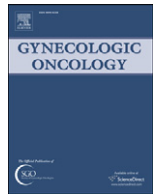




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## Case Report

## The case of a viable pregnancy post vaginal radical trachelectomy followed by combined chemo-radiation therapy

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## Case description

This is a 25 year-old G1P0A1 recently married woman who was referred from Texas to L'Hôtel-Dieu de Québec in 2004 for consideration of a radical trachelectomy following the diagnosis of cervical cancer. Clinical evaluation revealed the presence of a visible suspicious lesion measuring <2 cm. Cervical biopsies confirmed the diagnosis of a stage IB1 adenosquamous grade 2 cancer of the cervix. There was a single focus of lymphovascular invasion. She underwent a CT of chest, abdomen and pelvis and a pelvic MRI which were both unremarkable.

The patient underwent laparoscopic sentinel lymph node mapping followed by a bilateral pelvic node dissection and a radical vaginal trachelectomy on August 17th 2004. At the time of surgery, one sentinel node was identified bilaterally and the frozen section of both sentinel nodes was negative. However on final pathology, one micrometastasis was identified in the right obturator sentinel node. All the other 29 lymph nodes were negative. The trachelectomy specimen confirmed an adenosquamous carcinoma. The depth of invasion was 6 mm and lateral extension was 16 mm. Foci of

lymphovascular space invasions (LVSI) were present. Surgical margins were negative and the endocervical curettage was negative.

In view of the presence of lymph node micrometastasis, the patient was recommended to have adjuvant chemo-radiation. Before the start of treatment, she underwent ovulation induction and 11 embryos were frozen. She received a total of 4500 cGy in 25 fractions to the bilateral parametrial and lateral sidewalls as well as 540 cGy boost in 3 fractions to the right parametrial and right sidewall area with concomitant weekly cisplatin (40 mg/m<sup>2</sup>). A central block was used. She has remained free of disease since.

Following the radiation therapy, the patient has been completely amenorrheic. In 2007, she consulted a reproductive endocrinologist, and she was placed on high-dose estrogen (Estrace, 2 mg, 3 times per day) for 13 days. Follow-up transvaginal ultrasound scans confirmed that the endometrial lining was thickening, and it reached a maximal diameter of 10.4 mm with a trilaminar pattern. She underwent controlled ovarian stimulation which took 10 days to complete followed by oocyte retrieval 36 h later. A single 6-cell embryo was then transferred using a Wallace catheter under sonographic guidance, and implantation was successful. The patient was maintained on hormonal supplementation with a combination of oral estradiol and injectable progesterone in oil, and both were respectively weaned at 9 and 13 weeks of gestation.

The pregnancy evolved uneventfully until 23 4/7 weeks of gestation. The patient suddenly developed preterm premature rupture of the membranes (PPROM). Upon admission, her cervix was closed and she had no signs of infection. She was carefully observed and placed on prophylactic antibiotics and antenatal steroids. Three days later, she developed signs of chorioamnionitis and a classical cesarean section was performed at 24 weeks. She had a 454 g male infant with Apgar scores of 1 and 6. Unfortunately, the infant rapidly died from complications of septic shock, metabolic acidosis and prematurity 13 h later. Placental pathology showed signs of acute funisitis and cultures confirmed the presence of *Pseudomonas Aeruginosa*, *Klebsiella Pneumoniae* and *Bacteroides* species. The patient subsequently developed septicemia and a wound abscess which required prolonged antibiotic therapy and a home wound care.

Emotionally, this was a devastating experience for the patient and husband. After careful thinking, the patient elected not to try to get pregnant again. Instead, since she had other frozen embryos, a friend

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offered to be a surrogate mother. That pregnancy evolved uneventfully with the birth of a healthy boy at term. The patient is planning a second child with a gestational surrogate mother again.

## Discussion

Approximately 10% of patients undergoing radical trachelectomy for fertility preservation end up receiving adjuvant radiation therapy to the pelvis usually because of the inadvertent finding of positive nodes on final pathology [1]. Unfortunately, this form of adjuvant treatment causes permanent infertility in most patients either secondary to the radiation-induced menopause or because of damage to the uterine lining. We present the case of a young woman who got pregnant following a radical trachelectomy and node dissection plus adjuvant chemo-radiation. This case raises several oncological, obstetrical, reproductive and ethical issues.

## Literature review

A search of the literature identified only one other case of a pregnancy following radical trachelectomy and adjuvant radiation therapy [2]. It was a 33 year-old woman G2P2 with a stage IB1 cervical cancer treated by trachelectomy followed by radiation therapy for a suboptimal margin on the trachelectomy specimen (2 mm). The radiation therapy led to a clinical menopause with confirmed elevated FSH levels. She received a relatively low-dose radiation therapy with 32 Gy using centropelvic anteroposterior fields and 12 Gy using narrow lateral fields followed by a course of brachytherapy which delivered 20 Gy. She was placed on sequential hormone replacement therapy with reappearance of menstruation. The patient was found to be pregnant a year later, presumably spontaneously. At 26 weeks of gestation, oligohydramnios and onset of growth retardation were identified. Weakening of the vagoisthmic anastomosis and onset of preterm labor without cervical dilatation were initially treated with bed rest and ritodrine. At 27 weeks of gestation a “prophylactic” cesarean section was performed and a healthy baby was born. The mother resumed normal ovulatory function thereafter.

There are otherwise very few reported cases of pregnancy post pelvic radiation therapy in the literature. In 1986, Browde et al. reported a case of a pregnancy post pelvic radiation therapy and reviewed 13 other cases. Radiation doses varied significantly between cases and external radiation was usually not given. They observed severe fibrotic changes of the lower uterine segment and cervical canal suggesting that cesarean section is the delivery modality of choice post radiation therapy. However, no genetic damage to the offsprings were reported [3].

## Obstetrical issues

Preterm labor and delivery in patients post trachelectomy is felt to be primarily due to subchronic chorioamnionitis leading to activation of cytokine cascades and premature rupture of membranes (as was probably the case in our patient), and less likely due to true cervical incompetence (painless dilatation of the cervix). In most series, pregnancies post trachelectomy are associated with a higher risk of premature rupture of membranes and delivery. Despite careful monitoring, there is no good way to predict the onset of chorioamnionitis, no effective prophylactic measures to prevent it and no standardized protocol to manage those patients during pregnancy. A variety of regimens extrapolated from the literature on the management of premature labor have been proposed with uncertain benefits. Careful monitoring of cervical length and fetal growth by serial ultrasound is probably the best tool to monitor the pregnancy.

## Radiation therapy and effects on pregnancies

Pregnancies post VRT and radiation therapy pose additional challenges. Indeed, as was summarized recently by Noyes et al, the effects of radiation on the uterus are not insignificant in the event of a pregnancy [4]. First, the uterine vasculature can be damaged which can lead to intrauterine growth retardation (as was noted in the other case report). Second, radiation can cause myometrial fibrosis which can contribute to preterm labor in view of the reduced elasticity and distention of the uterine muscle. Third, radiation can damage the endometrium and interfere with optimal placental implantation which can predispose to placenta accreta and percreta which in turn can lead to preterm delivery and postpartum haemorrhage [4]. Clearly, those pregnancies are at very high risk of complications and should be managed by a multidisciplinary team.

## Oncologic issues

From an oncological point of view, it remains unknown if the presence of one isolated micrometastasis warrants adjuvant treatment, and if so, what is the most appropriate therapy. In our recent series of 125 completed vaginal radical trachelectomy, 5 patients were found to have positive nodes on final pathology despite negative frozen section [1]. Of those 5 cases, 2 received adjuvant chemo-radiation but 3 elected to be followed conservatively. Of note, all 3 had only one isolated micrometastasis in only one node (the sentinel node). So far, no recurrences have occurred. The indication for adjuvant therapy needs to be further studied in this group of patients. The option of systemic chemotherapy would seem appealing in those cases, as it could potentially reduce the risk of distant metastasis while preserving ovarian and uterine function.

This case also highlights the limitation of the frozen section analysis to detect nodal micrometastasis. In our series of trachelectomy, 36% of micrometastasis was missed on frozen section [1], thus confronting patients and physicians with the knowledge of metastatic disease and the need for adjuvant treatment “after the fact”. It is hoped that in the future, new technologies will improve the sensitivity of the frozen section analysis.

In the future, the increasing use of more sophisticated radiation therapy techniques such as 3D-CRT (Conformal Radiation Therapy) and IMRT (Intensity Modulated Radiation Therapy) may allow for a better preservation of uterine function while ensuring adequate coverage of the at-risk parametrial and sidewall areas in patients with positive nodes and negative endocervical margins.

Lastly, our patient could have undergone laparoscopic ovarian transposition to preserve ovarian function and allow for oocyte harvesting at a later time. When successful, this procedure is certainly valuable, however results in the literature have been controversial. Being married, our patient chose to immediately undergo ovarian induction and embryo cryopreservation and declined ovarian transposition.

## Summary

In summary, pregnancies following fertility-preserving surgery followed by adjuvant radiation therapy is a very rare event. However, with the growing ability of reproductive technologies to overcome reproductive barriers, these situations may occur more frequently in the future. The care of such challenging cases requires a multidisciplinary team and involves all aspects of our specialty including a gynecologic oncologist, reproductive endocrinologist, perinatal specialist and an obstetrician. This case also raises ethical issues considering the very small chances of carrying a viable child after pelvic radiation therapy and the high likelihood of prematurity and maternal/neonatal complications. We hope this case report will provide valuable information to help offer thorough counseling to patients confronted with such decisions.

**Conflict of interest**

Authors have no conflict of interest to declare.

**Acknowledgement**

We wish to acknowledge the exceptional courage of Mrs A.E. in her incredible journey to carry a child. She has forced us, as physicians, to go beyond the established limits of our comfort zone, and to go beyond «standard» treatment approaches. She was nearly successful.

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