Australian fertility preservation guidelines for people with cancer 2022: review and recommendations

Best practice in oncofertility care requires structured referral pathways, with access to fertility preservation counselling and technology

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Fertility preservation is a rapidly advancing field, and new strategies are continuously being developed and refined.[1] These strategies include oocyte and embryo cryopreservation, ovarian tissue cryopreservation and subsequent autografting for females, and sperm cryopreservation and testicular biopsy for males. Fertility preservation treatment is often urgent to prevent a delay in commencing cancer treatments. It requires effective communication and referral pathways between multidisciplinary teams, so that provision of fertility preservation care can be delivered consistently.[1]

In Australia, cancer incidence and survival have both increased.[2] In 2022, it is projected that over 8200 Australians under the age of 40 years will be diagnosed with cancer, with an incidence of 60.7 cases per 100 000 population.[2] This has nearly doubled from 4277 cases diagnosed per year in 1982.[2] The 5-year survival rate from all cancers has also improved in both the paediatric and young adult populations aged 0–19 years (75.5% survival in 1988 *v* 86.1% in 2017) and in the adult population aged 20–39 years (78.7% in 1988 *v* 88.6% in 2017).[2]

Currently, fertility preservation care is often underimplemented.[3] The barriers to overcome include limited models of care and uneven access due to cost, low health literacy, and patient education.[3] As the use of fertility preservation increases, further reporting on outcomes data is required.[1] In order to improve the quality of care, data collection by national and international registries is vital to identify the short and long term outcomes of fertility preservation interventions.[1]

As the Clinical Oncology Society of Australia (COSA) Fertility Preservation Taskforce, we have developed the 2022 guidelines,[4] with updates in management including:

- oocyte and embryo cryopreservation;
- ovarian tissue cryopreservation and transplantation;
- testicular sperm extraction; and
- testicular tissue cryopreservation in pre-pubertal boys.

The interdisciplinary working group designed clinically focused questions on important aspects of fertility for patients with cancer to inform guideline development. The draft guidelines were released for public consultation by professional societies and other interest groups in Australia from 2 to 28 June 2021, involving stakeholder input from the public. Using the National Health and Medical Research Council Levels of Evidence and grades for recommendations,[5] we made 26 evidence-based recommendations, with six consensus statements and two practice points.[6] The full *COSA guidelines for fertility preservation for people with cancer* can be accessed at www.cancer.org.au/clinical-guidelines/cancer-fertility-preservation.

Impact of cancer on fertility and discussing risk and referrals

Future fertility and the opportunity to have a family are among the most important concerns of people with cancer.[3] There is a wide variation in the awareness of health care professionals of the need for timely fertility discussion with people diagnosed with cancer.[3] The treatment of cancer in premenopausal women of childbearing age is associated with both decreased pregnancy and live birth rates[7] (Box 1). Women who receive cancer treatment may be more likely to have reduced ovarian reserve than those who have not undergone cancer treatment.[8] Furthermore, sperm quality is reduced in men previously treated for cancer compared with the general population.[9] Azoospermia may occur after cancer treatment including chemotherapy and radiation.

The lack of knowledge of current fertility preservation options is a barrier to this discussion. Optimising education and training of health care providers and implementing a formal oncofertility service reduces the risk of patient decisional conflict and regret regarding fertility preservation options.[10] Referral of patients with cancer to a fertility preservation specialist does not always occur, despite being acknowledged internationally as an important part of early cancer management[3] (Box 2).

The provision of a fertility preservation program within a multidisciplinary team is associated with improved referral pathways and timely fertility preservation discussion and treatment if required,[3,10] with guidance available from both the Australasian Oncofertility Consortium Charter[11] and the International Oncofertility Competency Framework.[12] Fertility counselling and the opportunity for fertility preservation are both associated with increased quality of life, including better physical, social and psychological health, and lower decisional regret. Studies evaluating decision aids have shown reduced decisional conflict and improved education in people with cancer and parents of patients with cancer.[13]

1 Impact of cancer treatment on fertility and discussing risks

Topic	Evidence-based recommendations	Level of Evidence	Grade for recommendation
Pregnancy and live birth	Health professionals should inform all people diagnosed with cancer, or parents in the case of children, that there is potential for cancer treatment to affect fertility	III-3	B
Ovarian function	Health professionals should advise female patients before cancer treatment about the risk of a reduction in their ovarian reserve after treatment	II	A
Testicular function	Health professionals should advise male patients before cancer treatment about the risk of loss of testicular hormone function and a reduction in sperm count	II	A
	Post-pubertal boys and men should have reproductive follow-up from 12 months after completion of cancer treatment		Consensus
Reproductive concerns	All patients with cancer, should receive age-appropriate information and support regarding the impact of specific cancer treatments on their future fertility	IV	C
	The desire of the person with cancer for future fertility should be taken into account when choosing systemic and local cancer treatments		Practice point
Health professional awareness	Continuing education for health professionals about reproductive health, risk of infertility and fertility preservation options is essential	IV	C
	Fertility discussions should be implemented and documented as part of the routine cancer plan for all patients. Age-appropriate materials should be provided to patients to assist with retention of information and for later reference	IV	C
Role of oncology services	Cancer services should develop organised oncofertility programs aligned with the Australasian Oncofertility Consortium Charter so that fertility care is incorporated into essential cancer care. Oncofertility programs should have a clear governance process that includes specific requirements for children	IV	C

2 Referral, service provision and psychological support

Topic	Evidence-based recommendations	Level of Evidence	Grade for recommendation
Referral rates and decisional conflict	Patients with cancer should have an opportunity to meet with fertility counsellors to provide decision-making and psychological support	III-3	C
Referral pathways	Cancer services should establish referral pathways with fertility preservation services to enable rapid referral of newly diagnosed patients with cancer	IV	C
Oncofertility service provision	Services planning on establishing their own oncofertility program are encouraged to refer to the International Oncofertility Competency Framework and the Australasian Oncofertility Consortium Charter	II	C
Fertility counselling	Fertility counselling should be offered to everyone with potentially curable cancer, ideally by a reproductive specialist and/or trained counsellor	I	B
Decision making	The use of decision support tools, such as fertility preservation decision aids, should be offered where available as they may assist with the decision-making process	I	A

Options for fertility treatment

Cryopreservation of semen before cancer therapy for post-pubescent boys and adult men is associated with a high chance of successful conception[14] (Box 3). A reported live birth rate of 62% using assisted reproductive technologies was comparable to that of the non-cancer population.[14] Testicular sperm extraction for post-pubertal males before chemotherapy, when production of a semen sample

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3 Options for fertility treatment

Topic	Evidence-based recommendations	Level of Evidence	Grade for recommendation
Sperm cryopreservation	It is essential to counsel post-pubertal adolescents and adult men and to provide an opportunity to freeze semen samples (ideally, multiple) before cancer treatment	III-2	C
	Screening of patients with cancer for infectious diseases concurrently with sperm cryopreservation is encouraged		Practice point
Sperm extraction (pre-pubertal boys)	Health professionals should consider discussion about testicular tissue biopsy and cryopreservation in pre-pubertal boys. This treatment is currently regarded as experimental and should only occur within an established research/ethical framework	IV	D
Sperm extraction (pubertal boys and post-pubertal men)	Health professionals should discuss the option of testicular sperm extraction and sperm cryopreservation in post-pubertal boys and men who cannot produce a semen sample	IV	D
Sperm extraction (pubertal boys and post-pubertal men)	Health professionals should discuss the option of testicular sperm extraction and sperm cryopreservation in azoospermic men who have had gonadotoxic cancer treatments and are desiring fertility treatment		Consensus
Embryo cryopreservation	Women of reproductive age at risk of gonadotoxicity from cancer treatment should be offered the opportunity to cryopreserve embryos before cancer treatment	III-3	C
Oocyte cryopreservation	The opportunity to freeze oocytes should be offered to post-pubertal girls and women at risk of gonadotoxicity from cancer treatment	II	C
Ovarian stimulation	Women with low risk breast cancer disease can be reassured that ovarian stimulation for fertility preservation is unlikely to contribute to cancer recurrence after treatment	II	C
Ovarian tissue cryopreservation	Ovarian tissue cryopreservation should be considered for pre-pubertal girls, and for young women at significant risk of premature ovarian insufficiency from gonadotoxic cancer treatments. The safety of grafting in patients with leukaemia has not been demonstrated	IV	C
Ovarian transposition	Ovarian transposition before radiotherapy to the pelvis may preserve ovarian function and may be considered for premenopausal women with pelvic cancers	III-2	C
Ovarian suppression with GnRH analogues	Premenopausal women with breast cancer should be offered a GnRH analogue before commencement of chemotherapy to reduce the risk of primary ovarian insufficiency	I	A

GnRH = gonadotropin-releasing hormone. ◆

is not possible, is an established option for fertility preservation, with few risks and with success rates of up to 60% sperm retrieval.[15]

Extraction and use of stem cells from testicular tissue biopsies from pre-pubertal boys is currently experimental.[16] Sperm dissection from testicular biopsy may also offer hope of future fertility in peripubertal or post-pubertal children who cannot provide a sample.[16] Recent evidence showing successful live births in a macaque monkey model is encouraging.[17] This represents the only opportunity for future fertility in pre-pubertal boys whose fertility may have been compromised by cancer treatment. However, caution should be used in boys with acute leukaemia, as there is a risk of contamination with disruption of the blood–testis barrier.

Mature oocyte cryopreservation provides a realistic opportunity for future pregnancy for female patients with cancer.[18] The age of the patient and the number of oocytes retrieved will influence the number of opportunities for pregnancy. Live birth rates are higher in women aged less than 35 years, with at least eight to ten mature oocytes necessary to achieve a success rate of over 40%, where oocyte numbers should be individualised in women aged over 36 years.[19] The outcomes after oocyte cryopreservation are similar to those after embryo cryopreservation, with live birth rates of 46% and 54% respectively in one study.[20]

Embryo cryopreservation is an established fertility preservation treatment that results in live births for women with a history of cancer.[21] Improvements in embryo cryopreservation have included a move towards using vitrification to freeze blastocysts. Blastocysts have a higher live birth rate per embryo transfer compared with cleavage stage,[22] and vitrification has demonstrated a significant improvement in embryo cryosurvival compared with slow freeze (risk ratio, 1.59; 95% CI, 1.30–1.93; $P < 0.001$).[23]

Ovarian stimulation for fertility preservation purposes in women with low risk breast cancer is unlikely to

result in cancer recurrence during the first 5 years after diagnosis.[24] No prospective studies on ovarian stimulation and cancer recurrence were found for tumour groups outside of breast cancer.

Ovarian tissue cryopreservation and transplantation for post-pubertal females is no longer considered experimental,[25] with increasing numbers of births after both spontaneous pregnancies and in vitro fertilisation. Of 20 cancer survivors who underwent ovarian transplantation of frozen–thawed ovarian tissue with the aim to conceive, 16 pregnancies were achieved: ten after in vitro fertilisation and six spontaneous.[25] The average age of ovarian tissue cryopreservation was 28.8 years, and age of 34 years at subsequent graft.[25] For pre-pubertal girls, ovarian tissue cryopreservation remains the main option for future fertility, and reported births suggest the future success of this technique.[18] In leukaemia and other relevant cancers, the risk of recurrence exists in subsequent ovarian grafting, as even advanced tests cannot entirely exclude cancer cells within the transplanted tissue.[25] As such, experimental models are investigating strategies to provide safe pregnancies for these patients.

Ovarian transposition before radiotherapy to the pelvis may reduce premature ovarian insufficiency in women with cancer, although there are few long term data or standardisation of transposition procedures among studies.[26] In premenopausal women with early breast cancer, concurrent gonadotropin-releasing hormone (GnRH) analogue administration with chemotherapy resulted in lower rates of chemotherapy-induced primary ovarian insufficiency.[27] This is known as medical fertility preservation.

Puberty, contraception, conception and pregnancy

Children who receive cancer treatment are at risk of hormonal disruption. The risks include developing late-onset hypothyroidism, growth hormone deficiency, abnormal timing of menarche or a need for medications to induce puberty[28] (Box 4).

Effective contraception is required during chemotherapy for women undergoing cancer treatment and immediately after treatment. But caution should be used with combined hormonal contraceptives containing oestrogen and progestin due to the risk of venous thromboembolism, for which both cancer and oestrogen are independent risk factors.[29] The Society for Family Planning clinical guidelines on cancer and contraception state that the data are insufficient to evaluate the risk of venous thromboembolism with progestin-only contraceptives in women with cancer.[29] Women who develop anaemia may benefit from the use of a progestin-containing contraceptive. However, those who develop osteopenia or osteoporosis following chemotherapy should avoid the progestin-only injection.[29] There is also a theoretical risk of breast cancer recurrence with hormonal contraception after cancer treatment. Therefore, non-hormonal methods

4 Puberty, contraception, conception and pregnancy

Topic	Evidence-based recommendations	Level of Evidence	Grade for recommendation
Pubertal development	Health professionals should be aware of the potential impact of cancer treatment on the pubertal development of children diagnosed with cancer. Appropriate follow-up care may include paediatric endocrinology and gynaecology/andrology	II	C
Contraception (during cancer treatment)	Health professionals should discuss the need for contraception with patients of reproductive age with cancer		Consensus
Contraception (after cancer treatment)	Health professionals should discuss sexual health and contraception with patients with cancer		Consensus
Interrupting hormone therapy to conceive	Limited existing data are reassuring for patients with low risk breast cancer who wish to interrupt hormone therapy to conceive		Consensus
Assisted reproduction and risk of cancer recurrence	Women with low risk disease can be reassured that it is generally safe to attempt pregnancy either spontaneously or with assisted reproductive technology. Consideration must be given to minimise the duration of time off adjuvant endocrine treatment		Consensus
Pregnancy and risk of cancer recurrence (breast)	Women treated for low risk breast cancer should be informed that pregnancy does not appear to increase the risk of disease recurrence or mortality	III-3	C
Pregnancy and risk of cancer recurrence (other)	Women treated for lymphoma and melanoma should be informed that pregnancy does not appear to increase the risk of disease recurrence. Women with a history of other cancers should seek specialist advice	III-3	C
Risk of pregnancy complications	Women with a history of cancer should be informed of the increased risk of pregnancy and birth complications, and care should be provided in an appropriate facility	III-2	C
	It is recommended that patients with cancer be reassured that their children are unlikely to have an increased risk of congenital anomalies. It is advisable that patients with cancer be offered pre-pregnancy counselling	III-2	C

of contraception, including the copper intrauterine device, are recommended for women with a history of breast cancer.[29]

In hormone-responsive breast cancer, little is known about the risk of recurrent cancer in women who pause endocrine therapy to attempt pregnancy. A study found no difference in recurrence rate between women who conceived spontaneously and those who conceived with assisted reproductive technology, regardless of hormone receptor status.[30]

Pregnancy in women with low risk breast cancer does not increase the risk of breast cancer recurrence or death.[30] Studies in other malignancies, such as borderline ovarian tumours, endometrial cancer, melanoma, and Hodgkin lymphoma, are limited but show no significant increase for recurrence in pregnancy, with no data available for other cancers. Women with a history of cancer are at increased risk of pregnancy and birth complications, including preterm birth, low birth weight, caesarean delivery, assisted delivery, and postpartum haemorrhage.[31] These women should seek appropriate pre-pregnancy counselling regarding increased risks.

Conclusion

The 2022 *COSA guidelines for fertility preservation for people with cancer* provide critically appraised evidence on best practice oncofertility care for health care providers in Australia. The guidelines highlight the importance of education for multidisciplinary team members, as well as pathways for referral of oncology patients to fertility specialists to discuss oncofertility options. Furthermore, improving patient communication on fertility risk and cancer is vital for quality in oncofertility care. New Australian resources, such as the online patient education video series Fertility after Cancer, have been developed to introduce fertility preservation options to patients and their families in an age-appropriate manner.[32]

There is scope for further research on referral and utilisation rates of fertility preservation services in Australia, as well as return-to-use of stored cryopreserved material and pregnancy outcome data. Current gaps in knowledge include the impact of non-cytotoxic oncological therapies and immunotherapy[33] on fertility and the role of laboratory techniques, such as in vitro oocyte growth and maturation, in oncofertility.

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