# Maternal Epithelial Ovarian Cancer

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*DOI: 10.17925/EOH.2009.05.1.64*

## Abstract

Maternal epithelial ovarian cancer is rare; its rarity is reflected by the paucity of reported cases in the literature. Its incidence appears to be increased in the older pregnant patient, and since childbearing among older patients has markedly risen in more recent years it is likely that this disease will become more common. Currently, there are no definitive guidelines regarding patient management in maternal epithelial ovarian cancer. Management should therefore be case-dependent, individualised and multidisciplinary in nature. Data centralisation for individual cases including detailed information on clinico-pathological variables, treatment regimens, maternal and neonatal outcomes may be beneficial in identifying optimal management strategies in these rare tumours.

## Keywords

Epithelial ovarian carcinoma, ovarian carcinoma, pregnancy, chemotherapy

**Disclosure and Acknowledgements:** The authors have no conflicts of interest to declare. Manu Vatish would like to thank the Fulbright Commission for its continued support.
**Received:** 21 April 2009 **Accepted:** 26 July 2009
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## The Clinical Problem

Malignant epithelial ovarian cancer diagnosed during pregnancy is rare, with an estimated incidence of 1:12,000 to 1:50,000 pregnancies.[1–3] A recent review[4] identified 28 publications pertaining to maternal malignant epithelial ovarian cancer, spanning a time period of 49 years. The paucity of published data and low incidence of maternal epithelial ovarian cancer is likely to reflect the low prevalence of ovarian cancer in younger women. The incidence of maternal primary epithelial ovarian cancer appears to be increased in the older pregnant patient.[4] In the UK there has been a two-fold increase in the birth rate in women >30 years of age and a three-fold increase in women >40 years of age since 1975.[5] Similarly, in the US since 1980 the proportion of first births has increased three-fold in women ≥30 years of age, six-fold in women ≥35 years of age and 15-fold in women ≥40 years of age since 1980.[6] Overall it is uncertain whether ovarian cancer associated with pregnancy is increasing,[7] although this seems possible as childbearing among older patients increases.

## Diagnosis

Patients may present with pain, abdominal distension or a mass, although many are asymptomatic at the time of detection.[4] Approximately 50% of maternal epithelial ovarian cancers are detected as an incidental mass on routine pelvic or ultrasound examinations, with the majority detected in the first and second trimester. Detection at the time of Caesarean section or in the postnatal period is less common.[4]

Higher-resolution imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) may be useful as an aid to diagnosis and staging of disease. The risk of radiation exposure to the foetus depends on the gestational age at the time of exposure, foetal cellular repair mechanisms and the absorbed radiation dose level.[8] Good-quality study data regarding CT scanning and adverse pregnancy outcome are lacking. We recommend that CT scanning, certainly in the first trimester, is avoided and that patients are fully counselled with regard to the possible implications of this method of imaging in pregnancy. There is currently no indication that MRI during pregnancy produces deleterious effects, but the safety of MRI procedures during pregnancy has not been definitively proved.[9] Whenever possible, it appears that MRI should be delayed until after the first trimester. Intravenous contrast media are not recommended, as they cross the placenta and their long-term effects are unknown.[10,11] Tumour markers are of limited value in pregnancy. CA-125 levels may be raised in normal pregnancy,[12–15] and as prior reports have tended to omit CA-125 levels no real clinical inferences can be made about the value of CA-125 in maternal epithelial ovarian cancer.[4]

## Management

Current management of epithelial ovarian cancer involves, where appropriate, staging laparotomy, debulking surgery and adjuvant chemotherapy, or tissue diagnosis with up-front chemotherapy followed by subsequent debulking surgery. There are currently no definitive guidelines in the literature regarding the management of epithelial ovarian cancer presenting during pregnancy.[16,17] Primary management of maternal epithelial ovarian cancer is dependent on the gestation of the pregnancy, disease stage, future fertility desires and the mother's wishes to continue with the pregnancy. Management is case-dependent; therefore, care should be individualised and multidisciplinary in nature.

### Surgical Management

Considering the relatively poor overall five-year survival in epithelial ovarian cancer, presentation of advanced-stage disease in early

**Table 1: Maternal Toxicity, Teratogenicity and Potential Long-term Risks of Carboplatin and Paclitaxel**

| | Carboplatin | Paclitaxel |
|---|---|---|
| Maternal toxicity | Myelosuppression, nephrotoxicity, neurotoxicity[25] | Myelosuppression, neurotoxicity, fatal anaphylaxis (rare)[25] |
| Early organogenetic period (animal models) | Intrauterine death, congenital malformations, external, internal and skeletal anomalies, (gastroschises, dilatation of cerebral ventricles, cleft sternum, fused ribs, malformed thoracic vertebrae)[26] | Craniofacial malformations, diaphragmatic hernias, kidney defects, cardiovascular system defects[27] |
| Foetal organogenesis (animal models) | Foetal growth inhibition, reduced brain weight[28] | No influence on pre-natal development was observed[29] |
| Post-organogenesis | Eyes, haematopoietic system, central nervous system remain vulnerable[30] | |
| Potential long-term risks | Compromised physical and neurological development, increased risk of malignancy in childhood and adult life, possibility of mutagenesis of germ-line tissue, increased risk of malignancy in future generations[31] | |

pregnancy warrants discussion and consideration of therapeutic termination. Pregnancy loss and loss of future fertility needs to be carefully measured against a potentially life-threatening condition.

In early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage Ia), staging laparotomy and salpingo-oophorectomy alone, followed by careful observation of both mother and foetus in a multidisciplinary setting, may suffice. If laparotomy is to be considered and continuation of pregnancy is desired, the second trimester is generally regarded as the best time for surgical intervention because the risk of miscarriage is minimised.[18,19] Surgical exploration in the third trimester is associated with premature labour and poorer pregnancy outcomes. In view of this risk, antenatal corticosteroids should be administered between weeks 24 and 36 to significantly reduce the risk of respiratory distress syndrome, neonatal death and intra-ventricular haemorrhage.[20] Although tocolytic agents should be available if uterine contractions occur post-surgery,[7,21,22] their routine use has not convincingly been shown to improve outcome.

In more advanced-stage disease, staging laparotomy and/or diagnostic biopsy alone may allow strategic multidisciplinary management planning. Conservative surgical management of malignant maternal ovarian cancer followed by antenatal chemotherapy has been reported in the literature[23,24] with the aim of postponing delivery until attainment of foetal maturity. Completion (or debulking) surgery has been described in numerous cases following delivery by Caesarean section.

## Chemotherapy

Platinum-containing agents, in combination with paclitaxel, are currently the primary chemotherapy agents used in the treatment of epithelial ovarian cancer. As all chemotherapy agents are potentially teratogenic, the effects of the drugs on the foetus and the potential long-term sequelae to the offspring[16] must be considered. The effect of pregnancy on the pharmacology of the chemotherapeutic agents used is also an important issue.[22]

Chemotherapy is contraindicated during the first trimester in patients wishing to continue with their pregnancy as it may cause severe foetal effects. However, chemotherapy may be delayed until the second or third trimester. In the post-natal period breastfeeding during cytotoxic chemotherapy is contraindicated.[25] At present no specific information is available regarding the teratogenic effects of carboplatin or paclitaxel in humans,[24] but data are available from animal studies (see *Table 1*). Thirteen prior reports have been identified[4] pertaining to patients undergoing chemotherapeutic treatment for epithelial ovarian cancer in the antenatal period. Varying regimens of cisplatin, carboplatin, paclitaxel and cyclophosphamide have been reported. Although no significant adverse effects were acknowledged, reporting bias is a possibility as only successful cases tend to be published. Platinum-based chemotherapy is reported to be generally well tolerated, and is not associated with malformation adverse outcomes, or neonatal toxicity.[23,24,32–42] While few case reports exist describing the use of paclitaxel in maternal epithelial ovarian malignancy,[35,38,41,43] there appears to be no significant foetal toxicity when administered during the second or third trimester. There is also no convincing evidence that increased malformation rates occur with the use of multiagent regimens.[44]

## Antenatal Complications, Labour and Delivery

Gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, pre-term labour and premature membrane rupture have been reported to occur in pregnancies complicated by epithelial ovarian cancer.[4] It is difficult to assess whether maternal antenatal complications are increased due to the relatively small number of cases reported in the literature. Although vaginal delivery has been reported, there exists the potential risk of tumour rupture or foetal dystocia during normal labour.[23] A literature review has shown the incidence of Caesarean section to be greatly increased,[4] with blood transfusion and post-partum stay more than five days also significantly more likely.[45] These findings are not surprising as in numerous cases[4] optimal staging procedures, completion surgery or debulking surgery has been performed at the time of foetal maturity with delivery performed by Caesarean section.

### Foetal Outcomes

It has been suggested that maternal ovarian cancer may cause sub-optimal intra-uterine conditions and haemodynamic alterations in uterine blood flow post-surgery or immunological changes leading to an increased risk of growth restriction or indeed stillbirth;[46,47] no substantial evidence is available to confirm this.

A foetal death rate of approximately 9% has been reported in maternal epithelial ovarian malignancy, with an overall foetal loss rate of 24% when including patients having a termination of pregnancy.[4] Neonatal follow-up in previous reports is extremely variable and longer-term data are lacking. No real assumptions on the long-term effects to the offspring of mothers undertaking chemotherapeutic treatment for epithelial ovarian cancer can therefore be made. However, patients must be thoroughly counselled with regard to the need for long-term surveillance of their children in view of potential long-term sequelae.

### Maternal Outcomes

Clinico-pathological survival prognosticators in epithelial ovarian cancer include FIGO stage, histological grade and the extent of

residual disease following tumour debulking surgery. The majority of reported malignant epithelial ovarian tumours diagnosed during pregnancy appear to be detected at an earlier stage (FIGO I–II), with distribution of histopathological sub-types similar to that of patients with non-maternal epithelial ovarian malignancy.[4] Placental histology has remained largely unrecorded in the literature, with only one prior case documenting focal metastatic carcinoma.[39]

Stage of disease appears unrelated to gestation at presentation and unconnected with earlier detection by routine ultrasound. Maternal prognosis regarding stage is reported to be similar to that in the non-pregnant patient,[1,36,40,49] yet on the whole it is difficult to draw any conclusions regarding overall survival due to reporting variations in the duration of follow-up of these patients. There is currently no evidence that pregnancy itself adversely affects the survival of patients with epithelial ovarian carcinoma;[48,50] nor is there evidence that pregnancy serves a beneficial effect on the disease process.

## Conclusion

The diagnosis of epithelial ovarian cancer during pregnancy is a rare event. The incidence appears to be increased in the older pregnant patient, and as childbearing among older patients becomes more common it is possible that a concomitant rise in the incidence of epithelial ovarian cancer in pregnancy can be expected.

Management is case-dependent; therefore, care should be individualised and multidisciplinary in nature. The potential limitations of the pregnancy on diagnostic and therapeutic procedures need to be thoroughly considered. Surgical and chemotherapeutic intervention in particular may cause deleterious physical and psychological effects in the mother, teratogenic effects in the foetus and developmental effects in the neonate. Furthermore, the potential long-term risks for the offspring of these mothers remains unclear.

There are currently no definitive guidelines regarding the management of epithelial ovarian cancer presenting during pregnancy. The paucity of data in the literature unfortunately makes it difficult to assess the true outcome of treatments, and the longer-term maternal and neonatal outcomes are even more difficult to substantiate. Data centralisation for maternal malignancies with long-term progeny follow-up would be beneficial in identifying optimal management strategies not only in these rare tumours, but also in other malignant tumours diagnosed and treated during pregnancy. ■


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