Ovarian cysts that persist or increase in size after several menstrual cycles are unlikely to be functional [50-52], for example mature cystic teratoma (dermoid cysts) has been shown to grow over time, increasing the risk of pain and ovarian accidents (torsion, rupture) [10,53].

Surgical management is therefore usually appropriate in these settings.

When encountering an endometrioma in women undergoing ART, the new ESHRE guidelines conclude that surgery should not be performed before ART only in the aim of improving pregnancy rate but for symptoms improvement. Surgery should be considered before ART for tissue diagnosis, reducing the risk of infection after oocyte retrieval and improve accessibility of follicles. The guidelines also conclude that if surgery is performed, cystectomy is the best option of treatment rather than aspiration or ablation [13,14].

When surgical management is indicated, the laparoscopic approach should be undertaken. Laparoscopic surgery for ovarian masses presumed to be benign is associated with lower postoperative morbidity and shorter recovery time and is preferred to laparotomy in suitable patients [54-57]. In a systematic review, that included six randomized controlled trials comparing the laparoscopic approach to laparotomy for ovarian cysts has shown reduced febrile morbidity, less postoperative pain, lower rates of postoperative complications, earlier discharge from hospital and lower overall cost [58]. It is also cost-effective because reduced hospitalization time and earlier return to work [59].

When performing laparoscopic surgery for the management of a benign ovarian cyst, complete removal of the capsule should be performed. Aspiration alone, either laparoscopically or vaginally, is less effective and carries a high rate of recurrences (46% - 84%) [60,61].

5. CONCLUSIONS

Ovarian cyst is a common occurrence in the reproductive-age group. Functional ovarian cysts are physiologic and usually resolve spontaneously within a couple of menstrual cycles. Combined oral contraceptives may be used to prevent the occurrence of these cysts; however, they do not accelerate cyst resolution.

Ovarian neoplasms are usually benign in women of reproductive age. The risk of an ovarian mass being in this age group is exceedingly small.

Measurement of CA-125 is not helpful in distinguishing between benign and malignant ovarian masses, reproductive-age women.

For functional cyst, conservative management is adequate since most cases will resolve spontaneously. There is no proven advantage in the use of combined oral contraceptives. Surgery will be reserved for cases of big or symptomatic functional ovarian cyst.

For benign cystic teratoma, surgical management is indicated when the cyst is growing or to provide better accessibility to follicle during oocyte retrieval.

For endometrioma, it is recommended not to perform

surgery unless in need of tissue diagnosis or performing surgery for another reason or to improve accessibility to follicle during oocyte retrieval.

Laparoscopy is commonly used to remove benign cysts above 60 - 70 mm in diameter.

Simple Ultrasonography, and if indicated, more advanced imaging techniques such as MRI enable expectant management and follow-up of ovarian cysts in women of reproductive age before deciding on surgical management. Successful introduction of Assisted Reproductive technologies and novel fertility preservation strategies have led to more awareness about the importance of ovarian reserve and its preservation.

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