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ORIGINAL ARTICLE

Clinical summary guide: reproduction in women with previous abdominopelvic radiotherapy or total body irradiation

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STUDY QUESTION: What is the evidence to guide the management of women who wish to conceive following abdominopelvic radiotherapy (AP RT) or total body irradiation (TBI)?

SUMMARY ANSWER: Pregnancy is possible, even following higher doses of post-pubertal uterine radiation exposure; however, it is associated with adverse reproductive sequelae and pregnancies must be managed in a high-risk obstetric unit.

WHAT IS KNOWN ALREADY: In addition to primary ovarian insufficiency, female survivors who are treated with AP RT and TBI are at risk of damage to the uterus. This may impact on its function and manifest as adverse reproductive sequelae.

STUDY DESIGN, SIZE, DURATION: A review of the literature was carried out and a multidisciplinary working group provided expert opinion regarding assessment of the uterus and obstetric management.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Reproductive outcomes for postpubertal women with uterine radiation exposure in the form of AP RT or TBI were reviewed. This included Pubmed listed peer-reviewed publications from 1990 to 2019, and limited to English language..

MAIN RESULTS AND THE ROLE OF CHANCE: The prepubertal uterus is much more vulnerable to the effects of radiation than after puberty. Almost all available information about the impact of radiation on the uterus comes from studies of radiation exposure during childhood or adolescence.

An uncomplicated pregnancy is possible, even with doses as high as 54 Gy. Therefore, tumour treatment doses alone cannot at present be used to accurately predict uterine damage.

LIMITATIONS, REASONS FOR CAUTION: Much of the data cannot be readily extrapolated to adult women who have had uterine radiation and the publications concerning adult women treated with AP RT are largely limited to case reports.

WIDER IMPLICATIONS OF THE FINDINGS: This analysis offers clinical guidance and assists with patient counselling. It is important to include patients who have undergone AP RT or TBI in prospective studies to provide further evidence regarding uterine function, pregnancy outcomes and correlation of imaging with clinical outcomes.

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WHAT DOES THIS MEAN FOR PATIENTS?

Cancer treatment can affect fertility and when radiotherapy is directed to the whole body or pelvis it may damage the ovaries and the uterus, making pregnancy unlikely and increasing the risk of complications. The uterus is more vulnerable prior to puberty, so the younger the age at which radiation treatment occurs, the more likely the uterus is to sustain damage. Each woman's individual situation needs to be discussed with the treating radiation oncology team to obtain information regarding techniques and doses used in the cancer treatment and to help quantify the damage to the uterus. We propose a number of tests which can help with understanding more about the function of the uterus after radiation treatment. These include an ultrasound, MRI and testing of a uterine lining sample. It is important to note, however, that there is no evidence demonstrating that the results of these tests will accurately predict the chance of fertility and safe pregnancy in a particular patient.

Introduction

In addition to primary ovarian insufficiency (POI), female survivors of cancer who are treated with abdominopelvic radiotherapy (AP RT) or total body irradiation (TBI) are at risk of damage to the uterus. This may impact on its function and manifest as infertility or adverse obstetric outcomes including preterm birth (PTB) and low birthweight (LBW), foetal growth restriction (FGR), uterine rupture, stillbirth and pre-eclampsia (Larsen *et al.*, 2004; Signorello *et al.*, 2006; Ataman *et al.*, 2016; Marklund *et al.*, 2018; van de Loo *et al.*, 2019; van der Kooi *et al.*, 2019). Tumours requiring AP RT include tumours of the rectum, anus, cervix and bladder, desmoid tumours and sarcomas.

The effects of radiation therapy on the uterus are 2-fold: direct radiation-induced changes, and those that are secondary to the hypo-oestrogenism caused by ovarian damage. It may be difficult clinically to distinguish the effects caused directly by irradiation from those caused by suppression of hormones (Arrive *et al.*, 1989; Urbano and Tait, 2004). In addition, there is some evidence that chemotherapy (which often accompanies radiation) directly damages the uterus, as summarized in Fig. 1 (Griffiths *et al.*, 2019; van de Loo *et al.*, 2019).

From early reports, it appears that the adverse pregnancy outcomes result from a radiation-induced reduction in the elasticity of the uterine musculature (Critchley and Wallace, 2005). Radiation-induced uterine vascular damage has also been proposed (Li *et al.*, 1987; Smith and Hawkins, 1989). There is a resulting loss of elasticity with restricted expansion of the uterus, impairment of vascularization and inadequate placentation. The mechanisms underlying the spectrum of the effects observed remain obscure (Li *et al.*, 1987; Hawkins and Smith, 1989; Rodriguez-Wallberg and Olofsson, 2019). Importantly, radiation may also impair endometrial receptivity, which is required to establish pregnancy, as well as endometrial function necessary to facilitate an ongoing and healthy pregnancy (Critchley and Wallace, 2005).

Prior to AP RT treatment, uterine transposition is the only fertility preserving option (apart from the radiation techniques such as shielding). This is experimental, with few case reports in the literature and no successful pregnancies to date (Ribeiro *et al.*, 2017; Ribeiro *et al.*, 2019). For carcinoma of the cervix treated with chemoradiation, there is no possibility of pregnancy with the patient's own uterus and existing options for having a baby include surrogacy or adoption. Uterine transplantation has been reported, but to our knowledge, only in one patient in the setting of cancer (Jones *et al.*, 2019) and it is not available in most centres.

The aim of this summary is to review the evidence and provide guidance regarding the management of women with a history of either AP RT or TBI involving a field containing the uterus, who wish to conceive.

The major concerns relate to: endometrial receptivity for implantation and placentation; uterine function for ongoing maintenance of pregnancy; and myometrial function.

Pubmed listed peer-reviewed publications from 1990 to 2019, and limited to English language, were reviewed.

Fertility outcomes following RT

Children and adolescents

AP RT

It is established that childhood cancer survivors have a lower fecundity and increased risk of adverse outcomes in pregnancy, which is related to many factors (Critchley *et al.*, 2002). Furthermore, most epidemiological studies have revealed important effects of radiation exposure on the reproductive health of female childhood cancer survivors. This is summarized in a meta-analysis of 14 cohort studies, with a total of 10 717 women with RT (AP) and 11 128 without RT (Gao *et al.*, 2015). This analysis demonstrated that childhood RT increases the risks of infertility (risk ratio (RR) 1.28, 95% CI 1.16–1.42), acute ovarian failure (RR 9.51, CI 5.03–17.96), low anti-Müllerian hormone <1 ng/ml (RR 14.79, CI 3.36–66.64), stillbirth (RR 1.19, CI 1.02–1.39) and LBW (RR 2.22, CI 1.55–3.17). Significantly, there was no increase in miscarriage or congenital malformations (Gao *et al.*, 2015; van de Loo *et al.*, 2019). This finding agrees with others showing no increased risk of malformation in the offspring of childhood cancer survivors who have had pregnancies (Green *et al.*, 2002; Mueller *et al.*, 2009; Reulen *et al.*, 2009; Sudour *et al.*, 2010; Nakamura *et al.*, 2013). Of note, the outcomes which may directly relate to the effect of radiation on the uterus (such as LBW, stillbirth, miscarriage), show only a modest or no increase compared to the overwhelming ovarian damage.

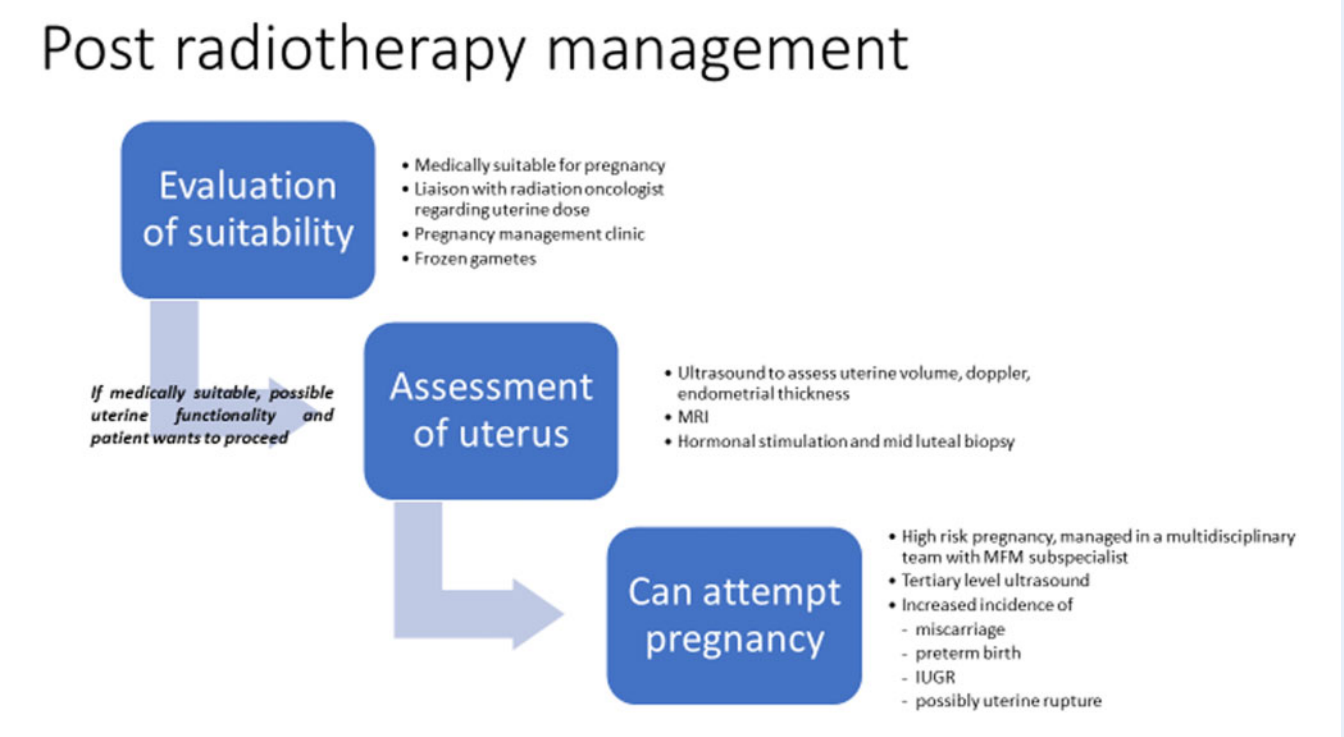

Figure 1. Assessment of damage to the uterus and patient management following radiotherapy (sometimes accompanied by chemotherapy). Adapted from Teh *et al.* (2014). IUGR, intrauterine growth restriction; MFM, maternal–foetal medicine.

Patients receiving radiotherapy treatment were at an elevated risk of preterm delivery compared with siblings (odds ratio (OR) 1.49; 95% CI 1.03–2.16). AP RT in particular increased the risk of preterm delivery (OR 3.81; CI 2.02–7.19) with 13 out of 72 survivors in this subgroup delivering before 37 weeks (Madanat-Harjuoja *et al.*, 2010). However, it is important to note that while the risk of LBW and prematurity may be partly due to decreased uterine volume as a result of pelvic radiation, other studies have observed these finding for cancers not typically treated with pelvic radiation and among those treated with chemotherapy only, suggesting that other factors may also contribute (Griffiths *et al.*, 2019).

TBI

The extent of damage to the uterus and ovaries during treatment of childhood cancer and in stem cell transplantation (SCT), is influenced by age at treatment and type of chemotherapy/conditioning regimen employed. Most of the available studies on the effect of these variables on ovarian and uterine function after treatment have included small numbers of patients, hampering subgroup analysis of radiation effects on the uterus (Critchley *et al.*, 2002; Jadoul *et al.*, 2011). In one of the largest clinical follow-up studies involving a cohort of 135 female survivors (three-quarters diagnosed prior to menarche) treated with chemotherapy, RT and/or SCT for childhood malignant and non-malignant diseases, TBI had the most damaging effect on subsequent uterine volume (OR 3.5, 95% CI 1.4–8.4) (Beneventi *et al.*, 2014). However, even the use of alkylating agents in stratified analysis was also associated with a reduced uterine volume.

In accordance with other studies, irradiation at a younger age was associated with smaller uterine volumes, suggesting that RT at a younger age results in more severe and irreversible uterine damage (Beneventi *et al.*, 2014). This may be due to effects on uterine development and vasculature, with the uterus unable to respond to puberty-induced growth (Critchley *et al.*, 2002). It has been observed that tissues with high rates of mitosis are more vulnerable to radiation damage than inactive tissues (Hall, 2009).

This same cohort of 135 women who were treated with chemotherapy, RT and/or SCT had further ultrasound analysis of uterine volume, ovarian volumes and uterine artery Doppler blood flow, which were then compared to healthy controls. Uterine volume was most reduced with TBI (82% reduction; 95% CI 71.8–87.8) followed by busulfan, compared with those who had not received a conditioning regimen. There are no studies which directly correlate reduced uterine volume with pregnancy complication rate.

Postpubertal girls and adults

AP RT

The risk of preterm delivery is increased in patients who have received RT (Tables I and II), however, in one of the largest studies of cancer survivors in Finland (Madanat-Harjuoja *et al.*, 2010), AP RT increased the risk of preterm delivery in paediatric and adolescent cancer survivors, but not in adult cancer patients receiving the same exposure (3/21; OR 2.44, 95% CI 0.67–8.92). Interestingly, in the young adults (20–34 years old) age group, risk of preterm delivery was significantly

Table I Data on radiotherapy in postpubertal girls and adults.

	Tumours	RT dose* (Gy)	Reported births[I]
AP RT	Cervix	60	No
	Rectal, anal	50	Yes
	Sarcoma (retroperitoneal and pelvic)	45–50	Yes
	Desmoid	50–54	Yes
	Bladder	55–66	No
	Lymphoma	30–40	Yes
	Ewing's sarcoma	45–54	Yes
TBI	Leukaemias (such as ALL, AML, CML, MDS)	10–14	Yes
	Lymphomas	10–14	Yes

Actual absorbed dose to uterus and ovary will depend on exact location of tumour with respect to these structures.
ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; AP RT, abdominopelvic radiotherapy; CML, chronic myeloid leukaemia; MDS, myelodysplastic syndrome; RT, radiotherapy; TBI, total body irradiation.
*Approximate doses only, based on commonly used dose ranges extracted from various international guidelines. Individual practises may vary.
[I]Refer to Table II for details.

elevated among 37/452 patients whose treatment regimens did not include RT (OR 1.49; 95% CI 1.03–2.15) (Madanat-Harjuoja *et al.*, 2010).

TBI

Successful pregnancies and deliveries of healthy children in women who have had SCT and preconditioning with TBI are well documented (Lasica *et al.*, 2016). However, due to reporting bias, the true incidence of pregnancy-related complications after SCT is unknown. In a large study of more than 35 000 European men and women who received SCT, there were 122 babies born to 113 women, of whom 23 had TBI. Increased pregnancy risks were seen in those who had received TBI compared to the general population and included preterm delivery (45% vs 6%, respectively) and LBW (50% vs 6%, respectively) (Salooja *et al.*, 2001). Surprisingly, these risks appear to be much higher compared to abdominal RT and demonstrate that more study is required in this area.

Similarly, Sanders *et al.* (1996) studied a group of 708 post-pubertal women who had received TBI for haematological malignancy. Among these, 110 had ongoing ovarian function and there were 32 spontaneous pregnancies. There was an increase in spontaneous miscarriage (38% vs 4%, respectively $P = 0.02$) and preterm delivery (63% vs 18%, respectively $P < 0.02$) among those receiving TBI with high-dose alkylating agents compared to alkylating agent treatment alone. An increased incidence of LBW and very LBW in babies compared to that expected in the general population (25% vs 7%, respectively $P < 0.0001$) was noted in those receiving high-dose alkylating agent, with or without TBI (Sanders *et al.*, 1996). Comparing the fertility of haematological malignancy survivors to their closest age siblings, Carter *et al.* (2006) demonstrated a reduced number of pregnancies in survivors (3% vs 72% in siblings, $P < 0.0001$), at least partially explained by ovarian damage, and an increased prevalence of nulliparity with later exposure to SCT or exposure to TBI. In contrast to the other studies (albeit with smaller numbers, i.e. n = 14), no significant increase in miscarriage, PTB or stillbirth was observed (Carter *et al.*, 2006).

Doses

Radiation affects fertility by damaging the ovaries and uterus, and their separate effects are difficult to distinguish. It appears that the LD_{50} (i.e. the dose required to kill 50% of oocytes) is 2 Gy or less in humans (Critchley and Wallace, 2005; Stroud *et al.*, 2009). The age-related response of the uterus and ovary to RT seems to differ. There appears to be an increase in radio-resistance of the uterus with age, but a decrease in resistance of the ovary to irreversible effects. This is evidenced by the fact that the sterilizing dose at which POI occurs immediately after treatment declines with age. Thus a younger patient with a larger oocyte reserve will have a larger residual reserve following treatment (Brougham and Wallace, 2005; Wallace *et al.*, 2005). The sterilizing dose for women aged less than 20 years is approximately 15 Gy (Brougham and Wallace, 2005). A study of fertility outcomes in 84 patients who had received abdominal and/or pelvic radiation in childhood, suggested that doses of less than 4 Gy caused no damage, while 4–15 Gy put patients at risk of subfertility.

When considering the uterus, doses between 14 and 30 Gy can impair uterine function (Critchley *et al.*, 1992; Bath *et al.*, 1999); however, this also occurs with lower doses in TBI (approximately 12 Gy), as described below. Doses for the treatment of rectal and cervical cancers are usually 30–50 Gy and a dose of >40 Gy has been traditionally regarded as sterilizing to the uterus (Critchley and Wallace, 2005). The tumour types and doses are summarized in Table I. Notably, there have been reports of successful pregnancies at doses of 30–54 Gy (see Table II). The main limitation is that the maximal radiation dose delivered to the tumour does not necessarily correlate with the uterine dose absorbed. This depends on tumour location and uterine proximity. Thus, there will be individual variation, even for patients with the same tumour type. A radiation oncologist may be able to provide a better estimation of uterine dose exposure.

Summary of evidence and gaps identified

The key findings of this review are that:

- The prepubertal uterus is much more vulnerable to the effects of radiation than after puberty.
- Almost all available information about the impact of radiation on the uterus comes from studies of radiation exposure during childhood or adolescence. There is significant population heterogeneity in these studies.
- These data cannot be readily extrapolated to adult women who have had uterine radiation and the publications concerning adult women treated with AP RT are largely limited to case reports. It

Table II Summary of the studies demonstrating fertility outcomes in the postpubertal and adult female population following AP RT.

Series	Study population/age	Radiation	Number of patients	Number of pregnancies	Adverse outcomes			
Haggar *et al.* (2014)	Western Australia survivors	TBI and pelvic	1894 total, 340 women	25% of all survivors. Unknown how many in RT subgroup		Tumour in pelvis	Radiation alone	Chemoradiation
			ChemoRT/RT alone		PTB (RR, 95% CI)	1.88 (1.24–2.87)	1.78 (1.53–3.74	1.05 (0.43–2.88)
					LBW	1.88 (1.24–2.87)	1.82 (1.26–2.59)	1.52 (1.01–2.43)
Madanat-Harjuoja *et al.* (2010) (Madanat-Harjuoja et al., 2010)	First deliveries of cancer survivors Finland. Sibling controls	Abdomino-pelvic		72 AP RT (37 paediatric, 14 adolescent, 21 adults)	PTB in 3/21 adults; OR 2.44, 95% CI 0.67–8.92 (not significant) Compared to paediatric group 7/37 (OR 4.01, 1.71–9.4) and 3/14 adolescents (OR 5.44, 1.45–20.48)			
Case reports: Rodriguez-Wallberg *et al.* (2015)	23 years Ewing's sarcoma sacrum	54 Gy		1	No reported complications Elective C/S at 38/40, 2970 g			
(Hurmuz *et al.* (2012)	25 years Anal cancer	30 Gy, lower segment/cervix 50 Gy		1	No reported complications Elective C/S 39/40			
Kurt *et al.* (2007)	24 years rectal cancer	50 Gy pelvis, ovarian transposition	1	1	Miscarriage at 21/40			
Wald *et al.* (2016)	36 years rectal cancer, Lynch syndrome	45–50 Gy pelvis, ovarian transposition	1	1 + 1	Spontaneous MCDA pregnancy, PPROM 28/40. Demise twin 1			
De Menezes and Tuck (2007)	17 years R ilium recurrence of Stage IV Hodgkin's Disease	36 Gy R hemipelvis	1	1 + 1	ETx2, DCDA twins C/S 35/40 for PET R lateral placenta accreta BWT 2.14 kg, 2.14 kg			
Ferreri *et al.* (2008)	29 years Primary uterine lymphoma	30.6 Gy Pelvis, ovarian transposition	1	1	Spontaneous pregnancy, no reported complications. NVD at term			
Bath *et al.* (2004)	14.9 years Ewing's sarcoma pubic ramus	55 Gy L pelvis. R ovary <16.5 Gy		1	No reported complications Elective C/S 38/40, 2940 (3–10th centile)			

BWT, birthweight; C/S, Caesarian section; DCDA, dichorionic diamniotic; ET, embryo transfer; L, left; LBW, low birth weight; MCDA, monochorionic diamniotic; NVD, normal vaginal delivery; OR, odds ratio; PET, pre-eclampsia; PPROM, preterm prelabour rupture of membranes; PTB, preterm birth; R, right; RR, risk ratio.

seems that uncomplicated pregnancy is possible, even with doses as high as 54 Gy. Therefore, tumour treatment doses alone cannot at present be used to accurately predict uterine damage.

- There is individual variation in radiation sensitivity and the pathogenesis of late radiation sequelae is complex and variable between individuals.
- Uterine damage is minimized by the newer technology and an increased awareness of fertility preservation within the field of radiation oncology. Intensity-modulated radiation therapy allows radiation dose to conform more precisely to the shape of the tumour, minimising dose to surrounding normal structures. Partial uterine radiation can also be used. This means that the radiation dose delivered to the uterus needs to be assessed separately to the tumour treatment dose.
- It is important to include patients who have undergone AP RT or TBI in prospective studies to provide further evidence regarding uterine function, pregnancy outcomes and a correlation of imaging with clinical outcomes.

Uterine assessment of radiation damage

Endometrial assessment as well as ultrasound and MRI are used to provide information about the uterus. There are no studies comprehensively assessing the extent of uterine damage, regarding endometrial receptivity for implantation, placentation and myometrial function. A multi-disciplinary consensus from a special interest group, including radiation oncologists, subspecialist obstetric and gynaecological sonologists, radiologists, gynaecologists and fertility specialists, suggested that a combination of endometrial sampling, ultrasound and MRI may be used to assess uterine morphology post-radiation (Teh *et al.*, 2014). However, it is important to recognize the limited data supporting these conclusions.

Endometrium

Endometrial receptivity is essential for successful embryo implantation (Zhao *et al.*, 2012) and radiation may impair the endometrial function of the uterus. While the reliability of standard methods for assessing and dating the endometrium based on histology have been challenged (Murray *et al.*, 2004), some groups have applied histological examination together with immunohistochemistry for markers of cellular differentiation to successfully demonstrate differences in receptivity in the female ART population (Evans *et al.*, 2012).

Endometrial biopsy samples can also be used to identify molecular changes associated with uterine receptivity to obtain a better insight into prospects for implantation success (Achache and Revel 2006). Recently, tests have been developed to diagnose endometrial receptivity based on endometrial gene expression patterns (Diaz-Gimeno *et al.*, 2011). While most of the published studies on endometrial receptivity have sampled fertile women for test validation or focused on patients with recurrent implantation failure (Diaz-Gimeno *et al.*, 2017), the method has been used in a small number of patients with persistently thin endometrium (<6 mm) (Mahajan, 2015).

Ultrasound

Ultrasound has been used to measure uterine volume, vasculature (using Doppler) and endometrial thickness. However, evidence for the value of ultrasound in assessment of the post-irradiated uterus comes predominantly from studies of childhood RT and cannot be extrapolated to women who have undergone RT in adulthood.

Uterine volume and Doppler

Reduced uterine volume and alterations in blood supply are common findings in survivors of childhood RT (Holm *et al.*, 1999; Beneventi *et al.*, 2015), and have been linked to poor fertility and pregnancy outcomes (Battaglia *et al.*, 2006; Raine-Fenning, 2008). However, there are no publications correlating these ultrasound findings with the degree of functional uterine damage and fertility outcomes.

There are conflicting data on whether hormone therapy (HT) can improve uterine size or blood flow, with Beneventi *et al.*, (2015) demonstrating a smaller uterus in a TBI-treated cohort, compared to controls, even with HT in patients. Similarly, two other studies suggest that the reduction in adult uterine volume when irradiation takes place at a younger age is probably irreversible (Critchley *et al.*, 1992; Larsen *et al.*, 2004). In a small longitudinal study of childhood haematological malignancy survivors who had received TBI, Bath *et al.* (1999) found that uterine volume improved after HT but remained significantly smaller than controls.

Endometrial thickness

An endometrial thickness over 7 mm has been related to better implantation rates in ART (Check and Cohen, 2011; Toth *et al.*, 2011; Zhao *et al.*, 2012). An unresponsive thin endometrium may be idiopathic or related to repeated curettages, infection, Asherman's syndrome or uterine irradiation (Shufaro *et al.*, 2008). While endometrial thickness (especially <6 mm) is associated with a trend towards a lower probability of pregnancy, the aetiology of the thin endometrium is very important and plays a significant part in its receptivity. Thus, radiation-induced damage, with the added impairment of vascularity and fibrosis, may be even more detrimental (Mahajan and Sharma, 2016) but there are no data assessing this directly in the RT-exposed uterus.

MRI

MRI of the female pelvis can provide morphological information and has been used to demonstrate radiation-induced changes, albeit in only two small studies (Arrive *et al.*, 1989, Milgrom *et al.*, 2013). Radiation changes in the myometrium may be demonstrated by decreased signal intensity on T2 images and may be seen as early as 1 month after RT. Other proposed effects include changes in cervical length, junctional zone anatomy and endometrial thickness (Arrive *et al.*, 1989). The pathophysiology underlying these findings is not certain but may reflect atrophy or fibrosis. Arrive *et al.* (1989) concluded that the changes seen are the same as those in the non-irradiated post-menopausal uterus suggesting oestrogen deficiency only, while Milgrom *et al.* (2013) (using controls who were similar in hormonal status, six patients) suggest that at least some degree of uterine change is a direct effect of RT on the uterus.

Pre-cancer treatment consultation

Before cancer treatment, all patients should be offered an appointment with a fertility specialist, as part of the multidisciplinary team managing their cancer, in order to address future reproduction. While this will often focus on the risk to fertility from loss of ovarian function and the potential options to mitigate against that, discussion should also include consideration of potential damage to the uterus (following the specialists' communication with the radiation oncologist regarding the treatment details). Where a significant risk is identified, discussion should include the realistic expectation of uterine functionality, including the potential need for surrogacy (Rentea *et al.*, 2018).

Clear documentation should be provided, and copied to the patient, of the information communicated from the radiation oncologist, as well as the discussion with the fertility specialist.

Post-RT assessment and management

Following treatment, the following assessment and management approaches are suggested for women seeking conception where there is a potential for RT-induced uterine damage (Fig. 1):

- Assessment of post-treatment fertility and endocrine status: all patients require discussion, even if treated for cervical cancer, to discuss surrogacy.
- If fertility is a possibility, a detailed discussion of potential obstetric risks, miscarriage, LBW/FGR, PTB and uterine rupture as well as failure to conceive.

The patient must be informed of the chance of unsuccessful fertility treatment and obstetric complications.

- Further discussion with the radiation oncologist regarding uterine dose, fractionation, and whole or partial uterine involvement.
- Clinical assessment in the short and medium term of endocrine status, including ovarian function and need for hormonal therapy.

Direct radiation to the uterus, either external beam or brachytherapy, used to treat cancer of the cervix is not compatible with successful pregnancy. Discussion of this with the patient should be clearly documented.

- Liaison with high-risk obstetrician for consultation.

If the radiation oncologist and high-risk obstetrician agree that there is potential uterine functionality and that the patient is medically fit for pregnancy, they may proceed with 'uterine assessment'. The patient must be informed of the heightened chance of unsuccessful fertility treatment and obstetric complications. This is especially so following AP RT, as compared to TBI.

- Assessment of uterine function (unnecessary if cancer of cervix): pelvic ultrasound (endometrial thickness, uterine volume and, if possible, uterine artery Doppler); MRI uterus (to assess myometrial fibrosis—T1 signal intensity, uterine volume, junctional zone anatomy and endometrial thickness); and consideration of endometrial biopsy following 5–7 days of progesterone to assess histology (Noyes criteria).
- Clear documentation, with the letter copied to the patient, regarding the discussion of risks and options

Management of pregnancy

Pregnancy in a uterus that has been exposed to RT is high risk, and needs to be managed by a multidisciplinary team with a high-risk obstetrician, and tertiary level ultrasound. Recommendations for management are as follows:

- increased frequency of appointments, growth scans and uterine Dopplers;
- deliver via Caesaran section by 38 weeks' gestation; and
- surveillance for the following potential complications: miscarriage, PTB, FGR, postpartum haemorrhage and pre-eclampsia.

Clinical guidance for women who wish to conceive following uterine radiation exposure is scarce and this summary can assist clinicians with patient management. It is important to perform prospective studies in this area to provide further evidence regarding uterine function, pregnancy outcomes and correlation of imaging with clinical outcomes.

Authors' roles

G.R., K.S., P.R. designed the study. G.R. performed the literature review, drafted the manuscript. This was critically reviewed by P.R., A.M., K.H., R.A.A., M.A., R.H., W.L., S.C., K.S., O.M., A.D., W.T.T., who also approved the final version.

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Conflict of interest

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