



# Management of fertility issues in cancer survivors

**BACKGROUND** With improved survival of cancer patients, the issue of fertility after treatment assumes greater importance. Consideration of fertility preserving measures before treatment needs to be considered.

**OBJECTIVE** To discuss an approach to management of fertility issues in survivors of cancer.

**DISCUSSION** Sensitive early counselling on fertility options is important to cancer survivors hoping to achieve a pregnancy. Assessment of fertility, the safety of a possible pregnancy and the impact of cancer treatments on future fertility treatments all need to be considered.

Cancer in the reproductive age group (patients younger than 44 years of age) is a relatively common problem, accounting for 10.8% of cancer diagnosis. In Australia this equates to in excess of 8000 new cases per year of cancer in people who may not have commenced or completed their family.<sup>1</sup> With average five year survival rates now exceeding 70%, many survivors of cancer are now in the enviable position of looking forward to a future that does include children.

The effect of cancer therapy on gonadal function is discussed in the article by Marsden and Hacker in this issue of AFP. Potential gonadotoxic cancer treatments are summarised in Table 1.

There are three principal issues concerning pregnancy in survivors of cancer treatment.

- Does the patient have a fertility problem as a result of treatment?
- Is pregnancy safe, both from the perspective of the cancer survivor and their future baby?
- How does the previous cancer or its treatment impact on future fertility treatment?

**Table 1. Potentially gonadotoxic cancer treatments<sup>13,14</sup>**

**Chemotherapy agents** with moderate to high risk of gonadal damage:

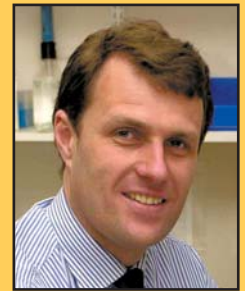
- Alkylating chemotherapy, eg. cyclophosphamide, ifosfamide, melphalan, busulphan, chlorambucil
- Alkaloids, eg. vinblastine
- Platinum agents, eg. cis-platinum
- Procarbazine

Methotrexate, cytosine arabinoside, anthracyclines and paclitaxel are low risk of producing gonadal toxicity.

**Radiotherapy thresholds**

Testicular radiation:	0.1-1.1 Gy	- oligospermia
	> 1.2 Gy	- azoospermia
	> 20 Gy	- possible Leydig cell disruption
Ovarian radiation:	Ovarian failure 5-20 Gy	(higher dose needed in young women)

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**Table 2. Features of gonadal dysfunction**

<b>Testis</b>	
Spermatogenesis	decreased testicular volume high FSH low inhibin B low sperm count/azoospermia reduced spermatogenesis on testicular biopsy
Leydig cell	low testosterone levels high LH levels
<b>Ovary</b>	delayed puberty or secondary amenorrhoea (more than 12 months) high FSH low oestradiol (may be high on day 3–5 in early POF) low inhibin B reduced ovary volume on ultrasound
<b>Uterus</b>	endometrial biopsy abnormalities decreased uterine size on ultrasound, impaired endometrial function (thickness, Doppler flow)

## Assessment of fertility

### In the male patient

Assessment of signs of normal pubertal development (adult distribution of pubic and facial hair, normal penis and testicle size) will give the clinician an idea of whether androgen production capacity has been damaged by cancer treatment in the pre-pubertal period. Similarly, the finding of low libido, poor energy levels and impotence may imply impaired testosterone production in the adult man. This could be confirmed by high serum levels of LH and low levels of testosterone (Table 2).

Semen analysis is the definitive measure of spermatogenesis in the adult male. Confirmation of testicular failure as the cause of azoospermia (absence of sperm in the ejaculate) rather than outflow obstruction can be implied by the finding of small testicles, high serum FSH and low inhibin B levels. However, testicular biopsy is the definitive investigation.

### In the female patient

Extensive destruction of the prepubertal ovary may result in failure of normal breast development and primary amenorrhoea. Pubic hair development is androgen dependant and therefore can be driven

by adrenal androgens, even in the absence of ovarian function. Total destruction of ovarian function in the adult woman will present as secondary amenorrhoea and symptoms of hypo-oestrogenism. It is important that the clinician does not diagnose premature ovarian failure (POF) until at least 12 months of secondary amenorrhoea and raised FSH have passed since some women may only experience transient ovarian failure.

The first sign of impending POF is usually a shortening in the menstrual cycle, followed by menstrual irregularity. Tests of ovarian reserve such as early follicular phase levels of FSH, oestradiol and inhibin B, combined with ultrasound assessment of ovarian size and follicle number are all useful (Table 2).<sup>2</sup> If a patient is found to have diminished ovarian reserve she should consider attempting pregnancy as soon as possible. If this is not appropriate due to a lack of a suitable male partner, she has several options. First she may consider undergoing ovarian hyperstimulation with the oocytes being frozen for later insemination once a partner is found. This process has resulted in live births but is relatively inefficient compared to routine IVF where embryos are frozen.<sup>3</sup>

Alternatively, she may wish to use donor sperm if legislation in the treating state allows for this. A final alternative is to take multiple biopsies of the ovarian cortex at laparoscopy and to freeze these for later use. This approach is currently experimental, as no pregnancies have yet been achieved, despite hormonal evidence of resumption of follicular activity following transplantation of the tissue back into the patient after cancer treatment was completed.<sup>4</sup> Furthermore, transplantation could potentially be dangerous if the ovarian biopsy harbours tumour cells.

Women who have had pelvic or abdominal irradiation should have some assessment of tubal patency since radiation may cause tubal pathology.<sup>5</sup> We favour endoscopic over radiological techniques for assessing tubal status since the operative technique allows for better assessment of radiation related endometrial damage.

## Safety of pregnancy following cancer treatment

Both male and female survivors of cancer should have an open discussion with their treating clinician about their long term prognosis before embarking upon starting a family. As a general

rule, once a patient reaches five years postdiagnosis without any evidence of recurrence, they are cured. Breast cancer is the unfortunate exception to this rule, with recurrences possible up to 20 years after the primary diagnosis.

Pregnancy in female survivors of cancer raises several issues. First, chemotherapy and radiation damages DNA in the surviving oocytes, especially those already embarking upon the long path to maturity. Most obstetricians would advise women to avoid pregnancy for one year after chemotherapy as data from pregnancies conceived greater than one year postchemotherapy show no increase in congenital anomalies.<sup>6</sup>

Second, the clinician should be mindful that pregnancy results in a massive increase in oestrogen levels. This theoretically could stimulate the growth of oestrogen receptor positive breast cancer tissue. Fortunately, the available evidence does not indicate a significant increase in cancer recurrence in women who become pregnant shortly following breast cancer treatment.<sup>7</sup>

Abdominal irradiation has the potential to damage uterine function, as well as ovarian activity. Radiation damages the small vessels within the myometrium and subendometrial layer, reducing uterine blood flow. The resulting endometrial atrophy can result in implantation failure, presenting as infertility or recurrent miscarriage. Furthermore, even if successful implantation does occur, there is an increased risk of fetal growth restriction and preterm delivery,<sup>6</sup> both leading to an 8-fold increase in perinatal mortality compared to controls.<sup>8</sup> Close surveillance of all pregnancies with serial growth scans is therefore mandatory.

## **Fertility treatment in survivors of cancer**

### **Female**

Women who develop POF following cancer treatment may achieve pregnancy using donor oocytes in combination with IVF. If the patient has had abdominal irradiation it is prudent to assess their endometrial function by measuring endometrial thickness during a hormone stimulated cycle, in combination with an endometrial biopsy, before placing them on a donor oocyte program. If the endometrium remains thin and atrophic despite high dose oestrogen stimulation, successful pregnancy following embryo transfer is unlikely and the couple would be better off to consider adoption.

Women exposed to chemotherapy or pelvic irradiation may not respond normally to ovulation inducing drugs during IVF treatment because of a reduction in ovarian reserve. This may be predicted by elevated FSH levels (>10 IU/L) taken on day 3–5 of the menstrual cycle. These women are then given higher doses of stimulation, often still with suboptimal results.

Ovulation induction during IVF treatment results in oestrogen levels 5–15-fold higher than normal cycles. For this reason, most fertility specialists would not advocate stimulated IVF treatment in a woman recently diagnosed with hormone sensitive breast cancer.

### **Male**

Today it is common practice for men to produce 2–3 semen samples for cryopreservation before embarking on chemotherapy or radiation treatment. This should ideally be performed before any cancer treatment has commenced as both treatments can damage sperm DNA, rendering them useless for future use. Damage to the sperm genetic material appear to be transient, resolving within six months of cancer treatment in men who do not become azoospermic.<sup>9,10</sup> Therefore, these men should be encouraged to delay plans for a family until after this six month period.

The type of fertility treatment offered to men who have stored semen depends upon the quality of the samples and the fertility status of their partner. If the female partner has patent tubes and there is abundant semen available, intra-uterine insemination is a useful approach. If the semen sample is poor, as often is the case with cancer patients, IVF with intracytoplasmic sperm injection (ICSI) may be required.

In men found to be azoospermic following cancer treatment, testicular biopsy can still identify small pockets of normal spermatogenesis within the testicle in approximately 50% of cases.<sup>11,12</sup> Testicular biopsy is therefore vitally important in this setting as it gives the patient a chance of fathering his own genetic child using IVF-ICSI technology.

### **Conclusion**

Advances in cancer treatment and reproductive medicine will enable many young cancer patients to experience parenthood in the future. When a diagnosis of cancer is made in a young person, thoughts of fertility are often furthest from their

minds. It is imperative that the general practitioner or treating specialist considers fertility preserving measures such as semen storage before commencement of cancer treatment. Sensitive early counselling about fertility options, with possible early referral to a gynaecologist with an interest in this area, may be useful.

Conflict of interest: none declared.

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### SUMMARY OF IMPORTANT POINTS

- If the proposed therapy places the patient at risk of gonadal failure, refer to a reproductive medicine unit for discussion of fertility preserving options before cancer therapy is commenced. Cryopreserve semen in all male cases of cancer.
- Assess reproductive function 12 months postcancer treatment, as described in Table 2. If signs of diminished reproductive function exist, refer early to a reproductive medicine unit so all fertility options can be discussed.
- Delay conception for at least 12 months after chemo/radiotherapy, so as to minimise the risks of treatment related congenital problems.
- Women receiving abdominal irradiation are at an increased risk of miscarriage, IUGR and preterm delivery and therefore should be managed by an obstetrician.
- Beware of the increased risk of POF in women exposed to cancer therapy, even if they resume normal menstrual function shortly after treatment.

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