Case Series

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Maternal and fetal outcome in pregnancy associated with malignancy: a case series at a tertiary care centre in India

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ABSTRACT

Malignancy in pregnancy is rare presentation with an estimated incidence of 1 per 1000. Pregnancy with malignancy poses a unique challenge for treating physician because of the safety concerns for the unborn child. The aim of the study was describing the maternal and infant outcomes of malignancy in pregnancy and to describe the various treatment options according to tumour type and gestational age. A prospective observational study was done at tertiary care centre for 6 months from December 2020 to June 2021. A case series of pregnancy associated malignancy were observed and followed up till postpartum period. Three cases were of ovarian tumors with good maternal and fetal outcomes as they were in early stages of the disease. Fourth case was of metastatic lung carcinoma with adverse maternal outcome due to advanced malignancy. The conclusion was that a multidisciplinary approach of obstetrician, pathologist, radiologist, oncologist, onco-surgeon, neonatologist is necessary in managing these cases. The treatment strategy should be discussed and structured on an individual basis. A combined approach of surgery and chemotherapy is advocated depending on the stage of the disease and gestation. Neonatal outcomes like prematurity, low birth weight are anticipated and good overall maternal and fetal outcome can be achieved.

Keywords: Pregnancy, Malignancy, Germ cell tumour, Maternal and fetal outcome, Chemotherapy

INTRODUCTION

Malignancy in pregnancy is a very rare presentation with an estimated incidence of 1 per 1000 pregnancies corresponding to 0.07 to 0.1%. According to the worldwide cancer data in 2018, 18 million patients with cancers were identified, of whom 8.5 million cancers were among women. Among the reproductive age group, about 35000 women develop cancer every year and 0.1% of pregnancies are affected by cancers.

Fortunately, malignancy in pregnancy is a very rare cause of maternal mortality. The order of decreasing frequency of cancers associated with pregnancy is breast tumors, leukaemia's–lymphomas, melanomas, gynaecologic cancer, and bone tumors, in that order. Since pregnancy is a state of altered immunity, malignant neoplasm

originating from various tissues may exacerbate during pregnancy. Also because of physiological and anatomical changes during pregnancy there can be increased risk of vascular and lymphatic dissemination of malignancy. The incidence of malignancy diagnosed during pregnancy is thought to increase with time due to increasing age of childbearing. Increased use of non-invasive prenatal testing as a screening test to detect foetal chromosomal abnormality, using cell free DNA from maternal blood, has been documented to have led to asymptomatic women being diagnosed with cancer during pregnancy.

Pregnancy with malignancy poses a unique challenge for treating physician. Because the safety and ramifications for the unborn child must be taken into consideration, pregnancy may make it more difficult to choose a cancer diagnosis and treatment plan. Clinicians should be aware of various types of clinical presentations associated with different types of malignancy in pregnancy and their maternal and neonatal outcomes so as to improve the treatment modalities by giving optimum maternal and foetal outcome. Here in this case series, we present 4 cases of different types of neoplasm diagnosed first time during pregnancy and described their maternal and foetal outcomes and various treatment options according to tumour type and gestational age.

CASE SERIES

Case 1

A 21 years old multigravida (G2P1D1) with previous caesarian section 2 years back with 38 weeks gestation was referred from a district hospital with dull aching pain in abdomen for 1 day. On general examination, her vitals were stable, on per abdomen, fundal height corresponded to 36 weeks of gestation, with deviation of uterus to right side. Firm, large mass was felt on the left side of uterus extending up to left costal margin.

Ultrasound was suggestive of single live foetus of 33 weeks 5 days with a large heterogeneously hyperechoic intraperitoneal solid mass lesion of size $13\times11.3\times11.7$ cm in left adnexa extending to left hypochondrium. Her tumor markers were done with CA 125 was 21.95 U/ml (normal level) LDH – 271.6U/l (normal level 45-90 U/l).

MRI was suggestive of large left adnexal mass, ovaries not visualized separately, no ascites, no evidence of metastatic deposit. Patient underwent caesarian section at 38 weeks and a 1.9 kg baby with good APGAR score without any gross congenital anomalies. Intraoperatively a solid mass of size 15×18 cm with lobulated surface arising from left ovary was removed with intact capsule. (Figure 1).

Right ovary was visualised normal and biopsy was taken. There was no evidence of metastasis on systematic exploration of all the intraperitoneal organs. Histopathological examination showed malignant germ cell tumor of left ovary (dysgerminoma). Patient's tumour was designated as stage 1 A (FIGO staging of ovarian tumours). After appropriate consultation with radio-oncologist patient was given 3 cycles of BEP chemotherapy (Bleomycin–Etoposide–Cisplatin) and is under follow up.

Case 2

A 22 years old multigravida (G2P1L1) with previous full term vaginal delivery with 27 weeks gestation was referred from private hospital of nearby district as case of ovarian tumour in pregnancy. On general examination, her vitals were stable, per abdominal examination 26 weeks gravid uterus was deviated to left side. A 30 weeks size firm mass with bosselated surface was felt separately from the uterus extending from right iliac region up to xiphisternum.

Ultrasound of abdomen and pelvis was suggestive of malignant neoplastic lesion in right adnexa of size $18 \times 17 \times 16$ cm likely a germ cell tumour. MRI confirmed the findings without lymphatic or peritoneal metastasis. Patient's serum LDH was elevated, 712 U/l and AFP was 122 (normal <40 mcg/ ml). Elective exploratory laparotomy was planned under spinal anaesthesia.

On inspection right ovary was replaced by a solid mass of $25\times20\times18$ cm occupying the abdominal cavity reaching up to epigastric region, a gravid uterus corresponding to 26 weeks size was seen deviated to left side. Left ovary and fallopian tube was appearing normal.

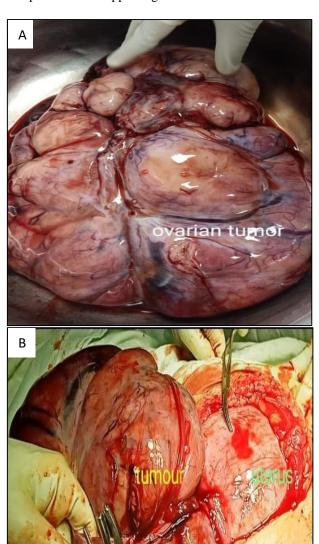


Figure 1: (A, B) Large solid ovarian mass with lobulated surface with intact capsule.

Minimal free fluid was present which was aspirated. Tumour was removed out by clamping, cutting and ligating right tubo- ovarian ligament. Omental biopsy was also taken. No evidence of metastatic deposits on intraperitoneal organs viz. contralateral ovary, omentum, liver, undersurface of diaphragm and intestinal loops. On gross examination mass was solid cystic with fleshy appearance and bosselated surface.

Histopathology examination showed malignant germ cell tumour likely to be dysgerminoma of right ovary. Peritoneal fluid cytology was negative for malignant cells.

Tumor was staged as stage 1A (FIGO). After discussing the case with radiation oncologist patient was allowed to continue the pregnancy and asked to follow up post-delivery for further management. Patient continued the pregnancy uneventfully and delivered spontaneously at 38 weeks gestation with good APGAR score without any gross congenital anomalies. She is following up with the oncologist without residual disease.

Case 3

35 years old primigravida, referred from a rural hospital with 12 weeks of gestation, came with a complaint of pain in lower abdomen for 8 days which was initially intermittent later continuous since last 3 days, pain was associated with two episodes of vomiting. There was history of fever 3 days back which subsided after taking treatment. On examination she was afebrile, pulse rate was 110 beats per minute, blood pressure was 90/60 mmHg, per abdomen she had mild tenderness in supra pubic region with no guarding and rigidity. Mass corresponding to 20 weeks size felt with restricted mobility, smooth surface, cystic consistency in left side of abdomen. Uterine size could not be made out.

n per vaginal examination-posterior forniceal fullness was present, mobile, cystic mass of 20 weeks was palpated, uterus 12 weeks size was felt separately. Ultrasound of abdomen and pelvis showed 12 weeks single live intrauterine foetus with large well defined, lobulated heterogeneously hypoechoic lesion of size $14.2 \times 10 \times 10.3$ cm in left adnexal region from which left ovary could not be separately visualized, lesion was crossing the midline and coming to right adnexal space.

Anechoeic necrotic area of size 3.5×3.2 cm noted within the lesion. On colour flow torsion of vessels was seen. Probe tenderness was present. Right ovary was separately visualized. On clinical assessment and ultrasonographic evaluation diagnosis of left ovarian cyst torsion was kept and taken for emergency exploratory laparotomy.

Intraoperative 12 weeks gravid uterus was present with left ovary replaced by 15×12×13 cm hemorrhagic cyst with irregular surface and bluish hue with single twist around ovarian pedicle. Torsion was released and pedicle clamped, cut and ligated. Flimsy adhesion was present between posterior surface of mass and bowel, adhesions were released and mass was removed. Left fallopian tube,

right ovary and right fallopian tube visualized and was normal. Peritoneal wash was given. No evidence of metastatic deposits intraperitoneally. Histopathological report was of left ovarian mass showed malignant germ cell (yolk sac) tumor. Patient's serum alpha fetoprotein in immediate post operatively was 60 ng/ml (normal is upto 40 ng/ml).

After consulting radio-oncologist patient was given 3 cycles of chemotherapy antenatally BEP following primary surgery. Patient was followed up with regular antenatal visits, with growth scans. Patient had oligohydramnios at 33 weeks and started with amino infusions.

Subsequently she developed fetal growth restriction and hence admitted at 35 weeks gestation and underwent emergency caesarean at 38 weeks gestation for fetal distress. A full-term baby with birth weight 2.2 kgs was born with good Apgar score. Post caesarean CT abdomen and pelvis did not show any residual disease and she was kept under follow up.

Case 4

37 years old third gravida (G3P1L1A1) with previous full-term caesarean at 6 years back, a booked case of our hospital presented at 35 weeks of gestation with excruciating lower back pain since 5th month of gestation and progressing gradually in severity. Pain did not respond to oral analgesics. Patient was evaluated since it was unusually severe and not related to obstetrics and referred to orthopaedician.

Patient was advised MRI lumbosacral spine that showed multiple lytic lesions in all the lumbar vertebrae with complete collapse of L5 lumbar vertebral body compressing thecal sac and cauda equina with similar lytic lesions in cervical vertebrae, sacrum and bilateral iliac bones favouring possibility of bony metastases.

Patient went into spontaneous labor at 36 weeks of gestation, emergency caesarean was done in view of previous caesarean, a late preterm child was born with birth weight 2.7 kg with good Apgar score. Patient was followed up with radio oncologist, Orthopedics and haematologist and was diagnosed as a case of lung adenocarcinoma with stage 4 metastatic disease.

Lung biopsy revealed non-small cell lung cancer. She was started on paclitaxel and cisplatin-based chemotherapy. In due course she had fracture neck femur got operated for the same. She received total 13 cycles of chemotherapy; PET scan was done which was suggestive of regressing disease. Later on, she was started on oral gefitinib which is an anti- cancer drug given for metastatic lung cancer. She was followed up but she expired after 8 months of delivery due to the metastatic disease.

Table 1: Clinico-pathological characteristics, obstetric and neonatal outcome of cases with pregnancy with malignancy.

Characteristic	Case 1	Case 2	Case 3	Case 4
Age at presentation (in years) Mean 28.7 years	21	22	35	37
Obstetric formula	G2P1D1	G2P1L1	Primigravida	G3P1L1A1
Referral	Yes	Yes	Yes	No
Presenting cpmplaint	Pain in abdomen	Mass in abdomen	Pain in abdomen	Excruciating lower back pain
Gestational age at the time of presentation (in weeks)	38	27	12	35
Type of malignancy	Ovarian malignant germ cell tumor (dysgerminoma)	Ovarian malignant germ cell tumor (dysgerminoma)	Ovarian malignant germ cell tumor (yolk sac tumour)	Non-small cell lung carcinoma
Tumor marker	Sr. LDH 271.6 U/l	Sr. LDH 712 U/I	Sr. AFP 60ng/ml	
Time of primary surgery (in gestational weeks)	38 weeks	27 weeks	12 weeks	NA
Stage	FIGO stage 1a	FIGO stage 1a	FIGO stage 1c	Stage 4 metastatic carcinoma
Type of delivery	Emergency caesarean at 38 weeks	Full term spontaneous vaginal delivery at 39 weeks	Emergency caesarean at 38 weeks	Emergency caesarean at 36 weeks
Antenatal complication	FGR*	None	FGR, oligohydramnios	None
Neonatal outcome	VLBW ^{\$}	LBW [#]	LBW	Late preterm
NICU admission	Yes	No	No	No
Adjuvant chemotherapy	Post delivery BEP 3 cycles	Not given	Antenatally BEP 3 cycles after primary surgery	Post delivery Cisplatin and paclitaxel 13 cycles followed by oral Gefitinib.

^{*}Fetal Growth Restriction, \$Very Low Birth Weight, #Low Birth Weight

DISCUSSION

Cancer diagnosed during pregnancy poses a decisional challenge for patients, family and clinicians. Despite a growth in research there is paucity of data available on cancer in pregnancy in Indian studies. In this study we analysed four cases of neoplasms during pregnancy and studied the characteristics, management and outcomes of patients diagnosed with cancer during pregnancy at a tertiary care centre in central India. All the above discussed neoplasms were detected incidentally during pregnancy. Mean age of the patients was 28.7 years. In a study done in UK, the median age was 33 years and in Indian study mean age was 26.9 years.^{7,8}

In our case series, adnexal masses of ovarian malignancy presented with acute abdomen, while adenocarcinoma of lung presented with severe back ache due to bony metastasis. Diagnosis may be delayed as symptoms of pregnancy like nausea, vomiting, breast changes, abdominal pain, anemia, backache, bleeding or vaginal discharge all these physiological changes may mimic malignancy symptoms. Ovarian malignancy occurs in 600

to 1 in 1500 pregnancies. The majority of these are benign and only 1%–3% are malignant. The most commonly encountered ovarian malignancy is germ cell, followed by sex cord stromal tumors, borderline tumors, and lastly invasive epithelial cancers. Because of its preponderance for reproductive aged women, malignant germ cell tumor accounts for 18–26% of all ovarian cancers complicating pregnancy. In our case series all were germ cell tumors. The most common symptom is abdominal or pelvic pain and one-third of ovarian cancers are diagnosed incidentally. A10,11 Two of our cases presented with pain in abdomen.

Pregnancy does not alter their prognosis but malignancy can affect fertility and complicate the pregnancy outcomes viz. increases risk of spontaneous abortion or preterm delivery, can cause acute abdomen due to torsion or rupture of adnexal mass, fetal effects such as uteroplacental insufficiency leading to FGR, preterm birth, fetal demise. Age at presentation for dysgerminoma in pregnancy (case 1 and 2) was in early 20 as it occurs usually in women under 30 years age, while for yolk sac tumor it was in mid 30s whose median age of diagnosis is

19 years. 12 Dysgerminoma patients both were multiparas while yolk sac tumor patient was primigravida. In case 1,2,3 of malignant ovarian germ cell tumour in pregnancy radiological imaging used here for diagnosis was ultrasound, could identify the size and complexity mass thus proving to be an essential tool assisting in making diagnosis. In order to avoid the effects of radiation to the fetus, nonradioactive imaging methods like magnetic resonance and ultrasound should be favoured during pregnancy. Many imaging methods deliver inferior ionizing radiation than the threshold dose of 100 mGys. Nevertheless, when adequate abdominal shielding is employed, they should not be withheld when necessary for proper oncologic management of the patient. Computed tomography of the abdomen and pelvis, fluoroscopic imaging used in procedures and some nuclear medicine techniques deliver higher doses to the fetus and should be avoided.1

Although serum tumor markers could be useful in the diagnosis, follow-up and management of cancer patients, they lack sensitivity and specificity during pregnancy, due to significant physiological variations in serum levels.¹³ Commonly used tumor markers CA 15-3, SCC, CA 125 and AFP levels are increased in pregnancy and consequently are not reliable. On the other hand, CEA, CA 19-9, LDH, AMH, and HE-4 levels are not commonly increased in pregnancy and may help. 1 For dysgerminoma, serum LDH is a tumor marker whose normal level ranges 45-90 U/l. In case 1 it was 271U/l and in case 2 it was 712U/l. During pregnancy and puerperium LDH level fluctuates very minimally unless the patient has preeclampsia. In both the cases it was raised and co-related with the disease activity. For yolk sac tumor also, it correlated with the disease as its level was raised in case 3 (60 ng/l).

The management of ovarian cancer in pregnancy has to take in consideration the mother, fetus, and malignancy, which must be managed simultaneously. Therefore, the decisions regarding each case should be on an individual basis, considering the patient's age, parity, desire for present pregnancy, future fertility, stage of the tumor, and duration of gestation. Surgical excision of the adnexal mass is necessary if the presentation is acute and also for diagnosing the type of malignancy. If pregnancy is to be continued exploratory laparotomy is performed usually during second trimester as in case 2 and case 3 when the risk of abortion is least and there is still space to operate.

Pregnancy is no longer a contraindication for laparoscopic surgery (<28 weeks) in skilled hands. Laparoscopic management of adnexal masses in pregnancy by an experienced team is a safe and effective procedure that allows a shorter hospital stay and a reduced rate of post-operative complications when comparing with laparotomy. Of the surgeries performed unilateral salphingo-oophorectomy is preferred than cystectomy and laparoscopic approach so as to ensure intact removal and to prevent rupture of the adnexal mass. ¹²

Guidelines are given by the society of American gastrointestinal endoscopic surgeons (SAGES) for laparoscopic surgery in pregnant women. 14 Indications: same as for nonpregnant women. Position: lateral recumbent. Entry: open technique, careful Veress needle, or optical trocar; fundal height may alter insertion site selection. Trocars: direct visualization for placement; fundal height may alter insertion site selection. In more advanced pregnancies, direct entry through a left upper quadrant port in the midclavicular line, 2 cm beneath the costal margin, may better avoid the fundus. Known as Palmer point. CO2 insufflation pressures: 10–15 mm Hg (lowest possible). Monitoring: capnography intraoperatively, **FHR** assessment preand postoperatively. Perioperative pneumatic compression devices and early postoperative ambulation

When performed laparoscopically, the procedure should be done with standard precautions to avoid the spread of malignant cells (particularly from tumor rupture). In patients with suspicion of malignant lesion on imaging, the procedure should include salpingo-oophorectomy of the affected side, peritoneal cytology, omental biopsy and selective removal of enlarged lymph node. Biopsy of normal contralateral ovary is not recommended. Presence of lymph node metastasis have no effect on long term outcome and that there is no role of systematic lymphadenectomy in malignant ovarian germ cell tumour. Intraoperative histological analysis of frozen-section specimen should be conducted in order to decide further management of the patient. ¹⁵

Currently there are more and more reports on a safe and effective use of anti-cancer drugs in pregnant women. There are guidelines for pregnant women with differentiation into epithelial and non-epithelial ovarian tumors, with particular emphasis on the safety aspects of pharmacotherapy. The administration of chemotherapy drugs up to 2 weeks after conception, in the time, when patients usually do not yet suppose that they are pregnant, does not cause congenital malformations. The period of organogenesis from the 3rd to the 8th week of pregnancy seems to be the most critical period of exposure to drugs. It is recommended to start chemotherapy only after the end of the 14th week of pregnancy. ¹⁶

The use of chemotherapy during the second and third trimesters of pregnancy appears to be safe. There are reports that the administration of cytostatics in these trimesters increases the risk of intrauterine growth restriction and contributes to low birth weight in children. Between the last chemotherapy cycle and the delivery, a 3-week interval is recommended to prevent the hematopoietic suppression in mother and fetus caused by chemotherapeutic agents. Hematological toxicity can result in an augmented risk for infections and bleeding complications during delivery. The treatment for Epithelial Ovarian Cancer should consist of surgical staging and chemotherapy (in all patients apart from staging IA, grade 1–2). As in non-pregnant patients, the

recommended chemotherapy regimen in pregnancy is carboplatin and paclitaxel. Neoadjuvant chemotherapy (NACT) should be administered in the advanced stages of the disease to maintain pregnancy. 19 Complications following the use of this group of drugs include neurotoxicity as well as toxic effects on the digestive and respiratory systems. In pregnancy, exposure to carboplatin during the second and third trimesters does not appear to increase the risk of serious malformations. In the treatment of non-epithelial cancers, surgical resection of the adnexal mass and staging are recommended. As in non-pregnant women, patients in advanced stages should undergo chemotherapy. The standard protocol is bleomycin, etoposide and platinum (BEP). 19 Its use during pregnancy was found to be associated with birth defects (ventriculomegaly, plagiocephaly, syndactyly, pectus excavatum), increased risk of FGR and neonatal complications.

It is recommended to abandon the use of bleomycin, which causes pulmonary fibrosis and to use the EP regimen based on etoposide and cisplatin.²⁰ In case of nonepithelial ovarian tumors in pregnancy, many authors recommend as well to follow the routine ovarian cancer regimen which is paclitaxel and carboplatin. There were no inferior results with this regimen when considering recurrences and overall survival.²¹ Carboplatin is preferred for gynecological malignancies except for germ cell cancers, in which a cisplatin-based schedule is standard of care. Paediatricians should be made aware of possible ototoxicity even if newborn hearing screening normal.

In our series, case 3 patients received chemotherapy during pregnancy. If patient is high risk for recurrence, chemotherapy after delivery is required. In our case series 1 patients of malignant ovarian germ cell tumour was given chemotherapy post -delivery. Since chemotherapy also carries risk of ovarian damage fertility preservation procedures like cryopreservation of oocyte, direct follicle aspiration during cesarean section and in vitro maturation to mature oocyte can be done for fertility preservation. Long term follows up data regarding about pediatric outcome of in utero chemotherapy exposure is not available. Malignant ovarian germ cell tumour can lead to fetomaternal compromise. FGR is the most common adverse event in live births of maternal malignant ovarian germ cell tumour which was seen in our case series as well.

CONCLUSION

Diagnosis and management of pregnancy complicated by malignancy is challenging due to variable presentation and a multidisciplinary approach of obstetrician, pathologist, radiologist, oncologist, Oncosurgeon, neonatologist is necessary. The treatment strategy should be discussed and structured on an individual basis. Fertility-preserving surgery can be done safely with a favorable outcome in the early stage in pregnancy. When chemotherapy is indicated, unless delivery can be accomplished within a few weeks of diagnosis, chemotherapy should be delayed until after

delivery. The platinum-based regimen seems to be the best choice after the first trimester. Good reproductive function and high survival rates can be achieved in patients treated with conservative surgery and adjuvant. Neonatal outcomes like prematurity, low birth weight are anticipated and good overall maternal and fetal outcome can be achieved.

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