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An ominous neighbour to the innocent foetus: 2 cases of ovarian malignancy diagnosed during pregnancy

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Abstract
The worldwide incidence of Ovarian Cancer in pregnancy is 0.04-0.11 per 1000, making it the second most common gynaecological malignancy in pregnant women. With an increase in the average age for child-bearing and routine use of ultrasonography during pregnancy, the grim diagnosis of ovarian malignancy during pregnancy is on the rise. The optimum management of such cases is challenging because of limitations in the diagnostic modalities and ethical concerns regarding chemo-radiotherapy and surgery. These cases require a multidisciplinary approach involving the obstetrician, medical oncologist, neonatologist and/or other specialities with the common goal of balancing the well-being of the mother against the survival of the foetus.
We report two cases of ovarian malignancy; one was an advanced case of high grade serous ovarian cancer and the other was a case of mucinous cystadenocarcinoma. While one patient had a favourable outcome with a healthy baby delivered at term, the other patient delivered a small for gestation (SGA) foetus at 32 weeks following which she had extensive chemotherapy and surgery followed by 2 episodes of recurrence.

Keywords: Ovarian malignancy in pregnancy, staging laparotomy, interval debulking surgery, hemotherapy, high grade serous ovarian carcinoma in pregnancy, mucinous cystadenocarcinoma in pregnancy

Introduction
The incidence of adnexal masses in pregnancy is reported at 0.15-5.7% [1]. Routine obstetrical ultrasounds often detect these masses in the first trimester, with 1-6% being malignant and requiring thorough evaluation [2]. Patients may present with vague symptoms like abdominal pain, lower back pain, discomfort, or anorexia, often mimicking uncomplicated pregnancy, or may be asymptomatic [3]. Tumour markers like CA 125, β-HCG, LDH, and α-fetoprotein have limited diagnostic or prognostic value for ovarian malignancies in pregnancy [4]. Due to the radiation limit of 0.5 Gy in pregnancy, ultrasound and MRI are the primary imaging methods. Although not validated in pregnant populations, the International Ovarian Tumour Analysis (IOTA) classification can describe ovarian abnormalities [5]. Dysgerminomas are the most common malignant germ cell tumours in pregnancy, accounting for 30% of ovarian malignancies, followed by serous cystadenomas. Borderline tumours, while having low malignant potential, may show aggressive features like microinvasion in pregnant women [6]. Ovarian cancers detected during pregnancy generally have a good prognosis due to early detection, often in Stage 1. The 5-year survival rate ranges from 72-90% in Stage 1 to 30% in Stage 4 [7].

Case 1: A 27-year-old primigravida was referred to our hospital at 28 weeks of gestation, 10 days after undergoing exploratory laparotomy at a private hospital in a different state in eastern India, due to abdominal pain. Her history, as provided by her and her relatives, revealed that she had been experiencing abdominal pain, distension, and weight loss for the past three months. An ultrasound at 12 weeks of gestation showed a single intrauterine live foetus at 12.3 weeks and a large right ovarian cyst measuring 15x10x11.7 cm with multiple septations and solid areas, along with moderate ascites. Her antenatal tests, including a complete blood count, liver and renal function tests, random blood sugars, and serology, were normal except for a CA 125 level of 3000 IU/ml.
She underwent exploratory laparotomy, but the operative notes were unavailable. However, her relatives provided a paraffin block containing a tissue section from the right ovary.

Upon admission, her general and systemic examination revealed moderate pallor, a midline vertical incision with staples in situ, and gross ascites. Obstetric examination indicated a singleton foetus at approximately 24 weeks of gestation. Routine investigations were repeated, and an ultrasound confirmed a single live intrauterine foetus corresponding to 26 weeks with an estimated weight of 736 grams and adequate amniotic fluid. The scan also showed gross ascites, mild hepatomegaly, and a multiloculated complex ovarian cyst measuring 19.2x16x15 cm with an ORADS score of 4.

Consultation with medical oncology and pathology confirmed high-grade serous epithelial carcinoma. After counselling with a multidisciplinary team, the patient and her husband chose to continue the pregnancy and proceed with chemotherapy. She received weekly carboplatin (AUC 2) for 5 cycles until delivery, with regular monitoring of blood count, renal, and liver functions. She also received two doses of intramuscular Betamethasone for foetal lung maturity after approval from medical oncology. Subsequent ultrasounds showed a small for gestational age foetus with oligohydramnios. She went into labour at 34 weeks and delivered a female infant weighing 1028 grams vaginally. The neonate was admitted to the NICU and discharged after 6 weeks at 1.8 kg.

The patient was transferred to a national cancer institute, where she received one cycle of Carboplatin (AUC 5) followed by one cycle of Paclitaxel (135 mg/m2) and Carboplatin (AUC 5). Neoadjuvant chemotherapy was followed by interval debulking surgery with R0 resection (total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and retroperitoneal and para-aortic lymphadenectomy) and three cycles of adjuvant therapy with Paclitaxel (80 mg/m2) and Carboplatin (AUC 5). She was staged at IIIC. (Figure 1) shows a magnified histological image of the tumour.

Unfortunately, the patient experienced a recurrence after seven months and began second-line chemotherapy (liposomal doxorubicin + carboplatin followed by letrozole). Due to a lack of response, her treatment was changed to cyclophosphamide + tamoxifen, which she responded to initially for three months before deteriorating. Eventually, in July 2023, she chose to return to her hometown for palliative care.

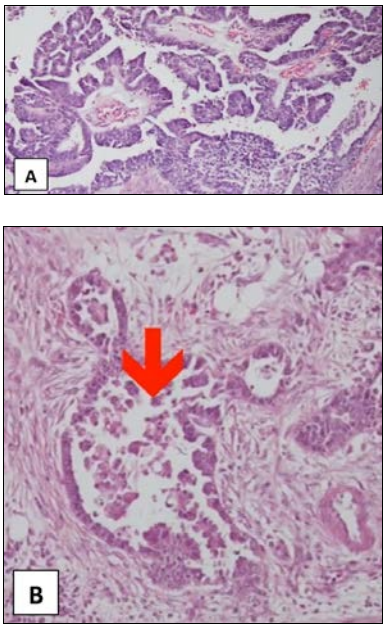

Fig 1: (A) High power photomicrograph of the tumour. (B) High power photomicrograph of omental metastatic deposit

Case 2: A 35-year-old woman, pregnant with her sixth child, was referred to our institute at 23.4 weeks of gestation due to a large right adnexal lesion detected during an anomaly scan at 22 weeks. She was asymptomatic, had no family history of ovarian or breast cancer, and had no similar findings in her previous five vaginal births. Her antenatal investigations and general/systemic examinations were normal. Her medical history included treated pulmonary tuberculosis five years ago.

An ultrasound at our institute showed a single live intrauterine gestation at 23.6 weeks, with an estimated foetal weight of 560 grams and adequate amniotic fluid. It also revealed a well-defined anechoic complex cystic lesion in the right adnexa, with internal echoes, papillary projections, and incomplete septations, measuring 14x14x19 cm without internal vascularity or calcifications. The right ovary was not separately visible from the lesion, which had an ORADS score of 4. Tumour marker results were: CA-125 = 19.8, CA 19.9 = 53.94, α-fetoprotein = 92.93, CEA = 7.47, β-HCG = 22,020.

The patient underwent an exploratory laparotomy, resulting in a right-sided salpingo-oophorectomy, and the specimen was sent for histopathology along with peritoneal washing. Intraoperative findings included a 22-week gravid uterus, a 15x15 cm multi-cystic right ovarian lesion with haemorrhage, and an adhered right fallopian tube (Figure 2). The left ovary and fallopian tubes were unremarkable, with no ascites or peritoneal lesions. The patient recovered well and was discharged with follow-up advice.

Cytology was negative for malignant cells, but histopathology reported "invasive mucinous carcinoma in the background of a borderline mucinous tumour." A second opinion from a national cancer institute confirmed mucinous adenocarcinoma with an intestinal phenotype and expansile tumour invasion. The ovarian capsule was intact, and the fallopian tube was pathology-free. Immunohistochemistry showed tumour cells positive for CK20, CDX2, and SATB2, but negative for CK7, PAX8, and ER.

The patient had regular follow-ups and was admitted at 40 weeks for elective induction of labour, delivering a healthy 3.5 kg male child. A contrast-enhanced computed tomography (CECT) scan a week later was unremarkable. Six weeks postpartum, she underwent total abdominal hysterectomy with left salpingo-oophoectomy. Post-operatively, recovered well and was referred to medical oncology for further management, with follow-up advised every three months. She remains in remission and continues biannual follow-ups at the cancer institute.

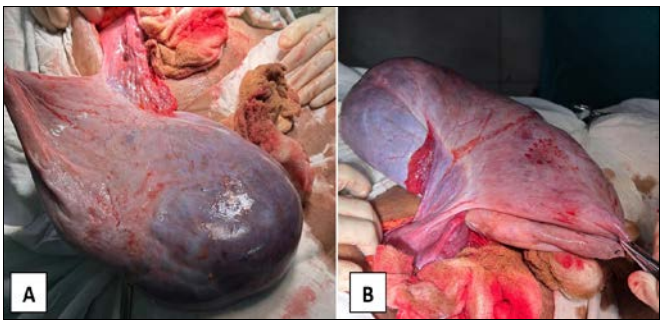

Fig 2 (A & B): Intra-operative image of the tumour along with the adhered right fallopian tube

Discussion

An ovarian tumour ranks fifth among the most common tumours during pregnancy, following breast, thyroid, cervical, and Hodgkin's disease [8]. Studies show that the histological types of ovarian cancer during pregnancy resemble those found in non-

pregnant women of reproductive age [9]. Ultrasound findings such as septations, solid components, nodules, papillary projections, ascites, or a mass larger than 5 cm suggest potential malignancy [10]. Further evaluation with transvaginal ultrasound or MRI helps confirm the diagnosis in suspicious cases [11].

Invasive epithelial cancer has the least favourable prognosis among ovarian cancers [12]. The standard treatment for epithelial ovarian cancer (EOC) usually includes primary surgery such as hysterectomy and bilateral salpingo-oophorectomy, along with peritoneal sampling (including peritoneal washing, omentectomy, multiple peritoneal biopsies, and removal of peritoneal implants) and lymph node biopsy/resection [13]. However, this approach is not feasible for pregnant patients. Poor maternal outcomes often lead to termination of pregnancy, but if the patient wishes to continue, the only option is to administer neoadjuvant chemotherapy until foetal maturity is reached, followed by interval debulking surgery after delivery [13, 14].

Elective surgery for adnexal masses should be postponed until the second trimester (around 17-19 weeks of gestation) when possible [15]. This timing reduces the risk of spontaneous abortion, coincides with the period when the corpus luteum is no longer hormonally dependent, and allows for the resolution of most functional cysts [15, 16]. Laparotomy is commonly used and generally has fewer side effects, but laparoscopic surgery should only be performed by experienced surgeons [17]. It is crucial to note that chemotherapy is not recommended during the first trimester due to its high risk of causing abortion and foetal abnormalities [18]. Chemotherapy can be considered in the second or third trimester since the risk of congenital malformations in foetuses exposed to chemotherapy is comparable to the general population [18, 19]. However, chemotherapy may have non-teratogenic effects such as intrauterine growth restriction or impacts on the developing central nervous system throughout pregnancy [20, 21]. Therefore, it is essential to counsel patients thoroughly on the treatment options and their associated risks and benefits.

Conclusion

In summary, managing ovarian cancer during pregnancy is a considerable challenge for healthcare providers. Due to its rarity and the absence of large randomized trials and extensive patient data, universal treatment guidelines have not been established. The complexity of deciding on optimal management stems from the need to balance the well-being of both the mother and the foetus. Therefore, a multidisciplinary team, including an obstetrician, oncologist, pathologist, anaesthesiologist, neonatologist, and psychologist, is crucial for effective management.

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Conflict of interest

None

Consent

The manuscript was prepared after taking valid informed consents from the patients.

Ethical Clearance

Not required

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