



2010

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Repository Citation

Al-Alem, Linah; Deokar, Amit M.; Timme, Rebecca; and Omar, Hatim A., "Ovarian Tumors in Children and Adolescents" (2010).
Pediatrics Faculty Publications. 258.

https://uknowledge.uky.edu/pediatrics_facpub/258

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Notes/Citation Information

Published in *Pediatric and Adolescent Sexuality and Gynecology: Principles for the Primary Care Clinician*. Hatim A. Omar, Donald E. Greydanus, Artemis K. Tsitsika, Dilip R. Patel, & Joav Merrick, (Eds.), p. 597-627.

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Chapter II

**OVARIAN TUMORS IN CHILDREN
AND ADOLESCENTS**

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Ovarian tumors are uncommon in the child and adolescent population, but **given** that cancer **is** a leading cause of **death** even **in** this age group it is important for the general practice physician to be aware **of** the signs and symptoms. These can include abdominal pain, increased abdominal girth, a palpable mass on pelvic or abdominal exam, nausea and vomiting, decreased appetite, weight loss, constipation, back pain, leg cramps, dyspareunia, urinary symptoms, abnormal uterine bleeding, and ascites, to name a **few**.

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The types of gynecological tumors seen in adults are also seen in children except in differing frequencies. The most common type of ovarian tumor in children is the germ cell tumor, of which there are several subtypes including dermoid cysts, dysgerminoma, yolk sac tumor, immature teratomas, and embryonal carcinomas.

INTRODUCTION

Ovarian tumors in children and adolescents are the most common genital neoplasms (1). In fact, ovarian tumors account for 1% of all neoplasms in girls under the age of 17 (1) and although ovarian tumors are relatively rare, they comprise about 70% of all childhood gynecological malignancies (2). Overall, ovarian cancer claims the lives of 8.8 women per 100,000 women in the total population (3). Ovarian tumors are diverse in origin, progression and treatment. All types of ovarian tumors that are seen in adults are also seen in children but their incidence is different (4). The most common types of ovarian tumors in adolescents are the functional non-neoplastic types and germ cell tumors (4,5). This is different from the adult population, where the majority of neoplasms are ovarian epithelial tumors (6,7). In addition, only 10% of the ovarian tumors occurring in adolescents are actually malignant (8). Nevertheless, cancer is a leading cause of death in the adolescent age group, after accidents and injuries, homicides and suicides (8). History taking and physical examination are the hallmarks of ovarian tumor diagnosis and treatment in the adolescent population. This is of extreme importance in order to ensure a healthy future (4). Unfortunately, ovarian neoplasm diagnosis is still a problem in today's clinics due to the vague symptoms with which the patient presents (3). This chapter aims to discuss the different ovarian tumors as well as their management focusing on the pediatric and adolescent population.

TYPES OF OVARIAN TUMORS

There are six main categories of primary ovarian tumors, namely: Functional cysts, benign ovarian tumors, borderline tumors, neoplasms of

germ cell origin (germ cell tumors), celomic (epithelial) origin tumors (epithelial ovarian cancer) and virilizing tumors. This classification is **based** on the present **day** concept of development **and** structure of **the** ovary (9). Other organizations, such as the WHO (World Health Organization), classify ovarian neoplasms into nine main categories and 26 subtypes. In this chapter we will be discussing the major six types of ovarian tumors that may be seen by the primary care provider. Usually after the primary finding of a tumor, the patient is usually referred to a gynecologic oncologist (1).

EPIDEMIOLOGY

The incidence of gonadal tumors in general increases with the onset of puberty. The incidence of all germ cell tumors, the most common **type** of ovarian tumors in children, is about 0.6-0.9 per 100,000 children. It is worthy to note that 25% of all pediatric germ cell tumors present as tumors with more than one histological type (10). Nevertheless, this varies significantly according to sex and age. As for the incidence of ovarian cancer, it tends to rise with age peaking in the eighth decade, and therefore rarely seen in the adolescent population (10). The majority of ovarian cancers are the result of sporadic mutations; approximately 10% are attributed to familial disposition. Females carrying deletions in the BRCA 1 and BRCA2 genes (tumor suppressor genes) make up the largest subset risk for ovarian cancer. These deletions are inherited in an autosomal dominant mode (10). Focusing on 76 subjects under 20 years of age with ovarian neoplasm, one report found that 63% had germ cell etiology (11). Thus, although the general incidence of ovarian tumors in the adolescent population is low, it does occur and early diagnosis is vital to ensure better survival as well as a better quality of life. What follows is a discussion of the 6 different subtypes of ovarian tumors.

CLINICAL PRESENTATIONS

It is of vital importance that primary care providers are aware of the different ways in which children and adolescents can present clinically. In contrast, older women may be asymptomatic. The symptoms of an individual ovarian mass are mentioned in the respective sections. Below is a list of symptoms that may mimic conditions such as appendicitis, urinary tract infections, gastroenteritis, sexually transmitted disease and constipation (12). This list of symptoms will help the provider decrease the probability of misdiagnosing ovarian tumor. They include the following:

1. Abdominal pain

This is a fairly consistent symptom in girls under the age of 10 years (13). It also is the main complaint in all adolescents (14). Occasionally there may be pressure symptoms in the abdomen or pelvis. Localization of the pain may depend largely on the age and development of the girl and is generally higher in the abdominal area due to the relative superior location of the ovary in young girls. Some children can present with an acute abdomen and surgical exploration is warranted in cases of adnexal torsion. Imaging is often helpful in aiding and confirming the diagnosis(15). It is very crucial for the provider to be aware of other acute situations such as appendicitis, but at the same time remember that ovary-related pain may mimic such presentation(12).

2 Increased abdominal girth and palpable mass

This could be fixed or nodular. The mass could also be bilateral (14-16). Palpating the mass can be challenging in an overweight individual.

3. Other symptoms includes (12-15):

- Nausea and vomiting
- Decreased appetite
- Loss of weight
- Constipation
- Back pain
- Leg cramps
- Isosexual precocious pseudopuberty (15)
- Dyspareunia
- Urinary symptoms such as, urgency, dysuria, etc.
- Menstrual abnormalities like abnormal uterine bleeding (AUB), amenorrhea/oligomenorrhea, menorrhagia, and dysmenorrhea
- Ascites
- Hydrothorax and difficulty breathing
- Virilization

4. Rare presentation(s):

- Thrombocytosis. especially with malignant tumors (17)
- Extranodal non-Hodgkin's lymphoma may present as an ovarian mass (18)

A. OVARIAN FUNCTIONAL CYSTS

Ovarian functional cysts are also known as benign cysts, simple cysts or physiological cysts. Functional cysts as well as benign neoplasms (discussed later on) are the most common ovarian masses among young adolescents (19). The etiology of functional cysts changes with each stage of development due to hormonal changes (20). In general, functional ovarian cysts are mostly non-neoplastic in nature and can be of a follicular, luteal or pregnancy-related luteoma. A functional cyst usually occurs in about 7.8% of reproductive aged women (9) and are the most common lesions in the pediatric age range (21). Functional cysts

occur due to an exaggerated cyclic ovarian function. Thus, most functional cysts resolve in a short period of time, usually within one or two cycles or put differently, 6 to 10 weeks (9) without treatment (20). If the cyst persists, the diagnosis should remain in question as potentially neoplastic in nature particularly if the patient has symptoms (20). Some reports consider lesions that are more than 10 cm as potentially neoplastic, while those that are less than 5 cm as non-neoplastic (9). It should be noted that all functional cyst subtypes are usually benign (22). Ovarian functional cysts are usually unilateral but may occur bilaterally (1).

Risk factors

The use of progestin only contraceptives may increase the risk of ovarian tumor development (9). But in general, the use of mixed (progestin and estrogen) oral contraceptives early acts as a protective agent against ovarian functional cysts (23). The development of functional cyst malignancies are more prominent in pre-pubertal girls especially if ascites is detected (9). Possible complications that may occur post cyst formation include cyst rupture, intracystic hemorrhage, ovarian torsion and necrosis (1).

Subtypes of ovarian functional cysts

Follicular origin

These cysts form as a result of anovulation. The follicle starts accumulating cystic fluid, rendering it larger than 25-30 mm when inspected with an ultrasound. Cysts should only be named 'functional cysts' when they are 5-10 cm in size. This is due to the notion that follicles can normally reach 5 cm (9). Most of the time, functional cysts resolve on their own (20).

Luteal origin

These cyst usually occur during the luteal phase. A patient may present to the clinic with severe acute pain, which may be due to a ruptured cyst.

Ruptured cysts may cause intraperitoneal bleeding or an unruptured cyst causing bleeding into the cyst cavity (hemorrhagic cyst). Functional cysts of luteal origin appear sponge like upon ultra sound inspection. In fact, they may even be confused with the development of ectopic pregnancies (9). Thus, when an ectopic pregnancy is suspected, functional cysts of luteal origin should be eliminated.

Pregnancy-related luteoma

This subtype of functional cysts is rare and is often asymptomatic. It is usually seen in adolescents that are pregnant and undergoing cesarean deliveries. These cysts are usually larger than 20 cm in diameter. In 50% of the cases presenting with pregnancy-related luteoma, female fetal masculinization is seen (9).

Symptoms

In general, functional cysts may cause acute pain, pressure, dull or achy pain that is often present for several weeks especially when the cyst is large, torsed or ruptured (9). It should also be noted that patients could be asymptomatic, particularly those that are of a pregnancy-related luteoma. Other symptoms that the patient may present with are complaints of pain during bowel movements or intercourse. In some cases, patients may complain of changes in menstruation (Irregular, longer, or shorter periods) (9).

Diagnosis

Ultrasonography is usually utilized to localize ovarian lesions but cannot be used to determine whether these lesions are malignant or not (21). Histological analysis is needed in order to determine the pathology of the cyst. Thus, ultrasound is the most common imaging used in making a functional cyst diagnosis, while MRI is rarely used (9). Pelvic exams are also helpful in view of the fact that it might indicate a palpable mass. This depends on the size of the cyst and the patient weight. An abdominal exam may reveal tenderness or rebound (9). Several lab tests

may be performed such as CA-125 (Cancer Anligen 125). It is important to note that CA 125 in adolescents may not help in distinguishing benign from malignant cysts and thus, although it may be helpful in some cases, it is not helpful in most cases. The most important lab test is human chorionic gonadotropin (?-HCG), which would indicate pregnancy but can be also be elevated in some tumors. In pregnancy-related lutcomas, testosterone and AFP (Alpha Feto Protein) can be elevated (9).

Other conditions causing similar symptoms

There are several medical conditions that usually present to the clinician with identical symptoms. These conditions should be eliminated before a functional cyst diagnosis is reached. These include conditions such as: PCOS (polycystic ovarian syndrome), endometriomas, ectopic pregnancies, appendicitis, other ovarian tumors (dermoid cysts, mucinous, serous cystadenomas, Fallopian tube carcinomas), PID (pelvic inflammatory disease) and hyperthecosis (9).

Treatment

Functional cysts tend to resolve on their own (20), and although oral contraceptive pills are often used, some state that combination oral contraceptives do not accelerate the regression of these cysts (9,23). In general, surgical procedures are not done unless absolutely necessary and should spare the ovary as much as possible (20). If functional cysts of follicular origin are the diagnosis, the follicle should be monitored for 1-2 cycles. Functional cysts should regress and become smaller with time and if they persist, surgery may be considered (9). If the patient presents with acute pain, the clinician should consider timing the pain with ultrasound images and characteristics to attempt to correlate the two. In addition, the clinician should consider the possibility of cystic rupture. Corpus luteum pain symptoms are usually treated with analgesics or narcotics although one should be careful with prescribing narcotic analgesics to adolescents for obvious reasons. This pain management would give the patient relief from the pain allowing the patient to be

monitored for 6 weeks. If after 6 weeks the cyst is enlarging or persistent then this might indicate malignancy of the cyst (9). Laparoscopy is the most common approach if the functional cyst is persistent (20). This approach is used in dermoid cysts, which will be discussed later (9). It should be noted that if the adolescent is pregnant, this will probably cause an added complexity in trying to differentiate between malignant and benign cysts (9). Surgery should be avoided as much as possible and is only used in enlarged or persistent cysts after a minimum of two cycles (9;23). Pregnancy luteomas have been shown to resolve on their own after delivery (9).

Follow-up

The rate of malignancy is very low in functional cysts (1). However, if malignancy is suspected, referral to an oncologist is necessary. In order to prevent future functional cyst formation, oral contraceptives may be used. Regular pelvic exams are usually used to monitor patients but repeated ultrasound imaging is not usually indicated (9).

B. BENIGN OVARIAN TUMORS

Benign ovarian masses are rare in the pediatric and adolescent population unless they are benign functional cysts. The incidence of benign tumors is not very accurate, but 2/3 of these benign tumors occur in 20-44 year old patients. Thus, the incidence in the pediatric and adolescent population is very low (9). Benign ovarian tumors are also known as ovarian cysts, tumor masses or adnexal masses. These tumors are often common in patients of reproductive age. Of all ovarian tumors, benign tumors account for 80-85%. The prognosis for benign ovarian tumors is often excellent.

Risk factors

Smoking in the adolescent population increases the risk of developing benign ovarian tumors by about three fold. Another risk factor is obesity. In contrast, pregnancy is associated inversely to ovarian tumor development. It should be noted that the presence of a benign ovarian tumor serves as a risk factor for the development of ovarian cancer later in life (9). Hence, it is necessary to follow up patients into their adulthood or inform them of their future risk.

Subtypes of benign ovarian tumors

Functional cysts

These usually do not require surgery and are asymptomatic and benign. Please refer to Function Ovarian cyst section for more information. Benign tumors do not have any staging system.

Endometriosis

These are also known as 'chocolate cysts' and often develop when the patient is diagnosed with endometriosis (9).

Benign cystic teratomas

These are also known as dermoid cysts and are considered benign germ cell tumors which are the most common tumors in adolescents and in fact, account for about 60% of neoplasms in women under 40 years (9).

Epithelial tumors

There are two main types of epithelial ovarian tumors. These are: serous and mucinous. Other epithelial benign tumors include endometrioid, clear cell, Brenner mixed epithelial and fibromas. Serous tumors are often benign but in 5-10% of the cases may present as borderline ovarian tumors and in 20-25% are malignant. Mucinous tumors in turn may become very large but only 5-10% are malignant in nature.

Symptoms

Ovarian tumors are usually asymptomatic but when symptoms are present they are often nonspecific, mimicking gastrointestinal complaints such as nausea, vomiting, bloating, constipation, and indigestion. In addition, urinary urgency, increased abdominal girth fatigue and weight loss or weight gain are also common. Ovarian torsion is sometimes seen when acute pain is a patients' chief complaint. Pelvic pain, menstrual irregularities may be present as well.

Diagnosis

A detailed history should be taken in order to assess familial risk, A breast exam is necessary since a history or presence of breast cancer is a risk for the development of ovarian tumors. Abdominal exams should test for the presence of ascites, a palpable mass or hepatomegaly, which would suggest the presence of an ovarian tumor. A pelvic exam is usually used to detect the presence of pelvic tenderness. Also, a pelvic mass with a size larger than 8-10 cm would suggest the presence of a neoplasm. Benign tumor diagnosis is done after surgical biopsy of the tumor and a histological exam. Nevertheless, a benign tumor does not usually lead to the accumulation of ascites nor peritoneal tumor studding. The precise basis and origin of ovarian epithelial tumors is still unknown (9). Ovarian torsion usually occurs in benign ovarian tumors but not malignant ones. There are several lab tests that can be performed to help rule out tumors. The most sensitive exams to detect ovarian tumors include: ultrasound, MRI, and CT. In contrast, the most specific exams that can be done include: Bimanual exams, MRI, PET scans (9). CA-125 is rarely used in premenopausal conditions and is not helpful in benign cases. A serum beta-HCG should always be done in order to rule out pregnancy.

Other conditions causing similar symptoms

Several other medical conditions may present in the clinic that have similar symptoms to the presence of ovarian tumors. These include PCOS, infections, ovarian malignancy, fallopian tube malignancy, functional cysts, and other gynecological conditions such as peritoneal cysts, uterine fibroid, and paraovarian cysts (9).

Treatment

Patients should undergo a period of 6-8 weeks of close monitoring if the results of ultrasound and MRI are benign. Surgery is only done as a last resort and several factors should be taken into consideration such as age, pain, and growth persistence over time. Surgery may be done in cases of ovarian torsion and masses that do not resolve over time. Oral contraceptives are used to inhibit ovulation and thus may help prevent the development of non-neoplastic. In the case of benign cystic teratomas, a cystectomy may be done in order to remove the cyst but preserve the ovary. If there are solid masses, surgical approaches should be followed by pelvic washings to prevent the risks of tumor cell spreading. Pathological exams should be performed in order to determine whether the tumor is for sure benign or not. If the tumor biopsy shows the presence of borderline or malignant tumors, refer to a gynecological oncologist (9).

Follow-up

Patients should be monitored with regular pelvic exams and if there are any abnormalities, ultrasound imaging should be used (9).

C. BORDERLINE OVARIAN TUMORS

Most borderline tumors occur in women between the ages of 30 and 50 years. Thus, borderline tumors are rare in adolescents. This type of ovarian tumor accounts for 15% of all ovarian malignancies and usually occurs 10-20 years prior to the development of ovarian cancer. Borderline ovarian tumors undergo a less aggressive course than malignant forms, although it should be noted that it has the potential to metastasize and reoccur after years of tumor-free status. Borderline ovarian tumors are also known as low malignant potential (LMP) tumors.

Risk factors

Unlike other ovarian tumors, borderline ovarian tumors are not affected by smoking, oral contraceptive use, nor BRCA-1 or BRCA-2 mutations. A family history of ovarian cancer also does not affect the risk of developing ovarian cancer. One major risk factor is nulliparity (9).

Subtypes of borderline ovarian tumors

About 65% of borderline ovarian tumors have a serous histological type while 30% are mucinous. The remaining 5% account for the remaining four subtypes: Endometrioid, clear cell, Brenner cell and mixed. Tumor cells can spread by various methods including implantation in the peritoneal cavity or by the lymph system to pelvic lymph nodes and eventually to other organs. Borderline ovarian tumors should be staged after excision using the International Federation of Gynecological Oncologists (FIGO).

Stage 1: The tumor is confined to the ovaries

1A: tumor growth is limited to one ovary without any malignant ascites

1B: tumor growth is limited to two ovaries without any malignant ascites

1C: tumor or stage 1A or 1B, but with ascites or ruptured capsules

Stage 2: The tumor has spread to the pelvis

2A: metastasis to the fallopian tubes or uterus

2B: both ovaries affected and extended to the pelvis

2C: a tumor of stage 2A or 2B, but with ascites

Stage 3: There are tumor seeds in the abdominal cavity or retroperitoneal lymph nodes

3A: confined to the pelvis

3B: metastasis to the peritoneal cavity but not >2cm mass

3C: metastasis to the peritoneal cavity but >2cm mass

Stage 4: Metastasis into other distant organs**Symptoms**

Major patient complaints include abdominal pain, constipation, bloating, nausea, weight changes, decreased appetite, dysuria and irregular menses.

Diagnosis

Physical exams often reveal solid or fixed masses and ascites or palpable mass upon abdominal exam. A CA-125 test should not be used in Borderline ovarian tumors since it is sometimes elevated in benign conditions, especially in pre-menopausal women with diseases such as pelvic inflammatory disease, endometriosis and liver disease. In order to distinguish between malignant and benign tumors, pelvic ultrasound and CT scans are often used. The presence of persistent pelvic mass upon serial imaging sessions, a mass larger than 8 cm, solid components, increased vascularity and bilateral ovarian involvements indicate a possible malignant tumor rather than borderline ovarian tumor.

Other conditions causing similar symptoms

Infections such as tubo-ovarian abscess may result in symptoms that mimic Borderline ovarian tumors. Benign, malignant and metastatic gynecological neoplasm also may be misdiagnosed as Borderline ovarian tumors. Other conditions include the presence of pelvic kidney (9).

Treatment

Treatments of Borderline ovarian tumors involve surgical removal of all visible masses. Chemotherapy is rarely beneficial due to the decrease/slow growth rate of this type of tumor. Surgery is typically used for diagnosis and treatment in this type of ovarian tumor. After tumor excision, proper staging is required by a gynecologic oncologist in order to ensure that all the mass is removed. The best removal is a total hysterectomy, although this should be done with care and only when the patient does not desire fertility. If histological analysis shows that the Borderline ovarian tumor is of mucinous origin, an appendectomy should also be performed. This is necessary due to the possible concomitant involvement of the appendix with the development of mucinous tumors. In recurrence cases, additional surgical excisions are done (9).

Follow-up

If the tumor is confined to the ovary and the surgery was successful no further surgical interventions are needed. The patient should be referred to a gynecologic oncologist for monitoring and to determine whether any other treatment would be helpful. There is a chance of recurrence, particularly after 10-15 years. Usually survival rates are about 99% for ovarian borderline tumors diagnosed at stage 1 or 2. Five and twenty year survival rates drop to 90% and 45%, respectively at later stages. Thus, diagnosis at earlier stages is essential. About 6% of the cases could develop into a low grade serous carcinoma. A physical exam and CA-125 is needed every three months for two years and imaging every six months for two years.

D.GERM CELL OVARIAN TUMORS

This type of ovarian tumor is the most common ovarian tumor in adolescents and young women (9, 24). The median age range is 16-20 years old but may occur in patients who are much younger, in fact, as early as 6 years of age. Thus, one of the important factors to consider is the preservation of fertility. These tumors originate from the germ cells of the ovary. Germ cell tumors account for about 5-7% of all ovarian cancers(9), 20% of ovarian tumors (25), and account for >60% of tumors occurring in patients younger than 20 years of age. One-third of the germ cell tumors diagnosed in patients younger than 20 years of age are malignant. The most common subtype is the benign cystic teratoma, also known as dermoid cyst. It is worthy to note that this type of ovarian tumor accounts for about 25% of all tumors in pregnancies.

Risk factors

This is the most common type of ovarian tumors in young women (9, 25).

Subtypes of germ cell ovarian tumors

Germ cell ovarian tumors have 5 different subtypes.

Dermoid cyst (mature cystic teratomas)

Most of these contain hair or sebaceous material, but may also contain substances derived from all three germ cell layers. These are usually benign, but may be squamous carcinomas in 1% of the cases.

Dysgerminoma

This subtype comprises about 50% of all germ cell tumors and therefore is the most common subtype of germ cell tumors. They also tend to form before the age of 30. They are usually unilateral but are bilateral in about 15% of the cases (2). In this subtype, due to the presence of enlarged cells, there is an elevation in lactate dehydrogenase (LOH) (2) levels and in 5% of the cases cells may produce HCG which may also be elevated (2, 9). An important aspect of dysgerminoma is that it has the highest

possibility of spreading to the peritoneal cavity and lymph nodes compared to other ovarian malignancies (2). There is a recurrence rate of about 17% after treatment(2).

Yolk sac tumors (endodermal sinus tumors)

This subtype accounts for 25% of germ cell tumors and is the second most common subtype of germ cell tumors (2). Upon microscopic examination, these tumors have a distinct reticular pattern and usually contain acid-schiff (PAS) positive hyaline bodies. As well as papillary structures, these cells usually contain and secrete AFP (alpha-fetoprotein) which may be measured in serum. The median **age** in which these tumors present is 19 (2). The most common symptoms that patients complain of are abdominal pain, fever, vaginal bleeding or an abdominal mass (2).

Immature teratoma

This is the third most common subtype and accounts for about 15-20% of all ovarian germ cell tumors (2). Similar to dermoid cysts, they contain substances derived from all three germ cell layers (9). The median age at presentation is 19. This type of tumor usually does not produce any tumor markers and are almost exclusively unilateral and are stage 1 at diagnosis (2). The survival rate is highly dependent on the stage of the disease. Those with grade I have a survival rate of about 93% while those with stage ID have a survival rate of about 33%. The mode of treatment is adjuvant chemotherapy as well as surgery (2).

Embryonic carcinomas and choriocarcinomas

Embryonic carcinoma is very rare and is often confused with Endodermal sinus tumors. Thirteen years is the median age of presentation and is usually unilateral (2). These tumors usually give a positive pregnancy test and in 60% of the cases show a hormonal profile that is consistent with precocious puberty in premenarcheal girls and abnormal vaginal bleeding in postmenarcheal girls. Choriocarcinomas are extremely rare and are also associated with an increased HCG level (2). These subtypes tend to produce HCG, rarely AFP and cause irregular uterine bleeding (9). The efficacy of treatment using adjuvant chemotherapy is not known due to the rarity of this tumor. The treatment regimen is thus usually identical to the Endodermal sinus tumors.

Juvenile granulosa cell tumors

These tumors often occur in the first two decades of life and in 80% of the cases, they present with menstrual irregularity or isosexual precocity. These patients may present with peritonitis, ascites and/or a pelvic mass. The majority of these tumors are unilateral and thus limited unilateral salpingo-oophorectomy is usually sufficient to confine the disease and the patient would not require any further therapy.

Germ cell ovarian tumors should be staged after excision using the International Federation of Gynecologic Oncologists (FIGO).

Stage 1: tumor is confined to the ovaries

- IA: tumor growth is limited to one ovary without any malignant ascites
- IB: tumor growth is limited to two ovaries without any malignant ascites
- IC: tumor of stage 1A or 1B but with ascites or ruptured capsules

Stage 2: tumor has spread to the pelvis

- 2A: metastasis to the fallopian tubes or uterus
- 2B: both ovaries affected and extended to the pelvis
- 2C: a tumor of stage 2A or 2B But with ascites

Stage 3: tumor seeds in the abdominal cavity or retroperitoneal lymph nodes

- 3A: confined to the pelvis
- 3B: metastasis to the peritoneal cavity but not >2cm mass
- 3C: metastasis to the peritoneal cavity but >2cm mass

Stage 4: metastasis into other distant organs

Symptoms

Patients usually present with acute abdominal pain which is likely due to ovarian torsion, hemorrhage or cyst rupture. There may be vaginal

bleeding, fever, as well as symptoms of hyperthyroidism or carcinoid syndrome.

Diagnosis

Diagnosis is done using CT of the abdomen and pelvis as well as an ultrasound. A physical exam is often used to detect an abdominal and pelvic mass. Primary amenorrhea, virilization and genital abnormalities should also be used as diagnostic events. HCG, AFP, CA-125 and LDH should be measured and monitored.

Other conditions causing similar symptoms

Germ cell ovarian tumors may present with symptoms that are also seen in appendicitis, ectopic pregnancy and ovarian torsion. Thus, these conditions should be eliminated prior to making a final diagnosis. Epithelial ovarian tumors, adrenal tumors and other pelvic masses may also be behind these symptoms.

Treatment

Due to fertility concerns, radiation is rarely used in germ cell tumors (9). These types of ovarian tumors are very chemosensitive to platinum-based therapies (25). Chemotherapy using bleomycin, etoposide, cisplatin (9, 24), actinomycin D and vincristine is sometimes used. Surgery is usually done in cases where a benign cystic teratoma is the diagnosis, as well as unilateral salpingo-oophorectomy (2). Staging after surgery is essential in determining what the next step is going to be (9). Dysgerminoma is treated by unilateral salpingo-oophorectomy making sure that a frozen section should be obtained, at the time of the laboratory, to confirm the diagnosis.

Follow-up

If there is a significant mass or abnormal HCG, AFP or CA-125, the patient should be immediately referred to a gynecologic oncologist. Lymph node metastasis depend on the histological subtype of the tumor and is indicative of poor survival (25).

E. MALIGNANT EPITHELIAL OVARIAN TUMORS

Epithelial ovarian cancer is the number one cause of gynecological death in women and the fifth leading cause of death in women overall (10). Accounting for about 90% of ovarian cancers, epithelial ovarian tumors are the most common type of ovarian cancer (6). This type affects mostly postmenopausal women. The lifetime risk of developing ovarian cancer in the population is about 1.4%. Ovarian cancer is very rare in the adolescent age group. About 2.3% of ovarian cancers occur in patients under 25 years of age, out of which only about 40% were under 19 years of age (26). In general malignant neoplasms are very rare in the pediatric and adolescent population (21).

Risk factors

There are several risk factors for developing epithelial ovarian tumors including early menarche, late age of menopause, no children, infertility and talc use. Some of the protective factors against epithelial ovarian tumors include pregnancy, oral contraceptive use and breastfeeding.

Subtypes of epithelial ovarian tumors

All epithelial ovarian tumors should be removed and staged after excision using the International Federation of Gynecological Oncologists (FIGO).

Stage 1: tumor is confined to the ovaries

1A: tumor growth is limited to one ovary without any malignant ascites

1B: tumor growth is limited to two ovaries without any malignant ascites

1C: tumor or stage 1A or 1B but with ascites or ruptured capsules

Stage 2: tumor has spread to the pelvis

2A: metastasis to the fallopian tubes or uterus

2B: both ovaries affected and extended to the pelvis

2C: a tumor of stage 2A or 2B but with ascites

Stage 3: tumor seeds in the abdominal cavity or retroperitoneal lymph nodes

3A: confined to the pelvis

3B: metastasis to the peritoneal cavity but not >2cm mass

3C: metastasis to the peritoneal cavity but >2cm mass (this is the most common stage of diagnosis)

Stage 4: metastasis into other distant organs

Upon histological analysis of the excised tumor, epithelial ovarian cancer is subtyped to mucinous, serous, endometrioid, clear cell, transitional, small cell, malignant mixed mesodermal, and unclassified (1).

Symptoms

Most of the time, patients are asymptomatic until the advanced stages are reached. In advanced stages, there is often abdominal fullness and pain (5, 9), urinary frequency, abnormal vaginal bleeding and pelvic pressure.

Diagnosis

A physical exam including a pelvic and abdominal exam should be done to detect any masses. Pleural effusions may be noted by decreased breath sounds and lymph nodes should be examined for any palpable masses.

CA-125 is often used to monitor and assess response to therapy, but should not be used as a diagnostic tool in women who are at low risk or asymptomatic (9). 80-85% of patients with advanced ovarian cancer have elevated CA-125 (3). A complete blood count and an abnormal metabolic panel may be used as an indicator for epithelial ovarian cancer. Unfortunately, there is no definitive test for early diagnosis. Imaging techniques such as ultrasound is most commonly used to detect ovarian masses with ascites or free pelvic fluid. A chest radiograph is sometimes performed to detect the presence of nodules. A CT scan often shows a pelvic or abdominal mass (9).

Other conditions causing similar symptoms

Tuba-ovarian abscess or other infections such as appendicitis may present with similar symptoms. An elevated CA-125 or the presence of ascites may be detected in patients with liver disease. In addition, several other tumors such as borderline, malignant and nonmalignant tumors may also have similar symptoms to epithelial ovarian tumors.

Treatment

A laparotomy must be performed and the tumor staged. Maximum cytoreductive surgery is often essential for a better prognosis if cancer is found. Peritoneal washings should be performed and typed. Also, total abdominal hysterectomy is favorable as well as samples from the diaphragm to detect any metastasis (9). Adjuvant chemotherapy is standard in treating ovarian cancer patients. Standard chemotherapeutic agents used include a platinum agent such as cisplatin and taxanes such as paclitaxel. For patients that develop recurrent disease, several other drugs may be used **but** are only **beneficial** in **10-25%** of the cases **and** are not curative (9).

Follow-up

Patients should be referred to a gynecologic oncologist if there is a high likelihood of ovarian cancer. If diagnosed at early stages, the prognosis is much better. In fact, the 5-year survival rate at stage I is 90% whereas at advanced stages, it is about 20%. CA-125 should be used to monitor the patient on a regular basis every 3 months. Most recurrences of cancer occur during the first 2 years after treatment (9).

F. VIRILIZING OVARIAN TUMORS

This type of ovarian tumor is extremely rare. In fact, it accounts for about 0.5% of all primary ovarian neoplasms. This type of tumor may occur at any age but mostly in the 2nd and 3rd decade of life. The hallmark of this tumor type is the production of androgenic steroid hormones. There are several substances that are released by this tumor that may often be used as markers (9). In the pediatric and adolescent population, the presence of a virilizing tumor should be taken into consideration when prepubertal girls present to the clinic with precocious puberty. This tumor develops from the cells that surround the oocytes (cumulus cells which are composed of granulosa cells). This tumor may be benign or malignant but is almost always firm, solid and have a smooth surface. Most of these tumors have low grade histology (9).

Risk factors

There are no known risk factors to date (9).

Subtypes of virilizing ovarian tumors

All epithelial ovarian tumors should be removed and staged after excision using the International Federation of Gynecological Oncologists (FIGO).

Stage 1: tumor is confined to the ovaries

1A: tumor growth is limited to one ovary without any malignant ascites

1B: tumor growth is limited to two ovaries without any malignant ascites

1C: tumor of stage 1A or 1B but with ascites or ruptured capsules

Stage 2: tumor has spread to the pelvis

2A: metastasis to the fallopian tubes or uterus

2B: both ovaries affected and extended to the pelvis

2C: a tumor of stage 2A or 2B but with ascites

Stage 3: tumor seeds in the abdominal cavity or retroperitoneal lymph nodes

3A: confined to the pelvis

3B: metastasis to the peritoneal cavity but not >2cm mass

3C: metastasis to the peritoneal cavity but >2cm mass (this is the most common stage of diagnosis)

Stage 4: metastasis into other distant organs

There are mainly three subtypes of virilizing ovarian tumors

- **Sertoli-stromal cell tumors:** These tumors may appear as well, poor or intermediate in differentiation.
- **Gynandroblastoma**
- **Steroid (lipid) cell tumors:** These include stromal luteoma, Leydig cell tumor or unclassified.

Symptoms

The chief complaint is usually abdominal pain and an increase in abdominal girth.

Diagnosis

There are certain findings during the physical exam that may help in the diagnosis of virilizing ovarian tumor such as a palpable adnexal mass, breast atrophy, hirsutism, deep voice, male pattern baldness and acne on the face or back. Certain lab tests such as inhibin, testosterone, AFP, DHEA, 17-hydroxyprogesterone and androstenedione may be performed to help confirm the diagnosis. A pelvic ultrasound and a CT scan of the chest and abdomen are also preferable (9).

Other conditions causing similar symptoms

PCOS and Cushing syndrome often present with similar symptoms and lab results. Thus, it is necessary to eliminate any suspicion regarding the presence of a virilizing tumor. Steroid use may also cause similar lab results (9).

Treatment

Surgery is the main mode of treatment. Chemotherapy is often used to treat metastatic disease such as cisplatin and bleomycin (9).

Follow-up

Patients will need to visit a gynecologist every 2-4 weeks and a routine physical examination as well as testosterone levels every 2-3 months afterwards (9).

RECENT ADVANCES IN TUMOR BIOMARKERS

There have been several reports regarding potential new ovarian tumor diagnostic markers. One of the most researched in the literature is

Lysophosphatidic acid (LPA) receptor. LPA receptors are G-protein coupled receptors. Two receptor subtypes, namely LPA 2 and 3 have been shown to be over expressed in most ovarian cancer cells. There are several studies underway trying to decipher the role of LPA receptors in ovarian tumor progression and are showing promise to its use (27).

OTHER CONCERNS

Due to the rigorous treatment measures and chemotherapy, adolescents often struggle with depression and poor body image even after the tumor has been removed. Thus, it is of utmost importance to take into account the psychological impact of the presence and treatment of ovarian tumors. In addition, fertility issues should be discussed extensively with the adolescent as well as their parents before any surgery is performed. It has been previously reported that there is a 15% decrease in fertility in survivors of pediatric gynecological cancers (28).

SUMMARY OF LAB TESTS HELPFUL TO THE DIAGNOSIS OF OVARIAN CANCERS

CA 125: usually elevated in epithelial tumors, and rarely in teratomas. It should not be used in asymptomatic patients

AFP: usually elevated in germ cell tumors, embryonic carcinoma, endodermal tumors and rarely but may be seen in polyembryoma and immature teratoma.

HCG: usually found in patients with choriocarcinoma, embryonic and germ cell tumors, and rarely in dysgerminoma

Carcinoembryonic antigen and LDH: this is usually seen in germ cell tumors and dysgerminoma

Estradiol: thecomas and adult granulosa cell tumors

CONCLUSION

Ovarian tumors are uncommon in the child and adolescent population, but given that cancer is a leading cause of death even in this age group it is important for the general practice physician to be aware of the signs and symptoms. These can include abdominal pain, increased abdominal girth, a palpable mass on pelvic or abdominal exam, nausea and vomiting, decreased appetite, weight loss, constipation, back pain, leg cramps, dyspareunia, urinary symptoms, abnormal uterine bleeding, and ascites, to name a few. The types of gynecological tumors seen in adults are also seen in children except in differing frequencies. The most common type of ovarian tumor in children is the germ cell tumor, of which there are several subtypes including dermoid cysts, dysgerminoma, yolk sac tumor, immature teratomas, and embryonal carcinomas. Each requires different laboratory workups and equally varied treatment plans. Functional cysts are typically benign in nature and can resolve on their own. Their etiology depends on the stage of the female cycle in which they occur. Other benign ovarian tumors such as endometriomas, cystic teratomas, and epithelial tumors along with borderline ovarian tumors, which may progress to a malignant stage, are rare in children and adolescents. Given the low probability of malignancy of these tumors, but poor prognosis if discovered at an advanced stage, it is important for the general practitioner and pediatrician to keep a high level of suspicion. Given the symptoms for ovarian tumors are common complaints seen daily in the outpatient setting, these can be difficult to differentiate from more common diagnoses, but is the reason to keep in mind other aspects of the child and their overall growth and development. Body image and fertility are significant issues to the adolescent female, therefore side effects as well as benefits of treatment should be given adequate discussion with the physician, parents and patient prior to initiation of treatment.

Table 1. Summary of ovarian tumors

Name	Benign Vs Malignant	Pathology	Treatment Recommendations
Functional Cysts Follicular Luteal Pregnancy luteoma	Benign	Exaggerated ovarian function, anovulation, follicular or luteal origin	Observation Possible role of combination contraceptive pills Laparoscopy evaluation in case of rupture
Endometrioma	Benign	Often accompanies endometriosis	As above
Epithelial Serous Mucinous	Benign, borderline, and malignant potential		As above
Benign Cystic Teratoma	Benign	Germ cell	Cystectomy
Borderline Serous Mucinous	Borderline		Excision ± hysterectomy in acceptable circumstances
Germ Cell Dermoid Cyst Dysgerminoma Yolk Sac	Benign or malignant depending on the type	All three germ cell layers	Chemotherapy and surgery where necessary

Immature teratoma Embryonal Carcinoma Choriocarcinoma			
Malignant Epithelial Virilizing Sertoli cell Gynaetroblastoma Steroid (lipid) cell Stromal Luteoma Lydig cell Unclassified	Malignam Benign or malignant	Epithelial	Surgery and chemotherapy As above

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