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Pregnancy in women who had cancer in childhood

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ABSTRACT

The majority of female cancer survivors will have normal reproductive function and would be expected to have a successful pregnancy. For the minority of young women who have received significant cytotoxic insult to the reproductive organs and yet still manage to conceive, pregnancy must be considered a high risk condition and these patients should be managed by a multidisciplinary specialist team.

Female survivors of childhood cancer who are able to become pregnant carry an excess risk of preterm delivery and low birth weight baby. This restricted foetal growth and inability of the uterus to carry the foetus to term is associated with radiation-induced damage to the uterus. Chemotherapy does not appear to be associated with adverse pregnancy outcomes. However, prospective follow-up of cohorts of patients treated with contemporary therapies, frequently involving more intensive therapies are required to determine the risk. A number of large multi-centre studies, are underway and will provide new insights into pregnancy outcomes in survivors of childhood cancer.

1. Introduction

With 5-year survival rates for childhood cancer of over 75% it is estimated that about 1 in 650 young adults, will be a long-term survivor.[1] Consequently, investigators are now focusing on improving our understanding of the late side-effects associated with successful cancer therapy. Long-term survivors are at risk of developing a number of late sequelae including impaired fertility, adverse pregnancy outcomes and health problems in the offspring.[2–5] Although not the highest priority at diagnosis, loss of fertility is one of the most devastating consequences of cytotoxic therapy for the survivor in the long-term.

Understanding the impact of cancer and cancer therapy on pregnancy and health of the offspring requires knowledge of the effects of chemotherapy and radiotherapy on female reproductive function. Cancer therapy may disrupt the neuro-endocrine axis, damage the ovaries and impair uterine function. This may result in pubertal delay or arrest, premature ovarian failure or subfertility.[5] When pregnancy does occur it must be considered as a high risk event because the woman may be at risk of having a miscarriage, premature delivery or delivery of a low birth weight infant. In this review, we discuss the evidence for increased adverse pregnancy outcomes, including low birth weight, prematurity and miscarriage, increased incidence of congenital abnormalities, altered sex ratio and cancer predisposition in the offspring.

2. Impact of cancer therapy on reproductive function

When considering the impact of cancer therapy on female reproductive function and the ability to have healthy offspring it is instructive to consider the normal physiological

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pathway involved in ovulation, pregnancy and delivery of a healthy baby. A healthy pregnancy requires the female to have an intact hypothalamic–pituitary–ovarian axis, an adequate ovarian follicle reserve and a normally functioning uterus. Surgery, chemotherapy and radiotherapy may adversely affect any of these processes.

Considering the neuro-endocrine pathway first, gonadotrophin deficiency following high-dose cranial irradiation (>24 Gy in the treatment of brain tumours) may manifest as delayed puberty or absent menses and can be treated by hormone replacement therapy. Interestingly, early puberty is often reported with lower irradiation doses (24 Gy, as previously used in CNS directed treatment for acute lymphoblastic leukaemia).[6] However, following low-dose radiotherapy (18–24 Gy), a subtle decline in hypothalamic–pituitary–ovarian function may occur with time, posing a clinical challenge which is of more concern. Decreased LH secretion, an attenuated LH surge and shorter luteal phases have been reported and may herald incipient ovarian failure or be associated with early pregnancy loss.[6,7]

Intact ovarian function demands a critical mass of primordial follicles in an appropriate endocrine milieu. At birth the human ovary has a fixed oocyte pool of about 2 million, which begins a process of depletion by atresia and recruitment towards ovulation, culminating in menopause at a median age of 51 years. Chemotherapy and radiotherapy may damage the ovary and hasten oocyte depletion resulting in loss of hormone production and premature menopause.[8] The ovaries may be damaged following total body, abdominal or pelvic irradiation and the extent of the damage is related to the radiation dose, fractionation schedule and age at the time of treatment.[9,10] The human oocyte is very sensitive to radiation, with an estimated LD_{50} of less than 2 Gy.[11] The number of primordial follicles present at the time of treatment, together with the dose received by the ovaries, will determine the fertile 'window' and influence the age of premature ovarian failure. Ovarian failure has been reported in 90% of patients followed up long term after TBI (10–15.75 Gy) and in 97% of females treated with total abdominal irradiation (20–30 Gy) during childhood.[12,13] It is now possible to predict the age at ovarian failure and the estimated sterilising dose following any given dose of radiotherapy at any given age based upon the application of the mathematical solution to the Faddy–Gosden model for natural oocyte decline (see Fig. 1).[14] This will help clinicians to provide accurate information when counselling women about fertility following treatment for childhood cancer.

The ovarian reserve is also susceptible to chemotherapy-induced damage particularly following treatment with alkylating agents such as cyclophosphamide.[12,15,16] Ovarian damage is drug and dose dependent and is related to age at time of treatment, with progressively smaller doses required to produce ovarian failure with increasing age.[17–19] Alkylating agents form an integral part of many treatment protocols and one of the most widely studied agents is cyclophosphamide. High-dose cyclophosphamide (200 mg/kg) is frequently used as conditioning therapy before bone marrow transplantation, either alone, where recovery of ovarian function is more likely, or in combination with other chemotherapeutic agents or total body irradiation.[12,15] In a study of 43 women

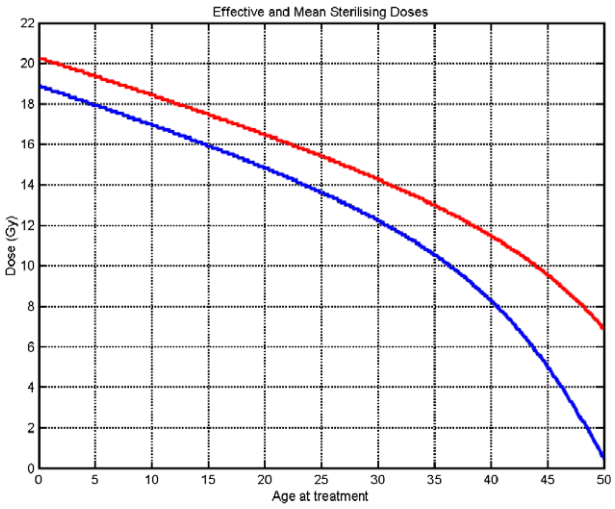

Fig. 1 – The effective (red, upper) and mean (blue, lower) sterilising dose of radiation for a known age at treatment.

with aplastic anaemia, cyclophosphamide (200 mg/kg) was associated with amenorrhoea in all women, with 36 showing recovery in 3–42 months after transplantation. For children treated prepubertally, normal ovarian function was reported in more than 95%, but of course this requires cautious interpretation as premature menopause may occur.[16]

Traditionally, treatment for Hodgkin's lymphoma with MOPP (mechlorethamine, vincristine, procarbazine and prednisolone) or ChLVPP (chlorambucil, vinblastine, procarbazine and prednisolone) have been associated with the development of premature ovarian failure in 19–63% of cases.[17–19] Amenorrhoea is more commonly encountered in the older women, although long-term follow-up is necessary, as a number of these young women will develop a premature menopause. In a recent study, the Amsterdam group explored premature menopause in survivors of Hodgkin's lymphoma treated before the age of 40. The cumulative risk for premature menopause (defined as cessation of menstruation before age 40) in these women was 48% (95% confidence interval (CI) 40–54%) when they had received chemotherapy, and only 2% (95% CI 0–4%) when they were treated with radiotherapy alone. Among girls treated with MOPP up to age 21 the cumulative risk of premature menopause was as high as 57% (95% CI 13–79%). The researchers also found that increasing total dose of procarbazine (>8.4 g/m^2) was associated with a premature menopause in 65% (95% CI 44–78%) of patients (Marie L. De Bruin, personal communication).

A number of women may have preservation of ovarian function if the dose to one or both ovaries can be relatively spared, for example in spinal or flank irradiation. However, even if the woman is able to conceive the pregnancy is still high risk. The uterus is at significant risk of damage following abdominal, pelvic or total body irradiation, in a dose and age dependent manner.[20] Normally the increase in ovarian oestrogen during puberty results in an increase in uterine size and change in shape from a tubular to pear-shaped organ.[21] Uterine function may be impaired following radiation doses

of 14–30 Gy as a consequence of disruption to the uterine vasculature and musculature elasticity.[22,23]

Efforts to improve uterine function have been tried in a limited number of studies. In young adult women previously treated with TBI, physiological sex steroid replacement therapy improves uterine function (blood flow and endometrial thickness) and may potentially enable these women to benefit from assisted reproductive technologies.[22] Another small study explored uterine function in 12 women, 4–10.9 years following treatment for haematological malignancies with TBI and BMT.[24] Of the group, 66% required sex steroid replacement for premature menopause and were found to have a 40% reduction in uterine volume compared to normal healthy women. Hormone replacement provided adequate endometrial exposure as demonstrated by withdrawal bleeding, however, it was not sufficient to achieve normal growth and development of the uterus. Larsen et al. studied uterine volume in 100 childhood cancer survivors and assessed uterine response to high-dose oestrogen replacement in three patients with ovarian failure and reduced uterine volume following abdominal and/or pelvic irradiation.[25] There was no significant difference in uterine volume, endometrial thickness or uterine artery blood flow following steroid therapy, suggesting that higher doses of pelvic radiation cause greater damage, compared to lower doses (as in TBI), and this damage may be irreversible.

3. Pregnancy to confinement in high-risk survivors

Cancer therapy may cause a spectrum of damage to the reproductive tract and not all females will be rendered infertile, despite significant gonadal damage. If there is a critical oocyte mass surviving, ovulation and conception may occur. Pregnancy in this group of females should be considered as high risk as the pregnancy may be associated with an increased risk of adverse outcomes, essentially related to uterine dysfunction.

Adverse pregnancy related outcomes in survivors of childhood cancer have been explored in a small number of studies, which have often been limited by the small size of the study cohort, diversity of diagnoses and, often historical, treatments. A number of studies have assessed pregnancy outcomes in female survivors of Wilms' tumour who received irradiation to the flank, abdomen or pelvis and have reported an increased risk of premature birth and/or low birth weight.[4,13,26–28] Abdominal or pelvis irradiation is associated with an excess of low birth weight offspring regardless of the cancer type.[28] The Childhood Cancer Survivors Study (CCSS) was established as a resource for investigating the long-term outcomes of a cohort of 5-year survivors of childhood and adolescent cancer, diagnosed between 1970 and 1986. With a cohort of more than 14,000 active participants it is the largest epidemiological study investigating long-term outcomes and quality of life in survivors who are now two or more decades after initial treatment. This cohort of adult survivors report great concern regarding their fertility and health of their offspring. Two large studies from the CCSS examined pregnancy outcomes in survivors in comparison to their sibling cohort. Green et al. reported that there was no significant increased risk of stillbirths, miscarriages or abortions when compared with foetal loss in the offspring of sibling controls.[29] Signorello et al. carried out in depth studies of pregnancy outcomes in singleton live births using data from the CCSS.[3] There were 2201 singleton live births in the group of 1264 survivors and 1175 children born to 601 female siblings. Children of survivors were more likely to be born preterm (<37 weeks) than the siblings' children (21.1% versus 12.6%). The apparent increased risk of low birth weight in the offspring of survivors was a consequence of prematurity rather than a result of being small for gestational age. Within the group of cancer survivors, increasing risk of preterm birth was associated with increasing cumulative dose of radiotherapy to the uterus. Children born to survivors who had received high-dose uterine radiotherapy (>50 Gy) were at a significantly increased risk of premature delivery than children of survivors who had not received uterine radiotherapy (50% versus 19.6%). High-dose radiation to the uterus was also significantly related to an increased risk of restricted foetal growth. In comparison to children of survivors who did not receive uterine irradiation, children of survivors who received high-dose uterine irra- diation were more likely to have low birth weight (<2500 g) (36.2% versus 7.2%) and to be small for gestational age (SGA: weight <10th centile; 18.2% versus 7.8%). Of the survivor cohort, the majority of patients (65%) underwent treatment with chemotherapy, however detailed analysis did not reveal any association between exposure to alkylating agents and preterm birth, low birth weight or SGA births.

It has been shown that final uterine volume is determined by the age and pubertal status at irradiation, which may explain the observation that the risk of preterm birth may also be greater for girls who receive irradiation treatment before menarche.[3,20] Although the exact mechanism for the increased risk of preterm delivery is unknown it may be due to the physical constraint of the decreased uterine volume. Impaired elasticity and uterine fibrosis may also be associated with cervical incompetence and contribute to the risk of preterm birth.[27] Interestingly, malpresentation has been reported as a risk factor for prematurity and malpresentations have been reported more frequently in female cancer survivors of flank irradiation.[29]

Cardiac decompensation is a concern during pregnancy for patients who have received significant doses of anthracycline therapy. Although a safe dose has yet to be defined, total cumulative dose is associated with increasing risk of toxicity.[30] Other risk factors include female sex and younger age at time of treatment. In a study, Van Dalen et al. explored clinical heart failure during pregnancy in 53 females treated for childhood cancer with anthracycline-based chemotherapy (mean cumulative dose 267 mg/m^2), none of the women developed clinical heart failure during pregnancy. This demonstrates that survivors of childhood cancer are at low risk of developing peripartum anthracycline-induced clinical heart failure.[31] Monitoring of cardiovascular risk factors is a routine part of the long-term care of all cancer patients who have received anthracycline therapy and it is recommended that these women have an echocardiogram at an early stage in their pregnancy.

4. Risks to the offspring

Concerns have been raised that potentially mutagenic chemotherapy and radiotherapy may cause germ line mutations and pose an increased risk of genetic abnormalities in the children born to survivors of cancer.[32,33] Reassurance is provided in two large international studies in the United States and Denmark involving a cohort of almost 25,000 childhood cancer survivors who gave birth to or fathered children. In the United States series, genetic abnormalities were reported in 157 of the 4214 (3.7%) childhood cancer survivors in contrast to 95 (4.1%) of the 2339 children of sibling controls. Similar findings were reported in the Danish series, providing further reassurance that cancer therapies do not confer a greater risk of inherited genetic disease in the offspring.[32] The Danish Cancer Registry identified 4676 survivors of childhood cancer diagnosed between 1943 and 1996 and compared them with a cohort of 6441 siblings. From this population-based study there were 2630 live offspring born to the survivors and 5504 live-born offspring of their siblings.[33] The Danish Cytogenetic Registry was used to determine the occurrence of abnormal karyotypes and of pregnancies terminated following prenatal diagnosis of a chromosomal abnormality. Taking these cases into account, and after exclusion of hereditary cases, there was no indication of increased risk of chromosomal abnormalities in the offspring. These results are in keeping with other studies of children of survivors of childhood cancer.[34,35] The Danish group have also investigated germline minisatellite mutations in the offspring of survivors of childhood cancer. The data from this pilot study demonstrate no statistically significant increase in germline minisatellite mutation rate associated with radiotherapy for childhood and adolescent cancer.[36]

Cancer survivors are understandably concerned about the development of cancer in their offspring. Multiple studies have explored the incidence of cancer in the offspring of cancer survivors and, excluding known cancer predisposition syndromes, there is minimal or no increased risk of cancer development in the offspring.[37] Reassuringly following potentially gonadotoxic chemotherapy and radiotherapy, if the surviving oocyte pool is sufficient for the woman to conceive there does not appear to be an increased risk of germline mutations in the surviving oocytes.[37]

5. Counselling young women about premature menopause

The majority of female survivors of childhood cancer will have regular menstrual cycles. However, for a minority of women, loss of ovarian function may occur unexpectedly resulting in premature menopause and infertility. Premature menopause will also be associated with loss of ovarian sex hormone production, and consequently these women are at increased risk of cardiovascular disease, psychosexual dysfunction and osteoporosis. Sklar et al. explored the risk and frequency of premature menopause in 2819 survivors of childhood cancer over 18 years who were participants in the multi-centre Childhood Cancer Survivor Study and compared them with a cohort of 1065 siblings.[38,39] Premature menopause developed in 126 subjects (4.5%) of the survivors group and 33 of the siblings (3.5%). However, the menopause had been surgically induced in 61 (48%) of 126 survivors and 31 (94%) of the 33 siblings. The risk of developing a non-surgical-induced menopause was 13-fold greater for survivors for cancer than that of siblings, with a cumulative incidence of 8% by age 40 years. The risk factors for non-surgical premature menopause included radiation exposure to the ovaries, increasing alkylating agent score (determined by number of alkylating agents and cumulative dose) and Hodgkins lymphoma. For survivors treated with both alkylating agent-based chemotherapy and abdominal irradiation the risk of non-surgical premature menopause approached 30%.

6. Preservation of fertility

At the time of diagnosis of cancer it is important to counsel the patient and the family about the potential risk to future reproductive function.[40] Attempts to preserve fertility are being explored.[41,42] A number of strategies to protect the ovaries and preserve fertility during cancer treatment have been attempted with limited success. Limitation of radiation dose to the ovary, although sometimes practiced in adults, is technically difficult in children. For prepubertal girls and the majority of young women options remain experimental.

Conflict of interest statement

The authors have no competing interests to declare.

REFERENCES

1. Campbell J, Wallace WH, Bhatti LA, Stockton DL, Brewster DH. Cancer in Scotland: trends in incidence, mortality and survival 1975–1999. Information and Statistics division, Edinburgh. www.isdscotland.org/cancer_information.
2. Blatt J. Pregnancy outcome in long-term survivors of childhood cancer. *Med Pediatr Oncol* 1999;**33**:29–33.
3. Signorello LB, Cohen SS, Bosetti C, et al. Female survivors of childhood cancer: preterm birth and low birth weight among their children. *J Natl Cancer Inst* 2006;**98**:1453–61.
4. Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Am J Obst Gynecol* 2002;**1887**:1070–80.
5. Critchley HO, Thomson AB, Wallace WH. Late effects of ovarian and uterine function and reproductive potential. In: Wallace H, Green D, editors. *Late effects of childhood cancer*. London (United Kingdom): Arnold; 2004. p. 225–38.
6. Bath LE, Anderson RA, Critchley HO, et al. Hypothalamic–pituitary–ovarian dysfunction after prepubertal chemotherapy and cranial irradiation for acute leukaemia. *Hum Reprod* 2001;**16**:1838–44.
7. Soules MR, McLachlan RI, Ek M, et al. Luteal phase deficiency: characterization of reproductive hormones over the menstrual cycle. *J Clin Endo Metab* 1989;**69**:804–12.
8. Thomson AB, Critchley HO, Kelnar CJ, Wallace WH. Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. *Best Prac Res Clin Endocrinol Metab* 2002;**16**:311–4.

9. Wallace WH, Shalet SM, Hendry JH, et al. Ovarian failure following abdominal irradiation in childhood: the radiosensitivity of the human oocyte. *Br J Radiol* 1989;**62**:995–8.
10. Byrne J, Fears TR, Gail MH, et al. Early menopause in long term survivors of cancer during adolescence. *Am J Obstet Gynecol* 1992;**166**:788–93.
11. Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. *Hum Reprod* 2003;**18**:117–21.
12. Sanders JE, Hawley J, Levy W, Gooley T, et al. Pregnancy following high-dose cyclophosphamide with or without high-dose busulphan or total body irradiation and bone marrow transplantation. *Blood* 1996;**87**:3045–52.
13. Wallace WH, Shalet SM, Crowne EC, et al. Ovarian failure following abdominal irradiation in childhood: natural history and prognosis. *Clin Oncol (R Coll Radiol)* 1989;**1**:75–9.
14. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys* 2005;**62**:738–44.
15. Sanders JE. The impact of marrow transplant preparation regimens on subsequent growth and development. *Sem Hematol* 1991;**28**:244–9.
16. Sanders JE, Buckner CD, Amos D, Levy W, Applebaum F, Doney K, et al. Ovarian failure following marrow transplantation for aplastic anaemia or leukaemia. *J Clin Oncol* 1988;**6**:813–8.
17. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG. The effect of combination chemotherapy on ovarian function in women treated for Hodgkin's disease. *Cancer* 1983;**52**:988–93.
18. Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM. Cytotoxic induced ovarian failure in women treated for Hodgkin's disease: a comparative study of MVPP and a seven-drug hybrid regimen. *J Clin Oncol* 1985;**13**:134–9.
19. Waxman JH, Terry YA, Wrigley PFM, Malpas JS, Rees LH, Besser FM, et al. Gonadal function in Hodgkin's disease: long-term follow-up of chemotherapy. *Br Med J* 1982;**285**:1612–3.
20. Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. *J Natl Cancer Inst Monogr* 2005;**34**:64–8.
21. Holm K, Laursen EM, Brocks V, Muller J. Pubertal maturation of the internal genitalia: an ultrasound evaluation of 166 healthy girls. *Ultrasound Obstet Gynecol* 1995;**6**:175–81.
22. Bath LE, Critchley HO, Chambers SE, et al. Ovarian and uterine characteristics after total body irradiation in childhood: response to sex steroid replacement. *Brit J Obstet Bynaecol* 1999;**106**:1265–72.
23. Critchley HO, Wallace WB, Shalet SM, Mamtora H, Higginson J, Anderson DC. Abdominal irradiation in childhood: potential for pregnancy. *Brit J Gynaecol* 1992;**99**:392–4.
24. Holm K, Nysom B, Brocks V, Hertz H, Jacobsen N, Muller J. Ultrasound B-mode changes in the uterus and ovaries and Doppler changes in the uterus after total body irradiation and allogenic bone marrow transplantation in childhood. *Bone Marrow Transplant* 1999;**23**:259–63.
25. Larsen EC, Schmiegelow K, Rechnitzer C, Loft A, Muller J, Andersen A. Radiotherapy at a young age reduces uterine volume of childhood cancer survivors. *Acta Obstet Gynecol Scand* 2004;**83**:96–102.
26. Hawkins MM, Smith RA. Pregnancy outcomes in childhood cancer survivors: probable effects of abdominal irradiation. *Int J Cancer* 1989;**43**:399–402.
27. Byrne J, Mulvihill JJ, Connelly RR, et al. reproductive problems and birth defects in survivors of Wilms tumour and their relatives. *Med Pediatr Oncol* 1988;**16**:233–40.
28. Chiarelli AM, Marrett LD, Darlington GA. Pregnancy outcomes in females after treatment for childhood cancer. *Epidemiology* 2000;**11**:161–6.
29. Green DM, Peabody EM, Nan B, et al. Pregnancy outcome after treatment for Wilms tumour: a report from the National Wilms Tumor Study Group. *J Clin Oncol* 2002;**20**:2506–13.
30. Sorensen K, Levitt GA, Bull C, et al. Late anthracycline toxicity after childhood cancer: a prospective longitudinal study. *Cancer* 2003;**97**:1991–8.
31. van Dalen EC, van der Pal HJ, van den Bos C, et al. Clinical heart failure during pregnancy and delivery in a cohort of female childhood cancer survivors treated with anthracyclines. *Eur J Cancer* 2006;**42**:2549–53.
32. Winther J, Boice JD, Mulvihill JJ, et al. Chromosomal abnormalities among the offspring of childhood-cancer survivors in Denmark: a population-based study. *Am J Hum Genet* 2004;**74**:1282–5.
33. Boice JD, Tawn EJ, Winther JF. Genetic effects of radiotherapy for childhood cancer. *Health Phys* 2003;**85**:65–80.
34. Byrne J, Rasmussen SA, Steinhorn SC, et al. Genetic disease in offspring of long-term survivors of childhood and adolescent cancer. *Am J Hum Genet* 1998;**62**:45–52.
35. Hawkins MM. Is there evidence of a therapy-related increase in germ cell mutation among childhood cancer survivors? *J Natl Cancer Inst* 1991;**20**:1643–50.
36. Rees GS, Trikic MZ, Winther JF, et al. A pilot study examining germline minisatellite mutations in the offspring of Danish childhood and adolescent cancer survivors treated with radiotherapy. *In J Radiat Biol* 2006;**82**:153–60.
37. Nagarajam R, Robison LL. Pregnancy outcomes in survivors of childhood cancer. *J Natl Cancer Inst Monogr* 2005;**34**:72–6.
38. Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: a report from the Children Cancer Survivor Study. *J Natl Cancer Inst* 2006;**98**:890–6.
39. Sklar C. Maintenance of ovarian function and risk of premature menopause in relation to cancer treatment. *J Natl Cancer Monogr* 2005;**34**:25–7.
40. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *JCO* 2006;**24**:2917–31.
41. Donnez J, Martinez-Madrid B, Jadoul P, et al. Ovarian tissue cryopreservation and transplantation: a review. *Hum Reprod Update* 2006;**12**:519–35.
42. Wallace WH, Anderson RA, Irvine DS. Fertility after the treatment of childhood cancer: who is at risk and what can be done. *Lancet Oncol* 2005;**6**:209–18.