Adnexal Masses in Pregnancy

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Introduction

With increasing use of first trimester aneuploidy screening, the incidental discovery of adnexal masses during early gestation is a clinically relevant problem that requires careful consideration. The purpose of this review is to summarize pertinent clinical issues surrounding women diagnosed with adnexal masses during pregnancy.

The overall estimated incidence of adnexal masses in pregnancy ranges from 2% to 10% [1]. Factors that impact the overall incidence of pregnancy related adnexal masses include method of diagnosis, criteria for defining a "mass," and the gestational age of the pregnancy. Prior to the use of routine first trimester ultrasound, adnexal masses only became clinically relevant if symptomatic or if they were large enough to palpate on physical examination. As ultrasound has become more commonly used in the first trimester, the reported incidence of adnexal masses has increased. Furthermore, as gestational age advances, the incidence of adnexal masses gradually decreases likely secondary to spontaneous resolution of many of these masses [2].

Observational studies evaluating adnexal pathology during pregnancy estimate a 1% - 4% incidence of sonographically detectable adnexal masses, with the majority of masses resolving spontaneously [3, 4]. A large retrospective analysis of three large population databases and estimated the incidence of pregnancy associated ovarian masses to be 9375 out of 4,846,605 (0.14%) [5]. Cases were identified in the prenatal, intrapartum and postpartum period. Of these 9375 masses, 2.1% (202/9375) were tumors of low malignant potential or ovarian malignancies. Studies that report surgical outcome data on patients with adnexal masses in pregnancy estimate the rate of malignancy or borderline tumors to be approximately 6% [6, 7].

Diagnosis

Ultrasound

Ultrasound serves a dual purpose during pregnancies complicated by adnexal masses, one is to characterize the mass and the second is to provide diagnostic assessment of a patient's symptoms in the acute setting. The majority of adnexal masses in pregnancy are incidentally discovered on routine prenatal sonographic examination. Despite numerous attempts, there is no reproducible sonographic scoring system with a high enough sensitivity to reliably diagnose ovarian malignancy on the basis of ultrasound alone [8-10]. However, there are numerous sonographic characteristics of adnexal masses that have been associated with increased risk of malignancy including size, solid components or heterogeneous/complex appearance, excrescences/papillary structures, internal septations, bilaterality, irregular borders, increased vascularity, low resistance blood flow and presence of ascites [1, 11, 12]. Taken alone each of these characteristics has been shown to have relatively reasonable specificity and/or negative predictive value for raising suspicion for malignancy; however, combinations of these factors are often more sensitive in predicting malignancy. Furthermore, given that pattern recognition by an experienced sonographer remains one of the best diagnostic modalities, it is imperative that clinicians are familiar with the characteristics that increase the suspicion for malignancy [13].

Adnexal mass size has been suggested as a viable screening tool for discriminating benign and malignant disease. Various size thresholds have been proposed above which an adnexal mass should be considered suspicious for malignancy. In a study of nonpregnant pre- and postmenopausal women performed by McDonald et al, tumor diameter greater than 10 cm was significantly associated with a diagnosis of malignancy. However, size alone was not a significant predictor of malignancy when multivariate analyses were performed. In addition, 27 unilocular cystic ovarian tumors measuring greater than 10 cm in this study were benign [12]. Among published series of adnexal masses in pregnancy, size thresholds ranging from 3 to 5 cm have been employed with reported malignancy rates ranging from 0-6.8%, and no reported malignancies were seen during pregnancy in lesions measuring less than 5 cm [6, 7, 14-16].

Ultrasound is also used as an adjunct to clinical evaluation to rule out ovarian torsion when patients present with abdominal and an ovarian mass. Sonographically ovarian torsion is demonstrated by visualizing an enlarged, edematous ovary with a concurrent mass or cyst. In addition, Doppler interrogation fails to demonstrate arterial and/or venous blood flow to the ovary. It is important to emphasize that ovarian torsion is a clinical diagnosis and ultrasound should only be used to provide additional supportive diagnostic information. This point is illustrated by findings of a recent study in which 19% of patients with torsion had normal preoperative Doppler flow to the affected adnexa [17]. The incidence of ovarian torsion during pregnancy varies widely depending on the size of the adnexal mass and its relationship to the gravid uterus making risk factors for torsion difficult to characterize. In a retrospective review assessing the risk of torsion among pregnant patients with adnexal tumors > 4 cm, 51% of torsions occurred in tumors measuring 6 to 8 cm in diameter with an overall incidence of 22% in this group of patients. Furthermore, the highest hazard rate of torsion occurred between 15 and 16 weeks' gestation with 60% of torsions occurring between 10 and 17 weeks' [18].

Tumor Markers

Tumor markers are typically measured among women with adnexal pathology to help distinguish as benign and malignant [12]. CA 125 is secreted by 80-90% of epithelial ovarian tumors and as a result it can be useful in monitoring patients with epithelial ovarian cancers. During a normal pregnancy, CA 125 concentrations can be variable and often peak during the first trimester, return to within normal limits for the remainder of gestation and then again peak in the postpartum period.

CA 125 is therefore of limited diagnostic utility in the antepartum and postpartum periods [19]. In addition, other established tumor markers are synthesized and secreted physiologically during fetal development [20]. For example, this is particularly true for inhibin, human

Mean CA-125 Levels Throughout Pregnancy

Adapted from: Spitzer M, et al. Maternal CA-125 levels in pregnancy and the puerperium. J Reprod Med. 1998 p 390 PMID: 9583073

Figure 1.   Click image to enlarge

chorionic gonadotropin (b-HCG), and a-fetoprotein (AFP) each considered markers for ovarian germ cell and sex cord stromal tumors of the ovary making them less useful during pregnancy.

Furthermore, during pregnancy, aberrations in HCG, inhibin or AFP can be associated with fetal aberrations like Down's syndrome and growth restriction as well as noncancerous maternal conditions like preeclampsia [21, 22]. Sarandakou, et al reviewed protein expression in both malignant and healthy fetal tissue and found normal levels of CEA, CA 15-3 and CA 19-9 in maternal sera documenting reliability of these markers in monitoring malignancy during pregnancy [23].   Collectively, these data point to the limited utility of serum marker evaluation during pregnancy.

Management

Given that the overwhelming majority of adnexal masses in pregnancy are benign and a good percentage will spontaneously resolve, an appropriate option for management of adnexal pathology in pregnancy is serial observation with ultrasound performed each trimester. Evidence supporting this recommendation is found in studies evaluating the incidence of adnexal masses in the first trimester of pregnancy. Zanetta et al found that 55% of masses resolve completely or significantly decrease in size [24]. In an attempt to predict characteristics of persistent adnexal masses, Bernhard et al, evaluated 432 masses discovered in pregnancy and found that 76% (320/422) were simple cysts with a mean diameter less than 5 cm. Of the remaining 102 masses larger than 5 cm, 70 (69%) resolved spontaneously. Multivariate analysis found that the best predictors of persistence were complex appearance and size greater than 5 cm [15]. Consequently, a reasonable option for patients with simple or functional appearing small adnexal masses would be surveillance with ultrasounds every trimester.

In patients that ultimately deliver via cesarean section, the adnexa should be evaluated at the time of surgery. In patients that undergo vaginal delivery, repeat imaging should be performed 6 to 8 weeks postpartum [2]. Support for this approach is seen in a single institution experience where surgery was reserved for patients with pregnancy-associated masses greater than 5 cm in size with characteristics suspicious for malignancy or symptoms of torsion and outcomes were compared to patients that were expectantly managed. Four patients in the antenatal surgery group had stage I ovarian cancers and one had a stage I borderline tumor. No cancers were identified in the expectantly managed group of patients [7]. Patients that have sonographic findings highly suspicious for malignancy or those that develop significant symptoms should undergo surgical resection.

Surgical Approach

The traditional approach involves a vertical midline laparotomy to provide the best exposure to the pelvis as well as access to the upper abdomen should surgical staging be indicated. Disadvantages to laparotomy include increased postoperative recovery time and increased incisional pain and discomfort that may limit a patient's mobility thereby potentiating risk of postoperative thromboembolism in a patient population that is already high risk. These factors raise the question as to the feasibility and safety of laparoscopy in pregnancy. In a retrospective comparative review of 88 pregnant women undergoing surgical intervention for adnexal pathology, 39 patients underwent laparoscopy in the first trimester compared to 54 patients undergoing laparotomy (25 in the first trimester and 29 in the second trimester). No operative or postoperative maternal complications occurred in either group with 5 women having first trimester miscarriages and 2 newborns having congenital malformations in the laparoscopy group compared to 2 first trimester miscarriages and 1 congenital malformation in the laparotomy group illustrating that laparoscopy is safe and should be considered if technically feasible [25]. The advantages to laparoscopy are evident in randomized comparisons of laparoscopy versus laparotomy for benign adnexal masses in which laparoscopy was associated with significantly less operative time, perioperative morbidity, length of hospital stay and postoperative pain [26-28]. Furthermore, laparoscopy is now widely used in most gynecologic malignancies, as such there is a role for laparoscopic staging in apparent early stage ovarian cancer [29].

The planned surgical dissection should be no different from a nonpregnant patient. Upon entry into the abdomen, a complete survey of the abdomen and pelvis should be performed and pelvic washings for cytology should be obtained. For benign appearing masses, if there is enough normal ovarian cortex and a clear border of the mass from the ovary, cystectomy should be performed with oophorectomy being reserved for more complex appearing masses. In the case of malignancy, careful attention must be paid to avoid cyst rupture as this would result in an upstaging of the patient and has the potential to induce more of an inflammatory response.

The timing of surgical interventions for adnexal pathology during pregnancy also requires careful consideration. There is evidence to support adverse pregnancy outcomes in patients undergoing abdominal surgery in the first trimester or after 24 weeks'; consequently, the ideal time for intervention is 14 to 22 weeks' gestational age. Patients that require intervention beyond the point of viability should be counseled on the risk of an undiagnosed malignancy and possibility of metastatic disease versus an adverse pregnancy outcome. When possible, patients undergoing antepartum surgery beyond 24 weeks' but prior to 34 weeks' should receive betamethasone to enhance fetal lung maturity. Furthermore, patients requiring intervention in the first trimester, particularly prior to 10 weeks should be given progesterone supplementation to support the early pregnancy should there be intraoperative disruption of the corpus luteum [2].

Histology

The majority of adnexal masses in pregnancy are benign. The most common histological diagnoses are dermoid cyst (37-50%), cystadenoma (20-24%), endometrioma (5-11%), and functional cysts (6-13%) [30-32]. The reported malignancy rates of adnexal pathology in pregnancy ranges from 0 to 8.5%, with the most common invasive pathology being epithelial ovarian malignancies (serous or mucinous), tumors of low malignant potential (serous or mucinous), and germ cell/sex cord stromal tumors, respectively [6, 7, 14-16, 30, 32].

Pregnancy Outcomes

Given that the majority of adnexal masses in pregnancy are benign and resolve spontaneously, the decision to proceed with surgical management should outweigh the risks of adverse perinatal outcomes. In a case-control study identifying women who had offspring with congenital abnormalities, there was no increase in surgery and anesthesia exposure in the congenital anomaly group. Lower birth weights were found among infants born to mothers that underwent surgery during pregnancy; however, this was accounted for by a subgroup of patients with cervical incompetence treated with cerclage [33]. Among the studies included in this review, surgical interventions for adnexal masses was tolerated to varying degrees with miscarriage

rates ranging from 0-4.7% [6, 7, 14-16, 30, 32]. In a retrospective review of surgical intervention for adnexal pathology by Usui et al, 12% of women experienced preterm delivery, 3.3% experienced spontaneous abortions and there were 3 perinatal deaths among 60 infants, 2 of which were for major congenital anomalies [16]. Whitecar et al found adverse fetal outcomes including preterm delivery and fetal loss were significantly less frequent if surgery occurred prior to 23 weeks' gestation [6]. Although there is a paucity of data regarding predictive markers for poor fetal outcomes, physicians should appropriately counsel women prior to proceeding with surgery for adnexal pathology.

Maternal and fetal outcomes should also be considered in the setting of a concurrent diagnosis of malignancy. Although most patients diagnosed with ovarian cancer during pregnancy have overall favorable prognosis with early stage disease, for a minority of patients with extraovarian spread or high risk features chemotherapy should be considered in the antepartum period. Chemotherapy in the first trimester should be avoided secondary to tetratogenic effects on the fetus; however, in the second and third trimesters growth and functional impairment are of greater concern than fetal malformation [34]. There is very limited experience with chemotherapy use for ovarian cancer during pregnancy. Ebert et al noted only 11 instances in which chemotherapy was given to pregnant patients with ovarian cancer over a 13 year time span [35]. Cisplatin is preferred over carboplatin during pregnancy secondary to decreased incidence of thrombocytopenia and decreased placental transfer secondary to cisplatin being less protein bound. There has been only one reported case of sensorineural hearing loss at 1 year in a child exposed to cisplatin in utero [36]. Although not specific to ovarian cancer, Aviles et al, reported on a cohort of children that were exposed to chemotherapy in utero and after extensive follow up have normal physical, neurological, psychological, hematologic, and immune function. This suggests that chemotherapy administered during pregnancy is not hazardous to the developing fetus [37]

Oncologic Outcomes

As discussed in this review, the majority of women are asymptomatic at the time of diagnosis of adnexal mass during pregnancy. Fortunately, for the minority of women diagnosed with ovarian malignancies, this yields favorable results in that the majority of ovarian malignancies and borderline tumors are low grade and stage at the time of diagnosis. Consequently, it is imperative that patients undergo comprehensive surgical staging at the time of diagnosis. Given the overall younger age of patients diagnosed with ovarian malignancies during pregnancy, it is appropriate for physicians to consider fertility sparing surgery for apparent unilateral disease. A recent multi-institutional retrospective review of patients treated conservatively for stage I invasive epithelial ovarian cancer defined favorable histologies as grade 1 or grade 2 adenocarcinomas excluding clear cell histology and found a 5 year overall survival and recurrence-free survival ranging from 93-100% and 92-97% respectively [38]. In particular patients with borderline tumors of the ovary are candidates for ovarian cystectomy. Although recurrence rates are higher, most are salvageable with additional surgery [39, 40]. In the rare instance where gross metastatic disease is identified, a decision regarding the status of the pregnancy must be rendered. Women in this situation in the first trimester may consider pregnancy termination secondary to the tetratogenic effects of chemotherapy in the first trimester. Women with more advanced gestations (2nd or 3rd trimester) may consider pregnancy preservation given the lack of adverse fetal outcomes based on limited clinical data [41]. In these rare instances, however, care should be directed by a multidisciplinary perinatal , neonatal and oncologic team.

Conclusion

In summary, the increased use of ultrasound in early gestation has led to an increase in the incidence of adnexal pathology diagnosed during pregnancy. Fortunately, the majority of adnexal masses diagnosed in pregnancy are benign and will resolve spontaneously without invasive intervention. Consequently, in the absence of symptoms or sonographic findings concerning for malignancy, patients should be expectantly managed. If surgery is indicated, laparoscopy is safe and feasible and both perinatal and maternal outcomes are favorable. Women diagnosed with ovarian malignancy during pregnancy are typically diagnosed with early stage disease making them ideal candidates for fertility sparing surgery.

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