**REVIEW ARTICLE**                                                                    **Open Access**

# Adnexal masses during pregnancy: management for a better approach

Simona Martone, Libera Troìa and Stefano Luisi*

## Abstract

The incidence of adnexal masses, due to large use of ultrasound during pregnancy, has considerably increased during last years. Large percentage of ovarian masses found during pregnancy consists in simple cysts and they tend to disappear spontaneously during pregnancy. There are still a percentage of masses that persist in second and third trimester that need to be monitored and, sometimes, surgically removed. If the mass increases in size, sometimes, it is itself an indication for delivery via cesarean section. Keeping in mind that adnexal masses diagnosed in pregnancy are generally benign, it is essential to consider that ovarian cancer still represents the second gynecological tumor for incidence after cervical cancer during pregnancy. Most patients are clinically asymptomatic and diagnosis is often a random finding during scheduled ultrasound for pregnancy follow-up. Sometimes, the finding of an ovarian mass requires other imaging technique such as magnetic resonance imaging. Computed tomography is avoided during pregnancy due to negative effects on fetus. Treatment option should be discussed and a multidisciplinary approach is required to set ad individualized plan, considering both mother and fetus. Sometimes the differential diagnosis between benign masses and malignancy is not feasible only through imaging, so that surgical intervention with histological examination is mandatory, even during pregnancy. Plus, although ovarian cyst torsion, hemorrhage, or rupture is uncommon in pregnancy, some women may require emergency surgery for these complications. Until 90s pregnancy was considered an absolute contraindication for laparoscopy, but nowadays both open surgery and laparoscopy can be performed considering mass diameter, gestational age, and surgical expertise. Emerging data are indeed confirming the advantages of laparoscopic surgery compared with laparotomy in term of recovery and need for medical care. The purpose of this review is to assess the incidence of adnexal masses during pregnancy and examine their impact on obstetric outcomes.

**Keywords:** Adnexal masses, Pregnancy, Ultrasound, MRI, Surgery, Laparoscopy, Laparotomy

## Introduction

Adnexal masses are one of the most common complications during pregnancy. Correct management of adnexal mass is of paramount importance both for maternal and neonatal safety. Due to the large spread of ultrasonography (US) technologies, adnexal masses incidence is increased over the years, diagnosed as random finding during scheduled pregnancy check-up [1]. Although, most adnexal masses are functional or benign, there are still a percentage of pregnancies complicated by ovarian

malignancy [2, 3]. Despite lots of physiological changes, including hormonal and metabolic changes, pregnancy does not seem to adversely affect maternal survival compared with non-pregnant patient [4]. On the other side, early diagnosis, which is extremely important for adequate management, could be difficult in this subgroup of patient due to ambiguous symptoms that easily overlap with symptoms of pregnancy. Risk of malignancy of adnexal mass, whether in pregnant or non-pregnant woman, can only partially be predicted through US. Several ultrasonography features can suggest benign o malignant nature of an ovarian mass, but sometimes histology confirmation is required. Moreover, there is still a percentage of adnexal masses incidentally discovered

* Correspondence: stefano.luisi@unisi.it
Obstetrics and Gynecology, Department of Molecular and Developmental Medicine, University of Siena, Policlinico "Le Scotte" Viale Bracci, 53100 Siena, Italy

during cesarean section. Surgical management has been recommended for ovarian masses over 6 cm in diameter or when symptomatic and in the second trimester to avoid the risk of miscarriage, torsion, rupture, and delayed diagnosis of malignancy [5]. In addition, large interrogative is determined by chemotherapy during pregnancy, due to the risk of miscarriage and congenital malformation. Previous studies have demonstrated overall favorable outcomes both with surgery and chemotherapy. The aim of the present review was to describing feto-maternal outcome of pregnancy complicated by adnexal masses, with a particular look at medical and surgical management.

## Epidemiology

Ovarian cancer during pregnancy is a rare entity, anyway, its prevalence is likely to rise since the always more frequent delay of childbearing to a later reproductive age [6].

Adnexal masses are one of the most common complications during pregnancy with an incidence of about 1-5.3% [7–9]. Most adnexal masses during pregnancy are functional or benign [10], only approximatively 5% are malignant [11]. Ovarian cancer still represents the most deadly type of gynecologic tumor worldwide. The average lifetime risk of developing ovarian cancer is 1.3%, 1 in 78 women. White women have the highest incidence of epithelial ovarian cancers (approximately 16.5 cases per 100,000 women). Although a large percentage of ovarian cancer is reported among women aged 60, there is still a percentage of cases that are diagnosed in women of reproductive age. Approximately 1 in 1000 pregnancies is complicated by malignancy and the incidence of ovarian cancer is estimated 2.8-11 per 100,000 pregnancies [1, 3]. However, most of the ovarian mass found during pregnancy are benign or staged I disease [12]. As an example, corpus luteum of pregnancy and simple functional cysts are very common during pregnancy with an incidence of 11-41%. They are hormone dependent and, in most cases, they are going to resolve spontaneously by 20 weeks [13]. Among hystotypes that persist beyond the second half of pregnancy, mature cyst teratoma is the most common diagnosis, along with serous and mucinous cystoadenomas and endometriomas [14]. Among malignancies, germ cell tumors, stromal tumors, and borderline tumors are the most common ovarian malignancy during pregnancy [12]. Epithelial cell cancer represents instead 35% of all ovarian malignancies diagnosed during pregnancy [14]. In addition, borderline ovarian tumors (BOTs) show more aggressive features during pregnancy compared to non-pregnant women [15].

## Diagnosis

Imaging during pregnancy is challenging because clinicians must take into account both maternal and fetal benefit. The mother, fetus, and tumor represent three identities that interact and influence each other and considering the mother's desire to continue pregnancy is fundamental.

At the present time, ultrasound (US) and magnetic resonance imaging (MRI) represent the two diagnostic imaging to use during pregnancy, due to lack of ionizing radiations. US is widely used during pregnancy for scheduled check-up and for the initial abdominal evaluation. It is not cost effective and does not have adverse effects on mother and fetus. Only doubts were pointed to use of Color Doppler in the first trimester for potential theoretical risk for the embryo.

A diagnosis of an ovarian mass during pregnancy should be directed to proper follow up. Any findings should be properly measured and described and the presence of suspicious feature detected. US plays a key role, especially in the first trimester, in the differentiation between benign form malignant masses. Sonographic assessment should include transabdominal (TA) and transvaginal (TV) examination, although, ideally, pelvis is best studied transvaginally. TV US has improved through the decades in the study of female pelvis anatomy since it allows imaging at a higher frequency providing increased resolution and discriminatory power. As the pregnancy progress, the uterus progressively obscures the pelvic organs and retroperitoneal space, reducing its sensitivity in discovering adnexal masses and malignancies. Color Doppler can be used to assess vascular flow within the mass or outside it and it can add further information. International Ovarian Tumor Analysis (IOTA) simple rules or simple descriptors are commonly used outside pregnancy noticing specific tumor features to predict malignancy [16]. Although their usefulness has not been proven in pregnancy, their rules can be applied to arise as suspect about a certain adnexal mass [17]. Doppler indices may change rapidly during pregnancy; therefore, this criterion should be applied carefully [18]. When a sonographic diagnosis is inconclusive, MRI is the second-line after US for diagnosis and staging gynecologic adnexal masses during pregnancy. It is highly accurate in the characterization of adnexal lesions; it offers larger imaging fields of view, excellent tissue contrast, and avoids radiations. Also, the American College of Radiology states safety of MRI with strengths up to 3 T with no adverse effect on the embryo or fetus and the organogenesis [19]. Due to radiations use, computed tomography (CT) is generally avoided during pregnancy. Its use is strictly limited to situations when information cannot be obtained through US or MRI. Patient informed written consent must be obtained. Tumor markers have limited role just as in case of non-pregnant women. Ca125, the most studied tumor marker, which is elevated in the majority of epithelial ovarian cancer, has limited utility since it rises also in other benign condition

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(fibroids and endometriosis). Furthermore, Ca125 levels are physiologically higher during the first trimester of pregnancy, making its relevance as a tumor marker even more limited in pregnant women [20]. Anyway, in a suspect of ovarian mass, Ca125 above the normal level may increase the suspect of ovarian malignancy and could be used as a baseline for follow-up. Germ cell tumors are the most common ovarian tumor among women of reproductive age, therefore, also during pregnancy. Germ cell tumor markers include alpha-fetoprotein (AFP), lactate dehydrogenase (LDH), and human chorionic gonadotropin (hCG), molecules that are normally elevated during pregnancy, making their use even more useless [20]. Other molecules used as makers, such as inhibin B, antimullerian hormone (AMH), human epididymis protein 4 (HE4), and Ca 19-9 are not expected to increase in pregnancy and could be used in some cases to strengthen diagnosis [12]. Imaging is helpful for presurgical evaluation of the extent of disease and to discover whether there are peritoneal implants and metastases or not. Another difficulty raised from pregnancy status is that adnexal masses may undergo pregnancy-related morphologic changes and mimic malignancy.

## Complications
Nowadays, the number of ovarian masses diagnoses incidentally during a routine US scan has increased [13]. However, there is still a percentage of adnexal masses that shows up as an acute event caused by torsion, rupture, or peritoneal hemorrhage [21]. Complications of an adnexal mass during pregnancy are similar to the non-pregnant population. Although there are several implications for applying surgery in a pregnant woman, when an emergency occurs, surgery should not be delayed.

### Adnexal torsion
Adnexal torsion (AT) is an emergent condition defined as a rotation of the ovarian peduncle around its own axis which might lead to ischemia and eventually to ovarian necrosis.

The real incidence of ovarian torsion is unclear but it seems increased during pregnancy [22], probably due to the displacement of the adnexa out of the pelvis. For this reason, its incidence seems more common during first and early second trimester that is the moment when adnexa are displaced. Pregnancies conceived by assisted reproductive technologies may be at increased risk for AT, particularly in the presence of ovarian hyperstimulation [23].

It has been reported an incidence of about 5% of pregnant women with an adnexal mass [24], and is more common, about 20%, for larger masses (> 6 cm) [23–25]. Koo et al., in 2011, showed that even for masses larger than 6 cm, in absence of symptoms and complications, surgery to prevent torsion is not justified [25].

Symptoms are similar to non-pregnant women and they include pain, nausea, vomit so it can be difficult to differentiate torsion symptoms to common symptoms pregnancy related. Plus, objective exam often shows no peritoneal signs.

### Rupture
The risk of rupture is less than 1%, but not uncommon indication for surgery during pregnancy [26].

### Obstetric outcome
Depending on their size and location, adnexal masses may be associated with a poor obstetric outcome caused by a mechanical effect. They have been linked to an increased risk of miscarriage, preterm delivery. Sometimes, very large adnexal masses can predispose labor dystocia, especially if they are close to lower uterine segment [27]. Furthermore, prenatal surgical approach to these lesions, both in emergency or in planned regimen, may be associated with significant obstetric risk [28].

### Malignancy
The occurrence of cancer in pregnancy is an uncommon event, with an overall estimated incidence of 0.02 to 1%. Although rare, ovarian cancer is the second most common gynecological cancer in pregnancy with an incidence of 1:12.500 to 1:25.000 pregnancies. The proportion of adnexal masses in pregnancy corresponding to malignant tumors varies considerably between the published series (0 to 10%) [29]. The lesion size (different cut-offs have been proposed) and a growth rate greater than 0.35 cm/week (10 times greater risk of malignancy) are also relevant [28]. In younger age groups, the most common malignant tumors of the ovary are germ cell tumors and epithelial tumors, and in pregnancy the latter may be even more common than the former [30]. Contrarily to the non-pregnant women, the majority of ovarian tumors are diagnosed in the early stages (80% in stage 1 of FIGO), with a large proportion of borderline tumors [25]. Decision regarding timing of staging surgery and chemotherapy requires a multidisciplinary team of experts.

## Management
Making the decision whether to operate an adnexal mass during pregnancy is often difficult. Taking into account both mother and fetus interests is of paramount importance. Literature lacks of prospective clinical trial in which women are randomized to surgery versus observation, and only retrospective review are available. Multidisciplinary team of specialists cooperates in making decision. Surgery performed during pregnancy carries additional intraoperative and perioperative risks. Depending on the clinical

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suspicion of malignancy, surgery could be delayed when possible, avoiding unnecessary risks for mother and fetus. On the other hand, observing an adnexal mass during pregnancy must take into account the possibility of malignancy or the occurrence of acute event that could require emergent surgery such as torsion, rupture, or obstruction of labor. Past studies showed that elective surgery performed during pregnancy is safe and not associated with increased rates of miscarriage, premature rupture of membranes and preterm delivery [27, 31]. When surgery is performed in emergency, on the other hand, it is burdened with a higher risk of obstetrical complication such as preterm labor. Lee et al. demonstrated that women who underwent emergency surgery had significantly higher risk of preterm labor (22% vs 3.8%) [32].

### Conservative management

Conservative management of adnexal masses is a reasonable choice in many circumstances. Since most adnexal masses during gestational age are functional or benign, a conservative management can be taken into account most of the times. Observational management is also supported by the fact that up to 71% of ovarian masses with benign appearance are going to either resolve spontaneously or decrease in size during pregnancy [33, 34]. The larger studies conducted by Zanetta et al. [35], Schmeler et al. [24], and Platek et al. [36] support a very low incidence of malignancy (0-3%) among adnexal masses during pregnancy. A smaller study by Kumari et al. [37] reported a slightly higher incidence of malignancy (about 10%). All these retrospective studies confirmed that malignancies during pregnancy were either early stage of low malignant potential. US (or, when necessary MRI) can be used to identify ovarian masses that looks benign in the pregnant population and in these cases observation is a reasonable option. Eventually surgery can be postponed after delivery even with complex masses in asymptomatic patient [10, 38]. If the mass is discovered during first trimester scan and US do not shows malignant features, further evaluation is required later in pregnancy (18-22 weeks). Similarly, if the mass is discovered during second trimester in absence of malignant features, it should be checked up at 32-36 weeks. During last trimester, a benign ovarian mass can be managed during cesarean section (if indicated) or after 6 weeks from delivery [1]. In 2013, a retrospective cohort study conducted by Goh et al. [39] about persistent ovarian masses was published. Between 2001 and 2009, of 24,868 obstetric patients, 1225 had an ovarian mass (4.9%) and only 171 had a persistent ovarian mass greater than 5 cm (0.7%). Applying observational management, they found an increased risk of hospitalization for pelvic pain (10.3%) but no increased risk regarding preterm birth, miscarriage, or peripartum complication.

Therefore, unless patient is symptomatic or US features suggest malignancy, pregnancy outcomes with expectant management can be favorable. In 2005, Schmeler et al. identified 63 ovarian masses greater than 5 cm in over 120,000 deliveries. Among the totality of those patients, 29% underwent surgery for suspected malignancy or complication whereas the others were observed and followed up. They found no difference in the two groups in terms of obstetrical complications. Plus, women diagnosed with cancer (6.8%) or tumor with low malignant potential (1.7%) had concerning US scan showing malignant features [24]. Zanetta et al. reported on 79 pregnant women diagnosed with adnexal mass who were followed conservatively. Only 4 women required intervention for torsion, 62% of all masses spontaneously resolved during pregnancy, the others were observed during pregnancy and eventually removed after pregnancy. No significant obstetrical complications were reported in the group of women that underwent expectation management, except for 2 patients that had cesarean section for obstructing labor. They concluded that expectant management is successful in the majority of cases [33]. Condous et al., in 2004, conducted a study on 3000 women and 182 ovarian masses were found (5.4%). Among these cysts 71.7% resolved spontaneously, 24.1% persisted during and after pregnancy, and 4.2% required intervention. According to the authors, scanning ovaries in first trimester could have very limited utility, because it can raise anxiety in the mother even though the risk of complication is very low [32]. Caspi et al., in 2000, followed up 68 women diagnosed with dermoid cyst < 6 cm during pregnancy. No one underwent surgery and no fetal or maternal complication was observed [40]. Also, some study from the past investigated expectant management. Bernhard et al. found that, over 18000 obstetric US scans, 76% of 432 ovarian masses were simple cyst less than 5 cm in diameter. No complication followed the expectant management in this group. Of the remaining 24% of complex and/or greater than 5 cm ovarian masses, nearly 69% resolved spontaneously [31].

### Surgery

When a benign etiology cannot be defined by imaging and surgery becomes necessary, a multidisciplinary team approach is recommended. It should include the obstetrician, the gynecology oncologist, the medical imaging specialist, the expert surgeon, the anesthetist, and the neonatologist to ensure the best care for both mother and fetus. Surgery should be reserved to symptomatic patients when an acute complication occurs or to asymptomatic patients if the adnexal mass is persistent or show ultrasound malignant features [41]. Ultrasound features suspicious for malignancy such as pelvic fluid, solid component, papillary excrescences, multiloculated

large tumor, gross internal septa, vascular nodules, and interval growing should arise suspect for malignancy therefore indicate surgery intervention. Because of the high risk of miscarriage during first trimester (about 15%), surgery should be particularly cautious in this period. When possible, delay surgery to early second trimester or until postpartum. It is preferable not to delay surgical intervention to the third trimester because, during this period, the larger uterus makes surgery more difficult. Plus, preterm delivery may be inducted. Therefore, when surgery is necessary during third trimester, one should consider to transfer patient to a hospital with a tertiary perinatal unit having in mind the possibility of corticosteroid administration and preterm delivery. Counseling is of paramount importance because the final decision is still up to the patient. When surgery is necessary, literature supports laparoscopy versus laparotomy [41, 42]. If frankly invasive ovarian cancer is identified, appropriate staging must be conducted. If a low malignant potential tumor is identified, fertility sparing surgery should be considered [43]. When acute complication occurs, surgery is indicated in any trimester. Only in recent years laparoscopy has become acceptable surgical alternative to laparotomy during pregnancy. Laparoscopy does not come with additional risk of fetal malformation or stillbirth [44, 45], but may be associated with risk of miscarriage and preterm labor. Only experienced laparoscopist should perform these procedures. According to American College of Obstetrics and Gynecology (ACOG) committee opinion of 2017, the second trimester is the best time to perform non-urgent laparoscopic surgery [46]. Anyway, emerging evidences are showing that laparoscopy could be safely performed in any trimester [47, 48]. In 2017, Liu et al. [49], in their review and meta-analysis on 240 women, compared the safety of laparoscopy versus laparotomy for suspected adnexal mass during the second trimester of pregnancy. The results suggested that, in the surgical management of adnexal masses, laparoscopic approach shows similar pregnancy outcomes, but better surgical outcomes than laparotomy. These include shorter hospitalization, lower post-operative pain, lower risk of post-operative adverse events. No significant differences were recorded for threatened spontaneous abortion or spontaneous abortion between the two groups. A majority of women with malignant ovarian tumors who are pregnant choose to undergo induced abortion and then undergo surgical and/or chemotherapy treatment [50]. For these patients who desire to continue pregnancy, surgical treatment is required. Laparotomy is preferred for malignancy, but especially in early stages or in borderline ovarian tumors, laparoscopy could find its application. Laparoscopy has been demonstrated to be safe for staging surgery for borderline ovarian tumors and this approach can preserve

fertility of younger patients [51, 52]. Clinicians should always counsel women about possibility of uterine perforation occurring. In 2014, Bogani et al. in their review and meta-analysis, analyzed perioperative and long-term survival outcomes in patients with early stage ovarian cancer who underwent either laparoscopic or open surgery. According to their study, neither 5-year disease-free survival nor overall survival was influenced by surgical approach. Plus, laparoscopic staging surgery was non-inferior to laparotomy in early stage ovarian cancer [53]. However, very few are the studies that have investigated application of laparoscopy for malignant ovarian tumors in pregnant patients; therefore, the safety and application during pregnancy remains limited and controversial. Another concern for laparoscopy during pregnancy has been arisen by the increased intra-abdominal pressure and fetal acidosis due to carbon-dioxide pneumoperitoneum. Increased abdominal pressure could reduce venous return, especially in women with impaired cardiac output [54], therefore, determining hypotension and hypoxia and consequent reduction in uteroplacental blood flow. Furthermore, fetus could absorb carbon-dioxide across peritoneum and experiment acidosis [55]. If maternal blood pressure is maintained stable and carbon-dioxide insufflation between 3.7-4.3 kPa, no adverse outcomes have been reported [56]. Establishment of pneumoperitoneum should be gradual, with careful monitoring of hemodynamic status [57]. In 2012, Candiani et al. [58] found no Doppler anomalies of fetal heart or maternal uterine arteries during laparoscopy on ovarian surgery if less than 12 mmHg pneumoperitoneum was used. Anyway, intrabdominal pressure between 8 and 12 mm Hg and not exceeding 15 mmHg should be maintained during laparoscopies in pregnant women with neither maternal nor fetal adverse outcome [59, 60]. The low impact technique, combining the use of minimally invasive surgical access with minimized risks related to a low- and stable-pressure $CO_2$ insufflation on the surgical peritoneal environment, allows for several potential benefits in terms of intensity of postoperative pain and time to full recovery. This technique seems particularly suitable in pregnancy where the low $CO_2$ pressures determine greater safety on the fetus, allow for adequate visualization while also avoiding the possible adverse effects on the hemodynamic and respiratory physiology of the gravid patient [61].

Gasless laparoscopic surgery comes with the advantage of avoiding hypercarbia and increased intraperitoneal pressure, but data from literature are lacking. Another concern about surgical approach is the potential adverse effect on the fetus of general anesthesia. Anyway, modern anesthetic agents, muscle relaxant, and opioids are not thought to be teratogenic [62]. A retrospective review by Hong et al. in 2004 reported that patients

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undergoing laparotomy for adnexal mass with regional anesthesia had higher risk of preterm labor compared with patients who received general anesthesia. But long-term studies are not available. General anesthesia comes with reduced risk of aspiration, good muscle relaxation, and controlled ventilation therefore is preferred to local approach [55]. A systemic review failed to demonstrate positive effects of routinary administration of tocolisis for women who underwent surgery during pregnancy [63]; therefore, its use should be tailored. The location of the primary port will depend on the level of the fundus, and Hasson technique may reduce the risk of uterine trauma [55]. There is no evidence that electrosurgery is harmful to the fetus. Amniotic fluid, in fact, due to its composition rich in electrolytes is thought to be protective for the baby. Literature does not suggest increased risk of energy related complications with any type of energy device [55]. According to Federation of Gynecology and Obstetrics (FIGO), for early stage ovarian cancer, stage I and II, surgical procedure consists of hysterectomy, bilateral adnexetomy, omentectomy, cytology, biopsies, and lymphadenectomy. For early stage disease, invasive epithelial ovarian carcinoma grade I stage Ia, fertility, and pregnancy preserving treatment may be considered, removing the adnex and going through staging [64]. Non-epithelial tumors are over 90% diagnosed at FIGO stage Ia and therefore could be treated conservatively [65]. For high-grade, stages I and II adjuvant chemotherapy can be considered with carboplatin and paclitaxel during second and third trimester. In case of higher stage disease in borderline tumors, since chemotherapy is not effective and given the indolent nature, it can be considered to perform adnexectomy and biopsy during pregnancy and then complete surgery after delivery. When there is a high probability of advanced stage ovarian cancer (FIGO stage III), medically induced abortion followed by standard treatment is an option, especially during first trimester. Chemotherapy can be considered in second and third trimester [63]. However data on long-term effects are limited.

## Conclusions

Adnexal masses are common during pregnancy. In most cases, they are functional or benign, even though there could still be a chance of malignancy. Diagnosis is of paramount importance for management. US is very useful tool to estimate the risk of malignancy and, when not conclusive, MRI can be safely used. In case of acute event, surgery is mandatory in any trimester, anyway, when feasible, surgery should be scheduled during second trimester. Laparoscopy is safe and recommended against laparotomy because of its benefit in terms of complications and recovery. Its application should be cautiously weight in the suspect of malignancy. In the

suspect of frankly invasive ovarian cancer appropriate staging must always be conducted. Whether for low malignant potential tumors, fertility sparing surgery should be an option. If chemotherapy is required, it can be considered in the second and third trimester. In addition, it is mandatory to send patients to referral center, and a multidisciplinary approach is required for a better management of adnexal masses during pregnancy.

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