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# *Management of Adnexal Masses in Pregnancy*

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**Abstract:** The identification of a pelvic mass during pregnancy can often change a time of happiness and exciting anticipation to 1 of anxiety and fearful unknown. Although diagnosed more commonly with the implementation of ultrasonography as part of routine prenatal care, discovering an adnexal mass during pregnancy remains a rare event. Fortunately, the majority of masses are benign and rarely negatively impact pregnancy outcomes; however, no specific protocols exist for the appropriate management of these women. This study will review the most current incidence, management, and outcomes for women diagnosed with an adnexal mass during pregnancy.
**Key words:** adnexal mass, pregnancy, surgical management

## *Incidence*

Depending on the method one uses and how one defines a clinically significant adnexal mass, the prevalence of pregnancies complicated by an adnexal mass varies, but has been reported to be between 1% and 4%.[1,2] The majority of these masses are small (< 5 cm) and represent corpus luteum or other functional cysts that typically resolve spontaneously by the second trimester. A small percentage of these, approximately 5%, will represent malignant tumors, making ovarian cancer the fifth most common cancer diagnosed during pregnancy.[3]

Identification of adnexal masses during pregnancy has made a major shift over the last 20 to 30 years with the use of routine prenatal ultrasounds. Previously, most adnexal masses were not detected until cesarean delivery or until they became symptomatic. Not surprisingly when discovered late in pregnancy or at the time of symptom development, there was a higher rate of complications (torsion, rupture, obstructed labor, etc.) and a higher rate of malignancy. Now, however, with routine use of ultrasounds, most masses are found incidentally, spontaneously resolve, and are not associated with poor pregnancy outcomes. In a review of nearly 20,000 obstetric ultrasounds, Bernhard et al[2] identified 422 (2.3%) patients with adnexal masses. The majority of 320 (76%) patients had simple cysts measuring < 5 cm. These cysts were asymptomatic and did not result in any adverse

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outcomes. The remaining 102 patients had complex masses or cysts >5 cm in diameter. Despite these more worrisome features, 70 of the 102 (69%) complex or larger masses resolved without incident.[2] When adnexal masses do not resolve, they are at risk for torsion, rupture, or hemorrhage. These complications can be seen in any trimester of the pregnancy.

## *Diagnostic Evaluations*

Although most ultrasounds that identify adnexal masses were obtained for obstetrical reasons, ultrasounds are quite good at determining the source of the mass and characterizing its morphology. Similar criteria used in the general population to triage an adnexal mass as benign or malignant also hold true during pregnancy. Masses that are complex, solid, and have papillations or mural nodules are more likely to be malignant. Likewise, masses with increased blood flow or decreased resistance index have a size >10 cm, or a growth rate of >3.5 cm per week have a significantly higher risk of malignancy.[4] Certain cysts, such as endometrioma or mature cystic teratoma, have very distinct ultrasound findings that lead to a high rate of accurate diagnosis. Although other imaging modalities exist, ultrasonography is usually sufficient to make decisions regarding management of an adnexal mass. If this is not the case, magnetic resonance imaging is preferred to computed tomography based on its superior soft tissue resolution and ability to avoid fetal exposure to ionizing radiation. Even without the routine use of gadolinium-based contrast (for which fetal safety has not been established), magnetic resonance imaging interpretations correlated with pathologic in the vast majority of cases.[5]

In a nonpregnant state, some investigators have tried to develop an ovarian cancer symptom index as a way to identify women at risk for ovarian cancer.[6] Many of the symptoms in the index, such as abdominal and/or pelvic pain, urinary urgency and/or frequency, increased abdominal size and/or bloating, and difficulty eating, are all very common in pregnancy. Using these symptoms, as a distinguishing evaluation, therefore, is quite limited during pregnancy. In addition, physical examination is often difficult or particularly uncomfortable for gravid patients, and palpation of masses or posterior cul-de-sac nodularity is hindered by the uterus.

Depending on the timing of a woman's first ultrasound, one of the first indications of a pelvic mass may be an elevation in maternal serum analytes obtained as part of the triple screen for Down syndrome or neural tube defects. Oncofetal antigens such as α-fetoprotein (AFP), human chorionic gonadotrophin, lactate dehydrogenase, estradiol, testosterone, and dihyroepiandrostenedione are involved in normal fetal development, and levels of all these antigens can be elevated during pregnancy normally or as a result of abnormal placentation or fetal anomaly. However, this elevation may also be indicative of a germ cell or sex cord stromal tumor.[7] Elevated AFP is often seen with germ cell tumors such as endodermal sinus tumors, embryonal tumors, or mixed germ cell tumors. Typical values seen in germ cell tumors are often 1000 ng/mL to 10,000 ng/mL or >9.0 multiples of the median.[8,9] This is contrasted by the AFP value of 500 ng/mL or 2.0 to 2.5 multiples of the median typically seen in pregnancies complicated by neural tube defects. When these significant AFP elevations are identified, concern for a germ cell tumor should arise and be excluded by ultrasonography if not already performed.

CA125 is a commonly used tumor marker for epithelial ovarian cancer. It is noted to be elevated in approximately 50% of early-stage and 80% of advanced-stage ovarian cancers. Unfortunately, CA125 is nonspecific and can be elevated with a variety of benign conditions including pregnancy. This is particularly true in the

first trimester or immediately postpartum.[10] Between 15 weeks gestation and delivery, however, a markedly elevated CA125 (range, 1000 to 10,000) can no longer be solely attributed to the pregnancy. If a mass is present with a persistently elevated CA125 before the first trimester, malignancy is more likely. A more modest CA125 elevation (value between 75 and 150) may still be pregnancy related or due to a poorly expressing ovarian cancer, so it loses its discriminatory ability. Another tumor marker, human epididymis protein 4 (HE4), has been used for surveillance of women with known ovarian malignancies and in conjunction with CA125, as a possible screening tool.[11] A small number of pregnant women have had this test performed all of whom had values of $< 300$ pM. When one considers that nearly 50% of women with ovarian cancers had HE4 value of $> 500$ pM, this may be a useful marker in pregnancy (HE4 package insert).

Finally, a new test, Ova 1, is being marketed to help triage patients with known masses to an appropriate surgical specialist. Used in conjunction with clinical assessment, Ova 1 detected 79% of stage I ovarian cancers and all stage II/III cancers.[12] This test is a protein-based in vitro diagnostic serum immunoassay using 5 different biomarkers—transthyretin, apolioprotein A1, β-2 microglobulin, transferring, and CA125. This test has never been reported for use in pregnancy, and given the effect of pregnancy on several of these markers, it is not likely to be useful in helping triage adnexal masses found in gravid women.

## *Differential Diagnosis*

When an adnexal mass is identified during a pregnancy, it is important to generate a differential diagnosis to help guide the management. This differential is guided by the ultrasound characteristics of the mass, clinical presentation, and potentially by tumor markers. The vast majority of masses detected during routine early obstetrical ultrasounds are simple cysts and $< 5$ cm in diameter. These small cysts are most physiologic functional cysts or perhaps unilocular serous or mucinous cystadenomas. When the masses contain some complex ultrasound features, the differential expands to include corpus luteum, teratomas, endometrioma, or theca lutein cysts. If the mass is solid in nature a fibroma or leiomyoma is more likely. Fortunately, only a very small percentage ($\leq 5\%$) of pelvic masses diagnosed during pregnancy are malignant. Of these, approximately 50% are epithelial tumors, a third are germ cell tumors, and sex cord stromal tumors or other tumors (sarcomas, metastatic disease) account for the remainder (Table 1).[13] This distribution is quite a bit different than that seen in the general population where germ cell tumors account for fewer than 5% of ovarian cancers, likely representing the younger age of women diagnosed with ovarian cancer during pregnancy. As far as the epithelial tumors are concerned, they are equally divided between frankly malignancy tumors and tumors of low malignant potential (Fig. 1). Approximately, 75% of the germ cell

***TABLE 1. Differential Diagnosis and Frequency for Pelvic Masses in Pregnancy***

| History | Percent |
|---|---|
| Benign mass (95%) | |
| Corpus luteum | 17 |
| Dermoid | 37 |
| Cystadenoma | 24 |
| Endometrioma | 5 |
| Leiomyoma | 5 |
| Other (paraovarian, luteoma, theca-lutein) | 12 |
| Malignancy (5%) | |
| Epithelial | 50 |
| Invasive | 33 |
| Low malignant potential | 66 |
| Germ cell tumor | 30 |
| Stromal/sex cord | 20 |

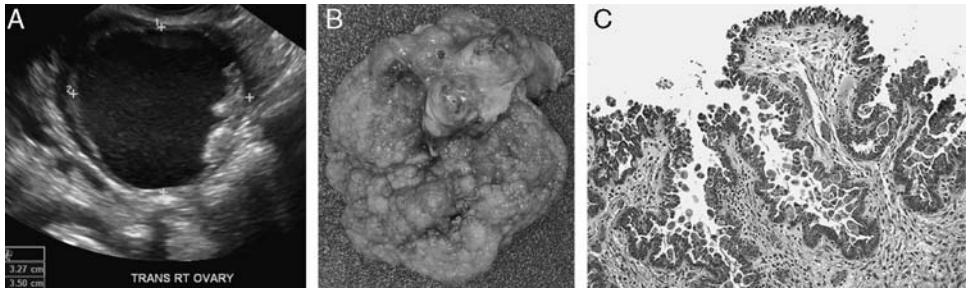


***FIGURE 1.*** Example of an ovarian serous tumor of low malignant potential. A, Ultrasound of the right ovary. Note the mural nodularity along the left wall of the cyst. B, Gross specimen of a serous low malignant potential (LMP) tumor. After opening the cyst, there were multiple excrescences and wall nodularity thorough the cyst. C, Microscopic histology of a serous LMP tumor. Diagnosis is made by the histologic features of epithelial papillae with detachment of atypical cell clusters or budding/tufting, cellular stratification, increased mitotic activity, and nuclear atypia all of which are present in this example.

tumors diagnosed during pregnancy are dysgerminomas (Fig. 2). Granulosa cell tumors and Sertoli-Leydig cell tumors account for approximately 50% and 33% of the sex-cord stromal tumors during pregnancy.[14]

## *Risks of Adnexal Mass*

Making the decision to operate on an adnexal mass diagnosed in pregnancy is often difficult and necessitates that the surgeon balance the competing interest of the mother and fetus. Unfortunately, there are no prospective studies randomizing pregnant women with adnexal masses to surgery versus observation, thus requiring the surgeon to rely on clinical acumen and data from retrospective reviews (Table 2). Often it is important that a multidisciplinary team of maternal fetal medicine specialists, gynecologic oncologists, and neonatologists be involved in the decision of whether to operate and in particular when to perform a surgery.

Surgery for an adnexal mass, whether performed during pregnancy or postpartum, carries some inherent intraoperative and perioperative risks. Previous reports

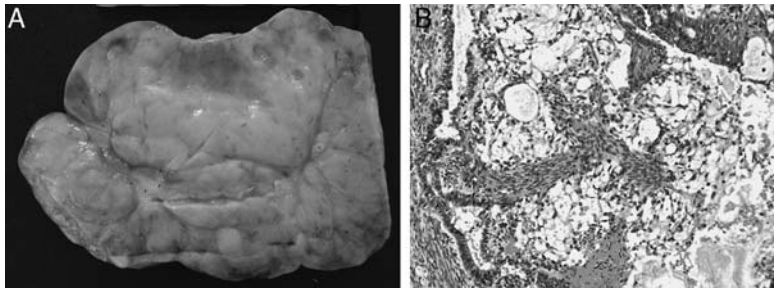


***FIGURE 2.*** Example of an ovarian dysgerminoma. A, Gross specimen of a dysgerminoma of the ovary. Typical of a dysgerminoma is the pale, lobulated, fleshy cut surface. B, Microscopic histology of a dysgerminoma. Note the uniform tumor cells with pale cytoplasm and a central round nucleus.

***TABLE 2. Published Series of Adnexal Masses in Pregnancy***

| Study | Incidence (%) | Cyst Resolution (%) | Rate of Intrapartum Surgery (%) | Rate of Malignancy or LMP (%) | Torsion (%) | Preterm Birth (%) | SAB or Neonatal Death (%) |
|---|---|---|---|---|---|---|---|
| Platek et al[15] N = 31 | 0.001 | 16 | 59 | 0 | 0 | NR | 10.5 |
| Bernhard et al[2] N = 102 | 2.3 | 92 | 25 | 1 | 1 | NR | NR |
| Whitecar et al[16] N = 130 | 0.001 | NR | 66 | 6.2 | 5.4 | 9.2* | 1.5* |
| Usui et al[17] N = 69 | 0.004 | NR | 100 | 2.9 | NR | 11.6 | 5 |
| Sherard et al[18] N = 60 | 0.15 | NR | 55 | 13 | 1.6 | 9 | 4.7 |
| Zanetta et al[19] N = 82 | 1.2 | 54.5 | 3.6 | 3.6 | 3.6 | NR | NR |
| Schmeler et al[20] N = 63 | 0.05 | 59.5 | 29 | 8.5 | 6.3 | 0 | 0 |

*Odds ratio for risk of preterm birth or SAB/neonatal death is 0.15 for surgery performed before 23 weeks of gestation. LMP indicates low malignant potential; NR, not reported; SAB, spontaneous abortion.

have shown that elective abdominal surgery during pregnancy is safe and not associated with increased rates of miscarriage, premature rupture of membranes, and preterm delivery.[21,22] This is sharply contrasted to the outcomes seen when surgery is undertaken in an emergent manner. As compared with those who had scheduled, elective surgery, Lee et al[23] demonstrated that those who had emergent surgery had a significantly higher incidence of preterm labor 22% versus 3.8%. Depending on the clinical suspicion of malignancy, delaying surgery may be feasible, thus avoiding any unnecessary risks to the pregnancy. The downside of observing a mass during pregnancy, however, is the risk of delayed treatment if malignant and the development of an acute event such as ovarian torsion, cyst rupture, or obstruction of labor that often necessitate emergent intervention. Ovarian torsion is most commonly (60% of the time) seen between the 10th and 17th week of gestation and has been reported to occur in up to 5% of pregnant women with adnexal mass. This rate is significantly higher (approximately 20%) for masses that are 6 to 8 cm in size.[20] Cyst rupture and obstruction of labor are less common complications.

## *Surgical Management*

Although there are no strict guidelines, most would agree that surgery is warranted for masses that persist into the second trimester and are $>10$ cm in size, are symptomatic, or are solid or have mixed solid and cystic ultrasound features suspicious for malignancy. The goals of the surgery include removal of the mass to avoid pregnancy complications, obtain a diagnosis, and to stage or debulk an ovarian cancer if a malignancy is identified. As in the nonpregnant state, surgery for an adnexal mass begins with obtaining peritoneal washings and a complete exploration of the abdomen with particular attention to the contralateral ovary. Traditionally, this has been accomplished through laparotomy and a midline incision. It is important to minimize manipulation of the uterus as this could increase the risk of placental abruption, premature labor, or fetal loss. If the clinical suspicion for malignancy is low and it seems technically feasible, a surgeon can perform a

cystectomy rather than salpingooophorectomy. If, however, the clinical suspicion for cancer is high (excrescences, ascites, etc.) or the mass is solid, the tube and ovary should be removed. In either case, a frozen section should be obtained. If a malignancy is confirmed and seems to be confined to the ovary, then a full staging surgery including peritoneal biopsies, omentectomy, and lymphadenectomy should be considered; however, the potential benefit of information gained from the more extensive surgery must be balanced against potential neonatal morbidity. For those women who are diagnosed with a dysgerminoma or grade 1 immature teratoma, staging is critical as adjuvant therapy is only initiated for those with advanced-stage disease. Routine biopsy or wedge-resection of the contralateral ovary is not necessary unless it seems to be involved with disease. If metastatic disease is identified, an attempt at cytoreduction should be undertaken. It is imperative, however, that the surgeon balance the fetal risk of an extended and radical debulking with the potential maternal benefit, realizing that interval cytoreduction after chemotherapy and completion of the pregnancy is a reasonable approach.

Timing of surgery for an adnexal mass is ideally in the early second trimester. Once in the second trimester, organogenesis is complete and the risk of spontaneous pregnancy loss has substantially decreased compared with the first trimester, thus minimizing the potential impact of surgery on pregnancy outcome. In addition, functional cysts should have resolved at this point hopefully eliminating unnecessary surgery. Finally, by the second trimester, the placenta, rather than the corpus luteum, is responsible for progesterone production; therefore, if an oophorectomy or cystectomy results in removing a corpus luteum, it should not affect the pregnancy's reliance on ovarian progesterone. If the corpus luteum is removed before 8 weeks of gestation, progesterone supplementation is necessary.

Depending on the timing of surgery, the operating room staff must be prepared to monitor fetal status. In the first and early second trimester, this entails checking fetal heart tones preoperatively and postoperatively. Once the fetus reaches viability in the late second trimester, this requires continuous fetal heart tone monitoring with the capacity for emergent cesarean section if needed. The role of prophylactic tocolytics in this setting is unclear.

Traditionally, the approach to surgery for adnexal masses during pregnancy has been with an open laparotomy. More recently, there has been a movement toward a minimally invasive surgical (MIS) approaches using laparoscopic or robotic surgery. Compared with laparotomy, MIS provides a quicker recovery time, lower surgical morbidity, and less discomfort, but also produces some physiologic challenges to a pregnancy. Given the elevated intra-abdominal pressures required for MIS, there is decreased maternal venous return and cardiac output, resulting in decrease uterine blood flow and can cause fetal hypotension and hypoxia. In addition, absorption of carbon dioxide can lead to fetal acidosis. Although less likely with a left upper quadrant insertion, a final challenge to MIS during pregnancy is injury/perforation of the uterus with the Veress needle or trocar. To date, there have not been any randomized trials comparing laparotomy to MIS for managing adnexal masses in pregnancy; however, case series have attested to the feasibility, safety, and benefits of MIS in pregnancy.[24,25] A recent Cochrane database review noted that the available case series on the topic were too limited to make any conclusions with regard to the risks and benefits of this technique in pregnancy and recommended a randomized trial.[26]

## *Conservative Management*

Alternative to surgery, conservative management of adnexal masses is a reasonable alternative in many circumstances. Two recent retrospective studies reported the outcomes of women with adnexal masses managed with observation (Table 2). In an effort to determine whether the delay in surgery impacted the risk of adverse maternal or fetal outcomes in women diagnosed with an adnexal mass during pregnancy, Schmeler et al[20] reviewed their experience with masses $>5$ cm in diameter. Of >120,000 deliveries, this group identified 63 (0.05%) patients with masses $>5$ cm, all but 4 of whom had follow-up data. Seventeen of the 59 (29%) patients had antepartum surgery whereas 42 (71%) were observed or had the mass removed at Cesarean section. Of those that had surgery before delivery, 13 patients were operated on for suspicious ultrasound findings and 4 patients were operated because of ovarian torsion. There was no difference in obstetrical outcomes between the 2 groups. All of the women diagnosed with a cancer (4 patients, 6.8%) or a tumor of low malignant potential (1 patient, 1.7%) had concerning ultrasounds; thus, the investigators concluded that observation is a reasonable approach if ultrasound features are not highly suspicious for malignancy. Zanetta et al[19] reported on 79 pregnant women diagnosed with adnexal masses who were followed conservatively. It is important to note that 68 of these women were asymptomatic and nearly 75% were diagnosed in the first trimester. Forty-two of the 68 (62%) women had their cyst resolve during pregnancy without any intervention. Four women required surgery during pregnancy for torsion. All of these torsions occurred shortly after the mass was identified in the first trimester. Of the 31 patients who had persistent masses after pregnancy, 19 patients ultimately underwent postpartum surgical management. No significant obstetrical complications were reported but 2 women had cesarean sections as a result of the mass obstructing labor. These investigators concluded that acute complications from stable cysts are rare, and expectant management is successful in the majority of cases.

## *Adjuvant Therapy and Outcomes of Ovarian Cancer in Pregnancy*

If malignancy is identified, management is dependent on the histology and stage of disease. For tumors of low malignant potential, regardless of stage, chemotherapy is generally not recommended. For epithelial malignancies, only well-differentiated cancers that are confined to the ovary (after comprehensive surgical staging) do not need chemotherapy. For all others, a platinum and taxane-based chemotherapy is the standard of care and has been successfully administered in pregnancy.[27,28] Chemotherapy for germ cell tumors, other than for stage I dysgerminoma, is typically bleomycin, etoposide, and cisplatin (BEP).[29] Clearly, the use of chemotherapy during an ongoing pregnancy carries risks and toxicities not only for the mother but also for the fetus. These risks are greatest during the first trimester when the fetus is undergoing rapid growth and organogenesis.[30] If chemotherapy is indicated and cannot be delayed, it is ideal to initiate chemotherapy in the second or early third trimester.

There is no evidence that pregnancy worsens the prognosis of ovarian cancer as compared with nonpregnant patients matched for tumor stage, histology, and grade. As a large percentage of ovarian malignancies are early stage and of favorable histology, 5-year survival rates for ovarian cancers diagnosed during pregnancy is between 75% and 90%. In 1 study, the risk of maternal death was associated with the timing of diagnosis,

with the mortality rate being 0 if the diagnosis was made 9 to 12 months before delivery, 5.6% if made 0 to 9 months before delivery, 6.3% if made at delivery, and 18.5% if made 0 to 12 months after delivery.[31] Diagnosing an ovarian neoplasm does not seem to have any adverse effects on neonatal outcomes such as low birth weight, prematurity, neonatal death, or neonatal hospital readmission.

## Conclusions

Overall, although adnexal masses are often diagnosed in pregnancy, the majority resolve spontaneously and those that do not rarely represent malignancy or negatively impact the pregnancy. The decision to expectantly manage versus operate on a pregnant patient with a mass is based primarily on ultrasound features and development of acute symptoms. When surgery is undertaken, it is best done in the second trimester. If a malignancy is diagnosed appropriate staging or debulking should be strongly considered and chemotherapy initiated as appropriate based on cancer histology, stage, and grade to ensure the best possible maternal outcomes.

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