# Female reproductive potential post-treatment for childhood cancer

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***Survival post-treatment for childhood malignancy is now in excess of 70%. Hence female reproductive potential following treatment must be addressed. Issues concerning subsequent uterine and ovarian function, fertility options and importantly the ethics and safety of treatment approaches are discussed herein.***

Childhood cancer is a rare event with a cumulative risk of 1 in 650 for a child developing a malignancy by the age of 15 years (Waring and Wallace, 2000). Throughout the last four decades advances in the treatment of childhood malignancy have resulted in a continued improvement in survival such that the overall 5-year survival rate is now in excess of 70%. In the UK there are now 10 000 adult survivors of childhood cancer with the number continuing to increase annually (Stiller, 1994). It has been estimated that the prevalence of adult survivors of childhood cancer approaches 1 in 1000 (Birch et al, 1988).

The improved survival rates have been achieved by combination chemotherapy with the addition of radiotherapy in selected cases. However, successful treatment regimens may be gonadotoxic, putting adult survivors at risk of premature ovarian failure and possible uterine damage.

Both chemotherapy and radiotherapy to a field that includes the gonads are known to be potentially gonadotoxic. Alkylating agents and procarbazine are the commonest gonadotoxic drugs while abdominal, pelvic or total body irradiation may also be gonadotoxic, depending upon dose and age at the time of treatment. High dose myeloablation alkylating agent therapy or total body irradiation are used as conditioning treatments in patients undergoing bone marrow transplantation.

As the number of children surviving increases, health services will be called upon to provide treatments to prevent the consequences of oestrogen deficiency and meet the fertility needs of this group of young adult survivors of childhood cancer. This review will look at the potential for competent reproductive function in these survivors.

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## REPRODUCTIVE ESSENTIALS

To achieve a successful pregnancy the female requires a normally functioning ovary, a patent fallopian tube and normal uterine function. If any damage or impairment of function occurs in these organs then reproductive potential may be impaired. Impairment may mean an inability to conceive or alternatively conception and implantation occur but then complications of pregnancy arise.

Reproductive function in childhood cancer survivors may be compromised as a result of the treatment they receive. Women who have had radiotherapy to the abdomen or total body irradiation, not chemotherapy alone, are more likely to require assisted reproduction for ovarian failure and pregnancies are more likely to end in spontaneous miscarriage. Even when pregnancies are ongoing there is an increased risk of preterm labour and children of low birthweight being born (Sanders et al, 1996; Byrne, 1999; Larsen et al, 2000; Salooja et al, 2001). Evidence to date where successful pregnancies have been achieved does not suggest the risk of congenital anomaly is greater than in the general population (Sanders et al, 1996; Blatt, 1999). However, as new assisted conception techniques emerge and develop this risk must be continually monitored.

## CONSEQUENCES FOR THE UTERUS

The uterus requires the sequential action of oestrogen and progesterone to establish and maintain a receptive endometrium that will allow embryo implantation. The uterus will then undergo extensive remodeling in pregnancy and greatly increase its blood supply by term.

Radiotherapy is the principal treatment modality that can directly affect uterine function. There

are few data that examine the effect of chemotherapy on uterine function. Failure to establish a receptive endometrium is an indirect effect of ovarian damage as a consequence of reduced sex steroid production. It has been hypothesized that the adverse pregnancy outcomes in radiotherapy-treated survivors may be the result of one or a combination of the following factors – impaired uterine blood supply, impaired uterine distensibility or impaired endometrial function (Bath et al, 1999). The effects of radiotherapy on the uterus have been examined in observational studies.

## UTERINE GROWTH AND FUNCTION

Radiation therapy can affect uterine size, uterine blood flow and may impair endometrial function. In the context of uterine size, one of the most important determinants of uterine size is the age at irradiation. Uterine volume has been shown to have a significant correlation with age at irradiation: the younger the age at irradiation the smaller the uterine volume (Bath et al, 1999) (*Figure 1*). At baseline, uterine volumes in women who had received radiotherapy were smaller than controls. The participants in this study were administered a physiological sex steroid replacement regimen (transdermal oestradiol; Critchley et al, 1990). Despite increasing in volume after this physiological regimen of sex steroid replacement the uterus remained significantly smaller (median uterine volume following replacement 16.5 ml and 41.5 ml in comparison group).

This confirmed earlier findings (Critchley et al, 1992; Holm et al, 1999) in patients with premature ovarian failure following whole abdominal radiotherapy where radiotherapy resulted in a significantly shorter uterine length compared with patients who had not received radiotherapy (*Figure 2* – data derived from Bath et al, 1999).

These studies also revealed abnormalities in uterine blood flow. At baseline in the reports by Critchley et al (1992) and Bath et al (1999), Doppler studies of the uterine artery failed to demonstrate uterine blood flow in patients previously treated with radiotherapy. Holm et al (1999) also described impaired vascular supply to the uterus, in their report illustrated by absent diastolic flow in eight of nine patients. However, Bath et al (1999) did show that after 3 months of physiological sex steroid replacement uterine blood flow was evident in three out of four patients where it had been absent before commencing physiological sex steroid replacement therapy. It remains to be determined if this improvement will be sufficient to adequately support placentation and pregnancy.

A physiological sex steroid replacement regimen was also shown to have an impact on the endometrium. Initially in the study by Critchley et al (1992) patients were treated with physiological sex steroid replacement for one cycle and did not see an increase in uterine length or endometrial thickness. Similarly Holm et al failed to produce any growth of the uterus in their radiotherapy patients who were treated with a standard hormone replacement regimen. However, Bath et al treated irradiated patients, chemotherapy-treated controls and healthy control patients with 3 months of physiological sex steroid replacement. Endometrial thickness was recorded by ultrasound at baseline and following treatment. Physiological sex steroid therapy induced endometrial growth as noted by increased endometrial thickness. As the endometrium of radiotherapy-treated patients responded following 3 months of sex steroid replacement therapy it is possible that the

*Figure 1. Correlation between uterine volume during third month of physiological sex steroid replacement therapy and age at irradiation. From Bath et al (1999).*

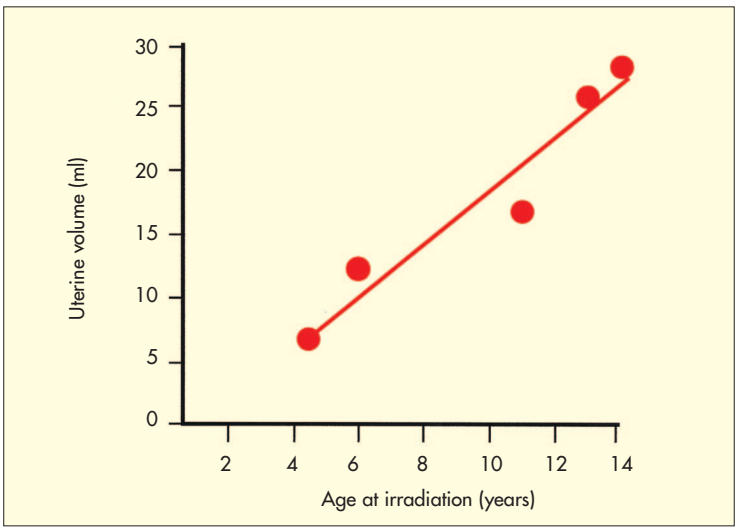
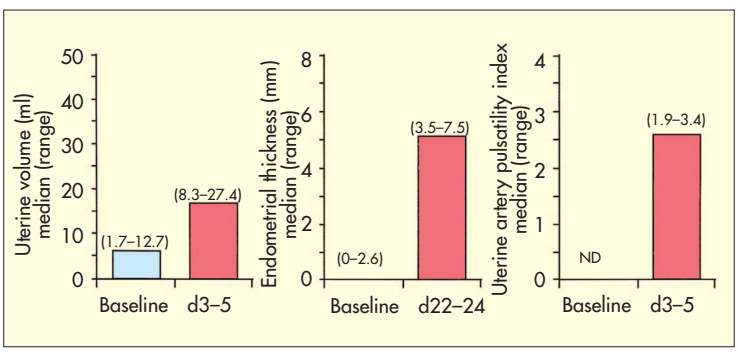



*Figure 2. Administration of physiological sex steroid replacement regimen increased uterine volume and endometrial thickness and re-established uterine artery blood flow in women (n=4) with premature ovarian failure after treatment with total body irradiation for leukaemia. Data derived from Bath et al (1999). ND = not detectable.*



endometrial response was a function of the duration of therapy. Further studies are required to establish the optimal dose and duration of oestrogen and progesterone to produce a maximal endometrial or uterine response.

The ability of the endometrium to respond to sex steroid replacement is important for patients with premature ovarian failure as the success of assisted reproductive techniques will depend upon the establishment and maintenance of a receptive endometrium. It has been shown that women with premature ovarian failure following total body irradiation can respond to physiological sex steroid replacement producing histologically normal endometrium that also exhibited evidence of oestrogen receptor-related function. (Critchley et al, 2002).

The importance of sequential sex steroid replacement was shown in the context of childhood cancer by Larsen et al (2000) who reported the pregnancy outcome of three survivors of childhood cancer who had received total body irradiation that resulted in premature ovarian failure. Subsequently they received sequential sex steroid replacement and underwent assisted conception with donor oocytes. Of the three patients two became pregnant, with one pregnancy progressing to a term delivery of a healthy girl and the other ending in miscarriage at 17 weeks gestation. Interestingly the patient with the healthy child was the only one of the three who had a normal uterine size. The other two patients had restricted uterine size as determined by ultrasound in a previous study 3 years before the assisted conception.

Radiation therapy may therefore affect uterine function by restricting uterine size, damaging uterine blood supply and indirectly reducing levels of endogenous sex steroids as a result of ovarian damage, and thereby preventing endometrial development. Encouragingly the endometrium, uterine vasculature and myometrium remain responsive to exogenous sex steroids, offering possibilities for assisted reproductive techniques for achieving pregnancy in these young survivors. However, caution should remain regarding pregnancy outcomes. If a pregnancy were to occur it should be treated as a high-risk pregnancy because of possible adverse effects upon the developing fetus such as miscarriage, intrauterine growth restriction, and preterm labour all secondary to uterine damage.

## CONSEQUENCES FOR THE OVARY

The ovary has its highest complement of oocytes in utero where at a gestation of 5 months the number of oocytes is approximately 7 million. By birth this number has declined to 1 million and by the menopause to less than 1000. Mathematical models based upon studies examining the follicle content of human ovaries at a range of maternal ages have shown this decline to be bimodal with a constant rate of decline from birth followed by a rapid phase of decline after the age of 37.5 years. This model suggested that large scale destruction of follicles, such as in the radiation or chemotherapy treatment of some childhood cancers, may hasten entry into the rapid phase of oocyte decline bringing about a premature menopause (Faddy et al, 1992).

The risk of damage to ovarian tissue is again dependent upon the dose, duration and age of the patient at the time of treatment. Prepubertal children appear to have the best prognosis. The younger the patient the higher the dose of chemotherapy or radiotherapy that is required to induce premature ovarian failure. This is supported by data from Byrne et al (1992) where children treated for cancer before the age of 12 years who did not suffer immediate ovarian failure and were menstruating at entry into the study had no increased risk of premature ovarian failure in their twenties compared to controls. However, children diagnosed and treated after the age of 12 years had a relative risk of 2.32 of premature ovarian failure in their twenties that was significantly greater than controls (Byrne et al, 1992; Byrne, 1999). When considering the effect of treatment they found that 13–19-year-old survivors treated with radiation below the diaphragm in conjunction with alkylating agents had a relative risk of almost 10 (Hodgkin's disease relative risk (RR) = 9.6 and all other cancers RR=8.56) for premature ovarian failure (Byrne, 1999). The relative protection of prepubertal children may be in part a result of the larger proportion of primordial follicles.

Gonadotoxic chemotherapies are most commonly alkylating agents such as cyclophosphamide and they have been shown to have an age- and dose-dependant effect (Blumenfeld et al, 1999). The results suggest that younger patients are relatively less susceptible to ovarian damage. A total dose of 5 g is sufficient to cause premature ovarian failure in a women older than 40 years while in the 30–40 years and 20–30 years age groups doses of 9 g and 20 g are required respectively. Other alkylating agents that have been implicated include busulphan, melphalan and ifosfamide (Blumenfeld et al, 1999). In an effort to prevent chemotherapy-

induced premature ovarian failure Blumenfeld et al (1999) undertook an observational study into the protective effect of 6 months co-treatment with gonadotrophin-releasing hormone (GnRH) agonists commenced along with chemotherapy. Their study showed that women co-treated with GnRH agonists were significantly less likely to suffer premature ovarian failure and they hope that such findings will be confirmed by larger randomized control trials (Blumenfeld, 2001).

The effect of radiotherapy on the ovary depends upon the site being irradiated, the dose and age of the patient. At risk are any patients receiving radiation below the diaphragm or spinal irradiation.

The dose of radiotherapy that is lethal to 50% of the oocytes (LD 50) has been calculated at less than 4 Gy (Wallace et al, 1989). Referring to the earlier model, the number of oocytes in a peri-pubertal female is much greater than in a peri-menopausal woman. Therefore the dose of radiation required to bring the number of oocytes in the peri-menopausal ovary below the threshold that will render her menopausal is much less than in the peri-pubertal ovary. This is reflected in the doses that in practice induce premature ovarian failure. A women over the age of 40 years requires 5–10Gy (Doll and Smith, 1968) while a significantly higher dose of 20 Gy is required in younger females to induce premature ovarian failure (Wallace et al, 1989).

For patients undergoing bone marrow transplant, total body irradiation is used as a conditioning treatment. The effect of total body irradiation is not known.

The impact that treatment will have upon reproductive potential is complex and often multifactorial. Chemotherapy or radiotherapy can damage the ovarian oocyte population and if sufficiently toxic will result in premature ovarian failure. The unique problem of reproductive potential in the survivors of childhood cancer poses many challenges for clinicians and scientists who wish to help these young women achieve a successful pregnancy.

## FERTILITY OPTIONS FOR PATIENTS

In this rapidly developing area there are a number of options for managing potential fertility problems. First, there is the possibility that there may be natural restoration of an individual's fertility. Second, hormonal manipulation may be used to protect reproductive tissues or to initiate restoration of reproductive function. Third, there may be the possibility of future use of harvested and cryopreserved gametes. Finally, there may be the collection, storage and manipulation of germ cells and tissues with the ultimate aim of allowing an individual the opportunity to extend their own genetic lineage (Wallace and Walker, 2001).

The age of patients at the time of diagnosis will mean that the vast majority will not be married or in relationships where consideration of embryo cryopreservation would be appropriate. Even if in a minority of cases it were to be considered, the negative impact of delay in treatment that can be minimized with new ovulation induction protocols using GnRH antagonists (Anderson et al, 1999), the anxiety, cost and inefficiency of the process must be taken into account. The use of physiological sex steroid replacement to improve uterine function has been discussed earlier in this review.

The remaining therapeutic options are otherwise discussed below and consideration is also given to the ethical and safety issues that are raised.

## PREVENTIVE STRATEGIES

The ideal therapeutic intervention would be a treatment for a patient's cancer that would not damage gonadal tissue while maintaining its effectiveness. Measures have been used to prevent ovarian damage. If radiotherapy is planned that would include the ovaries within the radiation field then an attempt may be made to remove the ovaries from the treatment field by laparoscopic ovarian translocation, thereby reducing the dose to which the ovary is exposed (Rutherford and Gosden, 1999).

The prepubertal ovary has also been noted to be relatively chemoresistant and attempts to mimic this situation in the postpubertal patient undergoing treatment have been attempted. Suppressors of the hypothalamic–pituitary axis have been used such as the combined oral contraceptive and GnRH receptor analogues (Blumenfeld et al, 1999; Pfeifer and Coutifaris, 1999; Blumenfeld, 2001). However, results to date have been mixed and no clear recommendations may be made.

## GERM CELL AND OVARIAN TISSUE CRYOPRESERVATION

Alternatives that are being researched include germ cell and ovarian tissue cryopreservation. Mature oocytes are more susceptible to damage at cryopreservation than immature oocytes. However, while immature oocytes are less susceptible to cryopreservation they cannot yet be

matured in vitro. Therefore the low survival and fertilization rates of oocytes preclude their consideration until advances are made in this field (Ludwig et al, 1999; Donnez et al, 2000).

The most promising area of current research is the cryopreservation of ovarian tissue. Research into this field began in the late 1950s. The ovarian cortex is rich in primordial follicles and cryopreservation of 1–2 mm strips is technically possible with follicles surviving the procedure (Gosden et al, 1999; Rutherford and Gosden, 1999). The follicles in the cortical strips contain immature oocytes and as previously noted there are as yet no techniques for in-vitro maturation. To circumvent the need for in-vitro maturation successful attempts have been made to autograft the strips into animals, e.g. mice (Parrot, 1960) and sheep (Baird et al, 1999), and more recently in humans (Oktay and Karlikaya, 2000; Radford et al, 2001).

Oktay et al (2001) laparoscopically replaced cryopreserved ovarian strips to the pelvic peritoneum of a patient suffering from a non-malignant disorder, 6 months after they had been removed. Following replacement the ovarian strips responded to gonadotrophin administration, producing ovarian follicles and endogenous oestrogen and progesterone. However, no pregnancies have yet been achieved with this technique.

A successful ovarian tissue orthotopic graft (grafting to normal anatomical position) in a patient treated for haematological malignancy has been reported by Radford et al (2001). Ovarian strips taken before commencement of treatment were replaced 19 months later when premature ovarian failure was confirmed. Following grafting, menopausal symptoms resolved and oestradiol levels rose transiently, with an associated fall in the follicle-stimulating hormone and luteinizing hormone levels (Radford et al, 2001). The grafted strips will, however, contain a finite number of follicles and graft lifespan may be restricted (Gosden et al, 1999). This is mainly because of the finite number of primordial follicles and the freeze thawing damage that results in loss of follicles. In the report by Radford et al (2001) the graft survived 9 months after which time the sex steroid levels were again consistent with ovarian failure.

As noted many of these techniques will depend upon a normally functioning uterus being present and in this group of patients there is currently still a risk of radiation damage to the uterus with certain regimens. Therefore, these cases may be complicated further as documented pregnancies in bone marrow transplant survivors with uterine damage have been subject to antenatal complications (Larsen et al, 2000; Salooja et al, 2001).

Further research in this area will address the in-vitro maturation of follicles and if grafting is orthotopic it may be possible to facilitate spontaneous conception without the need for oocyte recovery and in-vitro fertilization (Aubard, 2000).

## ETHICAL AND SAFETY ISSUES

Ethical and safety issues will also have to be considered. Safety issues that must be addressed include the risk of reintroducing malignant cells when replacing tissue, particularly in patients with haematological malignancies. Shaw et al (1996) highlighted this in studies on mice showing that lymphoma was transmitted by both fresh and frozen ovarian grafts, killing the recipients. It is hoped, however, that research may eventually allow oocytes to be cultured to maturity then fertilized and later transferred to patients free of contamination (Gosden et al, 1997).

The ethical issues to be considered include the provision of informed consent in this age group, storage of cryopreserved material, and who should be offered access to the technique (Donnez and Bassil, 1998). Guidelines have been formulated by the Royal College of Obstetricians and Gynaecologists (2000) and the British Fertility Society (Nugent et al, 2000). The guidelines suggest that ovarian tissue cryopreservation should be offered to those young children and adults at high risk of ovarian failure as a result of treatment. They highlight the importance of informed consent when counseling children and their families for the process of ovarian tissue retrieval and storage. Those involved with giving consent must understand the experimental nature of the technology. With the introduction of this service clear local protocols covering all above areas should be developed to facilitate its implementation. In addition a consensus statement also considered the role of the Human Fertilisation and Embryology Authority to be central in the supervision of storage and use of gametes and embryos (Wallace and Walker, 2001).

To enable the best advice and care to be given to patients it is crucial that a multidisciplinary approach is taken with maintenance of high standards in dealing with the tissue collected, research, record keeping and the follow-up data for patients involved (Wallace and Walker, 2001). HM

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Anderson RA, Kinniburgh D, Baird DT (1999) Preliminary experience of the use of a gonadotrophin-releasing hormone antagonist in ovulation induction/in-vitro fertilization prior to cancer treatment. *Hum Reprod* **14**(10): 2665–8
Aubard Y (2000) More to ovarian transplantation than meets the eye. *Fertil Steril* **74**(2): 423–4
Baird DT, Webb R, Campbell BK, Harkness LM, Gosden RG (1999) Long-term ovarian function in sheep after ovariectomy and transplantation of autografts stored at -196 C. *Endocrinology* **140**(1): 462–71
Bath LE, Critchley HOD, Chambers SE, Anderson RA, Kelnar CJ, Wallace WHB (1999) Ovarian and uterine characteristics after total body irradiation in childhood and adolescence: response to sex steroid replacement. *Br J Obstet Gynaecol* **106**(12): 1265–72
Birch JM, Marsden MB, Jones PH, Pearson D, Blair V (1988) Improvements in survival from childhood cancer: results of a population based survey over 30 years. *Br Med J* **296**: 1372–6
Blatt J (1999) Pregnancy outcome in long-term survivors of childhood cancer. *Med Pediatr Oncol* **33**(1): 29–33
Blumenfeld Z (2001) Ovarian rescue/protection from chemotherapeutic agents. *J Soc Gynaecol Investig* **8**(1 Suppl Proceedings): S60–4
Blumenfeld Z, Avivi I, Ritter M, Rowe JM (1999) Preservation of fertility and ovarian function and minimizing chemotherapy-induced gonadotoxicity in young women. *J Soc Gynaecol Investig* **6**(5): 229–39
Byrne J, Fears TR, Gail MH et al (1992) Early menopause in long term survivors of cancer during adolescence. *Am J Obstet Gynecol* **166:** 788–93
Byrne J (1999) Infertility and premature menopause in childhood cancer survivors. *Med Pediatr Oncol* **33**(1): 24–8
Critchley HOD, Buckley CH, Anderson DC (1990) Experience with a physiological steroid replacement regimen for the establishment of a receptive endometrium in women with premature ovarian failure. *Br J Obstet Gynaecol* **97:** 804–10
Critchley HOD, Wallace WHB, Shalet SM et al (1992) Abdominal irradiation in childhood; the potential for pregnancy. *Br J Obstet Gynaecol* **99**(5): 392–4
Critchley HOD, Bath LE, Wallace WHB (2002) Radiation damage to the uterus – Review of the effects of treatment of childhood cancer. *Hum Fertil* **5:** 61–6
Doll R, Smith PG (1968) The long term effects of X irradiation in patients treated for metropathia haemorhagica. *Br J Radiol* **41:** 362–8
Donnez J, Bassil S (1998) Indications for cryopreservation of ovarian tissue. *Hum Reprod Update* **4**(3): 248–59
Donnez J, Godin PA, Qu J, Nisolle M (2000) Gonadal cryopreservation in the young patient with gynaecological malignancy. *Curr Opin Obstetr Gynaecol* **12**(1): 1–9
Faddy MJ, Gosden RG, Gougeon A, Richardson J, Nelson JF (1992) Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Hum Reprod* **7**(10): 1342–6
Gosden RG, Rutherford AJ, Norfolk DR (1997) Transmission of malignant cells in ovarian grafts. *Hum Reprod* **12**(3): 403
Gosden RG, Picton HM, Nugent D, Rutherford AJ (1999) Gonadal tissue cryopreservation: clinical objectives and practical prospects. *Hum Fertil* **2:** 107–14
Holm K, Nysom K, Brocks V et al (1999) Ultrasound B-mode changes in the uterus and ovaries and Doppler changes in the uterus after total body irradiation and allogeneic bone marrow transplantation in childhood. *Bone Marrow Transplant* **23**(3): 259–63
Larsen EC, Loft A, Holm K et al (2000) Oocyte donation in women cured of cancer with bone marrow transplantation including total body irradiation in adolescence. *Hum Reprod* **15**(7): 1505–8
Ludwig M, Al-Hasani S, Felderbaum R, Diedrich K (1999) New aspects of cryopreservation of oocytes and embryos in assisted reproduction and future perspectives. *Hum Reprod* **14**(Suppl 1): 162–85
Nugent D, Hamilton M, Murdoch A: BFS Committee (2000) BFS recommendations for good practice on the storage of ovarian and prepubertal testicular tissue. *Hum Fertil* **3:** 5–8
Oktay K, Karlikaya G (2000) Ovarian function after transplantation of frozen, banked autologous ovarian tissue. *N Engl J Med* **342**(25): 1919
Oktay K, Aydin BA, Karlikaya G (2001) A technique for laparoscopic transplantation of frozen-banked ovarian tissue. *Fertil Steril* **75**(6): 1212–6
Parrot DMV (1960) The fertility of mice with orthotopic ovarian grafts derived from frozen tissue. *J Reprod Fertil* **1:** 230–41
Pfeifer SM, Coutifaris C (1999) Reproductive technologies 1998: options available for the cancer patient. *Med Pediatr Oncol* **33**(1): 34–40
Radford JA, Lieberman BA, Brison DR et al (2001) Orthotopic reimplantation of cryopreserved ovarian cortical strips after high-dose chemotherapy for Hodgkin's lymphoma. *Lancet* **357**: 1172–5
Royal College of Obstetricians and Gynaecologists (2000) *Storage of Ovarian and Prepubertal Testicular Tissue.* Working Party Report of the Royal College of Obstetricians and Gynaecologists. Royal College of Obstetricians and Gynaecologists, London
Rutherford AJ, Gosden RG (1999) Ovarian tissue cryopreservation: a practical option? *Acta Paediatr* **88**(433 Suppl): 13–8
Salooja N, Szydlo RM, Socie G et al (2001) Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. *Lancet* **358**: 271–6
Sanders JE, Hawley J, Levy W et al (1996) Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood* **87**(7): 3045–52
Shaw JM, Bowles J, Koopman P et al (1996) Fresh and cryopreserved ovarian tissue samples from donors with lymphoma transmit the cancer to graft recipients. *Hum Reprod* **11**(8): 1668–73
Stiller CA (1994) Population based survival rates for childhood cancer in Britain, 1980-91. *Br Med J* **309**: 1612–6
Wallace WH, Shalet SM, Hendry JH et al (1989) Ovarian failure following abdominal irradiation in childhood: the radiosensitivity of the human oocyte. *Br J Radiol* **62**(743): 995–8
Wallace WH, Walker D (2001) Conference consensus statement: ethical and research dilemmas for fertility preservation in children treated for cancer. *Hum Fertil* **4:** 69–76
Waring AB, Wallace WH (2000) Subfertility following treatment for childhood cancer. *Hosp Med* **61**(8): 550–7

## KEY POINTS

- The impact that treatment will have upon reproductive potential is complex and often multifactorial.
- Adverse pregnancy outcome in radiotherapy-treated cancer survivors may be caused by one or a combination of the following factors – impaired uterine blood supply, impaired uterine distensibility or impaired endometrial function.
- Uterine volume is directly correlated with age at irradiation.
- It is essential that the uterine volume factor is recognized as there may be associated problems in pregnancy, including risk of early pregnancy loss, intrauterine growth restriction and pre-term labour.
- The risk of damage to ovarian tissue is dependent upon total dose and age of patient at time of treatment. Pre-pubertal children may have a window of opportunity for fertility.
- Options for fertility preservation are limited and in children still remain experimental. Assisted reproduction technology has thus far focused on efforts to preserve ovarian tissue for future use.
- The optimal dose and preferred delivery route for sex steroid replacement has yet to be established and should aim to achieve adequate uterine growth in adolescence post anti-cancer treatment. Moreover it should also benefit bone and cardiovascular health.
- The unique problem of reproductive potential in the survivors of childhood cancer poses challenges for clinicians who wish to help these young women achieve a successful pregnancy.