We can now cure more than 70 per cent of all childhood cancers, and this cure rate approaches 90 per cent for some tumours. Enhanced supportive care for dose-intensive treatment regimens imposed on a cancer incidence that has been stable over the past 40 years is responsible for this success. Where survival is so high, however, further attempts to increase it must be balanced against the multi-organ toxicities to the majority of developing children. Though not necessarily impotent, 15–30 per cent of male survivors are rendered infertile, either from hypothalamo–pituitary–gonadal exposure to chemoradiation or from diseases such as Hodgkin’s lymphoma.

In today’s society, one in six healthy couples seeks help from reproductive clinics to conceive, with rapid advancements in assisted reproductive technology (ART) having being made in the past two decades. These include cryopreservation of gametes and embryos prior to gonadotoxic cancer therapies to preserve fertility in adults.

**IMPACT OF CHILDHOOD CANCER TREATMENT ON MALE FERTILITY**

Spermatogenesis begins only at puberty. This process requires meiotic division of diploid spermatogonia to produce haploid spermatozoa, a process that continues thereafter throughout adult life. Spermatogenesis requires sufficient intratesticular testosterone production maintained by pituitary-derived follicular-stimulating hormone (FSH) and luteinising hormone (LH) with negative gonadal feedback from inhibin B (Sertoli cells) and testosterone (Leydig cells). Both disease- and treatment-related factors can damage the hypothalamo–pituitary–testicular axis at one or multiple levels (Figure 1), thereby compromising male reproductive capacity.

**Chemotherapy**

The rapidly dividing sperm-producing testicular seminiferous epithelium is highly susceptible to cytotoxic damage, its extent determined by drug type, cumulative drug

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**Preserving reproductive capacity in young boys with cancer**

**HOONG WEI GAN AND HELEN A. SPOUDEAS**

In this article, the authors explore the possibilities and particular developmental and ethical issues surrounding sperm cryopreservation in young boys with cancer, and examine the unique legal implications of fertility counselling in adolescence.

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dosage and patient age at exposure. By contrast, the testosterone-producing Leydig cells are relatively robust. Consequently, pubertal sexual development may proceed normally (and sometimes early), the only sign of gonadotoxicity and future subfertility being small testicular volumes relative to the degree of virilisation and pubertal stage.

Because cancer treatment protocols are multidrug regimens, the individual effect of specific drug types has proved difficult to determine accurately. However, most alkylating agents (eg cyclophosphamide, busulfan, melphalan) and nitrosureas (eg lomustine) demonstrate dose-dependent gonadotoxicity; the UK Children’s Cancer and Leukaemia Group and the British Fertility Society (BFS) have provided helpful ‘guesstimates’ of the ‘gonadotoxicity risk’ of current common children’s cancer treatment regimens (Box 1).

Radiotherapy may affect fertility at more than one level on the hypothalamo–pituitary–testicular axis (see Figure 1). First, the testis is vulnerable to increasing doses of irradiation, which differentially affect the seminiferous epithelium and Leydig cells (Table 1). In adults, fractionated doses as low as 0.1 gray (Gy) may cause temporary azoospermia, while doses of 2–3Gy are likely to prevent spermatic recovery long term. Larger doses of 10–12Gy, as used in total body irradiation, damage both Leydig and Sertoli cell function and, if given concurrently with chemotherapy, have additive effects. Hypersecretion of LH can partially compensate for mild Leydig cell dysfunction with near-normal testosterone values (subclinical hypergonadotrophic hypogonadism), but the long-term impact on bone strength and cardiac health is unknown.

Disease
Occasionally, the disease itself can cause testicular dysfunction. Hodgkin’s disease has been associated with pre-treatment abnormalities in semen quality even in the absence of testicular infiltration. The pathogenesis of this phenomenon is poorly understood but is thought to relate to disease-induced inflammatory processes.

CURRENT FERTILITY PRESERVATION STRATEGIES
In mature adults, pre-treatment sperm cryopreservation has been the most successful method of fertility preservation since the 1950s. Spermatozoa are remarkably resistant to storage and freeze–thawing processes, and healthy offspring without congenital anomalies have been reported from sperm stored for up to 28 years. Separately stored ‘straws’ of spermatozoa can be thawed as required and used in fertility treatments, either directly by intrauterine insemination or by intracytoplasmic sperm injection, a technique available since 1992 that has markedly reduced the number of viable spermatozoa required to single numbers.

Requesting and obtaining masturbatory semen samples from older post-pubertal males is relatively straightforward. However, even ill adults may fail to produce a specimen in this way. For these patients and younger boys unable to...
to produce a sample because of psychological or sexual immaturity, religious or cultural beliefs, alternatives such as rectal electrostimulation, penile vibratory stimulation, surgical extraction under general anaesthesia, and even experimental techniques such as testicular tissue storage have been considered but not widely practised.

To facilitate service delivery, what remains unclear is exactly when during pubertal maturation boys are able spontaneously to ejaculate semen containing viable sperm. Spermaturia – the appearance of sperm in the urine by retrograde ejaculation – has been documented in healthy boys as young as 11.7 years of age and at a minimum testicular volume of 4.7ml, with little or no pubic hair development (Tanner stage P1, G2) and before peak height velocity. The age range for initial spermaturia, however, is wide and up to 17.5 years. Although it has been used as an estimate of true spermarche, there is no documentation of what triggers spermatogenesis, its correlation with pubertal staging and the ability to donate semen voluntarily, while spermatozoa obtained from urine are less viable and hence unsuitable for cryopreservation.

PIONEERING SERVICE FOR ADOLESCENT BOYS

More than 10 years ago, with the support of colleagues in child psychiatry, reproductive health and haematology/oncology contributing to the development of age-appropriate information leaflets, awareness campaigns and streamlined risk-assessments and referrals, we set up a pioneering endocrine/fertility assessment and counselling service for adolescents at University College London Hospital. This was targeted at males with cancer aged 12–18 years referred to our tertiary centre for high-dose therapies.

The repeated three- to four-yearly audit cycles of service in a total of 222 boys over that time have demonstrated a surprisingly consistent and unchanging counselling rate of some 70 per cent, but with an appropriately greater prioritisation of those at highest ‘gonadotoxicity risk’ over time. However, the relative paucity (30.0 per cent) of documented pubertal clinical examinations persists to date, in spite of good biochemical marker measurements (70.3 per cent) and high patient acceptability of the counselling process (68.4 per cent). 34.2 per cent of the total cohort (and 65.0 per cent of those actually attempting storage) banked viable sperm produced by masturbation, the youngest boys being 12.6 years at Tanner stage 3+ and/or with a testicular volume of ≥8ml (Gan HW, Williamson E, Cuddis Z, et al, personal communication). Importantly, it was hormone parameters of virilisation (testicular volume, plasma LH and
testosterone concentrations), not age per se, that correlated with successful storage, while parameters of spermatogenesis (plasma FSH concentration) determined the normality of sperm concentrations. The role of age came into play only as a surrogate marker of pubertal development and was not independently predictive of outcome.

Prepubertal boys
There are currently no proven fertility preservation techniques for prepubertal boys (testicular volume <4ml). Cryopreservation of diploid spermatogonial cells obtained by testicular biopsy for later post-cure autotransplantation or in vitro maturation to spermatozoa (as currently debated in young women) is still experimental, without successful conceptions, even in animal models. Auto-transplantation carries a theoretical risk of reintroducing malignant cells, particularly in haematological malignancies where the testes are potential sites of metastases. Other prophylactic techniques such as testicular shielding during radiotherapy or the administration of gonadotrophin-releasing hormone analogues or testosterone to render cell division quiescent and less susceptible to cytotoxins have limited, if any, practical success.

LEGAL, ETHICAL AND PRACTICAL CONSIDERATIONS
The storage and use of haploid gametes and embryos is governed by the Human Fertilisation and Embryology (HFE) Act14 – this mandates personal, not proxy, informed consent in line with reproductive rights. Thus, unlike for other paediatric procedures – for instance consenting for an appendicectomy – parents cannot give valid consent on a teenager’s behalf; any minor (under 18 or 16 years of age respectively in England and Scotland) must be judged intellectually (‘Gillick’) competent to consent without coercion. Written consent to disclosure, HIV, hepatitis B and C testing and the use of stored samples after death or mental incapacitation is additionally required at this difficult time.

Paradoxically, the legal loophole in which diploid prepubertal testicular tissue does not fall under HFE jurisdiction until such time as it becomes haploid leaves prepubertal boys potentially open to harm from experimentation – such as surgical removal of premeiotic spermatogonia – under the common law of parental consent, even if the sole intent to preserve fertility appears well intended.

There are few, if any, adolescent-tailored sperm banking and counselling facilities in the UK, and there is debate as to how adult services might be modified to meet their specific needs (eg the environment, written information and pornographic material provided). The increased press focus on fertility preservation and NICE recommendations suggest such a service might be offered more widely. However, while the young age of this increasing number of survivors would indicate a need for longer-term storage, historically, few stored samples have ever been used. This would suggest adult survivors either retain or do not ultimately want fertility, but also that patients at highest risk of subfertility are those most heavily treated and likely to die from aggressive disease or treatment-related complications.

ADOLESCENT FERTILITY COUNSELLING SERVICE
Oncologists may perceive reproduction as too sensitive and inappropriate a topic to broach with adolescents already undergoing a complex counselling and consent process for cancer treatment.15 However, the few studies in this area indicate surprising awareness among adolescents, who in fact welcome discussion and choice – a positive experience at this stage of their disease (Box 2).16

Pre-treatment fertility assessment
The young teenager has unique ethicolegal, physical, psychosexual and intellectual needs that are very different from those of the fully mature adult. To be fit for purpose, any adolescent fertility service should routinely, consistently and reliably measure and record pubertal staging and testicular volumes; this is but one step further than the routine examination of the testes required to exclude malignant involvement.

Paired with pre-treatment plasma endocrine biochemistry (LH, FSH, testosterone ± inhibin B where possible), this baseline assessment should form the gold standard against which service adherence might be judged and audited. It is vital not only to inform the

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**BOX 2. Summary of main points in the assessment and counselling for fertility preservation in adolescent boys**

**PRE-TREATMENT**
- Counsel within adolescent-tailored facilities (ideally)
- Counsel before commencement of treatment
- Allow sufficient opportunity to bank samples before treatment
- Clinical assessment – pubertal stage, testicular volume, best estimate of subfertility risk
- Biochemical assessment – LH, FSH, testosterone, inhibin B
- Gillick competence and informed consent including virology (HIV, hepatitis B and C)

**POST-TREATMENT**
- Streamlined late effects follow-up (may have other endocrine toxicities)
- Encourage post-treatment semen analysis (do not bank before three months)
- Contraceptive advice
- Testicular self-examination
counselling process and the individual patient’s chances of producing a viable sperm sample, but also to assess future serial change indicative of gonadotoxicity and/or spermatic recovery with time.

We have found that collecting sperm immediately after commencement of chemotherapy (even after only six days’ exposure) is likely to reduce sample viability by >75 per cent, and therefore this practice should be avoided. If it is to be successful in those judged to be at high risk (see Box 1), fertility preservation should be given earlier and higher priority in the cancer counselling process, even to the point of delaying cancer treatment to allow several attempts where possible.

Post-treatment fertility assessment
The long-term follow-up of teenage cancer survivors has not to date emphasised routine fertility assessment, semen analysis and/or sperm banking (against a future relapse) in those still minors (<18 years) at the end of cancer therapy.

However, counselling young boys and supporting them to donate interval post-treatment semen samples, together with routine pubertal and biochemical assessment, would provide the data needed to inform future age-appropriate services and sperm storage facilities based on the true gonadotoxicity (and time to recovery) of different cancer treatment regimens and their clinical correlates.

This would concur with the 2003 BFS consensus recommendation that where sperm was not cryopreserved before treatment, a further opportunity at least three months from the end of the chemotherapy (to reduce the risk of DNA damage) should be offered.7

For the counselling process to be truly complete, it should ensure understanding of the difference between potency (likely to be preserved or otherwise easily replaced) and fertility; for those unable or choosing not to cryopreserve sperm pre-treatment, there is still well-documented potential for recovery of natural fertility even five years after treatment13 and the consequent need for contraception in all. Testicular self-examination should be encouraged in the older teenager to monitor for tumour relapse or secondary malignancies.

CONCLUSIONS
As ART continues to evolve rapidly, fertility counselling in adolescence presents a specific and growing challenge. Government-level debate on the future role of the HFE Act would do well to give consideration to the needs of this cohort, who are increasingly campaigning for protection of their reproductive rights through patient groups such as the Teenage Cancer Trust. Meanwhile, clinicians can be reassured that the large majority of young teenagers welcome the discussion and can exercise appropriate informed choice even in the context of a life-threatening illness. There should thus be ample opportunity to discuss options available to them both before and after cancer treatment with concurrently improved documentation of consent and clinical examination to make the service truly tailored to the adolescent.

Declaration of interests: none declared.

REFERENCES