Successful cervical cancer treatment during a monochorionic diamniotic twin pregnancy in a patient with history of preterm delivery

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CASE PRESENTATION

This case concerns a woman in her mid-thirties, Gravida 5 Para 2, with two previous pregnancy losses, namely an early miscarriage and a termination of pregnancy. She has three surviving children, and currently has a spontaneous monochorionic diamniotic (MCDA) twin pregnancy. The woman presented at the high-risk obstetrics clinic at 14 weeks of pregnancy for a planned check-up. Our patient had a remarkable obstetric history: her first pregnancy was terminated because of an unknown congenital deformity. Her second pregnancy had been a spontaneous MCDA twin, for which she had undergone fetoscopic laser surgery at 24 weeks of gestation due to twin-to-twin transfusion syndrome (TTTS) stage III. She had given birth at 26 weeks of pregnancy after preterm pre-labor rupture of the membranes (PPROM) at 25 weeks. Her third pregnancy had resulted in a live birth at term. Her general medical history was unremarkable.

At the check-up, she mentioned a 4 month history of postcoital blood loss. At colposcopy, a large ulcerative tumor was visible on the anterior cervical lip. Bimanual vaginal examination revealed a dense tumorous mass measuring 25 mm in diameter with no evidence of parametrial or vaginal involvement. A biopsy was performed and confirmed the presence of an invasive squamous cell carcinoma.

Dr. Mearadji: What would be your proposed imaging plan and interpretation?

As part of the work-up at the hospital before referral, a transvaginal ultrasound was performed, showing a cervical mass of 22×14 mm from the anterior cervical lip to the anterior fornix. Magnetic resonance imaging (MRI) of the pelvis without contrast was performed. This confirmed the presence of a T2 hyperintense mass of 22×9 x 24 mm, with diffusion restriction in the anterior cervical lip, expanding to the anterior fornix (Figure 1). There was no parametrial or pelvic wall invasion, no spread to the adjacent organs and no lymphadenopathy visible on MRI.

Similar to non-pregnant patients, MRI with T2-weighted imaging (T2-WI) and diffusion weighted imaging (DWI) is the preferred imaging technique for staging cervical cancer in pregnant patients due to its reproducibility and excellent soft tissue contrast.[1] The appearance of cervical cancer is usually similar to that in non-pregnant patients and is T2 hyperintense, but could appear isointense to slightly hypointense in some cases due to increased T2 hyperintensity of the cervix in pregnancy.[2] Until now, there is no evidence of possible harmful effects on the fetus due to MRI exposure during pregnancy.[3 4] However, gadolinium based contrast agents can cross the placenta and exposure to these contrast agents in pregnancy is associated with an increased risk of stillbirth, neonatal death and adverse effects in early childhood.[3] Therefore
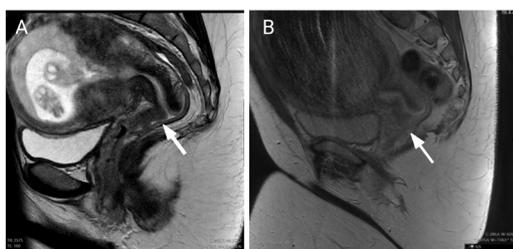
Figure 1 Sagittal T2-weighted image of the pelvis at 14 weeks of gestation at diagnosis (A), at 27 weeks of gestation after three cycles of carboplatin-paclitaxel (B). at 27 weeks of gestation, there was a limited decrease in tumor size, but a clear decrease in diffusion restriction, indicative of a good radiological response. However, at 31 weeks of gestation, we noted a stagnation of the oncological response. Arrow to cervical tumor.

gadolinium-based agents should be avoided during pregnancy. For staging of cervical cancer the use of intravenous gadolinium is not required, even outside of pregnancy, since it has little added value compared with T2/DWI.

Lymph nodes are assessed by looking at their size and appearance on T2WI, with DWI adding accuracy by increasing the detection of pathological nodes. However, While MRI can provide complementary information, surgical staging of lymph node status in pregnant patients with cervical cancer cannot be omitted.[1]

After evaluating radiological findings, at 14 weeks of a MCDA twin pregnancy, the patient was diagnosed with an invasive squamous cell carcinoma of the cervix, radiological stage 1B2 according to the International Federation of Gynecology and Obstetrics (FIGO).

Dr. Amant: What would be your recommendation at this time based on the gestational age of the patient and the stage of the cervical cancer?
Cervical cancer is one of the most challenging cancers during pregnancy, as the pregnant uterus itself is involved. Ideally, oncological treatment during pregnancy should deviate as little as possible from the standard treatment of non-pregnant patients and follow guidelines as closely as possible to preserve maternal prognosis. According to 2018 joint guidelines from the European Society of Gynecological Oncology/the European Society for Radiotherapy and Oncology/and the European Society of Pathology (ESGO/ESTRO/ESP) a radical hysterectomy or chemoradiotherapy should be considered for cervical cancer stage T1B1 or greater.[5] Unfortunately, these treatment options are incompatible with preservation of the pregnancy. At 14 weeks of pregnancy, termination of the pregnancy would allow standard-of-care treatment consisting of Wertheim hysterectomy or radiochemotherapy. Neoadjuvant chemotherapy during pregnancy followed by definitive oncological treatment after delivery has emerged in recent years as an option available to selected pregnant women with cervical cancer, but is still considered to some extent experimental given the lack of prospective studies.

The patient was fully informed about the different treatment options and consequences for the pregnancy. She was highly motivated to preserve the pregnancy, so we recommended to proceed

with a pelvic lymph node dissection during pregnancy. This procedure is crucial because lymph node status and number of lymph nodes involved are among the most important prognostic factors in cervical cancer.[6] Positive lymph nodes, even micro-metastases, found at the time of lymphadenectomy, are indicative of high-risk disease and can be an indication for termination of the pregnancy. In cases where all lymph nodes are negative, it is reasonable to administer neoadjuvant chemotherapy to achieve a tumor stabilization or reduction and delay the delivery until fetal maturity, with final treatment taking place after the delivery.

When chemotherapy is administered after 12 weeks of gestation, the incidence of congenital malformations is comparable between the general population whereas chemotherapy during the first 12 weeks of gestation is associated with an increased risk for congenital malformations.[7] Over the last decades, the trend to use chemotherapy during pregnancy has increased.[8] Long-term follow-up data show that children antenatally exposed to chemotherapy perform like their age- and gender-matched controls.[9] Alternatively, one could opt for neoadjuvant chemotherapy, irrespective of the nodal status, from the start.

Dr. Amant: What should be the considerations when performing surgery, and in particular lymphadenectomy, during pregnancy?
By positioning the patient in left-lateral tilt position from a gestational age of 20 weeks onwards in singletons, we reduce inferior vena cava compression by the gravid uterus and the resulting cardiac preload. Given the twin pregnancy we decided to apply this left lateral tilt position earlier. Adequate monitoring of the maternal condition is mandatory for maternal and fetal well-being. However, monitoring fetal distress by cardiotocography is not feasible during abdominal/pelvic surgery.

Pelvic lymphadenectomy can be performed until 22 weeks of gestation, both by laparoscopy or laparotomy. After 22 weeks of gestation, the size of the uterus precludes complete pelvic lymph node dissection and should be avoided.[6] Lymph node dissection can be performed by transperitoneal or an extraperitoneal approach. The advantages of extraperitoneal lymphadenectomy include shorter operating time and hospital stays compared with the transperitoneal method.[10] Due to easier access to both sides of the pelvis by extraperitoneal approach, perioperative uterine manipulation is reduced. At 16 weeks of gestation, a laparotomic extraperitoneal pelvic lymphadenectomy was performed. The procedure was not associated with excessive blood loss. As illustrated in Figure 2, we obtained an excellent view on the paravesical, pararectal and obturator space on both sides. A total of 32 pelvic lymph nodes were harvested and all were microscopically negative for cancer. At 18 weeks of gestation, the patient received the first cycle of 3-weekly neoadjuvant chemotherapy (NACT) consisting of carboplatin (5xAUC) and paclitaxel (175 mg/m²).

Dr. Amant: What would be your recommended oncologic surveillance during the pregnancy?
Both oncologic and obstetric follow-up during the pregnancy are necessary. However, there are no studies available that investigated the optimal mode and interval of surveillance of cervical cancer during pregnancy. Follow-up of tumor growth is important since disease response to chemotherapy is not guaranteed and
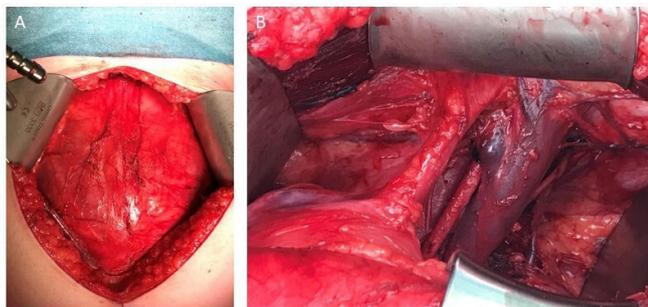
Figure 2 (A) Extraperitoneal approach during pregnancy after midline incision and separation of the mm. recti. (B) Proper exposure to the left pelvic sidewall, after removal of the regional lymph nodes.

stagnation or progression can occur after an initial response. After initiation of neoadjuvant chemotherapy, we recommend 3-weekly clinical follow-up of the tumor by speculum examination and 6-weekly MRI pelvis to assess radiological response.

Dr. Mearadji: What is the most accurate radiological examination to evaluate response to treatment?

MRI has shown a similar accuracy but higher sensitivity compared with ultrasound for response evaluation of stage IB1 to IIB cervical cancer; however, ultrasound may be subject to inter-observer variability. Transrectal ultrasound is preferred over transvaginal ultrasound in case of bulky tumor in order to reduce the risk of bleeding and to enable a better analysis of the distal cervix.[11] MRI is a reproducible imaging technique, which can be used to assess response to NACT during pregnancy. The MRI protocol for locoregional staging of cervical cancer during pregnancy and response evaluation should combine T2/DWI MRI and cover the entire abdomen.[1]

Initially, the patient did not have any more postcoital bleeding and speculum examination showed a good clinical response. MRI at 27 weeks of gestation, after three cycles of NACT, showed a limited decrease in tumor size and a clear decrease in diffusion restriction (Figure 1). A good clinical and radiological response to NACT was concluded. However, at 31 weeks of gestation, after four cycles of NACT, clinical examination showed a stagnation of the oncological response.

Dr. Painter: What should be the obstetric management in this complex case?

Twin pregnancies are associated with a higher risk of perinatal and maternal mortality and morbidity compared with singletons, especially MCDA pregnancies. Moreover, there is a sevenfold increased risk of neonatal death or neonatal and infant morbidity, primarily due to complications of preterm birth – a major risk factor in this case was the history of early preterm birth. In fact, the risk of preterm birth in multifetal gestations is six times higher than in singletons.[12] Not only are multifetal pregnancies more likely to be born preterm, they are at higher risk of sequelae of preterm birth in comparison to singletons. Twins have a two-fold increased risk of a high-grade intraventricular hemorrhage and periventricular leukomalacia when compared with singletons of the same gestational age.[13]

A history of preterm birth, as was the case for our patient, is a strong predictor of preterm birth in subsequent pregnancies. The recurrence risk ranges from 15% to more than 50% and it

is inversely related to the gestational age of the previous preterm birth.[14] In unselected twin pregnancies, the common strategies to prevent preterm delivery (ie, vaginal progesterone, intramuscular 17α-hydroxyprogesterone caproate, cerclage, or cervical pessary) failed to show an advantage in preventing preterm birth.[12]

Besides the increased risk of fetal growth restriction in all twin pregnancies, a monochorionic pregnancy has specific additional risks since the fetuses are dependent on a single, shared placenta. The vascular placental anastomoses that connect the fetal circulations of both members could lead to complications including TTTS, selective growth restriction (sGR), twin anaemia-polycythaemia sequence (TAPS), or twin reversed arterial perfusion (TRAP) sequence.[15] Each of these forms of placental pathology unique to MCDA twins can add to a further increase in spontaneous, but primarily medically indicated preterm birth.

In this patient, chemotherapy administration during pregnancy may have added additional risk of fetal growth restriction. A large cohort study showed that platinum-based chemotherapy is associated with increased incidence of small-for-gestational age neonates, whereas taxanes are associated with neonatal intensive care (NICU) admission. On the other hand, chemotherapy administration after 14 weeks of pregnancy is relatively safe in terms of fetal congenital anomalies.[8] Furthermore, the fact that chemotherapy during pregnancy allows delivery to be postponed in order to reduce preterm birth, which was historically the method available to garanteee oncological safety, could be viewed as a unique way of mitigating the lifelong sequelae of prematurity.

To minimize these obstetrical risks, the pregnancy was monitored regularly with 2-weekly serial growth assessments and weekly Doppler measurement. The fourth, and last NACT cycle was administered at 30 weeks and 2 days of pregnancy to allow recovery of both maternal and fetal bone marrow before the delivery. The fact that there was a markedly increased risk of preterm birth, that this multiparous patient was likely to deliver rapidly after the onset of spontaneous labor, and that her cervical cancer was a strong contraindication for vaginal delivery, meant her obstetric team had to be vigilant for signs and symptoms of preterm birth.

At 34 weeks and 6 days of gestation, a cesarean section was performed with corporeal incision of the uterus, 15 cm above the cervix to avoid any manipulation or disruption of the tumor during the cesarian section. Our patient gave birth to two healthy girls, weighing 2070 grams and 2535 grams respectively. Both neonates were admitted to the Newborn Intensive Care Unit (NICU) due to preterm birth.

After delivery, a Wertheim-Okabayashi procedure was planned, but proved technically unfeasible due to intra-abdominal adhesions secondary to the extraperitoneal lymphadenectomy. Transposition of the right adnexa was performed to prevent damage to the ovary during subsequent radiotherapy. The left adnexa remained in situ. Six weeks postpartum, the patient underwent curative pelvic radiotherapy with a total dose of 45 Gray (Gy) divided in 25 fractions of 1.8 Gy, followed by intracavitary brachytherapy. The patient remains in regular oncological follow-up at the time of writing with the last follow-up at 2 years and 8 months after diagnosis, showing no signs of disease recurrence.

CONCLUSION

Cervical cancer is the most frequent gynecological malignancy diagnosed during pregnancy. Similar to non-pregnant patients, MRI with T2WI and diffusion weighted imaging (DWI) is the preferred imaging technique for evaluation of local tumorous extent. In any case, surgical staging of lymph node status in pregnant patients with cervical cancer cannot be omitted with current image modalities. Treatment can be particularly challenging, especially when the patient wishes to preserve her pregnancy, as standard treatment for patients with cervical cancer consists of radical hysterectomy in early-stage disease or concurrent chemoradiotherapy in locally advanced cervical cancer. Fortunately, in recent years, the boundaries of oncological treatment during pregnancy have been expanded. Neoadjuvant chemotherapy has emerged as an alternative to concurrent chemotherapy and radiation, and it may offer patients the option to delay definitive treatment until fetal viability. A difficult obstetric history can make oncological treatment even more arduous. Indeed, chemotherapy administration during pregnancy has been associated with low birth weight and NICU admission. On the other hand, it should be considered that treatment during pregnancy allow clinicians to postpone the date of the delivery, avoiding the consequences of prematurity. To balance these risks and the benefits, a close monitoring of the pregnancy is recommended. To ensure a favorable outcome for both mother and baby, it is mandatory that such challenging cases are managed in tertiary referral centers, involving a multidisciplinary team of gynecological oncologists, obstetricians, radiologists, and pediatricians.

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