Live birth from ovarian grafted tissue after pelvic radiation for rectal cancer

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Objective: To study the management of a woman who returned to conceive after high-dose radiation treatment, with documentation of uterine dosimetry, and the efficacy of ovarian tissue grafted into an irradiated pelvis.
Design: Case report.
Setting: Private and public In Vitro Fertilization units.
Patient: A 26-year-old woman underwent radiation treatment for rectal cancer, with half of the uterus and the fundus being exposed to radiation doses of 50 and 25 Gy, respectively. We report the details of the uterine assessment, determining suitability of conception with her own uterus, pregnancy surveillance, and reproductive outcome.
Intervention(s): In Vitro Fertilization stimulation grafted ovarian tissue to assist with pregnancy.
Main Outcome Measure(s): Successful conception and live birth, pregnancy complications and management of high risk pregnancy.
Result(s): The results of magnetic resonance imaging and pelvic ultrasound showed a small uterus with preserved junctional zone anatomy, and although the endometrium was initially thin after high-dose estrogen administration, endometrial thickness increased with time. Twelve grafted ovarian tissue stimulation cycles led to 4 embryo transfers, the last of which resulted in a live birth. She had 2 cervical cerclage procedures because of cervical shortening and delivered a 3.3-kg healthy female neonate at 38 weeks of gestation via lower-segment cesarean section.
Conclusion(s): Successful pregnancy is possible from ovarian tissue grafted into an irradiated pelvis, with high-dose uterine exposure. Careful uterine assessment needs to be undertaken to determine suitability of conception attempt with a patient's own uterus, in consultation with the medical team. Further studies are needed to correlate imaging and biopsy findings with reproductive outcomes. (F S Rep® 2024;5:214–8. ©2024 by American Society for Reproductive Medicine.)
Key Words: Infertility, pregnancy, fertility preservation, radiotherapy, uterus

INTRODUCTION

Radiotherapy is known to cause significant ovarian damage leading to infertility and premature ovarian insufficiency (1). Additionally, clinical data suggest that the uterus sustains persistent damage after abdominopelvic and total body irradiation, particularly in young, prepubertal girls (2–4). The biologic changes, such as loss of elasticity and fibrosis and impairment of vascularization, can manifest in infertility, miscarriage, and increased rates of pregnancy complications such as preterm birth, low birth weight, uterine rupture, and stillbirth (5). The clinical questions regarding whether the uterus can establish and safely maintain a healthy pregnancy after radiation treatment (RT) are becoming more important because of factors such as increased uptake of fertility-preserving strategies including egg, embryo, and ovarian tissue cryopreservation, improved survival rates for patients with cancer, as well as more targeted RT with lower doses delivered or partial uterine exposure.

There are isolated case reports of healthy pregnancies after pelvic radiation doses traditionally considered to be sterilizing (>30–40 Gy), demonstrating that the uterus, especially when treatment occurs in adulthood, may be more resistant to RT damage than previously understood and there is a significant interindividual variation in radiosensitivity (4). Ultrasound (u/s) visualization and histology of the

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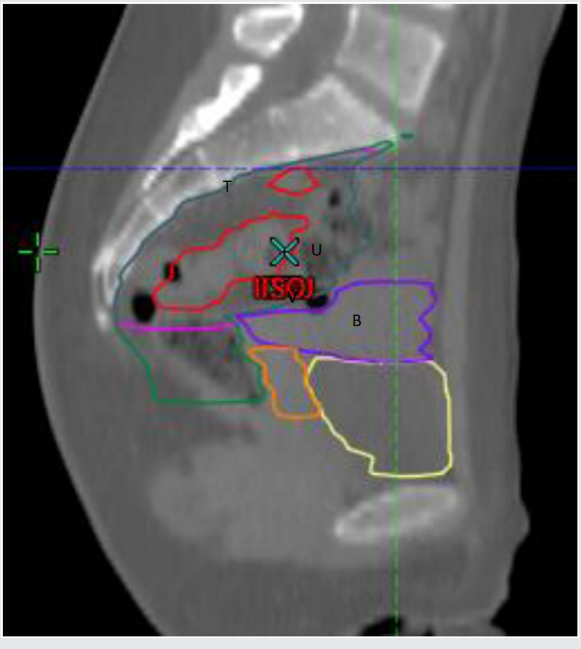
endometrium in response to estrogen and progesterone and u/s, Doppler, and magnetic resonance imaging (MRI) evaluation of the myometrium form the basis of assessment for feasibility of pregnancy (6). There is an additional concern regarding whether ovarian tissue grafting into an irradiated pelvis may be less likely to produce functional oocytes (7).

Most publications regarding fertility and pregnancy outcomes for RT-treated cancer survivors report cohort studies, lacking the granularity needed to manage individual patients, and include children/prepubertal girls with greater uterine radiosensitivity (8). Detailed, international case reporting of pregnancy outcomes in adult women treated with RT, incorporating details of dose distribution and volume of the uterus treated, can help inform regarding risks to fertility from RT and, most importantly, advise regarding feasibility of pregnancy for this complex but small group of patients. It can also help drive future interest in developing multinational registries and evidence-based function uterine assessments.

We report a successful term live birth with ovarian tissue grafted to the lateral pelvic side wall in a patient who received high-dose pelvic RT for rectal cancer. The doses delivered to half of the uterus and to the cervix were >40 (2 Gy per fraction) and up to 47.5 Gy, respectively (Figs. 1 and 2). To our knowledge, this is the first case reporting this information. Cervical surveillance diagnosed cervical insufficiency, and the patient underwent 2 cerclage procedures in the early second trimester.

FIGURE 1



Depiction of contours used for planning. The color green indicates the area planned for 45 Gy. The color dark green/pink indicates the area planned for 50 Gy (gross tumor and margins). B = bladder; T = gross tumor volume (red); U = uterus; V = vagina.

Rozen. Birth following rectal cancer. F S Rep 2024.

CASE REPORT

Patient

In January 2016, a 26-year-old woman (G0P0) was diagnosed with locally advanced, T3N1M0 rectal cancer, treated with neoadjuvant radiotherapy, delivering 50 Gy in 25 fractions to the tumor bed and completed in February 2016. Subsequently, the patient underwent surgery (laparoscopic ultralow anterior resection and loop ileostomy) in April 2016 and adjuvant chemotherapy with 5 cycles of capecitabine and oxaliplatin (CAPOX). She underwent loop ileostomy reversal in October 2016, 10 months after diagnosis.

The patient was referred for fertility preservation consultation, within a few weeks of diagnosis, and consideration of options, with a detailed discussion regarding the likely impact of RT on the uterus as well as the risk of ovarian insufficiency. She elected to undergo laparoscopic left salpingo-oophorectomy, with 221 ovarian tissue slices processed and slow frozen. After this, she underwent a random-start ovarian stimulation cycle with cryopreservation of 5 oocytes and 3 cleavage-stage embryos (to avoid any potential embryo wastage given low oocyte numbers). Radiotherapy was started 1 week after egg collection.

Procedures

Radiation therapy was delivered with a 5-field intensity-modulated radiotherapy technique using 6-MV photon beams. A dose of 50 Gy was delivered to the gross tumor volume with margin, and a prophylactic dose of 45 Gy was delivered to uninvolved pelvic lymph nodes. The dose distribution and dose volume histogram characteristics showed that the doses to the uterine fundus, half of the uterus, and cervix were 20–25, approximately 40–50, and 45–47.5 Gy, respectively (Fig. 2A).

Ethical approval

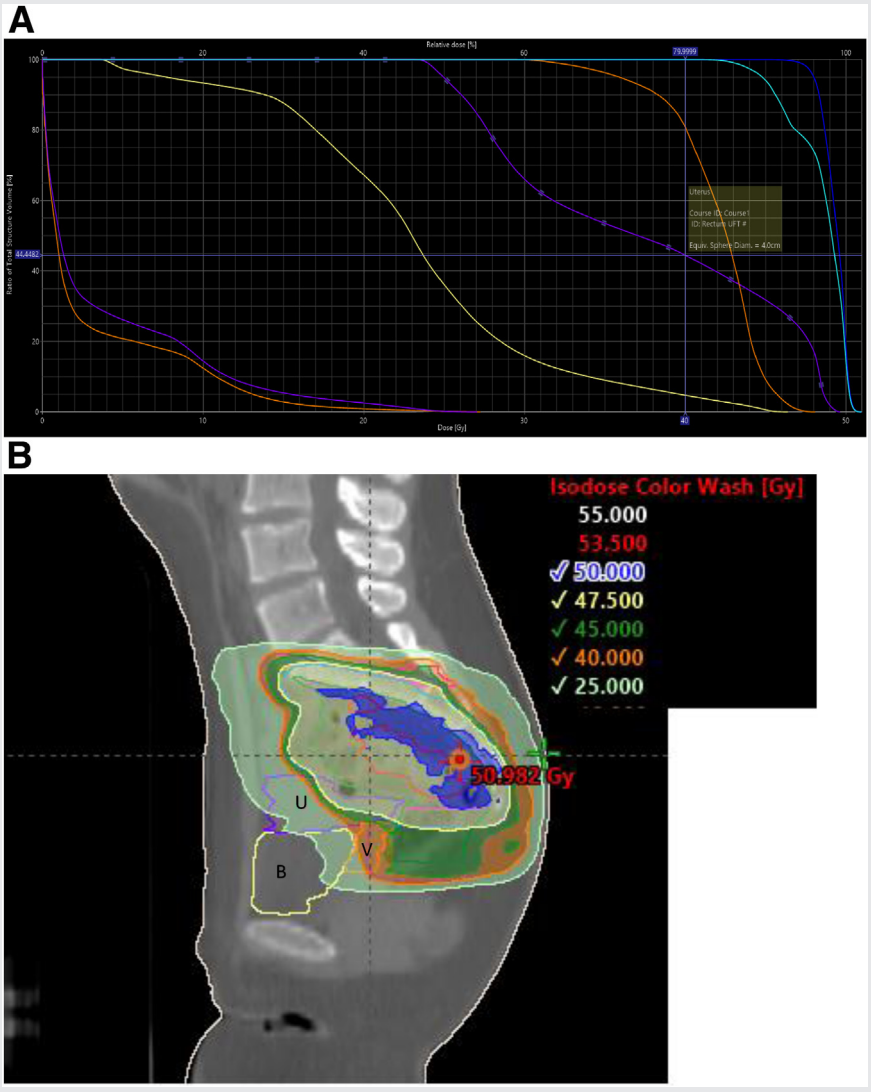
Informed consent was obtained from our patient to share de-identified information regarding her case. This study was approved by the Melbourne IVF Human Research Ethics Committee (HREC 103-23).

Results

Three and a half years after completion of her cancer treatment, the patient returned for consideration of pregnancy with her frozen gametes. She was using the oral contraceptive pill for hormone replacement due to iatrogenic ovarian insufficiency. The patient underwent an assessment of uterine functionality as per previously published guidelines for uterine RT (6), including pelvic MRI, u/s, and mock cycle endometrial histopathology.

Magnetic resonance imaging showed a normal-sized uterus, preserved endometrial-myometrial junction, 2-mm–thick endometrium, and atrophic right ovary. Similarly, the findings of pelvic u/s were consistent with those of MRI: uterine size of 7.4 × 5.8 × 3.6 cm (uterine volume, 82 mL); endometrial thickness of 4 mm; and normal blood flow. Her first medicated mock cycle using estradiol (E2) valerate 4 mg twice daily followed by the addition of 100-μg E2 patch twice weekly resulted in a maximum endometrial thickness of 3.7

FIGURE 2



(**A**) Dose volume histogram of the plan. Crosshair placed on V40Gy—traditionally thought to be regarded as the sterilizing dose to the uterus (U). (**B**) Sagittal view of the radiotherapy plan showing the various dose levels. The uterine fundus, vagina (V), and cervix received the doses of <40 (25–40), 40–45, and 45–47.5 Gy, respectively. MRI fusion was used to contour structures. B= bladder; MRI = magnetic resonance imaging.

Rozen. Birth following rectal cancer. F S Rep 2024.

mm on u/s after 35 days. Endometrial biopsy, collected via the Pipelle, was performed after the addition of progesterone vaginal pessaries 3 times per day, for 5 full days (with biopsy on the sixth day of progesterone administration). Histology was reported as low-volume inactive endometrium.

The couple was extensively counseled regarding risks related to failure of implantation, miscarriage, and adverse pregnancy outcomes, including stillbirth and uterine rupture. They decided to proceed with treatment. Three cleavage-stage embryos were transferred in 3 medicated thaw cycles, without success, and unexpectedly, the 5 frozen eggs did not survive warming and were noted to have cracked zonas, which are an unusual observation.

A second evaluation with MRI and mock cycle endometrial biopsy was undertaken 4.5 years after treatment completion. Again, MRI did not demonstrate any features to support myometrial fibrosis. The mock cycle using E2 valerate 4 mg 3 times a day, as well as 100-μg intramuscular E2 administered twice weekly, showed a thicker lining of 7.4 mm after 14 days, which further increased to 8.1 mm when progesterone was started a week later. The Pipelle biopsy histology at clinical postovulatory day (POD)+5 was reported as early- to mid-secretory endometrium, POD+4.

Because of these generally favorable findings and after careful consultation regarding the possibility of suboptimal graft take in an irradiated pelvic and poor folliculogenesis, as well as multidisciplinary support from her medical team, ovarian tissue transplantation was performed. This was almost 5 years after the completion of cancer treatment.

Four-port laparoscopy, using the Palmer point visual entry, with colorectal surgical assistance, was used for entry. Approximately 50% of the tissue was grafted to 4 locations: the left and right pelvic side walls and left and right anterior abdominal wall laparoscopic port sites. Hormonal activity, as evidenced by a decrease follicle-stimulating hormone level and increased E2 level, was detected after 3 months. A modified low-dose stimulation regimen was commenced, with a follitropin alpha level of 137.5 IU (9). As previously described, follicular growth was monitored with transvaginal (TV) and transabdominal u/s, with trigger administered at follicle sizes of $\geq$14 mm, and the ovum pick-up approach (TV or transabdominal) determined by graft location (9).

Nine stimulation cycles resulted in 2 embryo transfer procedures, with a total of 3 embryos transferred (2 cleavage-stage and 1 blastocyst-stage embryos). Three egg collections resulted in 0 egg pick-up. whereas 1–3 eggs were aspirated in the other 9 egg collection procedures. A further 2 medicated mock cycles were undertaken to assess endometrial progesterone responsiveness. The third and fourth biopsy histology reported poorly developed secretory endometrium and early secretory POD+3–POD+4 endometrium, respectively.

The patient did not conceive despite the transfer of 3 embryos into reasonably primed endometrium (thickness, 6–8 mm), with diminishing results from stimulation. Hence, a decision was made to perform a second graft with the remaining tissue. At this point, the option of surrogacy was raised again with the patient, who was adamant that she wished to continue with her own uterus. Laparoscopy was undertaken in November 2021, almost 1 year after the first transplant surgery. During this time, the remaining tissue was grafted to the left pelvic side wall and bilateral anterior abdominal wall sites. Three further stimulation cycles were undertaken, with 2 of these resulting in cleavage-stage embryo transfers. The last transfer of a day 3 embryo resulted in an ongoing pregnancy.

Pregnancy

The patient started low-dose aspirin and high-dose calcium for placenta-mediated complication prevention (e.g., preeclampsia and intrauterine growth restriction). Cardiac echocardiography, performed as part of prepregnancy workup, was repeated in the first trimester, and the results were within the normal limits. Cervical shortening to 13 mm and funneling were detected at 18 weeks of gestation and managed with the insertion of a McDonald cerclage with 1 nylon monofilament suture, which was a difficult procedure because the cervix was flushed with the vaginal walls. A second cerclage (McDonald with 1 nylon suture) was inserted at 22 weeks after funneling to 9 mm was observed on u/s at 21 $\pm$ 6 weeks. Fetal growth and TV cervical length were monitored weekly. The cervix remained stable at 10 mm, and the fetal growth remained at around the 50th percentile. A planned lower-segment cesarean section because of maternal request was performed as an emergency lower-segment cesarean section at 38 weeks of gestation after premature rupture of membranes, and the patient delivered a 3.3-kg healthy female neonate. They were discharged without complications, and normal development was noted at routine pediatrician follow-up.

DISCUSSION

This case report demonstrates both the possibility of successful pregnancy from ovarian tissue grafting into an irradiated pelvis and uterine functionality and term live birth after high-dose targeted pelvic irradiation. Aside from the possibility of uterine damage after high-dose RT, which is traditionally considered to be sterilizing, there is additional concern around ovarian tissue grafting into an irradiated pelvis, which may hinder graft take or folliculogenesis or result in oocyte impairment. In fact, no pregnancies were documented in 5 women after tissue transplantation who had previously received radiotherapy to the pelvis, despite the resumption of regular menstrual cycles, whereas there were 16 cases of successful pregnancies after the transplantation of ovarian tissue in women who have received chemotherapy (7).

The first case of successful pregnancy from ovarian tissue grafted to the irradiated pelvis in 2015 reported a dose of 54 Gy administered to the pelvis to treat sacral Ewing sarcoma (10). This is higher than our maximum uterine dose of 45 Gy; however, the radiation dose delivered to the uterus itself was not reported and likely lower than the maximum tumor dose. This highlights the importance of careful delineation of these structures during the time of radiation planning using image fusions with MRI, detailed reporting of dose distribution within the uterus, and use of dose volume histograms to compare data. Other parameters important for comparison include the total and per-fraction doses, biologically equivalent dose, and equivalent dose in 2-Gy fractions.

Although a maximum dose of 45 Gy was administered to half of the uterus, the fundus received a lower dose of 20–25 Gy. We propose a biologic hypothesis that the lower dose delivered to the potential embryo implantation site, than that to other parts of the uterus, may have been advantageous for pregnancy initiation. Endometrial responsiveness to oral and topical estrogen increased with time and was particularly noticeable between the first and second mock cycles, as demonstrated by improved endometrial thickness.

Moreover, this underscores the importance of obtaining more information about dose distribution within specific parts of the uterus and the value of advanced radiotherapy techniques. Modern radiation planning and delivery systems, such as volumetric modulated arc therapy and intensity-modulated radiotherapy, allow selective sparing of some areas of critical organs, if they are identified, assigning definite dose constraints during the planning phase.

Eleven previous case reports have described pregnancies after high-dose pelvic RT in adulthood, summarized by Lu et al. (11); however, these inconsistently report the uterine dose and site of exposure (only 6 report these parameters), which limits applicability of the findings. Eight of these pregnancies delivered at term, after 37 weeks, and 5 had no identifiable complications such as low birth weight (as shown in Table 1 in the study by Lu et al. (11)). These cases also highlight the importance of careful monitoring with regular u/s, Doppler, and cervical surveillance.

For our patient, and in agreement with Rodriguez-Wallberg et al. (10), repeated transplantation procedures were required to obtain what seemed to be improved follicular

development. Rodriguez-Wallberg et al. (10) noted that sequential ultrasonographic examinations demonstrated enlargement of the transplants over time and an increase in the size of the uterus. It is biologically plausible that repeated transplantations may be required in patients who have been exposed to high-dose pelvic RT.

CONCLUSION

This adds to the body of literature that suggests that successful pregnancy is possible after pelvic RT, even in cases where ovarian tissue was grafted to the RT-affected pelvis. We recommend comprehensive evaluation of the uterine condition as a prerequisite for commencing fertility treatment, as well as a team approach, with input from radiation oncologists and obstetricians, in managing these complex patients. Further studies are needed to correlate the imaging and biopsy findings with subsequent fertility and pregnancy outcomes.

CRediT Authorship Contribution Statement

Genia Rozen: conceptualization, methodology, investigation, data curation, writing original draft, editing, funding acquisition. **Sarat Chander:** methodology, validation, formal analysis, investigation, review and editing. **Alex Polyakov:** methodology, validation, formal analysis, investigation, review and editing. **Iniyaval Thevathasan:** validation, formal analysis, review and editing. **Catharyn J. Stern:** conceptualization, methodology, validation, investigation, resources, data curation, review, editing, supervision.

Declaration of Interests

G.R. has nothing to disclose. S.C. has nothing to disclose. A.P. has nothing to disclose. I.T. has nothing to disclose. C.J.S. has nothing to disclose.

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