

# Do doctors discuss fertility issues before they treat young patients with cancer?

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**BACKGROUND:** Many children treated for cancer are at risk of infertility, but for girls and prepubertal boys, all fertility preservation techniques remain experimental. We have assessed UK practice relating to information provision about the effects of cancer treatment on fertility and options for fertility preservation. **METHODS:** Paediatric oncologists prospectively completed a data form for each new patient registered over a 12 month period. **RESULTS:** Data were available on 1030 patients (68% of total registered). The effect of cancer treatment on fertility was discussed with 63% of patients. Of these, 61% were judged to be at high or medium risk of fertility problems. Discussions took place more commonly with boys than girls; the commonest reason for discussion not occurring was young age. The majority (83%) of post-pubertal boys assessed as high/medium risk of infertility were referred for semen cryopreservation. This rate fell to 39% of those in early puberty. Only 1% ( $n=4$ ) of girls were referred to an assisted conception unit. **CONCLUSIONS:** These data indicate a high awareness of the potential adverse effects of therapy on fertility among UK paediatric oncologists. High referral rates for older boys indicate that current guidelines are followed, but there is a need for fertility preservation techniques for girls and younger boys.

*Keywords:* cancer; fertility; puberty; children

## Introduction

A recent working party of the UK Royal Colleges recommends that all patients who require anti-cancer treatment should be fully informed about potential gonadotoxic side effects at the time of diagnosis and before potentially gonadotoxic treatment (Report of a Working Party of the Royal College of Physicians Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists, 2007). Furthermore, they recommend that sperm banking must be considered for all males before treatment that carries a risk of long-term gonadal damage. Improvements in the treatment of childhood cancers now mean that survival into adulthood is a realistic goal for the majority of patients. However, it is recognized that some cancers and treatments may compromise fertility and this raises new issues and options for the child and their family to consider (Sonmezer and Oktay, 2004; Wallace *et al.*, 2005).

Chemotherapy and radiotherapy regimens differ widely in their effect on fertility. Highly gonadotoxic chemotherapy regimens include alkylating agents and procarbazine (Howell and Shalet, 1998; Meirow and Nugent, 2001). Radiotherapy

carries a high risk where there is a direct or scatter dose to the gonad (Wallace *et al.*, 2003). Treatment regimens are constantly evolving, and there is a need for many years of follow-up for children treated before puberty before the effect on fertility can reliably be assessed. There are only a few retrospective or prospective studies assessing gonadal function and fertility in survivors of childhood cancer in relation to the treatment received (Byrne *et al.*, 1992; Bath *et al.*, 2003; Larsen *et al.*, 2003; Chemaitilly *et al.*, 2006; Sklar *et al.*, 2006). If there is uncertainty among professionals, there are particular difficulties in advising patients and parents on the most appropriate course of action.

For children and young people, the techniques available for fertility preservation are limited. For boys, the established method is cryopreservation of spermatozoa but this is only available for those who are sexually mature enough to be able to provide a semen sample by masturbation. No established options exist for pre-pubertal boys or girls, or for young women without a partner, although for both sexes, there is much interest in cryopreservation of gonadal tissue (Oktay *et al.*, 2001; Donnez *et al.*, 2006; Ehmecke *et al.*, 2006).

The development of strategies to overcome the effects of cancer treatment on fertility is still at an early stage. The aim of this study is to investigate current practice of UK paediatric oncologists regarding fertility preservation discussions and consequent referral patterns.

## Materials and Methods

This was a prospective observational study of UK practice relating to information provision about the effects of cancer treatment on fertility and referral patterns for fertility preservation over 1 year. All children and young adults presenting with cancer in the UK are registered with the Children's Cancer Research Group (CCRG) at the time of diagnosis. This provides an accurate denominator of the total number of new cancer cases with their age and sex, for comparison with the study population. Patients were recruited for 1 year from 1 November 2003. Eligibility criteria were a new diagnosis of cancer in a patient registered at a Children's Cancer and Leukaemia Group (CCLG) centre. Oncologists were asked to complete a proforma at the time of registration on their assessment of the risks of fertility (low <20%, medium 20–80% or high >80%) for each patient, and to indicate whether fertility preservation was discussed. Table I gives an overview of the main issues addressed on the proforma. Pubertal status was assessed as per the oncologist's normal clinical practice. The assessment of fertility risk was based on the oncologist's own knowledge and understanding. Thus, the data in this study reflect current clinical UK practice.

The study received UK Multicentre Research Ethics Committee approval. The primary analysis was descriptive, with Fishers exact test used to compare proportions.

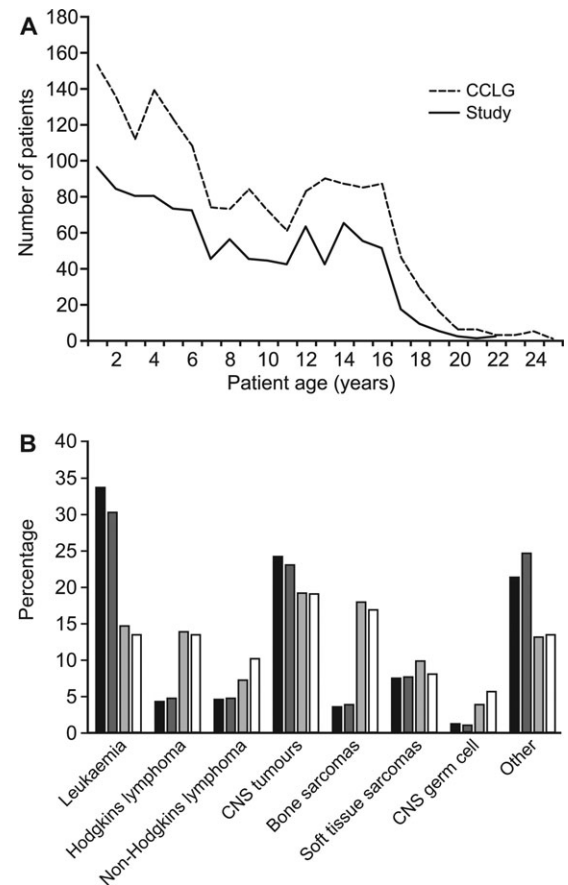
## Results

Forms were returned by 17 of the 22 CCLG centres in the UK. The remaining centres elected not to participate, the commonest reason being that their limited data management resources were already committed to other studies. A total of 1030 forms were returned, giving a return rate of 68% of patients registered by those 17 centres. The overall age distribution was very similar to that for the total population registered with the CCLG, and the distribution by diagnosis was also similar in the study compared with the total population (Fig. 1). In keeping with disease demographics, slightly more forms were returned for boys than girls (55%) and analysis of the sex ratio at each centre confirmed that none showed

marked disproportion. The majority of patients were pre-pubertal (76%), with 15% 'pubertal' and 9% 'post-pubertal' (Table II) with a similar distribution between boys and girls. The treatment plan for the majority of patients was chemotherapy regimens (76%), with a further 23% scheduled to receive radiotherapy. In 9%, there was uncertainty as to whether radiotherapy would be part of the primary treatment plan.

## Discussion of impact of treatment on future fertility

The possible impact of treatment on future fertility was discussed with 648/1030 (63%) patients overall. However, analysis by sex and pubertal stage showed that risk of fertility was discussed with 86% of post-pubertal girls and 76% of post-pubertal boys but only with 60 and 61% of prepubertal girls and boys, respectively (Table III). Pubertal status was therefore highly predictive of discussion in girls ( $P < 0.001$ ) but only approached significance in boys ( $P = 0.05$ ). The subject was usually raised by the oncologist, but had been instigated by the parent in 7%, and by the patient in 2%, of cases. In most



**Figure 1:** (A) Age distribution of all patients registered with the CCRG during the study period (solid line) and of patients included in this study (dashed line). (B) Distribution of all patients registered with the 17 centres taking part in this study ( $n = 1518$ ) by diagnosis compared with patients included in this study ( $n = 1030$ ). Black and darker shaded columns: all patients registered and study patients, respectively, ages 0–14; lighter shaded and white columns: all patients registered and study patients, respectively, ages 15–24. Data are expressed as a percentage of all diagnoses in each age group.

**Table I.** Summary of data recorded.

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- (i) Age, sex, diagnosis
  - (ii) Intended treatment plan
  - (iii) Pubertal status
  - (iv) Has the possible impact of treatment on future fertility been discussed?
    - Yes/no/reasons
    - If no, no further data required. Check list/open text
  - (v) What risk of infertility was given?
    - High, >80%; Medium, 20–80%; Low, <20%
  - (vi) Have fertility preservation techniques been discussed?
    - If yes, at whose instigation.
    - If no, why? Check list/open text
  - (vii) What fertility preservation techniques were discussed?
    - Check lists for male and female including 'not specified'
  - (viii) Whether the patient was referred to a fertility centre
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**Table II.** Distribution of study population by sex and pubertal status.

	Male	Female
Prepubertal	442	339
Pubertal	83	75
Post-pubertal	42	49
Total	567	463

Pubertal status was highly predictive of discussion in girls ( $P < 0.001$ ) but only approached significance in boys ( $P = 0.05$ ). Values are numbers of patients.

**Table III.** Analysis of study population where fertility risk was discussed.

	Male	Female
Prepubertal	61	60
Pubertal	71	55
Post-pubertal	76	86

Percentage of subjects with whom risk of fertility was discussed, analysed by sex and pubertal status.

cases, this discussion occurred at diagnosis, but in 7% this was delayed until during treatment.

Where the subject of impact on fertility was raised, the clinician was asked to record what degree of risk had been given. The risk to future fertility was scored as low (<20% chance of infertility) in 51%, with 11% given a high risk (>80% chance of infertility). Table IV gives a detailed analysis of these data by sex and pubertal stage. Boys were more likely to be considered at high risk than girls (51/362, 14% versus 21/286, 7.8%,  $P = 0.007$ ), but the proportions at medium and low risk were similar between the sexes.

Fertility was not discussed with 382 patients (37%). The most common reason for this, in 300 (79%), was that the risk of infertility was 'not significant', with 93 (15%) being regarded as too young. The severity of the patient's illness was significant in 19 (5%) and there was a poor prognosis in 48 (13%) patients. The explanation that techniques for fertility preservation were 'unproven' was only given as a reason for no discussion in nine cases and inadequate facilities and/or funding was given as a reason in only two cases.

A total of 125 boys in the study were classed as pubertal or post-pubertal and hence potentially able to produce semen for cryopreservation, and of these, the possible impact on fertility was discussed with 91 (73%). Of these, 51 (56%) were judged

to be at high or medium risk (Table IV). The main reason that the impact on fertility was not discussed in these two groups was because the risk was judged to be low (29 of 34 boys), with the remainder considered too ill or unlikely to survive; none was judged to be 'too young'. Thus, the potential effect of treatment on fertility was discussed with all pubertal and post-pubertal boys whose risk was considered to be >20%, and who were not too ill or whose prognosis was not too poor.

The majority of boys included in this study were pre-pubertal ( $n = 442$ ). The possible impact of treatment on fertility was discussed with 271 (61%) of them (Table IV), a slightly smaller percentage than with the more mature pubertal and post-pubertal boys (73%). Risk was judged to be high or medium in 169 of these 271 pre-pubertal boys (62%) (Table IV). Of the 171 pre-pubertal boys with whom fertility was not discussed, 130 (76%) were regarded as not being at significant risk, and 55 (32%) were regarded as 'too young'. Thus, even with this less mature group where the options for fertility preservation are experimental at best, the impact of treatment on fertility was discussed with most boys at risk.

Data from all girls have been analysed together. The impact of treatment on fertility was discussed with 286 (62%) of the total of 463 girls, and 175 (61%) of these were judged to be at high or medium risk.

#### *Discussion of methods for preserving fertility and referral to fertility centres*

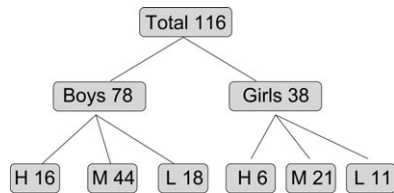
Fertility preservation techniques were discussed in 116 cases (18%), of whom 30% of each sex were at high risk and 78 (67%) were boys (Fig. 2). Techniques were discussed significantly with more boys than girls (22 versus 13%,  $P = 0.007$ ), which is probably accounted for by the greater number of boys at medium risk (31 versus 20%), with similar proportions of boys and girls at high or low risk (~30 and 10%, respectively). For 31 (27%), information was provided by a reproductive specialist.

Discussion of fertility preservation techniques included electro-ejaculation and epididymal aspiration for just three boys in addition to ejaculation in all. Of those with whom the impact of treatment on fertility was discussed, 15 of 18 (83%) post-pubertal boys and 13 of 33 pubertal boys (39%) at high or medium risk and six of 40 (15%) at low risk were referred to an assisted conception clinic. In the case of pre-pubertal boys ( $n = 442$ ), techniques were discussed in only

**Table IV.** Detailed analysis of risk to fertility by sex and pubertal stage.

Risk to fertility	Male			Female		
	Pre-pubertal <i>n</i> (%)	Pubertal <i>n</i> (%)	Post-pubertal <i>n</i> (%)	Pre-pubertal <i>n</i> (%)	Pubertal <i>n</i> (%)	Post-pubertal <i>n</i> (%)
High (>80%)	39 (14.4)	5 (8.5)	7 (21.9)	14 (6.9)	2 (4.9)	5 (11.9)
Medium (20–80%)	130 (48.0)	28 (47.4)	11 (34.4)	120 (59.1)	14 (34.1)	20 (47.6)
Low (<20%)	102 (37.6)	26 (44.1)	14 (43.7)	69 (34.0)	25 (61.0)	17 (40.5)
Total at risk	271 (100)	59 (100)	32 (100)	203 (100)	41 (100)	42 (100)

Number (*n*) and percentage of children with whom fertility was discussed (total  $n = 648$ ) by pubertal stage and by risk to fertility of their proposed treatment as assessed by the treating clinician.



**Figure 2:** Distribution of fertility risk in patients with whom fertility preservation methods were discussed. H, high risk (>80%); M, medium risk (20–80%); L, low risk (<20%).

20 (7.4%) cases and only one boy (at high risk) was referred to an assisted conception service.

Fertility preservation techniques were discussed with 38 girls. Techniques discussed included oophorectomy ( $n = 4$ ), ovarian tissue cryopreservation ( $n = 21$ ), oocyte cryopreservation ( $n = 11$ ), embryo cryopreservation ( $n = 4$ ) and hormone protection ( $n = 3$ ). A total of four girls were referred to an assisted conception service: one high risk pre-pubertal girl, and two high risk and one medium risk post-pubertal girls. The most common reasons for not discussing techniques included ‘not at significant risk’ in 123, ‘too young’ in 116 (all pre-pubertal), ‘techniques unproven’ in 95, ‘no facilities’ in 41 and ‘no funding’ in 34. More than one reason could be given.

Fertility preservation techniques were not discussed with 532 patients; in 258 (48%) this was because they were judged to be ‘not at significant risk’. This means that in the other 274 cases (52%), techniques were still not discussed despite the patient being perceived as, and informed to be, at significant risk. The most common reason given for lack of discussion was that in the opinion of the clinician the patient was too young (299/532, 56%). Other reasons were: that the techniques were unproven (133); that the patient was too ill (69) and unlikely to survive (13). Inadequate funding and/or facilities were indicated in 62 cases.

## Discussion

The aim of this study was to investigate current practice regarding counselling of patients and their carers about the effects of therapy on future fertility and the use of fertility preservation techniques. This prospective study was open to all children and young people presenting with a diagnosis of cancer in the UK over a period of 1 year. Of the 22 CCLG treating centres, 17 agreed to participate and we achieved a return rate of 68% of all patients from those centres. Although we acknowledge that incomplete data collection may lead to bias, the age distribution and lack of sex or disease diagnosis bias confirm that the survey responders are representative of a whole national cohort. Additionally, it is possible that the existence of the study, i.e. the request to complete a form, may have encouraged further discussion of fertility issues. It is not possible to estimate the extent of this, but the absence of the biases noted above suggest that this is not likely to have had a major impact.

Some treatments for childhood cancer can lead to infertility in later life (Wallace *et al.*, 2005) but there is little clear

evidence-based consensus on which patients are assessed as being at high, medium and low risk of sub-fertility in adulthood. This study did not address whether paediatric oncologists were classifying patients correctly, but what information was provided in the light of perceived risk. Apart from sperm cryopreservation for post-pubertal boys, all fertility preservation techniques remain experimental but it is important to consider other experimental techniques before treatment starts in patients deemed to be at high risk of infertility. Fertility preservation requires specialist reproductive knowledge with which the treating oncologist may be unfamiliar. A recent study of paediatric oncology providers in the USA highlighted the difficulties they found finding both proper facilities and specialists for fertility preservation for their patients (Goodwin *et al.*, 2007).

Schover *et al.* (2002a, b) found that fatherhood is important to young men surviving cancer (Schover *et al.*, 2002a). Over half of the men in that study would like to have children in the future, and 75% were childless at diagnosis of their cancer. In this group of mature men, selected because of the high likelihood that their cancer treatment could impair their fertility, only 60% recalled a discussion about fertility before treatment began, with only 51% being offered sperm banking. Despite our younger cohort of patients, of 125 peri/post-pubertal boys, the possible impact of their treatment on fertility was discussed in the great majority (73%) with the rest being considered at low risk or a few as too ill or unlikely to survive. Surprisingly, pubertal status did not prove to be as strong a determinant of whether fertility risk was discussed in boys as in girls, despite the expectation that semen cryopreservation, i.e. the only established method of fertility preservation, would be discussed with more pubertally advanced boys. However, analysis of the reasons why fertility was not discussed revealed that discussion did not occur with pubertal and post-pubertal boys at high/medium risk only where they were too ill or the prognosis too poor.

In a further study of oncologists’ attitudes and practices regarding banking sperm before cancer treatment, 91% agreed that sperm banking should be offered to all men at risk of infertility because of cancer treatment, but only 10% were able to deliver this service (Schover *et al.*, 2002b). In fact, almost half the oncologists either never mentioned sperm banking or offered it to <25% of their patients aged over 14 years. The most common barrier to sperm banking was lack of time to discuss this difficult issue. Discussion of fertility issues was mostly initiated by the oncologist. The high level of fertility awareness among UK paediatric oncologists and their readiness to discuss and refer for sperm banking in boys and young men who are at significant risk of infertility is a major finding of our study.

In a study of sperm and oocyte conservation in North American children’s cancer centers (Glaser *et al.*, 2000), there was little agreement regarding appropriate indications or methods for gamete cryopreservation. They concluded that unresolved medical, legal and ethical issues necessitate the development of a voluntary code of practice and guidelines in order to ensure good clinical practice. A recent cross-sectional survey of all paediatric oncology services in Australia

and New Zealand found inconsistencies in the indications for and methods of gamete conservation being offered to newly diagnosed children with cancer (Heath and Stern, 2006). In 2003, The British Fertility Society Guidelines (British Fertility Society, 2003) recommended that sperm banking should be offered to all pubertal young men at high or medium risk of infertility. These guidelines, together with the establishment of links between assisted conception centres and oncology units, may have contributed to improving knowledge and awareness of these issues in the UK paediatric cancer community. While these guidelines thus reflect current practice in the UK for post-pubertal boys as revealed in this study, the referral rate for pubertal boys was markedly lower, at 39%. These results therefore indicate the need for further improvements in referral patterns for this group at risk.

Semen cryopreservation is an established and effective way of preserving fertility for the post-pubertal male. It can be very difficult for teenagers who have been given a devastating diagnosis to discuss fertility, understand the difference between it and potency, and then produce a semen specimen (Edge *et al.*, 2006). It is also recognized that the disease itself can reduce the quality of the semen specimen and make it unsuitable for storage. On the positive side, however, many patients and their families benefit from open discussion regarding fertility, as this places emphasis on looking to the future and provides reassurance that curative treatment is the aim (Wallace and Thomson, 2003; Saito *et al.*, 2005).

At present, there are only two established practices of fertility preservation in female patients receiving potentially gonadotoxic cancer therapy (Wallace *et al.*, 2005), oophoropexy and cryopreservation of embryos. The former may preserve ovarian function, but radiation-induced uterine damage may reduce the chances of carrying a successful pregnancy. The latter is only applicable to sexually mature females, and requires sperm for fertilization. For women without a partner, cryopreservation of mature oocytes is a potential alternative, but subsequent pregnancy rates are significantly lower as these cells sustain more damage during the freeze–thaw process than do embryos (Oktay *et al.*, 2006). These techniques also involve delaying treatment to allow ovarian stimulation. For pre-pubertal patients or women without a partner, ovarian tissue can be removed (Donnez *et al.*, 2006) without delaying treatment (Burns *et al.*, 2006). The proof of principle for this was demonstrated in sheep, with both the return of cyclical ovarian activity and production of offspring (Baird *et al.*, 1999). The recent reports of human embryo development after heterotopic transplantation of cryopreserved ovarian tissue (Oktay *et al.*, 2004) and of live births after orthotopic transplantation of cryopreserved ovarian tissue (Donnez *et al.*, 2004; Meirow *et al.*, 2005; Demeestere *et al.*, 2007) are important advances in demonstrating that it may be realistic to restore ovarian function following sterilizing treatment.

The impact of treatment on fertility was discussed with 62% of the girls overall in our study, rising to 86% of the post-pubertal girls. Discussion was instigated by the oncologist in the majority of cases, indicating a high awareness of this issue, and was more commonly raised by girls and their parents than by boys and their parents. A total of four girls

were referred to an assisted conception service. As with boys, the increasing awareness among UK paediatric oncologists and their patients is reflected in the percentage of girls with whom the impact of treatment on fertility was discussed. The small number referred to assisted conception services probably reflects awareness among oncologists of the experimental nature of all fertility preservation methods in young women. The fact that some cases were referred indicates that UK paediatric oncologists do not regard it as unethical for patients to be offered these treatments (Dudzinski, 2004).

In conclusion, this study demonstrates a high awareness among paediatric oncologists in the UK of the potential adverse effect of cancer treatment on fertility, and that discussion of this issue with patients and their families is the norm. Sperm cryopreservation was discussed with most boys, and referral rates were high where this was most clearly appropriate, although it appears that more pubertal boys should be referred. In girls, the level of awareness and interest among both oncologists and patients regarding fertility preservation is high, indicating that techniques, when established and available, will be widely used.

The recent report of a working party of the Royal Colleges recommends that long-term sperm banking should be universally available and fully funded for patients at risk of long-term gonadal damage (Report of a Working Party of the Royal College of Physicians Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists, 2007). National funding bodies are strongly encouraged to fund the development of a small network of research-based oocyte and ovarian tissue storage facilities which will be able to provide universal access to techniques which aim to preserve fertility. With increased awareness among paediatric oncologists of fertility issues in their patients, it is important that an evidence-based approach to the management of this small number of young patients requiring these techniques is developed as a matter of urgency.

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