Provisionally accepted for publication

ORIGINAL ARTICLE

Clinical outcomes among pregnancy complicated by cancer: analysis of 41 cases.

Outcomes of pregnancies with cancer

Madhva **Prasad** *, Anahita **Chauhan**, Priyanka **Deshpande,** Shreshta **Mahanti**

Department of OBGYN, Seth GS Medical College and KEM Hospital, Mumbai, India

***Corresponding author:** Madhva **Prasad**, c/o Dept of OBGYN, St Johns Medical College Hospital, Bangalore 560097, India.
Email: madhva@gmail.com.
ORCID: 0000-0001-5507-7812

DOI: 10.36129/jog.2026.259

ABSTRACT

Objective. With a rising incidence of cancer in the reproductive age group and a rising contribution of indirect causes towards maternal mortality, the entity of cancer in pregnancy deserves more attention. Data from India is largely limited to individual case reports. To describe the demographic details, details regarding cancer, obstetric and neonatal outcomes among patients with cancer in pregnancy.

Materials and Methods. A retrospective observational study was conducted by screening delivery and MTP records for the terms “cancer”, “malignancy” in the “risks” column to identify patients. Three years data (January 2016-December 2018) was collected. Relevant obstetric history, pregnancy course, cancer treatment details and obstetric/ neonatal outcomes were noted. Results were tabulated. No comparison group was taken.

Results. Over a 3-year period, 41 pregnancies with cancer with an average age of 28.7 years, majority second gravida were identified. Malignancies of the reproductive tract (11) and breast (7) were the most common, followed by other organs. Nineteen patients (46.34%) had cancer prior to pregnancy. 28 patients underwent MTP and nine were preterm deliveries. Only four patients delivered at term. Six mothers needed ICU care and there were three mortalities.

Conclusions. Cancer in pregnancy, though rare, can pose several challenges to the obstetrician and the oncologist. Further prospective data is needed on the topic of cancer and pregnancy.

Key words

Cancer-survivor; indirect maternal mortality; high-risk pregnancy; critical care obstetrics.

Introduction

While the vast majority of pregnancies are uneventful and uncomplicated, obstetricians are well-versed in dealing with medical conditions complicating pregnancy such as hypertension, diabetes etc. However, as a rarity, some medical conditions with grave prognosis may occur first or be noticed first in the course of pregnancy. An example of one such grave condition is cancer. What happens when these two conditions – pregnancy and cancer occur simultaneously, is the focus of this article.

Most recent cancer registries estimate that the incidence of cancer has been rising over the last few decades (global estimate of 14.9 million incident cancer cases and 8.2 million deaths in 2013) [1]. Mathur et al [2] have confirmed such a trend (an estimated 13 lakh patients with cancer in India). Based on an observation in Tunisia, Dimassi et al [3] suggest that cancer appears to be the most common cause of death in women belonging to the reproductive age group, with a recommendation that cancer in the reproductive age group should receive more attention.

In general, gynecologists are looking for many ways to prevent cancer too [4]. The contribution of cancer of maternal mortality is quite low (only 1 % in a large analysis of indirect maternal mortality) [5]. However, with the reducing prevalence of direct causes of maternal mortality [6], due to the robust improvement in maternal healthcare, the proportion attributed to rare causes like cancer may become more prominent.

Cancer with pregnancy is in itself very rare. A study in Nepal showed a prevalence of around 1 in 1000 deliveries [7]. In the western literature, cancer attributable maternal mortality is also very less (around 3.16 per 100,000 live births) [8]. Most literature pertaining to cancer and pregnancy are in the form of case reports or very small case series [9-13]. In this context, the objectives of the study were to describe the demographic details, details regarding cancer, obstetric and neonatal outcomes among patients with cancer in pregnancy.

Materials and Methods

This was a retrospective observational study involving review of records in a tertiary care centre located in Western urban India. The labour ward register and the medical termination of pregnancy register were screened by the investigators of the study for the terms “cancer”, “malignancy” or any other similar were identified and noted. The admission papers were retrieved from the medical records department were reviewed and patient details were noted by two investigators. All MTPs which had been conducted in patients with malignancy, for any reason, were identified and the indoor papers of these patients were also scrutinized. Data was collected for a duration of 3 years. (January 2016-December 2018). All patients with pregnancy and cancer (immaterial of the trimester of presentation, registration status and all types of cancers) were included. Those who had delivered elsewhere, those who had inadequate data or missing records were excluded. Demographic details obstetric history details course of the pregnancy (terminated or continued, need for hospitalization, antenatal complications) details of the cancer treatment (nature of malignancy, site, histological type, time of diagnosis, treatment details- chemotherapy, radiotherapy etc, relationship between cancer diagnosis and pregnancy), and the outcomes of the present pregnancy were noted in detail. Gestational age at the time of delivery, the type of delivery, need for intensive care unit admission and any attendant complications were noted. Neonatal outcomes in terms of need for NICU admission were noted. If there was a mortality, the relevant details were noted with more detail.

Study registration, ethical and methodological standards

This study was performed after Institutional Ethics Committee clearance (EC/OA-130/2018)

Statistical analysis

The results were tabulated and represented using appropriate statistical methods of representation using Microsoft excel. No comparison groups were taken, and advanced statistical analysis was not required.

Patient and public involvement

Being a retrospective review of records, no patient involvement was required.

Results

Over a 3-year period, 41 pregnancies with cancer were identified.

Demographic details

The average age was 28.7 +/- 4.05 years, the youngest being 21 years and the oldest being 40 years. Being a tertiary care referral institute, most of the patients were referred from a geographical location away far from the treating institute.

Obstetric details

The gravidity distribution is shown in table 1. Majority of the patients were second gravida. Among the multigravida (35) patients, there were 5 patients who did not have any living issues.

Tissue of origin of the cancer

There were 11 malignancies of the reproductive tract and remaining 30 were of other organs. The details of these types of malignancies are presented in table 2. As a single entity, cancer of the breast was the most common

Time of diagnosis malignancy in relation to pregnancy

Out of the 44 patients, 19 (46.34%) were known to have cancer prior to occurrence of pregnancy. 5 (12.1%) were detected during the first trimester of pregnancy. 17 patients (41.4%) were detected in 2nd trimester. None of the patients were detected in 3rd trimester or postpartum period. (table 3)

Treatment details of patients who had cancer prior to pregnancy (n=19)

Out of 19 patients who had cancer prior to pregnancy, 14 had received chemotherapy, 10 had received radiotherapy and 11 had undergone an operative procedure.

Operative details

The operative procedures that the patients (11) had undergone were Unilateral adnexectomy omentectomy (1), Adrenalectomy (2), Radical esophagectomy (1), Radical mastectomy (3), Radical resection of colon (1), Total thyroidectomy (2) and Unilateral salphingoophorectomy (1). Out of these 11 patients who had undergone an operative procedure, 4 patients had undergone operative procedure less than 1 year before detection of the index pregnancy.

Contraception history of the patients who had cancer detected prior to index pregnancy

Among the 19 patients who were known to have cancer prior to pregnancy, 18 were not on any contraceptive method. In one patient's records, there was no mention of contraception history at all.

Treatment details of patients who were diagnosed during pregnancy (n=22)

Eleven patients were initiated on chemo-radiotherapy as appropriate soon after termination of pregnancy (4 first trimester MTPs and 7 second trimester MTPs). Seven patients needed

chemo-radiotherapy but had to wait till the completion of pregnancy (MTP could not be performed). Eleven patients underwent operative procedures peri-delivery/ peri-abortion, the distribution of which is shown in table 4.

Pregnancy outcomes (n=41)

Pregnancy outcomes are presented in a composite format in table 5. Twenty-eight patients underwent termination of pregnancy. With respect to trimester, 15 were in the first trimester and 13 were in the second trimester. With respect to time of detection, 11 MTPs were in patients who had been diagnosed in the index pregnancy and 17 were in patients who had been diagnosed prior.

Thirteen patients delivered beyond period of foetal viability. Of these, four patients delivered at term and nine were preterm deliveries. All these deliveries yielded live births. There were 13 deliveries, out of which one was twins. Of 14 neonates, 8 were male and 6 were females. Though 10 neonates needed NICU admission, there were no neonatal deaths.

Pregnancy morbidity and mortality

Number of admissions needed in antenatal period

The number of admissions (excluding the one needed for completion of pregnancy- MTP or delivery) were noted. Majority of the patients 31/41 (75.6%) required only no admissions. Among the remaining 10 patients, 5 required one admission, and the remaining five needed more than one admission. The average duration of stay was calculated to be 8.87 days.

ICU care

Six patients needed ICU care for decompensation in the general condition. Out of these six patients, three were in the post-delivery period

Mortality

In this study, there were three mortalities. A brief description of the three cases is presented below.

25-year-old G3P1L0A1 who was detected to have Acute Myeloid Leukemia in the late 3rd trimester of pregnancy. She underwent induction of labour at 38 weeks of gestation and delivered live female child (No PPH). Post-delivery, she was started on chemotherapy. Succumbed on day 14 of postnatal life despite multiple blood and blood product transfusions including G-CSF injections, due to severe bleeding diathesis.

24-year-old G2P1L1 with Ewing's Sarcoma Femur. Deep Venous thrombosis (paraneoplastic syndrome) occurred in antenatal period needing anticoagulation. She went into spontaneous preterm labour and delivered a fresh stillbirth. Due to persisted DIC despite

therapy, operative procedure could not be performed, and she succumbed on day 34 of delivery

34-year-old primigravida with sudden seizures and unconsciousness diagnosed with large oligodendroglioma. Due to raised ICP unresponsive to medical therapy, emergency craniotomy was needed in antenatal period, wherein there was brief recovery in GCS. Three days post-procedure she went into spontaneous labour and delivered a live birth. She succumbed on day 9 of delivery due to neurological complications.

Discussion

Main findings

This was a retrospective analysis of 3 years of cancer cases in pregnancy, and an entire range of malignancies was noted, breast cancer being the most common one. It was surprising to note that there were no cases of gestational trophoblastic neoplasia.

Cancer and pregnancy: A rare interplay of two otherwise common conditions

Boussios et al have reported nine cases of lung cancer in pregnancy, in an international collaborative study [14]. Girault et al identified only 20 cases of brain tumours over 8 years in a single centre study [15]. Yu et al have reviewed the available evidence of thyroid cancer in pregnancy, have suggested that more patient data needs to be generated [16]. Blake et al reviewed epithelial ovarian cancers in pregnancy and found only 105 cases over 50 years eligible for review [17]. Rare cancers like vulval cancers have also been reported in pregnancy [18]. The one type of cancer with a high incidence and probably adequate literature is breast cancer [19]. Azim et al in their article titled “Managing cancer during pregnancy: what evidence do we have?” have emphasized the fact that adequate data is not available in this matter, and with further data, complex management issues can be looked into with better light [20]. None of these analyses have attempted in giving any incidence/ prevalence statistics because of the inherent risk of hospital bias. The same principle is followed in the study also, and only the numbers (and no proportions) have been presented.

Strengths and limitations of the present study

It is hoped that this data presented here adds to the existing pool of knowledge regarding this otherwise rare topic. The authors acknowledge that, being a retrospective observational

study, despite meticulous attempts at analysis, there may be some cases which may have been missed, and this is a drawback of this study.

Interpretation Comparison with other studies

Management of each case is individualized

Usually, patients are sent to high volume tertiary care centres for obstetric care, be it delivery or for medical abortion. In the analysis, a detailed description of each individual case and the course is not possible due to need for brevity. In most situations, management is highly individualized and decided on a case-to-case basis, involving a multi-disciplinary approach, following the risk-benefit ratio principles, taking care of both maternal and fetal well-being. The diagnostic techniques, chemotherapy protocols compatible with pregnancy, and decision-making processes regarding timing of delivery and cancer treatment, definitely need further refinement.

Cancer cervix – impact of HPV and pregnancy

In this study, there were 6 patients with cancer cervix but none of them had undergone a Pap smear during early antenatal period. The utilization of pregnancy as a time for early diagnosis of cervical cancer needs better clarity and consensus. The concept that performing Pap smear during pregnancy may lead to “over-diagnosis” is counteracted by the advancing average of pregnancy world over, as noted by Nygard et al [21]. A recent meta-analysis [22] focussed on the natural history of High-grade CIN lesions detected during pregnancy. The results of 10 studies were reviewed and the authors concluded that “it is worth noting that a small percentage of high-grade CIN would progress to cervical cancer during pregnancy.”

Fertility issues among cancer survivors

A recent review analyzing the the bidirectional effects of HPV on male and female reproductive health highlights its influence on pregnancy outcomes and fertility-sparing management advances. All these sensitize us towards the importance of integrating vaccination and fertility-preserving strategies in preventive care. These findings should positively impact our policy towards integrating HPV screening during pregnancy and the peripartum period. [23] In the recently reported ETERNITY project, 36 patients with early-stage cervical cancer (stages IB2, IB3) were treated with neoadjuvant therapy and conization, and followed up for arond 36 months. Among 6 participants seeking fertility, 5

had successful conception, highlighting that specific interventions for cancer can preserve fertility, without increasing morbidity or mortality. [24]

Similar encouraging results are observed in a systematic review of 443 early stage cancer cervix patients with 443 patients. [25]

Contraception usage among cancer survivors

In our study, out of the 19 patients who had been diagnosed to have cancer prior to detection of pregnancy and on regular follow-up, none were on any contraception. Out of these 19 patients, barring three patients (One was primigravidae and two multigravidae did not have a living issue), 16 already had a living issue. This phenomenon of non-usage of contraception among this set of cancer survivors, draws parallel to the non-usage of contraception among women with high-risk medical conditions [26].

Poor implementation of contraceptive advice and lack of regular practise of referral to contraception counselling is a trend noted among many specialist physicians [27], and this study shows that oncologists also fall in the same bracket.

"Methods of fertility preservation after cancer treatment" is a well-researched topic. [28, 29]. However, not much is known about whether fertility is preserved without any intervention after cancer treatment.

Balachandren et al [30] have reviewed the topic of fertility and ovarian reserve after cancer diagnosis, and have highlighted the dearth of knowledge about the topic.

Hypothetical patient's thought processes such as "*I have cancer, hence, I won't conceive*" and "*I have cancer, let me enjoy my life as long as I live*" can paradoxically lead to increased coital frequency, though has not been be substantiated in contemporary literature. The study here, though small in size, shows that a sizeable number of women can remain fertile after cancer diagnosis/ treatment.

Occurrence of pregnancy prevents optimal cancer management

Cancer mortality is high, and there are many reasons for the same, which is common medical knowledge, and rapid strides are being made in the management of cancer [31-33]. Cancer needs surgical, chemotherapy or radiotherapy. Diagnosis of pregnancy may prevent or delay the prompt administration of appropriate cancer therapy. Even among patients "in remission", side-effects of anti-neoplastic agents and pregnancy-related changes can push patients towards life-threatening emergencies [9]. In such scenarios, the valiant efforts by the oncologist team are set aside by the occurrence of pregnancy. Through this article, the authors would like to highlight that pregnancy occurence should not be a deterrent to

receiving optimal oncological care. To prevent such a catastrophe, introduction of the term “onco-contraception”, on similar lines to “onco-fertility” can be considered.

Conclusions

Pregnancy with cancer presents unique challenges to the obstetrician and the oncologist, which must be handled with a multidisciplinary effort, vigilance and care. Policy upgrades regarding utilization of pregnancy as a time for cervical cancer and HPV screening is needed. Follow-up among cancer-survivors merits consideration regarding fertility concerns (both fertility preservation and contraception). Further prospective studies on the topic of cancer and pregnancy overlap are to be encouraged.

COMPLIANCE WITH ETHICAL STANDARDS

Authors’ contribution

MP: Conceptualization, methodology, formal analysis, supervision, writing - original draft, reviewing and editing.

ARC: Conceptualization, project administration, supervision, validation, writing - reviewing and editing

PD and SM: Data curation, resources, software, formal analysis, methodology,

Funding

None.

Study registration

Not applicable.

Disclosure of interests

No interests to declare.

Ethical approval

EC/OA-130/2018.

Informed consent

Not needed in retrospective studies

Data sharing

Data can be shared if needed

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Table 1. Distribution of Parity

Gravida status	Number (%) (n=41)
Primigravida	6 (14.63%)
Gravida 2	16 (39.02%)
Gravida 3	10 (24.39%)
Gravida 4 and above	9 (21.95%)

Table 2. Tissue of origin of the cancer (n =41)

System involved	Type of malignancy	Number
Reproductive organs (11)	Squamous cell carcinoma cervix	4
	Adenocarcinoma cervix	2
	Ovarian epithelial	2
	Adenocarcinoma endometrium Uterus	3
Breast (7)	Adenocarcinoma Breast	7
Gastrointestinal (6)	Esophagus (adenocarcinoma)	1
	Krukenberg tumour	1
	Rectum (all adenocarcinoma)	4
Endocrine (5)	Pancreas (adenocarcinoma)	1
	Adrenal Carcinoma	1
	Malignant Pheochromocytoma	1
	Thyroid (Papillary)	1
	Thyroid (Medullary)	1
Brain (4)	Oligodendroglioma	1
	Glioblastoma multiforme	2
	Hemangiopericytoma	1
Haematological (3)	Acute myeloid leukaemia	1
	Chronic myeloid leukaemia	2
Soft tissue / bone (3)	Ewing sarcoma	2
	Giant Cell Tumour	1
Lung (1)	Squamous cell carcinoma	1
Tongue (1)	Squamous cell carcinoma	1

Table 3. Time of diagnosis malignancy in relation to pregnancy

Time of diagnosis	Number (%) (n=41)
Before pregnancy	19 (46.34%)
During pregnancy 1st trimester -	5 (12.19%)
During pregnancy 2nd trimester	17 (41.46%)
During pregnancy 3rd trimester/ peripartum	0
Postpartum period	0

Table 4. Operative procedures performed among patients detected to have malignancy during pregnancy (n=11)

Operative procedures performed with fetus-in-situ	**Number**
Craniotomy with excision of lesion	2
Diversion Sigmoidostomy	1
Procedures done in the immediate postpartum period	**Number**
Breast Conservation surgery	2
Sigmoidectomy	3
Bilateral salpingoophorectomy	1
Hemi-tongue resection	1
Thyroidectomy	1

Table 5. Pregnancy outcomes (n=41)

Gestational age	Details	Number
Upto 12 weeks (n=15)	MTP	14
	Spontaneous abortion	1
12 – 20 weeks (n=13)	MTPs	13
	Spontaneous abortions	0
Preterm (n=9) <28 weeks: 3 28-34 weeks: 4 34-37 weeks: 2	Preterm caesarean	6
	Preterm vaginal Delivery	3
Term (n=4)	Caesarean	1
	Vaginal delivery	3