



## Case Report

# A Stage 1B1 Clear Cell Cervical Cancer Patient who fell Pregnant whilst Awaiting Fertility Sparring Surgery Managed with Neoadjuvant Chemotherapy to Arrest Disease Progression until Delivery at 36 Weeks Gestation

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### Abstract

We present a case of a 25 years old woman who presented to the gynaecological oncology unit before pregnancy with a histological and clinical diagnosis of cervical squamous cell carcinoma stage 1B1. She desired fertility and hence an elective admission for vaginal trachelectomy (for fertility sparing) was planned. She fell pregnant whilst awaiting surgery and opted to continue with the pregnancy after counselling. She received neoadjuvant chemotherapy and was delivered at 36 weeks and a caesarean radical hysterectomy and pelvic lymphadenectomy was done. There is no disease recurrence after 2 years of follow up. This case highlights the challenges of prolonged waiting periods for surgery in our setting as well as the presentation of a rare histopathology of clear cell carcinoma. Clear cell adenocarcinoma of the cervix is associated with exposure to diethylstilboestrol (DES) in utero.

**Keywords:** Caeserean radical hysterectomy, chemotherapy in pregnancy, clear cell cervical adenocarcinoma in pregnancy

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The incidence of cervical cancer in pregnancy is between 1 in 1000 to 1 in 2500. This makes it the most frequent malignancy diagnosed during pregnancy. It is unclear how pregnancy has effect on tumor biology and the management of pregnant patient is not well defined.<sup>[1]</sup> Clear cell adenocarcinomas of the cervix are generally rare with a reported incidence of between 4-9 % of cervical adenocarcinomas.<sup>[2]</sup> They arise in two distinct population groups (exposed to diethylstilbestrol (DES) in utero and sporadically).

<sup>[3, 4]</sup> Clear cell adenocarcinomas may be associated with human herpes virus infection.<sup>[4, 5]</sup>

The use of neoadjuvant chemotherapy (NAC) is described as an option to achieve disease control until fetal viability. It is administered until gestation of 35 weeks or preferably at 3 weeks' intervals.<sup>[6]</sup> When the interval is short, there is increased risk of delivery related maternal/fetal hemorrhage and infection. An inadequate elimination of cytotoxic drugs by fetus result in increased fetal risk.<sup>[6]</sup>

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Radical operative procedures, including hysterectomy, as well as radiotherapy and/or chemotherapy may lead to premature ovarian failure (POF).<sup>[7]</sup> Safe fertility preserving procedures are vaginal radical trachelectomy (VRT), abdominal radical trachelectomy (ART) or simple trachelectomy with lymph node dissection.<sup>[8]</sup> The prognosis of clear cell adenocarcinomas appears to be similar to other variants.

Due to the rarity of clear cell adenocarcinoma of the cervix, only a few published case reports have implied that fertility-preserving treatment is possible in patient with early stage cancer.<sup>[9]</sup> In this case report, the patient received in-depth counselling with the gynecological oncologist, gynecology and obstetrics teams regarding the risk of progression of disease as well as fetal complications. She was also offered opportunity to discuss her options with the family. The decision to proceed with the pregnancy, using neo-adjuvant chemotherapy until fetal maturity even though she was still 18 weeks, was made after much discussions.

## Case Report

We present a case of a 25 years old Primigravida who was HIV negative with normal ante-natal booking blood results. She presented to the gynaecological oncologist unit before pregnancy with a histological and clinical diagnosis of cervical squamous cell carcinoma stage 1B1. She desired fertility and hence an elective admission for vaginal trachelectomy (for fertility sparing) was planned. On admission date, urine pregnancy test was positive and pregnancy of 18 weeks gestation was confirmed by ultrasound with a singleton live fetus. She expressed her need to continue with pregnancy. The patient declined surgical management in pregnancy such as radical trachelectomy due to lack of guarantee to preserve the current pregnancy. She was thoroughly counselled on the risk of neo-adjuvant therapy at this gestation regarding progression of the cancer and she opted to take the risk and continue with the pregnancy. She opted to delay therapy for pregnancy. Her antenatal follow up was continued at our fetomaternal unit of the obstetrics department. The management of her disease was also discussed with the medical oncology unit and a total of 4 cycles of three weekly chemotherapy with taxane 280 mg and addition of carboplatin 600mg on the fourth cycle were administered to this patient in an attempt to arrest disease progression. She suffered scalp and body hair loss complications of chemotherapy. Fetus monitoring ruled out fetus growth restriction and oligohydramnios. Maternal follow up evaluation was by both clinical examination and ultrasound done by an experienced sonographer due to challenges with MRI availability. No

clinical progression of the lesion was reported. Delivery was planned for 34 weeks gestation and above. She was admitted at 34 weeks for steroids and subsequently discharged for a planned Caesarean-Radical Hysterectomy and Lymph nodes dissection (CRHLND) at 36 weeks due to unavailability of neonatal critical care beds.

Surgery was performed by the gynaecological Oncologist with assistance from the obstetric labour ward team as well as neonatal ward team. The caesarean section was uneventful and radical hysterectomy had no immediate complications. Intraoperatively, the disease had not progressed and there was no suspicion of nodal involvement. The placenta appeared normal with no areas of infraction, haemorrhage or metastasis. The baby had a birthweight of 3200 grams and Apgar scores 9/10 and 10/10 in first minute and 5 minutes respectively. The patient was admitted for four days post operatively and no complications observed in the ward.

She was seen at follow clinic after 6 weeks and then 2 months and no surgical complications were noted. She will be followed up with vault smears every 6 months for a period of 2 years and subsequently annually if vault smears are negative.

## Histopathology

A radical hysterectomy with left and right pelvic lymph node dissection specimen was sent to the National Health Laboratory Services (NHLS) for histological evaluation. On macroscopic assessment, there was no visible cervical mass. Microscopic cervical sections examination showed involvement of the Endocervical tissue by a clear cell adenocarcinoma. The tumour was solid and had tubulocystic growth pattern with cuboidal cells. It displayed marked nuclear pleomorphism and occasional hobnailing with abundant clear to eosinophilic cytoplasm. Depth of invasion from surface was 23.2 mm. No involvement of Pouch of Douglas, parametria, endometrium or adnexa. The 27 lymph nodes examined were tumour free. There was evidence of low grade squamous intraepithelial neoplasia (LGSIL) which was completely excised. The patient is classified as a stage IB2 cancer according to the TNM classification of malignant tumours.

The placenta weighed 397 g and histological examination showed no significant pathological changes. There was no evidence of a metastatic carcinoma.

## Discussion

The treatment modalities for cervical cancer in pregnancy are determined by the gestational age, stage of disease and the wish of the patient to preserve the pregnancy.<sup>[6]</sup>

## Delivery Delay with Neoadjuvant Chemotherapy for Cervical Cancer Patients During Pregnancy

Fruscio et al found that the oncological outcome of pregnant women with cervical cancer is similar to non-pregnant women. They also found that chemotherapy does not seem to affect fetal health and development, even with longer follow up period. Therefore, they concluded that neoadjuvant chemotherapy for the treatment of locally invasive cervical cancer during pregnancy seems to be a reasonable option to delay definitive treatment until fetal viability.<sup>[10]</sup>

## Protocol for Management of Cervical Cancer in Pregnancy ( $\leq 20$ Weeks Gestation)

Women who have a stage 1A disease can have deliberate delay of therapy if pregnancy is desired. Women with stage 1B1 disease who do not want to continue pregnancy can have radical hysterectomy and lymphadenectomy with fetus in utero. If pregnancy is desired, deliberate therapy is acceptable with a plan for radical hysterectomy and lymph nodes dissection at Caesarian section at 34-36 weeks following administration of steroids for fetal lung maturity.<sup>[11]</sup>

Patients with stage 1B2-2A who do not desire pregnancy receive chemoradiation with fetus in utero with subsequent spontaneous abortion. Neo-adjuvant chemotherapy is acceptable if pregnancy is desired in this stage and radical hysterectomy and lymph node dissection at 34-36 weeks of gestation. Patients who are stages 2B-4 disease, receive chemoradiation with no surgery.<sup>[11]</sup>

## Period from Diagnosis to Delivery and Outcome

Fruscio et al.<sup>[10]</sup> found that the median duration of therapy delay from diagnosis until delivery was 16 weeks. There were no observed cases of spontaneous preterm birth or premature rupture of membranes. The deliveries were made between 30 and 36 weeks of gestation by elective caesarian section. There were no metastases to the placenta, congenital defects and no children who presented with neuropsychological and physical development.

## The Surgical Management and Outcome

Yan H et al.<sup>[12]</sup> reported an average postoperative hospitalization time of 10.6 days for women who had CRHLND. The average number of excised pelvic lymph node was 20.

When deciding therapy for invasive cervical cancer in pregnancy, the stage of the disease and duration of pregnancy is considered.<sup>[11]</sup> Radical trachelectomy is an acceptable surgical method for patients who desire fertility preservation. Yan et al found that for patients who had radical tra-

chelectomy followed by a cerclage, there was a pregnancy rate of 86% (36/42) after the procedure and patients were delivered by the elective cesarean section between the 37<sup>th</sup> and 38<sup>th</sup> weeks.<sup>[12]</sup> Those diagnosed prenatally have higher rate of caesarian section, hospitalization longer than 5 days, low and very low birthweight, prematurity and fetal death.<sup>[11]</sup>

## The Role of MRI in Assessing Operability

The use of MRI in pregnancy is advocated as it has no known deleterious effects on the fetus. MRI helps in assessing the prognosis for both the mother and the fetus. It is also the only reproducible examination that can assess response to treatment (chemotherapy) administered during pregnancy.<sup>[12]</sup>

## Neo-Adjuvant Chemotherapy and Outcome

Dawood et al concluded that the use of neoadjuvant chemotherapy (NAC) in treating cervical cancer in pregnancy with Cisplatin seems to be the most reliable form of treatment and permits a good outcome for most patients.<sup>[12]</sup> Patients with FIGO stage 1B2 and greater who refuse interruption of pregnancy should be offered a single agent of cisplatin 75 mg/m<sup>2</sup>. There is also interest in combination therapy of cisplatin 50mg/m<sup>2</sup> plus vincristine 1mg/m<sup>2</sup> with favorable outcome.<sup>[10]</sup>

The recurrence and mortality rates after NAC on the study by Robova et al. was 20% and 10%, respectively. The mortality rate in the fertility-sparing group of node-negative patients was 10%.<sup>[8]</sup> They predict that in the future, adjuvant chemotherapy after NAC followed by trachelectomy in women with residual disease would reduce the number of recurrences.<sup>[8]</sup>

Ahn et al. concluded that Concurrent Chemo-photodynamic therapy (CCPDT) could be a new treatment option for uterine cervical cancer that can preserve fertility. However further studies and multicenter trials remain to elucidate the safety and therapeutic mechanisms.<sup>[13]</sup>

## Conclusion

Clear cell cervical cancer is rare. The use of chemotherapy is safe during pregnancy. There is no evidence of disease recurrence after 2 (two) years of follow up even though literature reports recurrence rate of 20.8% after VRT and 20% after ART on women with tumor larger than 2 cm.<sup>[8]</sup> It is safe to use neoadjuvant chemotherapy after thorough counselling on women who desire future fertility or to maintain current pregnancy as the response rate to neo-adjuvant platinum based chemotherapy is between 60 and 95% and tumor volume can be decreased before surgery to enable complete removal of the tumor with negative margins.<sup>[8]</sup>

Prolonged period between diagnosis and surgery is likely to results in tumour progression and pregnancy related complications. In our setting, there was prolonged period due to lack of resources. Fortunately, there were no observed tumour related and pregnancy related complications.

#### Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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