

## Incidence and Clinical outcome of ovarian neoplastic tumors in pregnancy

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### **ABSTRACT**

**Objective:** The purpose of this study was to review patients diagnosed with ovarian cancer in pregnancy and to assess their incidence, the effectiveness of the available methods of treatment and prognosis of these tumors.

**Methods:** A review of 11 women diagnosed to have cancer of the ovary associated with pregnancy who delivered at a tertiary care institute between Jan 2013 to Dec 2016. The clinical presentation, time and mode of diagnosis, treatment, pregnancy outcome and maternal survival were noted. The role and effect of surgery and chemotherapy on maternal and fetal outcome was noted.

**Results:** The incidence of ovarian carcinoma associated with pregnancy in this study was 0.265 per 1000 deliveries. Out of these women 63.6% (7/11) were primigravidas. 45.45% (5/11) women were asymptomatic at the time of presentation and diagnosed on routine ultrasonography. 7 patients had ovarian epithelial malignant neoplasia. Fetal survival rate was 81.81%.

**Conclusions:** Ovarian tumors in pregnancy are usually diagnosed early due to frequent routine examinations. Epithelial tumors constitute a majority of ovarian carcinomas. The surgical staging and management should follow the standard protocol, since outcome depends on the stage of lesion. Early diagnosis and prompt treatment offers the best prognosis for the patient

**Keywords:** Ovarian neoplasm; pregnancy; surgical staging; chemotherapy; tumour markers

### **INTRODUCTION**

Gynecological cancers account for 22% of all new cancers cases among women in developing countries [1]. Ovarian cancer is the second most frequent gynecological cancer diagnosed in pregnancy, after cervical carcinoma [2]. Ovarian neoplastic tumors associated with pregnancy present a thorny scenario. It not only endangers maternal and fetal life but malignancy itself and its management also poses threat to future reproductive capacity of woman. In spite of its rare occurrence, the tremendous financial burden on health care system and emotional burden on patient and her family caused by ovarian cancers presses the need for future research in this field.

### **MATERIALS AND METHODS**

The study included 11 women with ovarian carcinoma diagnosed during pregnancy at our institute (a tertiary level care center) between Jan 2013 to Dec 2016. The study protocol was approved by the institutional ethics committee, following which the patients were included in the study after obtaining informed consent.

All cases were followed up from diagnosis of ovarian carcinoma till termination of pregnancy, purpuration and thereafter for variable period of time follow-up period of ranged from 4 to 20 months. Parameters like patients age, parity, presenting symptom, gestational age at diagnosis were carefully recorded. All these patients under went surgical staging procedure followed by chemotherapy as per the requirement of individual case. FIGO cancer staging system® was applied to each case. Chemotherapy was given either during pregnancy or postpartum. Chemotherapy consisted of Cis-platin in cases of adeno carcinomas and BEP (bleomycin, etoposide and Cis-platin) in case of dysgerminomas. All and BEP (bleomycin, etoposide and Cis-platin) in case of all patients requiring Chemotherapy were administered drug in consultation with and under monitoring of a medical oncologist at the institute. All histopathologic evaluation were performed by specialist pathologist from pathology department cases which diagnosed to diagnosed to have simple cyst or benign neoplastic growths were excluded from the study.

## OBSERVATIONS & RESULTS

During the study period there were 41410 deliveries in the institute. Out of these 11 pregnant women were diagnosed with ovarian malignant neoplasm, giving a ratio of 0.265 per 1000 deliveries. During this period a total of 186 staging laparotomies were performed for ovarian malignancies at our hospital which make the rate of surgeries for ovarian cancers in pregnant patients to be 5.91%. Majority of women were in second decade of life at the time of diagnosis. The mean age of women in the study was 26.27 years with a range of 22-33 years. Out of these women 63.6% (7/11) were primigravidas. The gestational age at the time of diagnosis of cancer varied from 12-32 weeks with a mean of 18.72 weeks.

45.45% (5/11) women were asymptomatic at the time of diagnosis and routine ultrasonography for pregnancy suggested the presence of tumour. 27.27% of women presented with signs and symptoms of torsion. Another 9.09% presented with abdominal distension, uterus large for dates or abdominal pain of varying intensity. Ascitis was present in one patient while one patient presented with diffuse chronic abdominal pain. Size of the tumour in largest dimension ranged from 4-25 cm. Mean size of tumour was 10.27x 6 cm. 63.63% patients had ovarian epithelial malignant neoplasia out of which two were borderline tumour. Germ cell tumors were present in 27.27% cases and all cases were having dysgerminomas. Metastatic cancer (Krukenberg tumour) accounted for the remaining one case. (9.09%).

The surgical procedure varied from simple cystectomy to unilateral oophorectomy to total abdominal hysterectomy and bilateral salphingo- ophorectomy, omentectomy, lymphadenectomy and debulking surgery. Patient 6 and 8 underwent LSCS at the time of surgery. Adjuvant chemotherapy was given in 45.45% cases. Most cases were diagnosed early although 18.18% cases were stage @ IV at the time of diagnosis. Two cases belonged to FIGO cancer stage II.

Fetal survival rate was 81.81%. 54.5% babies delivered preterm while 36.36% delivered at term. 27.27% fetuses were exposed to intrauterine chemotherapy out of which one aborted at 18 weeks of gestation. No gross congenital abnormality was found in any of fetuses. There was one neonatal death due to aspiration at 28 days of life.

**TABLE no: 1** Patient demographics, tumour presentation, size, tumour stage, type and management

Patient No.	Age in years	Parity	Period of Gestation At diagnosis In weeks	Presentation symptoms	Size of Cyst in cm	Type of surgery	FIGO stage	Tumour marker	Histo- pathology	Chemo-therapy
1	33	1	14	Asymptomatic	10 X 12 X 8	BSO+Left Ovarian biopsy+ LND+Om	IC	CEA1 25- Elevated	Serous adenocarcinoma	Cis-Platin Post-partum
2	22	0	15	Abdominal Pain, distension	25 X 20 X 8	LSO	IA	CEA1 25- WNL	Mucinous Adenocarcinoma	no
3	25	0	21	Abdominal Pain, vomiting	20 X 18 X 10	LSO	IA	CEA1 25- WNL	Mucinous Adenocarcinoma	no
4	28	2	15	Asymptomatic	4 X 4 X 3	LSO+ Right Ovarian Biopsy+ LND+ Om	IC	CEA1 25- Elevated	Serous Adenocarcinoma	Cis-Platin started ante-partum
5	22	0	16	Asymptomatic	6 X 6 X 5	BSO+Left ovarian biopsy	IA	CEA1 25- WNL	Serous Borderline tumour	no
6	26	0	32	Chronic Abdominal pain	15 X 10 X 8	LSCS+ optimum cytoreduction could not be performed as mass was retroperitoneal	IV	LDH- Elevated highly	Dysgerminoma (FNAC)	BEP post partum
						encasing aorta and IVC				

**TABLE NO. 2:** Gestational age at intervention and perinatal outcome

Patient No.	Gestation at time of surgery In weeks	Intrauterine Chemotherapy exposure	Pregnancy outcome	Congenital abnormalities
1	14	no	Elective LSCS at 34 weeks, 2000 gm	Nil
2	16	no	Term, 2500gm	Nil
3	18	no	36 weeks, 2500gm	Nil
4	15	Yes, started at 28 weeks	34 weeks, 2000	Nil
5	16	no	Term, 3200	Nil
6	34	no	34 weeks, neonatal death after 28 days	Nil
7	14	Yes, started at 16 weeks	Abortion at 18 weeks	No gross CA
8	31	no	31 weeks, 1200gm	nil
9	16	no	Term, 2600gm	Nil
10	18	Yes, started at 22 weeks	33 weeks, 1800gm	Nil
11	14	no	Term 2800 gm	Nil

**Table No. 3:** Incidence of ovarian neoplastic tumors in pregnancy

STUDY	YEAR of publication	INCIDENCE ( per 1000 deliveries)
Zhao et al. [5]	2006	0.073
Machado et al. [9]	2007	0.11
Behdash et al. [24]	2008	0.083
Gezginc et al. [3]	2011	0.75
Present study		0.265

## DISCUSSION

Cancer of the reproductive system in pregnancy is a perplexing situation as not only two lives are involved but also woman's future reproductive ability is at stake. Although considered to be a rare malignancy associated with pregnancy ovarian cancer is the second most common gynaecologic cancer complicating pregnancy only next to cervical carcinoma [3].

There is wide variation in the incidence of ovarian cancers quoted in the literature from 1/10,000 to 1/100,000 [4]. Various studies give incidence of ovarian cancers as low as 0.073/1000 deliveries [5] to as high as 0.75/1000 deliveries [3]. In the present series the incidence of ovarian cancer complicating pregnancy is 0.265/1000 deliveries. The figure is on higher side as the study center is a tertiary care centre and a referral hospital.

The parity of women in present series ranged from 0 to 2 with mean of 0.45. Majority of women were primigravida. Beral et al have shown a clear inverse relation between average completed family size and mortality from ovarian cancer and according to their study this protection seems to persist throughout life [6]. Gwinn et al in their study revealed a strong trend in decreasing risk of epithelial ovarian cancer with increasing cumulative months of pregnancy [7]. Clear trends of decreasing risk were evident with increasing number of pregnancies (regardless of outcome) by Whitt more et al [8]. The present study supports these findings.

A large number of patients with adnexal tumors are asymptomatic at diagnosis [2,3,9]. The corresponding figure in our study was 45.45%. Torsion was the presenting feature in 27.27% cases. One patient (case no.6) presented at 32 weeks of gestation with complaint of long standing mild to moderate abdominal pain. Her chronic pain was considered to be preterm labour pain and she was managed on that line of treatment at peripheral centres until MRI showed the presence of a retroperitoneal mass which on ultrasound guided FNAC came out to be dysgerminoma. Another patient (case no.8) presented at 30 weeks of gestation with severe preeclampsia, abdominal ascites and deranged liver and renal function tests. Initially diagnosed as a case of HELLP syndrome, it later turned out to be a case of bilateral ovarian malignancy with ascites. Pelvic imaging during the course of management helped us nail the diagnosis.

Ovarian cancers tend to be diagnosed at an early stage because of frequent obstetrical examinations [9,10] and pelvic ultrasonography for obstetrical reasons in asymptomatic patients. In a study by Nelson et al [11], 87% of ovarian cancers among pregnant patients were detected in FIGO stage I-

II. In present study 81.8% cases belonged to FIGO stage I-II. Advanced stage at time of diagnosis and invasive epithelial cancer are the most important predictors of poor outcome in a patient of ovarian cancer [4,12,13]. Presence of ascites

implies advanced disease and adversely affects patient survival [5].

In the current study 2 patients had advanced disease (stage IV dysgerminoma and stage IV mucinous adenocarcinoma). The patient with stage IV adeno-carcinoma had massive ascities and deranged liver and renal functions and had to be put on ventilator just after surgery. This patient died on 3<sup>rd</sup> post-operative day in ICU. The patient with stage IV dysgerminoma received BEP chemotherapy and was in remission at 15 months of follow-up.

In 1963, over an 80-year review period, Jubb reported 34 cases of primary ovarian carcinoma associated with pregnancy, with only 54% being of epithelial type<sup>[14]</sup>. Germ cell tumors are reported to be more prevalent than other histological types of ovarian carcinoma diagnosed during pregnancy by several other authors also<sup>[5,15]</sup> a finding consistent with the age-matched, non pregnant setting<sup>[16]</sup>. But more recent studies in this field have shown epithelial ovarian malignancies as the more prevalent histological type associated with pregnancy than germ cell tumors<sup>[2,9,4,17]</sup>. Guidelines published by International consensus meeting on gynaecological cancers in pregnancy held on 3<sup>rd</sup> of July 2008 in Belgium<sup>[4]</sup> state that ovarian epithelial malignancies constitute 49-75% of all ovarian malignancies in pregnancy. In the present series 63.63% cases were of epithelial cancers out of which 28.57% were borderline while rest 71.42% were invasive epithelial malignancies. Germ cell malignancies accounted for a minority of cases. This review of literature shows changing trend from prevalence of germ cell malignancies to epithelial malignancies associated with pregnancies, a finding corroborated in the present study as well Serum CA125 is not of substantial prognostic or diagnostic importance in ovarian epithelial malignancies<sup>[4]</sup> complicating pregnancy. Halila et al in their study found raised CA125 levels in 69% of ovarian cancers, 33% of patients with pelvic inflammatory disease and 24% of normal pregnancy<sup>[18]</sup>. Serum CA125 levels may be raised in normal pregnancy with a usual peak in the first trimester<sup>[19]</sup> and return to normal limits (or <65 µ/ml) in the second trimester<sup>[18,20]</sup>. A lower level rise in serum CA125 level may not help to substantiate a diagnosis. There for the CA125 control values from non-pregnant patients cannot be applied to pregnant women with ovarian cancers<sup>[21]</sup>. This observation was confirmed in the present series as well with the measured CA125 levels showing no correlation to epithelial ovarian malignancies. On the other hand LDH was found to be elevated in all cases of dysgerminoma and can be used as a diagnostic marker.

About 0.75% -2% pregnant women undergo surgery during pregnancy for various reasons<sup>[4]</sup>. The second trimester is generally regarded as the best time for surgical intervention because the risk of miscarriage is minimised<sup>[3,4,22]</sup>. One in three risk of spontaneous miscarriage following laparotomy in the first trimester has been reported<sup>[23]</sup>. The present study shows that surgical procedure is safe for mother and fetus during second trimester. 81.81% cases in this study underwent surgery during early second trimester. There was no abortion observed except one abortion (case no.7) at 18 weeks.

In this case chemotherapy was started at 16 weeks of gestation, soon after surgery. Surgical exploration in the third trimester is associated with premature labour, hence poorer pregnancy outcomes<sup>[13,17,22]</sup>. In present series 2 patients were operated in 3 trimester. Their infants were born at 34 and 31 weeks. Both infants were followed in neonatal intensive care unit, with one neonatal death at 28 days of life (patient no.6).

The decision as to which type of surgery to perform is based on the histology and stage of tumour, gestational age and patient's desire for future pregnancy. In early-stage epithelial ovarian cancer (FIGO stage Ia), staging laparotomy and salpingo-oophorectomy alone, followed by careful observation of both mother and fetus in a multidisciplinary setting may suffice<sup>[22]</sup>. The management of advanced stage ovarian cancer during pregnancy includes various different strategies like primary debulking with termination of pregnancy followed by post-partum chemotherapy<sup>[4,9]</sup>, expectant management<sup>[9]</sup>, cytoreductive surgery during pregnancy followed by chemotherapy during pregnancy with final surgery during/after delivery<sup>[1,3,4,24]</sup>. In present study unilateral salphingo- oophorectomy, omentectomy and peritoneal biopsies were performed for early stage cancers. In patient no.6 optimum cyto-reduction could not be performed as growth was encasing major vessels and patient received BEP chemotherapy post-partum. Patient was under remission at 15 months of follow-up. In patient no 8 complete curative surgery was aimed for after LSCS. In one patient (patient no.7) surgical procedure was limited to establish the diagnosis and salphino-oophorectomy and patient received antenatal chemotherapy.

Cyto-toxic drugs used in gynaecological cancers are cis-platin, pacli-taxel, bleomycin, etoposide and vinblastin. All cyto-toxic agents are teratogenic and are contraindicated in first trimester of pregnancy<sup>[22]</sup>. Amant F et al at the international consensus meeting on gynaecological cancers in pregnancy reviewed 37 available case-reports on intra-uterine exposure of chemotherapy in second and third trimester of pregnancy and found normal neurological development and absence of congenital anomalies in 35/37 cases. Sensori- neural deafness, ventriculo-megaly and prematurity were found in one case report<sup>[4]</sup>.

Similarly normal neonatal outcome was found in fetuses exposed to combined BEP for germ cell cancers<sup>[3,4,12,17]</sup>. In present series 27.27% fetuses (3/11) were exposed to ante-natal cyto-toxic agents. Although no congenital anomaly was found one patient had abortion at 18 weeks while others had preterm deliveries. In rest of the cases chemotherapy was administered post-partum.

## CONCLUSIONS

Ovarian cancer during pregnancy is a demanding problem and a multidisciplinary approach with expertise is required for optimum management of these cases. Individualisation is crucial when ovarian malignancy is diagnosed during

pregnancy. Epithelial cancer constitute most common histological type of all invasive ovarian cancers malignant ovarian tumors are diagnosed at an early stage because of frequent obstetrical examinations in asymptomatic patients. Staging and treatment of ovarian cancers should follow the standard approach as much as possible. Outcome of pregnancy depends upon the stage of tumour. Oncological surgery and chemotherapy after first trimester seems to be safe from fetal point of view. Chemotherapy causes a slight predisposition for prematurity. Tumors markers are less reliable in pregnancy so close surveillance instead of adjuvant chemotherapy propagated earlier can be a recipe for disaster. Unnecessary delay in treatment of ovarian tumour in pregnancy should be avoided.

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