Treatment Options for Pregnant Women With Ovarian Tumors

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Diagnosis of ovarian mass during pregnancy is a rare event. Treatment of ovarian malignancies during pregnancy depends on histology, grade, stage, and gestational weeks. When possible, surgical excision is indicated, and sometimes, fertility-sparing surgery is recommended. Administration of systemic treatment before or after surgery is indicated as in nonpregnant women. Preliminary data suggest that platinum salts and taxanes are safe during pregnancy. Management of ovarian tumors in pregnancy requires a multidisciplinary approach to guarantee an optimal treatment for the mother and the fetus.

Key Words: Ovarian tumor, Pregnancy, Surgical approach, Systemic treatment

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The diagnosis of malignancies during pregnancy is infrequent, with approximately 1 of 1000 pregnancies complicated by cancer. The most common tumors occurring during pregnancy are breast cancer, cervical cancer, melanoma, and hematopoietic tumor.[1]

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Ovarian tumors complicate approximately 1 of 10000 pregnancies. Most adnexal masses during pregnancy are functional or benign, with a limited percentage (3%–6%) of malignant lesions.[2] The most frequent malignant ovarian tumors in pregnancy are germ-cell tumors, followed by borderline ovarian tumors (BOTs) and epithelial ovarian cancer.[3] It has been claimed that pregnancy does not worsen the prognosis of ovarian cancer, but the presence of a viable fetus calls for a balance between the optimal therapy for the mother and the lowest possible fetal toxicity. The occurrence of an adnexal mass during pregnancy poses a number of issues, including the most appropriate diagnostic workup, surgical management, and systemic treatment. As data about patients' management are scanty and few guidelines are available, each woman should be treated within a multidisciplinary setting, after a thorough discussion of each individual case. Gestational age at diagnosis, stage of the disease, patient's willingness to keep the pregnancy, and fetal risks secondary to maternal treatments are all factors that should be considered. The aim of this article is to review the available evidence about diagnosis and treatment of ovarian tumors during pregnancy.

Search Strategy

All articles published from 1979 until July 2013 regarding ovarian tumors during pregnancy were extracted from Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) using the

search items *ovarian tumours*, *pregnancy*; *ovarian carcinoma*, *pregnancy*; *surgery*, *pregnancy*; or *chemotherapy*, *pregnancy*. Potentially eligible articles were identified based on the evaluation of the title and abstract. Seventy-eight articles were identified.

Diagnostic Workup

Most pelvic masses diagnosed during pregnancy are discovered during routine fetal ultrasound.[4]

Ultrasound examination is safe, and an experienced examiner can confidently distinguish between benign and malignant pelvic masses on the basis of gray scale evaluation and color Doppler findings, correctly discriminating them in greater than 90% of all cases.[5] The reported sensitivity and specificity for malignancies are 88% and 96%, respectively.

Simple ovarian cysts will resolve spontaneously in most cases, and they are usually treated expectantly, at least if they are not causing any symptoms.

Women with simple adnexal cysts of 5 cm or less in diameter have been managed expectantly also outside pregnancy, without any adverse effects being noted.

Large masses with multiple septa, solid components, nodules, or papillae or symptomatic masses should be further investigated,[6] and surgery should be considered.

In a study by Whitecar et al,[2] 89 of the 91 masses diagnosed as simple cysts were confirmed to be benign at pathologic examination; all 6 malignancies in their series were correctly identified by ultrasound characteristics.

Computed tomography might clarify the extraovarian spread of the disease but exposes the fetus to at least 2 to 4 cGy, and it should be avoided during pregnancy. Magnetic resonance imaging allows accurate evaluation of large masses that are difficult to visualize with ultrasound. It can also determine whether the tumor is widespread in the abdomen and discriminate acute bowel processes, such as appendicitis and inflammatory bowel disease. Using magnetic fields and not ionizing radiation, magnetic resonance imaging is deemed safe during the whole pregnancy.[3]

The role of serum tumor markers during pregnancy is debated. CA125 levels increase during the first trimester, with concentrations greater than 65 IU/mL in 16% of the patients.

Thus, the usefulness of serum tumors markers during pregnancy should be carefully considered.[7]

Surgical Management

When there is a low probability of malignancy, the option of watchful waiting without surgery might be considered.[8] Surgical management of ovarian masses during pregnancy is indicated when the patient is at high risk of an acute abdomen, secondary to ovarian torsion or rupture. Moreover, the persistence of an adnexal mass during the second and third trimesters is considered by many authors an indication for surgery, as up to 10% of persistent ovarian masses will be ultimately diagnosed as malignant tumor s.[9,10] Whenever possible, midgestation (12-27 weeks) should be elected for ovarian surgery during pregnancy, but the risk of premature delivery remains quite high, reaching 22% in some series. Surgery can be performed by laparotomy or laparoscopy.[9] Laparoscopy drawbacks include possible injury to the pregnant uterus by Verres needle or trocar and the potential fetal acidosis due to carbon dioxide.[11] On the other hand, laparoscopy is associated with less postoperative pain, reduced use of narcotics, and shorter hospital stay. Currently, there are no prospective studies comparing laparotomy and laparoscopy during pregnancy. However, multiple observational studies have demonstrated that laparoscopic management of adnexal masses in pregnancy is technically feasible and is associated with a lower risk of pregnancy complications.[9] The ideal procedure for a suspicious adnexal mass during pregnancy is peritoneal cytology and unilateral salpingo-oophorectomy of the affected side with frozen-section analysis. Results of the frozen section should guide further surgical management.

Borderline Ovarian Tumor

The BOTs account for 10% to 20% of all ovarian malignancies. They are characterized by younger age distribution, lower stage at diagnosis, and favorable prognosis. When BOT is diagnosed, resection of the neoplasm and all macroscopic diseases is required. The macroscopically normal ovary can be left in place, as bilateral oophorectomy does not improve prognosis.

A recent series of 40 patients with diagnosis of BOT during pregnancy highlights a trend to more aggressive characteristics and higher frequency of advanced stage than in nonpregnant women. This emphasizes the need for accurate inspection of the abdominal surface and biopsy of any suspicious lesion.[12]

Nonepithelial Ovarian Tumor

Most patients with nonepithelial ovarian tumors (germ-cell and sex-cord stromal tumors) have bulky masses, sometimes measuring up to 30 cm.[13] Nonetheless, more than 90% of the patients have stage I disease. In 1 series, 24 of the 27 patients with dysgerminoma during pregnancy were diagnosed at stage IA.[13] In another series, all patients with sex-cord tumors were diagnosed at stage I, but 13 of the 36 had tumor capsule rupture during the procedure.[14] Because prognosis of stage I nonepithelial tumors is good, fertility-sparing surgery is recommended.

Epithelial Ovarian Cancer

In nonpregnant patients with early-stage epithelial ovarian cancer, standard surgeries are hysterectomy and bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, and lymph node sampling. Only young patients with early-stage lesions who are interested in subsequent pregnancies may be treated conservatively. Surgery is followed by chemotherapy for all stages except for stages IA and IB and grade 1 tumors.[15]

During pregnancy, hysterectomy is not possible unless the patient decides to terminate the pregnancy. If the patient chooses to continue her pregnancy, preservation of the uterus with peritoneal staging should be offered as the primary surgical treatment.

In nonpregnant patients with an advanced disease, standard surgical management consists of debulking surgery with a complete resection of all macroscopic diseases.[15] In

patients with unresectable disease, 3 courses of neoadjuvant chemotherapy followed by interval debulking and 3 more courses of chemotherapy should be discussed.[16] During pregnancy, in most reported cases,[17] patients with an advanced disease chose to terminate pregnancy, but in some patients, neoadjuvant chemotherapy has been administered.

Systemic Treatment

Outside pregnancy, standard chemotherapy regimens include carboplatin plus paclitaxel with or without bevacizumab for epithelial cancer and bleomycin, cisplatin, and etoposide (BEP) for nonepithelial cancer. Preclinical data indicate that platinum derivatives are mutagenic and teratogenic,[17–19] particularly during the first trimester. The risk of congenital malformations is around 10% to 20% in the first trimester but decreases to 1% to 3% thereafter. Chemotherapy administered during the second and third trimesters can be associated with preterm delivery, intrauterine growth restriction, low birth weight, and neonatal blood count reduction.[20] It should not be given after the 35th week of gestation to reduce the risk of neonatal neutropenia.[21,22]

Cisplatin and carboplatin are highly bound to plasma proteins, and only the unbound fraction may cross the placenta. During pregnancy, lower albumin levels are observed; thus, higher levels of unbound cisplatin may be associated with higher risks of maternal and fetal toxicity. Ex vivo studies suggest that carboplatin transfer from the maternal to the fetal circulation remains very limited. In a unique pregnant baboon model, transplacental transfer of carboplatin, paclitaxel, and docetaxel has been studied. The concentration of carboplatin in the fetal plasma was half of that measured in the maternal plasma and was relatively stable. Conversely, platinum concentration in amniotic fluid gradually increased, possibly for the platinum excretion through fetal kidneys.[23]

Mir et al[24] identified 36 articles documenting the use of cisplatin and 7 cases of patients treated with carboplatin during pregnancy: platinum-related maternal toxicity during pregnancy was described equivalent to nonpregnant women. In 1 patient treated with BEP during the second trimester, a cerebral atrophy with ventriculomegaly was reported. Other anomalies included polyhydramnios and intrauterine growth restriction in 4 and 3 cases, respectively. Moreover, neonatal creatinine elevation was reported in 1 case, suggesting that cisplatin may be nephrotoxic in the fetus. In other patients treated with BEP during pregnancy, preterm labor, myelosuppression, and neonatal alopecia were reported.[25] Detectable levels of cisplatin or platinum-DNA adducts were reported in 2 newborns who were exposed to cisplatin during the third trimester and in 2 newborns exposed to carboplatin, suggesting a late transplacental transfer of these drugs.[26] In 2009, an international consensus on the treatment of gynecologic cancers during pregnancy was published: authors proposed to replace BEP with paclitaxel-carboplatin or cisplatin-vinblastine-bleomycin (PVB).[25] The PVB was used in some cases without maternal or fetal complications. Fetal morbidity and the potential high risk of secondary leukemia related to etoposide administration support the use of these alternative regimens in pregnant women with nonepithelial ovarian cancers. Other and more recent data support the safety of platinum analogues in pregnancy; patients were treated with cisplatin or carboplatin for ovarian cancer during pregnancy, with normal neonatal outcome, as shown in Table 1.

Paclitaxel has been used during pregnancy for breast and ovarian cancers, but long-term data are scanty. As taxanes have low molecular weight, they would be expected to easily cross the placenta. In the pregnant baboon model previously cited,[23] very low levels of paclitaxel and docetaxel were detected in fetal compartments, with a concentration ratio of 1:100 in fetal and maternal plasmas, respectively. Taxanes are substrates for P-glycoprotein, a placental transporter that highly reduces placental transfer, limiting the drug concentration in fetal tissue.

Cardonick et al[27] reported data of 15 women treated with taxanes during pregnancy, 12 with a diagnosis of breast cancer and 3 with a diagnosis of ovarian cancer. In 2 patients, there was a preterm delivery secondary to preeclampsia. Three newborns had a weight at delivery below the 10th percentile, and a hypertrophic pyloric stenosis was diagnosed in 1 infant. Even if the treated patients were few, apparently, there were no statistically significant differences in obstetric and neonatal outcomes in pregnant women treated with taxane-based regimen compared with other chemotherapeutic agents.

Smith et al[28] published a case report of a pregnant woman with ovarian cancer treated from the 14th week of gestation with intraperitoneal carboplatin along with systemic paclitaxel. At 32 weeks, the patient developed mild preeclampsia and thrombocytopenia, and at birth, bilateral talipes equinovarus was described.

From these data, it clearly seems that the use of chemotherapy during pregnancy should be thoroughly discussed for the potential risk of fetal damage and potential pregnancy complications.[29] Table 1 reports a summary of all ovarian cancer patients treated with chemotherapy during pregnancy.

Aviles and Neri[18] reported the long-term outcomes of 84 children whose mothers received chemotherapy during gestation. All children reached adequate learning and educational performance in the long-term follow-up. A multicenter study by Amant et al[30] showed normal cardiologic and neurologic development in 70 children treated with different chemotherapy regimens in the uterus. Median gestational age at birth was 35.5 weeks, with a birth weight under the 10th percentile in 14 of the 70 children. The incidence of fetal malformations was similar to the general population. Neonatal neurologic examination was normal in 91% of the babies with transient anomalies (hypotonia, contracture). After a median follow-up of 22.3 months, a normal cognitive development was reported for most children, with a prevalence of lower performances mainly in the preterm group. No structural cardiac defect nor conduction abnormalities were detected.

Few data are available about monoclonal antibodies treatment during pregnancy. Bevacizumab, the VEGF-specific monoclonal antibody indicated for advanced epithelial ovarian cancer, is assigned to pregnancy category C by the FDA for its teratogenic effect in animal models. No reports on the use of bevacizumab in pregnant ovarian cancer patients have been published; thus, it should not be administered during pregnancy.[31]

TABLE 1. Report of ovarian neoplasms treated with chemotherapy during pregnancy

Author	Ptsn.	Histotype	Chemotherapy	GA at Delivery, wk	Obstetrical Outcome	Neonatal Outcome
Germ-cell ovarian tumors						
Robova et al (2007)	1	Endodermal sinus tumor	Cisplatin, 4 courses	35	Normal antenatal US examination	Anemia with red cell transfusion at birth Healthy at F-U (24 mo)
Han et al (2005)	1	Endodermal sinus tumor	Cisplatin, etoposide, bleomycin	40	IUGR	Healthy newborn Healthy at F-U (72 mo)
Viana et al (2011)	1	Endodermal sinus tumor	Cisplatin and etoposide, 6 courses	35	IUGR, oligohydramnios	Anemia and thrombocytopenia at birth Healthy at F-U (24 mo)
Malone et al (1989)	1	Endodermal sinus tumor	Cisplatin, vinblastine, bleomycin	32	NA	Healthy newborn F-U: NA
Elit et al (1999)	1	Endodermal sinus tumor	Cisplatin, etoposide, bleomycin	28	Ventriculomegaly at US examination	Ventriculomegaly with cerebral atrophy; moderate RDS (related to prematurity) F-U: NA
Motegi et al (2007)	1	Endodermal sinus tumor	Cisplatin, vinblastine, etoposide	31	Normal antenatal US examination	Healthy newborn F-U: NA
Karimi Zarchi et al (2008)	1	Immature teratoma	Cisplatin; etoposide; bleomycin, 2 courses	39	Normal antenatal US examination	Healthy newborn Healthy at F-U (18 mo)
Han et al (2005)	1	Immature teratoma	Cisplatin; etoposide; bleomycin, 2 courses	38	Normal antenatal US examination	Healthy newborn, intussusception at 7 mo Healthy at F-U (26 mo)
Christman et al (1990)	1	Immature teratoma	Cisplatinum; vinblastine; bleomycin, 1 course	40	NA	Healthy newborn Healthy at F-U (60 mo)
Hubalek et al (2007)	1	Dysgerminoma	Carboplatin; paclitaxel, 3 courses	36	Normal antenatal US examination	Minor RDS, mild anemia at birth Healthy at F-U (22 mo)
Buller et al (1992)	1	Dysgerminoma	Cisplatin; etoposide, 4 courses	38	IUGR	Low weight at birth Healthy at F-U (9 mo)
Horbelt et al (1994)	1	Mixed germ-cell tumor	Cisplatin; etoposide; bleomycin, 3 courses	39	NA	Anemia at birth F-U: NA
Stromal ovarian tumors						
Tomlinson et al (1997)	1	Sertoli-Leydig tumor	Cyclophosphamide; cisplatin, 3 courses	34	NA	Healthy newborn Healthy at F-U (12 mo)
Epithelial ovarian tumors						
Otton et al (2001)	1	Papillary serous adenocarcinoma with a clear-cell component	Cisplatin, 4 courses	31	Normal antenatal US examination	Healthy newborn Healthy at F-U (12 mo)
Henderson et al (1993)	1	Papillary serous adenocarcinoma	Cisplatin; carboplatin, 3 courses	36	Normal antenatal US examination	Healthy newborn Healthy at F-U (12 mo)

King et al (1991)	1	Papillary serous adenocarcinoma	Cyclophosphamide; cisplatin, 5 courses	36	NA	Healthy newborn F-U: NA
Malfetano et al (1990)	1	Papillary serous adenocarcinoma	Cyclophosphamide; cisplatin, 7 courses	37	NA	Healthy newborn Healthy at F-U (19 mo)
Bayhan et al (1999)	1	Mucinous adenocarcinoma	Cyclophosphamide; cisplatin, 2 courses	35	Polyhydramnios	RDS at birth Healthy at F-U (18 mo)
Sood et al (2001)	1	Papillary serous adenocarcinoma	Cisplatin; paclitaxel, 3 courses	37	Normal antenatal US examination	Healthy newborn Healthy at F-U (30 mo)
Ferrandina et al (2005)	1	Papillary serous adenocarcinoma	Cisplatin, 6 courses	36	Normal antenatal US examination	Healthy newborn Healthy at F-U (42 mo)
Mendez et al (2003)	1	Papillary serous adenocarcinoma	Carboplatin; paclitaxel, 6 courses	36	Normal antenatal US examination	Healthy newborn Healthy at F-U (15 mo)
Picone et al (2004)	1	Endometrioid adenocarcinoma	Carboplatin, 2 courses	34	Normal antenatal US examination	Unit care for prematurity Healthy at F-U (18 mo)
Modares Gilani et al (2007)	1	Papillary serous adenocarcinoma	Carboplatin; paclitaxel, 4 courses	35	Normal antenatal US examination	Healthy newborn Healthy at F-U (6 mo)
Huang et al (2004)	1	Mucinous adenocarcinoma	Cisplatin, cyclophosphamide	30	Preterm premature ruptured membrane	NA NA
Smith et al (2013)[28]	1	Serous adenocarcinoma	Intraperitoneal carboplatin; intravenous paclitaxel, 4 courses	37	Preeclampsia, IUGR	Low birth weight, congenital talipes equinovarus (familiarity) Healthy at F-U (6 mo)
Cardonick et al (2012)[27]	3	NA	Carboplatin, paclitaxel; cisplatin, paclitaxel; carboplatin, paclitaxel	36 38 39	IUGR, normal twin pregnancy, normal antenatal US examination	Healthy newborn Twin A: healthy Twin B: jaundice, Tourette syndrome, dyslexia, Asperger syndrome, speech delay Healthy newborn
Tabata et al (2008)	1	Undifferentiated carcinoma	Carboplatin, 4 courses	33	Normal antenatal US examination	Healthy newborn Healthy at F-U (12 mo)
Serkies et al (2011)	1	Mucinous adenocarcinoma	Cisplatin; paclitaxel, 2 courses	34	Normal antenatal US examination	Healthy newborn Healthy at F-U (73 mo)
Doi et al (2009)	1	Mucinous adenocarcinoma	Carboplatin; paclitaxel, 5 courses	37	Normal antenatal US examination	Healthy newborn Healthy at F-U (40 mo)
Mantovani et al (2007)	1	Serous adenocarcinoma	Paclitaxel, 5 courses	38	Normal antenatal US examination	Healthy newborn Healthy at F-U (16 mo)
Rouzi et al (2009)	1	Papillary serous adenocarcinoma	Cisplatin; docetaxel, 4 courses	34	Anhydramnios and ventriculomegaly diagnosed before starting chemoterapy	The baby died 5 days after delivery because of multiple anomalies

F-U, follow-up; GA, gestational age; IUGR, intrauterine growth restriction; NA, not available; RDS, respiratory distress syndrome; US, ultrasound.

CONCLUSIONS

Ovarian tumors in pregnancy are rare, and a multidisciplinary approach involving oncologists, gynecologists, pathologist, perinatologist, and psychologists is necessary to define the most adequate treatment strategy. Therapeutic choices should consider both maternal and fetal well-being, whenever possible. Surgery can be performed during pregnancy, ideally at midgestation and by a laparoscopic approach. Benign pelvic masses and BOTs are treated by surgery alone. Data suggest that chemotherapy can be administered during the second and third trimesters, but close monitoring of pregnancy course and fetal growth remain mandatory. Carboplatin- and paclitaxel-based regimens should be chosen for epithelial ovarian cancer, whereas BEP, PVB, and carboplatin-paclitaxel can be considered for nonepithelial ovarian cancer.

As malignant ovarian tumors during pregnancy are rare, patients should be referred to centers with specific experience and to cooperative registries (www.cancerinpregnancy.org).

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