Fertility Preservation Service

The Royal Children's Hospital fertility preservation principles of care and guidance

A reference document for health professionals to use when helping newly diagnosed patients and families make choices about fertility preservation

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The Royal Children's Hospital Fertility Preservation Principles of Care and Guidance

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Table of contents

Message to readers

Dear Colleagues,

Families report that information about fertility is one of their highest unmet needs at the time of cancer diagnosis. It is an international standard of care to inform families about the risks of infertility due to gonadotoxic treatment in a timely manner. [1,2] **The benchmark of care is to provide clear and consistent information about the impact of treatment on fertility where there is curative intent in line with the Australasian Oncofertility Charter**.[3] It is important to reduce disparities in clinical practice so that all families may receive good quality care irrespective of gender, culture, education and socioeconomic status.

This guidance aims to provide clear and consistent information and resources for healthcare professionals for use in the introductory discussion of fertility for families of children and adolescents receiving medical therapy or having medical conditions that can affect fertility. While guidelines are provided, the decision to undertake a fertility preservation procedure is an individualised one, based on clinician judgement, medical safety and patient/family preference.[4]

The fertility preservation procedures are approved as a novel technology at The Royal Children's Hospital (RCH), with research governance for data collection and clinical ethics approval for select individual cases.[5] This provides a governance framework for safe practice. The ethical principles underpinning provision of care include the high value placed on fertility by the growing pool of cancer survivors; the low risk of the FP procedures with careful selection; the irreversible impact of gonadotoxic therapy; the long lag phase to using the reproductive tissue during which time the reproductive technology rapidly advances; as well as the recognition of a child's right to an open future.

These pathways are under continuous renewal, informed by research as well as consumer and clinician voices. To access clinical resources please see the RCH intranet: https://www.rch.org.au/fertility/

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[1]Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2019;112(6):1022-33.

[2] Kieu V, Stern C, Harris J, Jayasinghe Y, Bradford N, Cui W, Deans R, Hunter T, Allingham C, Kane SC, Lau LS, Logan S, McLachlan R, Neville K, Peate M, Phillips M, Saunders C, Tome M, Upreti R, White K, Anazodo A, Hart RJ. Australian fertility preservation guidelines for people with cancer 2022: review and recommendations Med J Aust 2022 Dec 12;217(11):564-569

[3]Anazodo A.C, Gerstl B, Stern C, McLachlan R, Agresta F, Jayasinghe Y, Cohn R, Wakefield C.E., Chapman M , Ledger W, Sullivan E.A . Utilising the experience of consumers in consultation to develop the Australasian Oncofertility Consortium Charter. Journal of Adolescent and Young Adult Oncology 2016 5(3):232–9

[4]Jayasuriya S, Peate M, Allingham C, Li N, Gillam L, Zacharin M, Downie P, Moore P, Super L, Orme L, Agresta F, Stern C, Jayasinghe Y. Satisfaction, disappointment and regret surrounding fertility preservation decisions in the paediatric and adolescent cancer population. J Assist Reprod Genet. 2019 Sep;36(9):1805-1822

[5]Jayasinghe Y, Gillam L, Orme L, Zacharin M, McCarthy M, Sullivan M, Heloury Y. RCH Novel Technologies submission 2014.

1. Background principles in Oncofertility care

1.1 Fertility Discussions

All patients and families receiving gonadotoxic therapy, where there is curative intent, have the right to know if their fertility is at risk, even if:

- There is no time to do anything about it.
- There is nothing that can be done.
- Prognosis is poor.
- We do not think it is a good idea or medically safe to preserve fertility.
- Infertility risk is low
- Treatment is completed.

Note: It is important to discuss sexual health and menstrual management and refer to Gynaecology (birth assigned females) or Endo-oncology (birth assigned males) after completion of treatment irrespective of whether or not the patient had fertility preservation.

1.2. Consumer value-driven care

Providers often underestimate the importance of a fertility discussion with families. A study undertaken at the RCH has demonstrated that those families at most regret about their Oncofertility care are those who had no or suboptimal fertility discussion, even if they were at low risk for infertility. If families are informed from the start, they have reduced anxiety, have the opportunity to instigate coping strategies and are less likely to have future regret or conflict about their care [4].

1.3 Fertility preservation procedures in general populations:

1.3.1 Established FP procedures

Sperm collection, before starting chemotherapy, is considered an established procedure in mature patients. If there is time it may be ideal to collect more than one specimen. Documented clinical pregnancy rates from thawed sperm collected prior to cancer treatment range from 18-57%[6]. Higher success rates are seen with intracytoplasmic sperm injection (requiring an average of 3 cycles to achieve

[6] Chen L, Dong Z, Chen X. Fertility preservation in pediatric healthcare. Front Endocrinol 2023; 14: 1147898

a pregnancy compared to 8 cycles form IVF). Testicular sperm extraction may be considered for mature birth assigned males who have been unable to collect a sperm sample if time permits and risks of the procedure are low. The procedure is inappropriate in pre or peri-pubertal birth assigned males. Assessment of testicular volume and tanner staging must be undertaken beforehand. Successful retrieval in adult birth assigned males when there is no cause for obstruction is 30-50%.

Oocyte collection is not feasible in many patients (for example Acute Leukaemia) at diagnosis, due to the time critical nature of starting oncology treatment. There may be opportunities to offer this procedure during survivorship. In healthy adults under 35 years the chance of a live birth is around 3-5% per oocyte, depending on the numbers collected[7]. A systematic review has demonstrated the median number of oocytes collected in adolescents prior to cancer treatment was 12 (range 1-23)[8] hence multiple stimulation cycles or additional collection of ovarian tissue is beneficial where time permits. Usually, tissue collection is undertaken prior to oocyte collection, or there would need to ideally be a three week window after oocyte collection to reduce surgical risks for tissue collection. There has only been one livebirth from oocyte collection from a teenager[9] and egg quality is unknown in very young teenagers, therefore it **should be regarded as innovative in very young teens[8]**.

1.3.2 Innovative FP Procedures

- Ovarian tissue preservation is considered innovative (transitioned from a research technique), but outcomes in children are not very well established (only three births to date). In adults the chance of a livebirth per birth assigned female is around 25% (with variation seen between centres)[10,11]. It is not routinely offered to Leukaemia patients on diagnosis due to the urgency of cancer treatment, and also because of the known presence of Leukaemia cells in the tissue. It may be offered prior to moderate to high risk treatment such as HSCT. Currently the tissue from Leukaemia patients is not autografted in Australia, but has been successfully reported internationally[11].

1.3.3 Experimental FP Procedures

- Avenues to mature the oocytes in vitro or clear Leukaemia cells from the tissue are experimental.
- Testicular tissue preservation in pre-pubertal patients is experimental[1].
- GnRH is effective for menstrual suppression and national guidelines (ACOG, ASRM) do consider its

[7] Cobo A, Garcia-Velasco JA, Coello A, Domingo J, Pellicer A, Remohi J. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil Steril. 2016;105(3):755-64 e8

[8] Slonim M, Peate M, Merigan K, Lantsberg D, Anderson RA, Stern K, Gook D, Jayasinghe Y. Ovarian stimulation and oocyte cryopreservation in females and transgender males aged 18 years or less: a systematic review. Frontiers in Endocrinology May 2023

[9] Kim TJ, Hong SW. Successful live birth from vitrified oocytes after 5 years of cryopreservation. Journal of Assisted Reproduction and Genetics. 2011;28(1):73-6.

[10] Donnez J, Dolmans MM, Diaz C, Pellicer A. Ovarian cortex transplantation: time to move on from experimental studies to open clinical application. Fertil Steril. 1038 2015;104(5):1097-8

[11] Shapira M, Dolmans MM, Silber S, Meirow D. Evaluation of ovarian tissue transplantation: results from three clinical centers. Fertil Steril. 2020 Aug;114(2):388-397

use for this indication [1,12]. Meta-analyses suggest that if there is a protective effect on fertility it will be very small[13]. There is very little data on teenagers regarding fertility protection and it should be considered experimental for this indication. The decision to administer GnRH and include add back hormone therapy should be made by gynaecology in consultation with oncology, for each dose. Patients should be referred after treatment for assessment of bone mineral density. Side effects can include hot flushes, vaginal dryness, and in the longer term reduced bone density due to hypo-oestrogenism.

1.4 Governance of Fertility Preservation at RCH

- Oncofertility is run as a special service, reporting to the new technologies committee, RCH strategy, RCH HREC for data collection and we abide by a Clinical Ethics Framework. There are many checks and balances in place when procedures are being undertaken so that there is organizational oversight, and protection for families, staff and the institution.
- Under a new distributed model of care, the role of the Oncofertility team is to provide consultation, support, resources, and education to clinicians and families; enroll families onto the Melbourne Oncofertility REgistry (MORE); monitor key performance indices (KPIs) in Oncofertility care administered by clinical teams; and implement practice changes (guide strategic direction and implement new ways to protect fertility that are acceptable to families). Multidisciplinary meetings (MDMs), huddles, and guidance for medically complex cases, are overseen by the Director of the Oncofertility Program, [currently Chair of the Australian New Zealand Consortium in CAYA Oncofertility (ANZCO) and Australia's representative on the Practice Committee of the Global Oncofertility Consortium]. The consultant oncologist is responsible for initiating Oncofertility discussion, referral if required, and initial documentation, and also referral after treatment is completed. Clinical teams (Gynaecology, surgery, Endo-Oncology) are responsible for implementing and documenting care upon referral.

1.5 Who to offer FP procedures

In very broad terms,

- Non-experimental procedures may be considered for low, medium and high gonadotoxic risk patients where time permits, where it's medically safe and ethically appropriate.
- Usually, ovarian tissue cryopreservation (OTCP) and testicular tissue cryopreservation (TTCP) are reserved for patients at moderate to high risk of infertility, and only when it's medically safe, and where the families value fertility highly.
- Any family who requests referral regardless of risk should be referred for discussion in a timely

[12] American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care. Options for Prevention and Management of Menstrual Bleeding in Adolescent Patients Undergoing Cancer Treatment: ACOG Committee Opinion, Number 817. Obstet Gynecol. 2021 Jan 1;137(1):e7-e15.

[13] Chen H, Xiao L, Li J, Cui L, Huang W. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in premenopausal women. Cochrane Database Syst Rev. 2019 Mar 3;3(3):CD008018

manner. Occasionally this may be prior to the diagnosis or treatment plan.

- Therefore each decision should be individualised depending on family values, medical risks of intervention, as well as infertility risk. Experimental fertility preservation procedures should not be regarded as standard practice, but considered decisions every time. There is no right or wrong decision when it is medically safe and logistically sound. If the risks of the intervention are more than low risk but can be managed, then FP may be permissible where the value placed on fertility by the family is high. If the risks of the FP intervention pose high morbidity, which can't be managed, then FP is unlikely to be permissible.
- If you need help with fertility discussions and decision-making you can
    - call the Oncofertility team (CNCs, Director & Paediatric Gynaecologist, Endo-Oncologist)
    - refer through the usual clinical pathways
    - review our website: Home page (Internet): https://www.rch.org.au/fertility/For_health_professionals/
    - request a Clinical ethics review for ethically complex cases or an MDM for medically complex cases
    - attend an Oncofertility huddle
    - speak to a member of the CCC Oncofertility advisory committee

1.6 Assessing risk of infertility

Risk prognostication for infertility is not an exact science. Risk tables published by Meacham et al (2020)[14] and based on Green et al (2014)[15] are currently used to stratify risk for infertility (known as The Paediatric Initiative Network of the Oncofertility Consortium Risk stratification). It broadly categorises risk to fertility into three groups (minimally increased risk, significantly increased risk, and high level of increased risk). These terms have replaced the traditional terms of low (≤20%), moderate, and high (≥80%) risk given the lack of long-term studies with self-reported infertility as an outcome, however the terms are not always interchangeable for birth assigned males. According to Meacham et al.,[14] the dose of ≥4.0g/m2 Cyclophosphamide equivalent dose (CED) is considered.

- Minimally increased gonadotoxic risk for pre-pubertal birth assigned females (CED <8 g/m2)
- Significantly increased gonadotoxic risk for post-pubertal birth assigned females (CED 4-8g/m2)
- High level of increased risk for pre and post-pubertal birth assigned males (CED ≧4g/m2)

Long-term follow up of male childhood cancer survivors has demonstrated that 25% may experience azoospermia, and 28% oligospermia after chemotherapy with cyclophosphamide equivalent doses less than 4000 mg/m2[16]. Chow et al 2016 demonstrated that males who received cyclophosphamide,

[14] Meacham LR, Burns K, Orwig KE, Levine J. Standardizing Risk Assessment for Treatment-Related Gonadal Insufficiency and Infertility in Childhood Adolescent and Young Adult Cancer: The Pediatric Initiative Network Risk Stratification System. Journal of Adolescent and Young Adult Oncology 2020 Dec;9(6):662-666

[15] Green DM, Nolan VG, Goodman PJ, Whitton JA, Srivastava D, Leisenring WM, Neglia JP, Sklar CA, Kaste SC, Hudson MM, Diller LR, Stovall M, Donaldson SS, Robison LL. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer. 2014;61(1):53-67.

[16] Green DM, Liu W, Kutteh WH, Ke RW, Shelton KC, Sklar CA, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. Lancet Oncol. 2014;15(11):1215-23.

ifosfamide and procarbazine in the upper tertile doses (≥7412 mg/m2 [HR 0.58], ≥53 000 mg/m2 [HR 0.46], and ≥5060 mg/m2 [HR 0.3], respectively) reported a significantly decreased likelihood of siring a pregnancy compared with those not exposed to each drug[17]. Cyclophosphamide at a dose of 7500 mg/m² of more was reported as an important threshold for male survivors of childhood cancer, although even survivors who received doses of more than 5000 mg/m² were at risk. They concluded that a cyclophosphamide equivalent dose of around 5000 mg/m² [HR 0.82], and particularly doses exceeding 10 000 mg/m² [HR 0.53], were strongly associated with a reduced likelihood of siring pregnancies. This data would suggest that birth assigned males exposed to a CED of 4.0 g/m2 would be at moderate risk of infertility with those at high risk receiving close to 7.5g/m2.

1.7 Interval fertility preservation

1.7.1 Gonadal tissue preservation after gonadotoxic treatment has commenced:

When urgent cancer treatment is required gonadal tissue preservation may be undertaken as an interval procedure. There is a paucity of data about the impact of receiving fractionated doses and further research is required. For birth assigned females prior delivery of **low dose** gonadotoxic therapy does not preclude subsequent ovarian tissue preservation due to the high follicle density found in children[18,19]. In a study of 70 adult women from three centres in (Tel Aviv, Belgium and Missouri) who underwent autografting, 50% of women had at least one live birth[11]. There was no difference in success in those who had previous chemotherapy (with a low dose CED), compared to chemo naïve women. The decision to collect ovarian tissue after receiving **moderate or high dose** gonadotoxic therapy requires individualized expert consultation. The recommendation may be to see if it were possible to collect mature eggs after treatment is over.

For birth assigned males, a study by Moussaoui et al (2022)[20] reported that those who received alkylating chemotherapy prior to TTC (average CED 5.4 g/m2, range 2-15.6 mg/m2) (n=16 out of 35), had a significantly reduced median number of spermatogonia compared to patients who had not yet received alkylating chemotherapy (0.5 with a range 0–4, and 2.75 with a range 0–6 respectively, p = 0.0017). In another worldwide study of 189 patients where 44 had received lower dose alkylators (average CED = 2.8 g/m2, range .5–7.0 g/m2) there was no difference in the number of germ cells and spermatogonia according to previous chemotherapy exposure (Valli-Pulaski et al 2019)[21]. However, results should be interpreted with caution as the future utility of testicular tissue after gonadotoxic exposure is unknown in

[17] Chow et al. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. Lancet Oncol. 2016 May ; 17(5): 567–576

[18] Fabbri et al. Obstet Gynecol Int. 2012;2012:910698. doi: 10.1155/2012/910698

[19] Lim J Establishing Normative Data of follicle density according to age in Paediatric and Adolescent Females. Honours Thesis University of Melbourne 2021

[20] Moussaoui D, Surbone A, Adam C, Diesch-Furlanetto T, Girardin C, Bénard J et al. Testicular Tissue Cryopreservation for Fertility Preservation in Prepubertal and Adolescent Boys: a Six Year Experience from a Swiss Multi-center Network. Frontiers in Endocrinol August 2022

[21] Valli-Pulaski H, Peters KA, Gassei K, Steimer SR, Sukhwani M, Hermann BP, et al. . Testicular tissue cryopreservation: 8 years of experience from a coordinated network of academic centers. Hum Reprod. 2019 34:966–77.

humans.

1.7.2 Oocyte and sperm collection after gonadotoxic therapy has commenced:

It is not recommended that mature gamete collection (of oocytes or sperm) be planned once chemotherapy (whether high or low gonadotoxic risk) has commenced due to the risk of DNA damage, fragmentation and mutagenesis[22]. Such adverse effects are not observed in primordial follicles that survive long term after chemotherapy exposure, because there is no increased risk of birth defects in birth assigned females who conceive years after chemotherapy[23]. Furthermore, there is a high chance of no response to ovarian stimulation or azoospermia within three months of treatment. It is recommended that survivors delay natural conception and oocyte collection for at least 6 months after completion of gonadotoxic therapy[24] and sperm collection for 6 to 24 months (allowing time for damaged mitotic and meiotic cells to be cleared)[25]. In special circumstances where there are no other options and the risks to fertility are very high and the family places high value on fertility, collection at three months or sooner may be considered with fully informed consent of the patient/family.

This is why it is often recommended that sperm collection occur prior to any treatment where possible even if it is low gonadotoxic risk. If a patient then requires high gonadotoxic risk treatment the only option for FP is testicular biopsy. The sperm cannot be dissected for use from the affected tissue (they may be absent or have DNA damage), thus the patient relies on experimental maturation of germ cells from that tissue.

In summary we can collect gonadal tissue after gonadotoxic therapy but we cannot collect mature eggs or sperm for 3-6 months.

1.8 Preparing for a fertility consultation

The following points will help prepare you for a discussion.

1.8.1 Prepare

We have included talking points below. The following chapters present risk stratification systems for infertility based on treatment, potential recommendations according to risk of infertility, and fertility preservation options. We have also included clinical ethics guidance, and a list of forms/hand-outs (clinical and research) which are also readily available on the RCH intranet. This information is a general

[22] Meirow D, Schiff E. Appraisal of chemotherapy effects on reproductive outcome according to animal studies and clinical data. JNCI Monogr 2005;34:21–5

[23] Winther JF, Boice JD Jr, Mulvihill JJ, Stovall M, Frederiksen K, Tawn EJ, et al. Chromosomal abnormalities among offspring of childhood-cancer survivors in Denmark: a population-based study. Am J Hum Genet 2004;74:1282–5.

[24] Chung et al. Emergency IVF versus ovarian tissue cryopreservation: decision making in fertility preservation for female cancer patients Fertil Steril 2013;99:1534-42

[25] Bujan L, Walschaerts M, Brugnon F, Daudin M, Berthaut I, Auger J, Saias J, Szerman E, Moinard N, Rives N, Hennebicq S. Impact of lymphoma treatments on spermatogenesis and sperm deoxyribonucleic acid: a multicenter prospective study from the CECOS network. Fertil Steril. 2014 Sep;102(3):667-674.e3.

summary and we endeavor to update it regularly. All consultations should be highly individualised.

1.8.2 Who should be there?

Sometimes health providers can struggle to provide all of the critical information families require during fertility consults or may not consider it within their scope of practice[26]. At The RCH, there are many providers who now feel confident in the quality of their fertility consultations and are happy to play a leading role[27]. If you are uncomfortable or unsure about discussion of this topic, you may find it helpful to contact the Director of Oncofertility, Oncofertility Coordinator or identify another individual who can lead the discussion in your place, until you feel ready. It is helpful to have another team member present.

Give some thought to the age and gender of the young person, and whether it is appropriate for them to receive age-appropriate explanation and discussion separately. Cognitive capacity, unwellness, emotional distress and pubertal status are important factors to consider, as well as the cultural background of the family. It is important not to exclude families from fertility discussions based on their background, age and gender of the child or the risk to fertility as families cope and adjust in different ways.[28,29]

Young persons should, if possible, be key participants in the discussion, and supported through decision making about fertility in a way that is comfortable to them. There is a heavy reliance on parents during this time who are surrogate decision makers for young children[30]. Be sure to ask mature adolescents and/or families who they would like involved in this conversation. Pubertal patients may feel most comfortable discussing fertility matters including sperm preservation privately with a parent or a health professional.

1.8.3 Timing and documentation

Fertility discussions should occur prior to commencement of cancer therapy whenever possible, and discussed after therapy or if treatment changes. This KPI is being measured and reported to novel technologies. If you are discussing the details of the cancer diagnosis at the same time, consider taking a break and having a separate fertility discussion. Some families have reported that they prefer the discussion to happen in a different space so that they can pay more attention to the issue of fertility after

[26] Kemertzis M, Ranjithakumaran H, Peate M, Gillam L, McCarthy M, Super L McQuillan S, Drew S, Jayasinghe Y*, Orme L*. Fertility Preservation Toolkit: A clinician resource to assist clinical discussion and decision making in pediatric and adolescent oncology. J Pediatr Hematol Oncol. 2018; 40 (3): e133–e139

[27] Hand M, Kemertzis M, Peate M. Gillam L, McCarthy M, Orme L, Heloury Y, Sullivan M, Zacharin M, Jayasinghe Y. A Clinical Decision Support System to assist paediatric oncofertility: A short report. JAYAO 2018; 7 (4): 509–513.

[28] McQuillan S, Malenfant D, Jayasinghe Y, Orme L, Grover SR. Audit of current fertility preservation strategies used by individual paediatric oncologists throughout Australia and New Zealand. Journal of Pediatric Oncology, 2013: 1:112–118.

[29] Wang Y, Logan S, Stern K, Wakefield CE, Cohn RJ, Agresta F, Jayasinghe Y, Deans R, Segelov E, McLachlan RI, Gerstl B, Sullivan E, Ledger WE, Anazodo A. Supportive oncofertility care, psychological health and reproductive concerns: a qualitative study. Support Care Cancer. 2019 Jun 1.

[30] Li N, Jayasinghe Y, Kemertzis M, Moore P, Peate M. Fertility Preservation in pediatric and adolescent oncology patients: The decision-making process of parents. Journal of Adolescent and young Adult Oncology 2017 6(2): 213–222

receiving the diagnosis. It is vital to provide written resources to families and to document your discussion in the notes. There are specialised fertility templates in the EMR for documentation and referral, designed to assist medical decision-making about fertility preservation.[27]

1.8.4 Discussion points

1.8.4.1 Risk to fertility

1. Discuss young person's level of risk to fertility based upon your assessment of diagnosis and treatment (even if the risk attributable to treatment is zero).
2. Discuss flexibility of timing for initiating treatment.
3. Explain what the level of risk means if no action is taken.
4. Explain that experimental procedures are undertaken as a novel technology rather than standard practice.

1.8.4.2 FP Options:

1. Individualised discussion of appropriateness or not of FP procedures, based on gender, pubertal stage, cancer, treatment plan, medical and surgical comorbidity and other relevant factors.
2. Clearly describe what is experimental and what is considered standard, and pros and cons.
3. Describe future options available if no action is taken.
4. Consider referral for fertility preservation (FP) according to medical/surgical risks, age and interest of patient (if mature) and family.
5. Usually the final decision for experimental procedures will rest with the medical teams (a medical recommendation for example if it is not safe to proceed) and family. It is important to understand that the surgical teams may occasionally decline the procedure depending on potential surgical morbidity. Sometimes it may require Clinical Ethics or medical MDM.
6. Address any issues regarding sexual health in a confidential manner.
7. Document the discussion in the electronic medical record (EMR) using a smart set or your own notes.
8. Provide written resources to patient/family.
9. Call upon the expertise of the Oncofertility team if you need advice, particularly if the family place a high value on fertility.

1.9. Quality Assurance

RCH is undertaking one of the largest studies on the safety and efficacy of paediatric fertility preservation (Melbourne Oncofertility REgistry (MORE). We recommend that all families be provided with information on this and invited to participate whether they decide to pursue fertility preservation or not, allowing outcomes to be compared between groups. In this research, parents can give permission for researchers to use information from the medical record. Optional consents include permission for data linkage (with the register of births, IVF centres), and permission for contact for future research.

2. RCH fertility preservation principles for birth assigned males

2.1 Purpose

To ensure that consistent discussion of infertility risk occurs with patients and their families having gonadotoxic treatment with curative intent, including the discussion of relevant preservation options for those having options available.

2.2 Principles

The RCH Children's Cancer Centre, RCH Endo-Oncology, RCH Immunology, RCH Nephrology, RCH Rheumatology, RCH Surgery, RWH Andrology and RWH Reproductive Biology Units will work collaboratively to:

1. Provide education and consultation to all birth assigned male patients and/or families where there is curative intent, about potential fertility impairment as a result of treatment in a clear and consistent manner with use of appropriate resource tools.
2. Discuss the pros and cons of fertility preservation (FP) options with these families including transparent discussion of standard versus experimental options (Table 1).
3. Infertility risk can be based on risk stratification tables, but all situations are to be considered individually (Table 2)
4. The medical teams must judge if FP is medically safe, in which case, the decision to proceed is value driven, made by patient/family in consultation with treating team.
5. Involve clinical ethics as appropriate.
6. Provide age-appropriate discussions with patients when a FP procedure is being considered.
7. Document fertility discussions in the medical record.
8. Discuss participation in the Melbourne Oncofertility REgistry (MORE) for all patients having a fertility discussion whether they have a FP procedure or not.
9. Provide feedback of results, and appropriate follow up over the treatment journey and during survivorship.

2.3 Fertility preservation team can include:

1. Director of Oncofertility
2. Oncofertility coordinator
3. Oncology or other treating team
4. Endo-Oncology consultant
5. Surgical team
6. Reproductive Biology Unit/Andrology liaison
7. Oncology liaison
8. Clinical ethics

9. Lines coordinator

2.4 Eligibility for the discussion

1. All new birth assigned male patients having gonadotoxic treatment with curative intent should have a discussion about the impact of cancer treatment on fertility.
2. Birth assigned males with relapsed disease and a new gonadotoxic treatment plan.
3. Other conditions with gonadotoxic risk (nephrology, rheumatology, immunology, other).
4. At request of patients or families.
5. Birth assigned males who have completed treatment and having long term follow-up who require surveillance.

2.4.1 Initial discussion

It is recommended that the initial fertility discussion be undertaken by the treating clinician (e.g. Oncology, Renal, Rheumatology, Immunology) and include:

1. Assessment and discussion of risk of infertility attributable to planned chemotherapy, radiation or surgical procedure even if the risk is zero.
2. Discussion of possible fertility preservation (FP) options as appropriate.
3. Address any issues regarding sexual health in a confidential manner.
4. FP consultation can be formally documented in EMR using a template or just use your own notes.
5. Provide written resources to patient/family depending on age and type of FP procedure:
    a) RCH Testicular Tissue Cryopreservation information sheet
    b) RCH Sperm Banking information sheet
    c) RCH Adolescent and Young Men Undergoing Cancer
6. Invitation and consent for participation in the Melbourne Oncofertility REgistry (MORE)

2.5 Sperm collection

2.5.1 When to refer for Sperm collection

1 Post-pubertal patients at any risk of infertility.

2 Prior to the start of gonadotoxic therapy (chemotherapy, radiation or TBI) for the following reasons
    a. Even low risk treatments may cause sperm DNA fragmentation which increase the risk of mutagenesis, which can persist for up to 2 years.
    b. A significant decline in sperm count and quality or even Azoospermia may occur by three months increasing the risk of unsuccessful semen collection.

3 Interval FP or FP after treatment: Collection would be advised after one year off treatment. If sperm collection is being undertaken within one year of gonadotoxic therapy, a sample may be stored on patient/family request, however documentation of the risks should occur and a disclaimer form signed and they should receive recommendations to collect a revised sample a

year after treatment if possible, and if the quality of semen is normal the previous sample may be discarded. For those patients at very high risk of infertility who place a high value on fertility and have already received gonadotoxic treatment, seek advice to discuss the most appropriate management.

4 If the semen analysis is normal, it is recommended that the patient freeze 10 straws (each straw is o.5ml of which half is cryoprotectant) and potentially 15-20 straws if there are atypical results. This means the patient should be given the opportunity to collect multiple sperm samples if medically safe to do so.

5 **Normal semen analysis results are as follows**:

- Ph 7.2-8
- Volume ≥ 1.5 to 6ml
- Concentration ≥ 16M/ml or 39M/ejaculate
- Motility 42%
- Vitality 58%
- Morphology 4%
- Leukocytes <1M/ml

2.5.2 Inpatient procedures for sperm preservation:

If you have a patient who would like to bank sperm while an inpatient, important principles include:

1 Ensuring the patient has privacy during collection. It is unacceptable for others to be present in the room unless requested by the patient.

2 Sometimes patients may not be able to produce a sample due to a range of factors including distress, immaturity and sickness. Sometimes a produced sample contains no viable sperm due to concurrent illness. Therefore, it is best to discuss fertility preservation early, as multiple collections may be required or other options explored such as TTCP.

3 Adolescents should be offered confidential discussion and receive sexual health and contraceptive advice.

4 More information (Intranet only): Inpatient procedures for sperm preservation (intranet only)

2.5.2.1 If it is a weekday follow the instructions below for inpatient sperm collection:

1. Inform Oncofertility coordinator by email or EMR chat.
2. Please assess Tanner stage (>3), testicular volume (>10mls) and patients understanding of sperm collection
3. Please contact the Andrology Unit on 8345 3991/3992 to speak with a team member to arrange a time for the patient to produce their sample. You must speak with the Andrology team **prior** to speaking with your patient.
4. Order the following tests on EMR:
    a. Semen Analysis

b. Cryopreservation of Seminal Fluid/Spermatozoa

5. Give the patient/designated family member the following:
6. RWH Andrology Request for Sperm Storage in a Minor Consent Form (minors need a parent/guardian to consent) RWH Andrology consent form
7. Please ask the patient/designated family member to take their Medicare card & photo ID.
8. Give the patient a specimen cup (that has been clearly labelled with a patient label) and a paper bag.
9. Secure a private space e.g. single patient room and hang a "Stop Sign".
10. Ensure that all members of staff are aware not to enter the room.
11. Instruct patient to remove the sign when finished.
12. Once the patient has provided their sample, please check the following:
    a. Specimen is in the cup and closed tightly
    b. Cup is in the bag (please put paper bag inside a plastic biohazard specimen bag)
    c. Sperm banking consent forms have been completed
13. Please ensure that the patient or family member delivers the specimen to the Andrology lab within **1 hour of collection and at the allocated time** to 321 Cardigan Street, Carlton.
14. Arrange follow-up with Endo-oncology after treatment.
15. Invite the patient to participate in the MORE Registry. Patients can be invited whether they decide to pursue fertility preservation or not.
16. Document notes in the EMR.

2.5.3 After Hours sperm collection

In the case of needing to commence emergency cancer treatment, when sperm must be collected and stored after hours, please contact the On Call Andrology Scientist in Charge via RCH or RWH switchboard. If you are unable to reach a member of the team, please contact Dr Gulfam Ahmad via switch (Scientist in Charge at Andrology).

2.5.4 Outpatient procedures for sperm preservation

If you have a patient who would like to bank sperm as an outpatient, please take the following steps:

a. As previously outlined for inpatient

b. Direct the patient/family to make an appointment directly with the Andrology Service on:

Andrology Unit/Sperm Bank

The Royal Women's Hospital, Carlton Campus 321 Cardigan Street

Carlton Vic 3053

Tel: (03) 8345 3991

Hours: Monday–Friday 8.30am-5pm

More information can be found here: The Royal Children's Hospital Fertility Preservation Service Sperm Banking Guidelines for an Outpatient

2.5.5 Unable to collect a specimen

Upon completion of testing, it is important to discuss the results with the family and decide if further collection is required. Scientists in the Andrology lab will be able to help you interpret the results and advise if repeat collection is recommended. Sometimes patients may not be able to produce a sample due to a range of factors including distress, maturity and health. Sometimes a produced sample contains little or no viable sperm due to concurrent illness. If this is the case, please speak with the Oncofertility team to discuss this further. If time permits, TTCP with sperm dissection (at RCH) or TESA (at The RWH) may be a possibility.

2.5.6 Funding for sperm banking

The charity MyRoom will pay the fees for semen analysis and storage for 3 years for all oncology patients. After this period, they will be contacted by the Andrology lab. The yearly fee after the initial 3 years is $220 ($165 if patient has a concession card).

2.6 Testicular sperm aspiration (TESA)

2.6.1 When to refer for TESA

Post-pubertal birth assigned males, same criteria as above with inability to ejaculate and physically and emotionally mature (Tanner stage (≥3) and testicular volume (≥10mls))

Exclusions/caution: High bleeding or infection risk. Usually done under local. Patient may be able to have this procedure under sedation/GA if they are needle phobic or have procedural anxiety.

2.6.2 Procedure for TESA

1. Oncology please send FP referral to Endo-oncology if it has not already happened (for assessment of physical and emotionally maturity (Tanner staging and testicular volume measured)
    a. Outpatient: Referral to Outpatient Oncofertility (born biologically male fertility preservation)
    b. Inpatient: Fertility Preservation (born biologically male) Inpatient Consult
2. Oncology assess if it may be undertaken under local or general anaesthetic. It may not succeed and family need to be informed.
3. Oncology to consider and mitigate risks of bleeding and infection (risks are higher with TESA compared to testicular biopsy as it is a blind procedure)

4. Oncofertility team will liaise with RBU at the RWH to assess logistics. If proceeding, medical team to refer to RWH RBU with internal EPIC referral to RSU Public Fertility Service and follow up phone call to Reproductive Fellow on call.
5. RBU clinicians will undertake procedural and storage consent and arrange laboratory.
6. RBU clinicians undertake a verbal post procedure check via phone call. It is recommended that the RCH clinician review the patient.
7. Results review: RBU clinician notify treating team of results. If normal OC CNC discuss with family. If abnormal, endo oncology or treating oncology to discuss with family and notify Director.
8. Discuss RSU results with family: OC CNC if normal, endo-oncology team if abnormal and notify Director
9. Summary of care letter to family (by OC CNC)
10. Follow-up appointments: OC will coordinate with CCC CNC's, Endo-Oncology to order appointment

2.6.3 Who do I contact for further information?

Please contact the Oncofertility team at RCH.

Oncofertility Team – Director of Oncofertility Program (via switchboard) or CNC's (via below)

The Royal Children's Hospital

50 Flemington Road

Parkville 3052

T: (03) 9345 5309

Spectra link: 52382 (please call switch on 03 9345 5522 and ask for this extension)

E: fertility@rch.org.au

2.7 Testicular Tissue Cryopreservation (TTCP)

2.7.1 When to refer for Testicular tissue cryopreservation:

1. Pre-pubertal patients at moderate to high risk of infertility.
2. Post-pubertal patients with inability to ejaculate or poor quality of sperm where open surgery rather than needle aspiration is advantageous.
3. At request of patient/family, (note: investigational procedures are not usually undertaken if risk of infertility is low).
4. At discretion of treating team.
5. Patients may include:
    a. Oncology (potential number: 20–30/year).
    b. Nephrology (nephrotic syndrome, lupus — 2 to 4/year).
    c. Others may include rheumatology, immunology, haematology.

2.7.2 The role of the oncologist or other treating team:

1. Assessment and discussion with family of risk of infertility attributable to planned chemotherapy, radiation or surgical procedure even if the risk is zero.
2. Consider and discuss medical and ethical suitability of fertility preservation based on medical history sociocultural considerations, CED calculations and other factors.
3. Provide opportunity for confidential discussion for adolescents, regarding fertility and sexual health
4. Formally document likely impact of treatment on fertility and discussion with the family in EMR using a 'fertility' template or just use your own notes.
5. Determine requirements for other co-existent operative procedures (CVL, LP, BMA).
6. Please provide written information to families as appropriate and clearly discuss experimental nature of procedure TTCP Information Sheet
7. Oncofertility team accepts clinician-to-clinician referrals. If a referral is required, oncology clinician to phone Endo-oncology consultant so that referrals do not get lost.
8. Oncology CNC please also notify Oncofertility CNC.
9. Oncology clinician complete fertility preservation referral form
10. Fertility Preservation (born biologically male) inpatient consult; a phone call to endo-oncology is imperative as these referrals are not flagged in the EMR.
11. Referral to Outpatient Oncofertility (born biologically male fertility preservation) gets sent to the Oncofertility triage pool.
12. Referrals should include:
    a. Brief history.
    b. Developmental maturity of patient (tanner stage testicular volume).
    c. Planned gonadotoxic treatment (drug names doses), urgency (with clear indication of acceptable timeframe), prognosis, indication of infertility risk (high >80%/medium/low <20%) and CED mg/m2 or g/m2
    d. **note: CED can be determined using CED calculator on Fertility intranet page*- CED calculator
    e. Handover of patient/family's understanding of the diagnosis, prognosis, FP options/response to introductory discussion.
    f. Other procedures planned.
    g. Other factors pertinent to cancer/reproductive potential (e.g. prognosis, likelihood of RT, likelihood of relapse).
    h. Factors that may specifically increase surgical risk such a mediastinal mass, significant immunosuppression, bleeding disorder.
    i. Social concerns within the family such as custody issues and parental disagreement.
    j. The level of complexity of the young patient's situation that would necessitate consultant review.
    k. Any specific concerns the treating oncologist has with respect to proceeding with an FP procedure.
13. If the referring clinician feels the patient/family should not yet be approached, they will let the

Endo-oncologist know how and when it is best to see the patient. The oncology team should always have introduced the fertility discussion before the fertility team sees the family for consultation.

14. Notify Director of Oncofertility if any deviations to protocol (anything atypical, contraindication, complaints) or for complex cases. These can be further discussed at Oncofertility huddles or Fertility MDMs.

2.7.3 Initial discussion with Oncofertility CNC (In the absence of the OC CNC, oncology will undertake role)

1. The Oncology team will have introduced the fertility risk with the family.
2. The OC CNC will notify the Director for ethically or medically complex cases
3. The Oncofertility CNC will see the family after discussion with oncology, endo-oncology and at times Director, to orientate family to program and discuss fertility preservation based on team discussion
4. Oncofertility CNC will provide written information based on team discussion (information sheets, links to fertility videos, decision aid, Oncofertility registry consent)
5. Please note the final decision about suitability for fertility preservation and surgery will be made in consultation with all teams including the Oncofertility clinicians and surgeons. If any surgical concerns, involve surgery in discussions prior to definitive decision making

2.7.4 Endo-oncology consultation for TTCP (In the absence of endo-oncology, oncology will undertake role):

1. Referrals will be made by oncology staff, sometimes other departments (e.g. Renal, Immunology),
2. Often at short notice before chemotherapy. Oncofertility consult needs to fit in with:
    a. Timing of other essential tests (e.g. MRI, CT etc.).
    b. Timing of GA for port insertion.
    c. Availability of staff at the RWH for tissue storage/examination.
3. Patients may be seen a) in the ward or b) brought to endo-oncology clinic by a CCC staff member or c) sent there by oncology staff or d) at the Day Cancer Centre.
4. Often a preliminary discussion has been made by oncology staff and the Oncofertility coordinator and written documents provided. If not the documents are easily available on: TTCP Information Sheet
5. An Endo-oncologist needs to discuss issues which differ depending on:
    a. If the patient is pre-pubertal.
    b. Peri-pubertal (e.g. testes 10 ml, pubic hair stage 3).
    c. Post-pubertal.
6. Explanation of role as Endo-oncologist and purpose of visit.
7. Assess and discuss young person's level of infertility risk based upon age, pubertal stage diagnosis and treatment plan.
8. Assess medical surgical ethical risk
9. Explain the level of risk to fertility if no action is taken.
10. Introduce potential options for preserving fertility.

11. Clearly describe what is experimental and what is considered standard, and pros and cons of the most appropriate FP plan for the individual.
12. Clear statement that TTCP is currently experimental in humans – has been successful only in animals so far. It is undertaken at RCH as a novel technology.
13. Details of testicular biopsy and the procedure[31].
14. Explain that we always examine any biopsy at RCH, just in case there is some entirely unexpected abnormality such as no germ cells or spermatogonial cell lines, or malignancy.
15. For patients who are peri-pubertal at the time of a testis biopsy, tissue may also be dissected to look for mature sperm and any sperm found can be stored for intracytoplasmic sperm injection (seen in those as young as 11–12 years of age)[32]. This incurs the same cost as per sperm storage.
16. Please note that for patients with haematological malignancy it is important to have a fertility discussion. However, the ability to sift cell lines and remove any potential cancer cells is not perfect at this time. Risks of malignant reseeding can be high and at the current point in time, tissue is not being autografted back into the body at local institutions.
17. Makes shared decision with family about risks and benefits of proceeding, and decide if FP is permissible
18. Decide if decision requires clinical ethics referral or MDM. All pre-pubertal testicular tissue preservation cases do need to be referred to ethics. Post-pubertal TTCP only needs ethics referral if there are additional risks or ethical complexities.
19. Decide and arrange if family needs review again
20. Discuss sexual health needs for adolescents
21. Freezing immature testicular tissue is free until 21 years of age at RWH. After this time— storage may not be essential if fertility is proven in the future by semen analysis, but is still recommended. Decisions to cease storage should be made in consultation with adult provider.
22. High quality documentation in the EMR

2.7.5 If family decides to go ahead with Fertility Preservation

Please keep all original forms and give to the Oncofertility CNC:

- RWH Collection and Storage of Gonadal Tissue in a Minor Consent Form
- RWH RBS FPS Male Patient Referral

1. Endo-oncology provides final decision to oncology fellow who will refer to paediatric surgeons
2. Clinician (endo-oncology or oncology) arranges to see the patient/family to sign the consent forms
3. Document they have read and understood testicular tissue information sheet and consent forms which go through the experimental nature of TTCP.

[31] Faure A, Bouty A, O'Brien M, Thorup J, Hutson J, Heloury Y. Testicular biopsy in prepubertal boys: a worthwhile minor surgical procedure? Nat Rev Urol. 2016 Mar;13(3):141–50. doi: 10.1038/nrurol.2015.312.

[32] Ho WLC, Bourne H, Gook D, Clarke G, Kemertzis M, Stern K, Agresta F, Heloury Y, Clark H, Orme L, Jayasinghe Y, Zacharin MR; Paediatric & Adolescent Fertility Preservation Task Force, Melbourne. A short report on current fertility preservation strategies for boys. Clin Endocrinol (Oxf). 2017 ;87(3):279-285.

4. Clinicians (endo-oncology or oncology) sign RWH Collection and Storage of Gonadal Tissue Consent Form
5. CNC or clinician signs Oncofertility Registry consent
6. Clinicians (endo-oncology or oncology) complete the RSU FPS Patient Referral Form
7. Leave all forms with OC CNC (pigeon hole in CCC office 2nd floor)
8. The Oncofertility CNC will email both the completed RWH consent and RSU FPS referral form to RWH Lab: rsuivflabsupervisors@thewomens.org.au The lab can be contacted for urgent matters on 03 8345 3232. In the absence of the OC CNC, oncology will need to email the forms

2.7.5.1 Involvement of clinical ethics in decision-making for TTCP:

1. Guidelines are as per the Ethics Checklist for Fertility Preservation Procedures.
2. If a clinical ethics meeting is needed, Clinical Ethics Service Referral Form 3A to be completed for pre-pubertal patients and Form 3B to be completed for post-pubertal patients. This should be regarded as an important medico-legal document for filing in the medical record.
    a. Pre-pubertal ethics referral (Intranet): https://www.rch.org.au/fertility/health-prof/male/
    b. Post-pubertal ethics referral (Intranet): https://www.rch.org.au/fertility/health-prof/male/
3. If required, oncology complete electronic Ethics Referral Form with as much information as possible and email to: lynn.gillam@rch.org.au and CC: fertility@rch.org.au & bioethics@rch.org.au (Clinician)
4. If a clinical ethics meeting is held, the expected invitees include the Director of Oncofertility, Oncofertility CNC, a representative from Oncology, Endocrinology and special experts where appropriate (e.g. Haematology/Genetics).
5. If the sole issue is that the child is pre-pubertal then an expedited review may occur upon written referral.

2.7.5.2 If patient is having TTCP with the insertion of a line

1. Oncology team will liaise with family, refer to surgeons, lines coordinator
2. Oncofertility CNC and oncology will coordinate with lines meeting on Thursday @ 4pm. Email Sara Tennison (lines coordinator) to join this meeting sara.tennison@rch.org.au
3. Lines coordinator will coordinate with surgeons, theatre and anaesthetists, and endeavor to book cases for the morning. There is no reproductive lab service after 1.30 pm week days and no service on weekends or holidays.
4. Oncology and Endo-oncology consultant to be notified if there are any delays to expected commencement of cancer treatment due to the FP procedure itself and make decision regarding risk-benefit. Notify Director of Oncofertility.

2.7.5.3 If patient is having TTCP with a procedure other than a line (e.g. BMA or LP)

1. Oncology Fellow will coordinate with surgeons and notify Oncofertility CNC of planned date for TTCP by either EMR chat or email fertility@rch.org.au

2.7.5.4 If patient is having TTCP as a standalone procedure

1. Oncology fellow will refer to Paediatric Surgeons and notify Oncofertility CNC of planned date for TTCP by either EMR chat or email fertility@rch.org.au

2.7.5.5 All teams to understand requirements for theatre:

1. Request time of surgery as early as possible on the list (am is best).
2. Once the panel is booked oncology please order histopathology and write:
3. Type of malignancy
4. Site: testicle
5. Histopathology check for malignancy and stage of spermatogenesis
6. The specimen should be labelled

2.7.5.6 The day before the surgery (Oncofertility CNC will do this, in the absence of the OC CNC oncology will do this)

1. Please contact RWH laboratory to confirm theatre: 8345 3232/3233
2. Ensure the following documentation has been completed (will be on EMR)*:
3. RWH storage consent signed
4. RBU FPS completed
5. Ethics referral signed by Ethics team
6. Registry form signed

*best way to check for these is to enter the patient file on EMR and search for key words (fertility) on the left hand side search box

2.7.5.7 Day of theatre

1. Reproductive lab to arrange storage eskis and collect tissue
2. Theatre sign off when tissue delivered to reproductive services

2.7.5.8 After surgery

1. Postop check (by the surgical team)
2. Histology review: sign off by Endo-oncology or oncology.
3. Discuss histology and RSU results with family: OC CNC or oncology if normal, endo-onc team if abnormal, and notify Director (eg if malignancy in tissue).
4. Summary of care letter to family (by OC CNC) and copy to oncology and GP.
5. Follow-up appointments: The patient/family should be referred after treatment to Endocrine Oncology Clinic for medical follow-up, confirmation of storage arrangements and discussion of the evolving technology. This provides an opportunity to answer questions and manage expectations.
6. Timing of follow-up by Endocrinology is at the discretion of oncologist (around 12 months).
7. Transition to an adult facility for discussion with an andrologist is recommended when appropriate.

Table 1. Infertility risk and potential recommendations in biological males

Age	Risk category	Potential to recommend FP
Pre-pubertal	Low	Not recommended
	Significant	May consider experimental options
	High	May consider experimental options
	Uncertain	Not recommended
Pubertal	Minimal	Preserve sperm if able
	Significant	Preserve sperm. Consider TESA/ TTCP if unable to produce sample
	High	Preserve sperm. Consider TESA/TTCP if unable to produce sample
	Uncertain	Preserve sperm if able

Table 2. Male level of risk for gonadal failure / infertility above that for the general population (Paediatric Initiative Network Risk Stratification)[14]

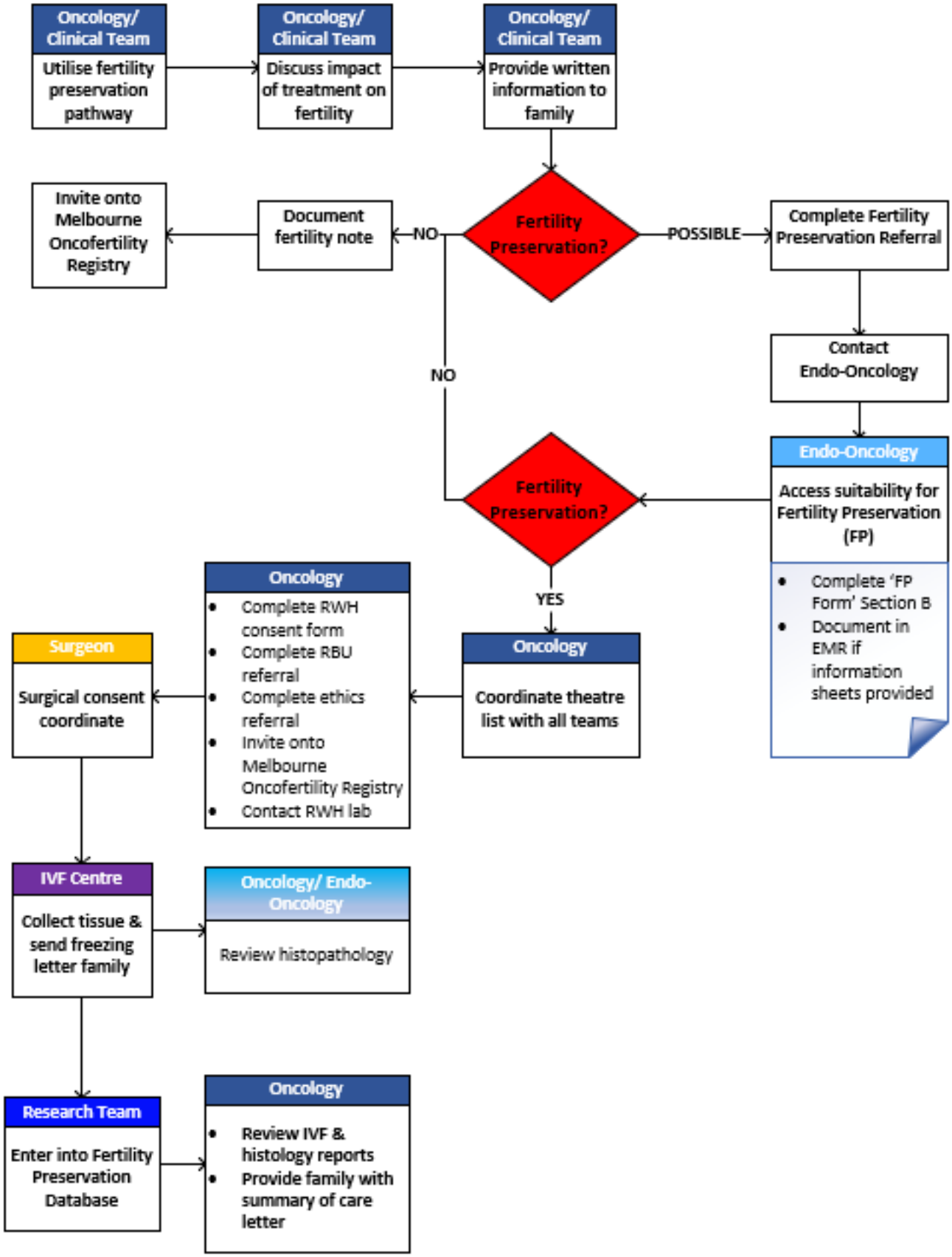
		Minimally increased risk	Significantly increased risk	High level of increased risk
Alkylators CED* gm/m²		CED <4		CED ≥4
Hematopoietic stem cell transplant				Alkylator +/- TBI Myeloablative and reduced intensity regimens
Heavy metal mg/m²		Cisplatin Carboplatin	Cisplatin >500	
Radiation exposure	**Testicular**	0.2–0.6 Gy	0.7–3.9 Gy	≥4.0 Gy
	Hypothalamus	26–29.99 Gy	>30–39.9 Gy	≥40 Gy
Surgery			RPLND^	

*CED = Cyclophosphamide Equivalent Dose[15]

To standardize risk estimates Cyclophosphamide Equivalent Dose

CED (mg/m2) = 1.0 (cumulative cyclophosphamide dose (mg/m2)) + 0.244 (cumulative ifosfamide dose (mg/m2)) + 0.857 (cumulative procarbazine dose (mg/m2)) + 14.286 (cumulative chlorambucil dose (mg/m2)) + 15.0 (cumulative BCNU dose (mg/m2)) + 16.0 (cumulative CCNU dose (mg/m2)) + 40 (cumulative melphalan dose (mg/m2)) + 50 (cumulative Thio-TEPA dose (mg/m2)) + 100 (cumulative nitrogen mustard dose (mg/m2)) + 8.823 (cumulative busulfan dose (mg/m2) D ^RPLND = Retroperitoneal Lymph Node Dissection

Figure 1. Testicular tissue cryopreservation pathway birth assigned males



3. RCH fertility preservation principles for birth assigned females

3.1 Purpose

To ensure that consistent discussion of infertility risk occurs with all cancer patients and their families, including the discussion of relevant preservation options when suitable.

3.2 Principles

The RCH Children's Cancer Centre, RCH Paediatric and Adolescent Gynaecology and Reproductive Biology Units will work collaboratively to:

1. Provide education and consultation to all birth assigned female patients and/or families about potential fertility impairment as a result of treatment in a clear and consistent manner with use of appropriate resource tools.
2. Discuss and consider the following potential fertility preservation (FP) options with birth assigned female patients/families where the patient is to receive any chemotherapy, radiation or surgical procedure that could impair fertility
    a. Post-pubertal birth assigned females (>12y and ≥Tanner3):
        i. Hormone stimulation and oocyte cryopreservation, requires maturity and takes approximately two weeks.
        ii. Ovarian tissue cryopreservation (limited outcome data).
        iii. GnRH agonist (limited outcome data and considered more an adjunct rather than an alternative to other measures).
        iv. Oophoropexy (limited outcome data).
        v. Ovum donation.
    b. Pre-pubertal birth assigned females:
        i. Ovarian tissue cryopreservation (limited outcome data).
        ii. Oophoropexy (limited outcome data).
        iii. Ovum donation.
3. Discuss FP recommendations based on risk of infertility versus risk of intervention, but all situations are to be considered individually and decisions made by patient/family in consultation with treating team (Table 3).
4. Involve Clinical Ethics as appropriate.
5. Provide age appropriate and confidential discussions with patients around sexual and reproductive health
6. Document fertility discussions and use of resources in medical record.
7. Discuss participation in Melbourne Oncofertility REgistry (MORE)
8. Provide feedback of results, and appropriate follow up over the treatment journey and during survivorship care.

3.3 Fertility preservation team to include:

1. Director of Oncofertility
2. Oncofertility coordinator
3. Paediatric and Adolescent Gynaecology (PAG) fellow
4. PAG consultant
5. Reproductive Biology Unit liaison
6. Oncology liaison
7. Clinical Ethics
8. Lines coordinator
9. Surgical team as required

3.4 Eligibility for fertility discussion

Birth assigned female patients are to be identified by the Children's Cancer Centre or treating team staff. The eligible population includes:

1. All new birth assigned female patients with a proven cancer diagnosis with intent to cure.
2. Birth assigned females with relapsed disease and a new gonadotoxic treatment plan and intent to cure.
3. At request of patients or families.
4. Birth assigned females who have completed treatment and are having ovarian reserve surveillance.

3.5 Indication for FP referrals to Gynaecology:

1. For all pubertal birth assigned females at any risk of infertility.
2. Pre-pubertal birth assigned females at moderate to high risk of infertility.
3. At the request of patient or family (investigational procedures are generally not recommended for prepubertal patients at low risk of infertility).
4. At the discretion of the oncology team.

3.5.1 Initial discussion by oncology clinician

The treating oncologist or other team member has an initial discussion with all eligible patients. This includes:

1. Assessment and discussion of risk of infertility attributable to planned chemotherapy, radiation or surgical procedure even if the risk is zero (Table 4).
2. Consider medical and ethical safety of FP and relay any concerns around supportive care to gynaecology team.
3. Offer additional reproductive and sexual health discussions with adolescents to discuss menstrual and contraceptive needs.
4. Fertility discussion can be formally documented in EMR using a template (in notes search

'fertility' or just use your own notes.

5. Written resources may be distributed to the patient and her family:
    a. OTCP Information Sheet
    b. Egg Freezing Information Sheet
    c. Zoladex Information Sheet
    d. RCH Oestrogen Patch information sheet
    e. Adolescent and Young Women Undergoing Cancer

3.5.2 Oncology Process for referral to gynaecology if required

1. Oncology clinician to call the Gynaecology Fellow/Gynaecologist so that referrals are not lost.
2. Oncology CNCs to notify Oncofertility CNC
3. Make a referral to the Oncofertility pool using the Biological Female Oncofertility Referral Form in the EMR.
    a. Inpatient: Fertility Preservation (born biologically female) inpatient consult
    b. Outpatient: Referral to Outpatient Oncofertility (born biologically female fertility preservation)
4. Referrals should include:
    a. Brief history.
    b. Developmental maturity of patient (tanner stage and menarcheal status).
    c. Planned gonadotoxic treatment (drug names doses), urgency (with clear indication of acceptable timeframe), prognosis, indication of infertility risk (high >80%/medium/low <20%) and CED mg/m2 or g/m2
5. **note: CED can be determined using CED calculator on Fertility intranet page: CED Calculator (Intranet Only)*
6. Handover of patient/family's understanding of the diagnosis, prognosis, FP options/response to introductory discussion.
7. Other procedures planned.
8. Other factors pertinent to cancer/reproductive potential (e.g. prognosis, likelihood of RT and relationship to uterus and ovaries, likelihood of relapse).
9. Factors that may specifically increase surgical risk such a mediastinal mass, significant immunosuppression, bleeding disorder, battle-scarred abdomen, malignant abdominal retroperitoneal mass.
10. Social concerns within the family such as custody issues and parental disagreement.
11. The level of complexity of the young patient's situation that would necessitate consultant review.
12. Any specific concerns the treating oncologist has with respect to proceeding with an FP procedure.
13. If the referring clinician feels the patient/family should not yet be approached, they will indicate how and when it is best to see the patient.

3.5.3 Role of Oncofertility CNC (in the absence of OC CNC, Gynaecology will undertake)

The Oncofertility coordinator will see the family to provide preliminary information and provide an overview of potential fertility care, prior to gynaecology consultation when appropriate.

1. The Oncology team will have introduced the fertility risk with the family.
2. Will notify Director of Oncofertility of medically and ethically complex patients
3. The Oncofertility CNC will see the family after discussion with Oncofertility clinician (gynaecology) to orientate family to program and discuss fertility preservation based on team discussion.
4. Oncofertility CNC will provide written information based on team discussion (information sheets, links to fertility videos, decision aid, Oncofertility registry consent).
5. Please note the final decision about suitability for fertility preservation and surgery will be made in consultation with all teams including the Oncofertility clinicians and surgeons. If any surgical concerns, involve surgery in discussions prior to definitive decision making

3.5.4 Gynaecology FP consultation:

1. PAG fellow or consultant will be available for consultation on new patients as soon as possible to further discuss the impact of cancer therapy on the patient's fertility. Consultations may occur beyond the 24-hour mark if the oncology team indicate that chemo/radiation treatment is less urgent.
2. Those patients who are inpatients, will have this discussion on the ward in an appropriate private space such as a single patient or interview room. Those who are outpatients may have this discussion in the oncology or gynaecology clinic as a drop-in.
3. Undertake a careful medical/surgical/social risk evaluation. The clinician will research and relay to the family the expected effect of cancer treatment on fertility (via published peer reviewed articles, reputed fertility risk calculators, and discussion with oncology and reproductive teams where appropriate). They will discuss potentially beneficial FP options with the family.
4. Consider if partial or complete oophorectomy is suitable. In general we would recommend:
    a. ½ of the cortex to be collected in children and adolescents.
    b. Oophorectomy for those having pelvic radiation, (usually of the irradiated side, as long as risk of malignant contamination from a solid tumour is low). For those receiving BMT with very high CEDs (>12g/m2 pre-pubertal; >8g/m2 post-pubertal) or TBI at high doses we would also consider oophorectomy as an individualised decision.
5. Consider pre-op bloods in those who may have already been exposed to gonadotoxic treatment or have a predisposing condition that may impair ovarian function, which could influence the decision to proceed to FP.
6. Make their own notes in the EMR or use the special 'fertility' templates which assist with fertility decision-making.
7. Provide age appropriate education and logistical information to the young patient on fertility preservation options.
8. Address any issues around menstrual management and sexual health.

9. Arrange any further consultations if required.
10. Makes shared decision with family about risks and benefits of proceeding, and decide if FP is permissible
11. Decide if patient will have concomitant Zoladex® insertion and place medication order
12. Decide if requires clinical ethics referral or MDM
13. Communicate back to the oncology clinician the treatment plan, exact nature of surgery (partial or complete oophorectomy, laterality) particularly any impact on the start of treatment.
14. Refer to Reproductive Services if consideration of oocyte collection

3.5.5 Clinical ethics:

1. Clinical ethics must be carefully considered according to the clinical ethics checklist.
2. For birth assigned females, staff do not need to routinely refer pre-pubertal ovarian tissue preservation cases to the Clinical Ethics Service prior to surgery, as long as there are no additional risks or ethical complexities. The same applies for post-pubertal fertility preservation.
3. If a clinical ethics opinion is needed, complete Referral Form 3A for pre-pubertal patients and Form 3B for post-pubertal patients. This should be regarded as an important medico-legal document.
    a. Pre-pubertal ethics referral (Intranet): Pre-pubertal form
    b. Post-pubertal ethics referral (Intranet): Post-pubertal form
4. If required referring department to complete Ethics Referral Form (edit Word document) with as much information as possible from EMR and email to: lynn.gillam@rch.org.au and CC fertility@rch.org.au & bioethics@rch.org.au (Clinician).
5. Expected invitees: Director of Oncofertility, Oncofertility CNC, a representative from Oncology, Gynaecology, and special experts where appropriate e.g. Haematology/Genetics.

3.6 If Ovarian Tissue Preservation to proceed:

1. Gynae arrange to see the patient/family to sign the consent forms. To book an Outpatient appointment, please contact Clinic coordinator on ext 57019 (A2 clinic) or message via in basket.
2. Gynae document in the notes that parent has read and understood RCH OTCP information sheet (as suggested by RCH Legal). This form goes through the innovative nature of the procedure.
3. Gynae complete the RWH consent to Gonadal Tissue Storage for Minors and FPS storage form, FPS Referral form
4. Gynae or CNC invite family to participate in Melbourne Oncofertility Registry.
5. Give forms to Oncofertility CNC
6. The Oncofertility CNC will email RWH storage consent and RBUFPS referral form to RWH Lab: rsuivflabsupervisors@thewomens.org.au, upload forms into the EMR, and arrange for Zoladex® to be sent to theatre if required. The lab can be contacted for urgent matter on 8345 3232

3.6.1 If patient is having OTCP with the insertion of a line:

1. Gynae to liaise with the Oncology Fellow re exact nature of surgery.
2. Onc Fellow will organise the line
3. Onc fellow will refer to surgery and outline exact nature of OTCP surgery , and request Zoladex® on

surgical referral if required

4. Lines coordinator will liaise with surgeons, theatre and anaesthetists, and endeavour to collect tissue in the morning as each biopsy takes several hours to process by the scientists. There is no reproductive laboratory service after 1.30pm and no service on weekends or holidays.
5. Surgery to book panel, Gynae to liaise with surgery to convey any special aspects of surgery

3.6.2 If patient is having OTCP with a procedure other than a line (e.g. BMA or LP)

Oncology Fellow will coordinate with Gynaecology and notify Oncofertility CNC of planned date for OTCP by either EMR chat or email fertility@rch.org.au

3.6.3 If patient is having OTCP as a standalone procedure:

Gynaecology team to organise theatre and undertake the procedure and notify Oncofertility CNC of planned date for OTCP by either EMR chat or email fertility@rch.org.au

3.6.4 All teams to understand requirements for theatre:

1. Request time of surgery as early as possible on the list (am is best). Once the panel is booked Gynaecology please order histopathology and write:
2. Type of malignancy
3. Site: ovary
4. Histopathology check for malignancy and follicle count
5. The specimen should be labelled

3.6.5 Day before surgery (in the absence of the OC CNC, oncology to complete)

1. Oncofertility CNC to contact RWH laboratory to confirm theatre: 8345 3232/3233
2. OC to arrange Zoladex® to be delivered from pharmacy;
3. If OC is unable to administer Zoladex® OC then Onc fellow to coordinate someone to administer
4. Ensure the following documentation has been completed (will be on EMR)*:
    a. RWH Storage Consent signed
    b. RBU FPS completed
    c. Ethics referral signed by Ethics team
    d. Registry form signed

    **best way to check for these is to enter the patient file on EMR and search for key words (fertility) on the left hand side search box*

3.6.6 On day of theatre (in the absence of the OC, oncology to complete)

1. Oncofertility CNC to ensure Zoladex® in theatre and someone to administer
2. Gynaecology and oncology consultant to be notified if there are any delays to expected commencement of cancer treatment due to the FP procedure itself and make decision regarding

risk-benefit.

3. Director of Oncofertility may be consulted for advice

3.6.7 Follow-up: (in the absence of the OC CNC, gynaecology to complete)

1. Review histology (Gynae team)
2. The Oncofertility coordinator will discuss reproductive findings with family postoperatively,
3. The Oncofertility coordinator will provide a summary of fertility care letter to the family and copy to referring clinician and GP
4. It is recommended that families have a follow-up discussion after acute treatment with Gynaecology whether they had FP or not. This allows questions to be answered regarding storage, technology, and monitoring of pubertal development, reproductive, sexual and bone health.
5. Timing of follow-up by gynaecology is at the discretion of oncologist (around 12 months) or from around nine years of age.
6. Transition to an adult facility is recommended when appropriate.

3.7 If Oocyte collection is being considered:

1. Gynaecology undertake consultation as per usual then refer to RWH RSU with internal EPIC referral to RSU Public Fertility Service and follow up phone call to Reproductive Fellow on call.
2. Order FSH, LH, Oestradiol and AMH
3. Multiple stimulation cycles or additional collection of ovarian tissue is beneficial where time permits.
4. Usually tissue collection is undertaken prior to oocyte collection, or there would need to ideally be a three week window after oocyte collection to reduce surgical risks for tissue collection.
5. Oocyte collection is not advised if gonadotoxic therapy has been administered in the last 6 months due to mutagenic risk: liaise with reproductive team for advice.

3.8 Goserelin Acetate (Zoladex®) injection for use in patients receiving gonadotoxic therapy

1. Please see medication guideline: Intranet: Medication Guideline (Intranet only)
2. Subcutaneous 3.6 mg implant every 4 weeks OR Subcutaneous 10.8 mg implant every 12 weeks
3. Commence with the 10.8 mg implant every 12 weeks. In some cases, the patient will be transitioned to the 3.6 mg implant every 4 weeks towards the end of treatment.

3.8.1 Contraindications to Zoladex®

1. Contraindicated in patients with known hypersensitivity to LHRH, LHRH agonist analogues or any of the components of Zoladex®
2. Undiagnosed vaginal bleeding: please seek advice from the gynaecology team

3. Thrombocytopenia: please seek advice from the treating medical team for consideration of platelet transfusion.
4. Zoladex® should not be used in pregnancy as there is a theoretical risk of abortion or foetal abnormality if LHRH agonists are used during pregnancy. It is important to exclude pregnancy prior to administering the Zoladex® implant in sexually active females of childbearing age

3.8.2 Side effects of Zoladex®

1. Hot flushes or sweating
2. Headaches
3. Mood changes
4. Vaginal dryness
5. Reduced bone density

3.8.3 Preparation

1. Personal Protective Equipment (PPE)
2. Zoladex® injection
3. Alcohol swab
4. Sharps container
5. Cotton wool ball
6. Small dressing
7. Ensure implant is visible in the applicator window; do not expel air bubbles.

3.8.4 Administration

Never administer intravenously

Procedure

1. Prepare patient and obtain consent
2. Complete the six rights of medication administration and complete documentation on the MAR
3. Perform the five moments of hand hygiene · Prepare equipment as per Aseptic Technique · Don PPE if required as per the RCH Hazardous medicines procedure
4. Position patient in a safe and comfortable position Procedure Management Guideline
5. Consider the use of comfort techniques such as distraction
6. Landmark injection site (see image on Zoladex® packaging for example if required))
7. Clean site with an alcohol swab
8. Pinch the skin
9. Inject the needle halfway at a 45-degree angle (see image on Zoladex® packaging for example if required)
10. Then lower the needle so that it is flat against the skin (90-degree angle) and insert the needle fully so that the hub is against the skin
11. Inject the medication at a slow and steady pace until you hear the devise click. The needle will

automatically retract

12. Apply a cotton ball with pressure for 1-2 mins, until bleeding has stopped
13. Apply a small dressing
14. Place the syringe in a sharps container
15. Remove PPE (if required)
16. Perform the five moments of hand hygiene

3.8.5 Monitoring after Zoladex® insertion

1. Monitor for immediate adverse reactions e.g., fever, rash, vomiting, shortness of breath
2. Advise patient/family to remain in the hospital for 15 minutes following their injection
3. Inform the patient/family/nursing team to monitor injection site for bleeding or oozing
4. Keep the area clean and dry until the injection site has healed
5. Observe for redness, oozing, warmth, or signs of infection
6. Gynaecology to review patient after one month (by phone) to assess for hypooestrogenic side effects

3.8.6 Repeat Zoladex® doses

1. Place a reminder in the EMR for 2 weeks prior to the next anticipated dose, to be sent to gynaecology, Oncofertility CNC and treating oncologist
2. Oncologist to provide information regarding duration of ongoing treatment
3. Gynaecology to assess patient regarding side effects, dose, decision for add back estrogen patch

Table 3. Infertility risk and potential recommendations biological females

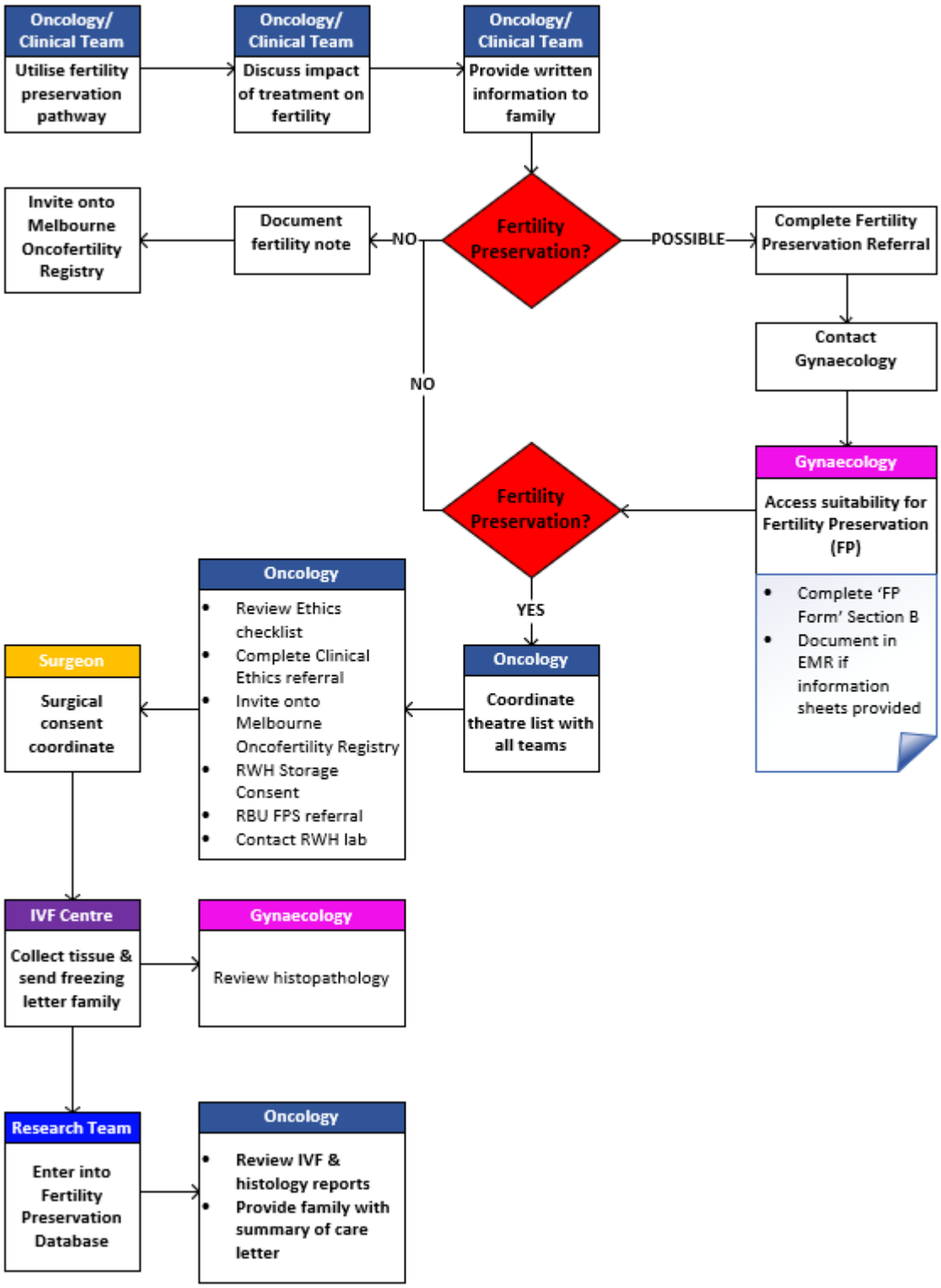
Age	Risk category	Pre-treatment FP recommendation
Pre-pubertal	minimal	No
	significant	Yes, for consideration
	high	Yes, for consideration
	Uncertain	No
Pubertal	minimal	No, but up to patient/family
	significant	Yes. Consider oocyte harvest if time Consider OTCP
	high	Yes. Consider oocyte harvest if time Consider OTCP
	Uncertain	Up to patient if >16

Table 4. Female level of risk for gonadal failure / infertility above that for the general population (Paediatric Initiative Network)[14]

			Minimally increased risk	Significantly increased risk	High level of increased risk
Alkylators CED* gm/m²		**Pre-pubertal**	CED <8	8–12	>12
		Pubertal	CED <4	4–8	>8
Heavy metal			Cisplatin Carboplatin		
Hematopoietic stem cell transplant					Alkylator +/- total body irradiation Myeloablative and reduced intensity regimens
Radiation exposure	**Ovary**	**Pre-pubertal**		<15 Gy	≥15 Gy
		Pubertal		<10 Gy	≥10 Gy
	Hypothalamus		22–29.9 Gy	>30–39.9 Gy	>40 Gy

*CED = Cyclophosphamide Equivalent Dose

Figure 2. Ovarian tissue cryopreservation pathway birth assigned females



4. Fertility preservation principles for children with Leukaemia

4.1 Purpose

This protocol was originally developed for patients on the TOTXVII protocol, however general principles also apply to other patients with a Leukaemia diagnosis. The aim is to ensure that consistent, evidence-based discussion regarding estimated infertility risk occurs with patients and their families, when they are receiving treatment for acute lymphoblastic Leukaemia (ALL) or acute lymphoblastic lymphoma (LLy). This discussion should include options for fertility preservation procedures when indicated.

4.2 Background regarding TOTAL XVII

On 1st December 2021 the SJCRH TOTALXVII study opened to recruitment at the Royal Children's Hospital (RCH) for the treatment of newly diagnosed ALL or LLy. On this protocol, children receive therapy on one of three treatment strata dependent on their 'risk group'. Each stratum carries different risks to fertility based on their chemotherapy protocol, defined by the cumulative equivalent alkylator dose (CED), in addition to other factors that contribute to risk (pubertal status and gender)[i].

Risk group stratification is determined following completion of remission induction chemotherapy, which lasts approximately 6 weeks.

- Approximately 42% of patients will be treated on the 'low risk' arm with a CED of 1g/m2 patients, which is expected to have a low risk to fertility (<20%) for both birth assigned males and birth assigned females. In comparison, infertility affects 8-12% of couples in the general population)[33]. Those with low-risk disease do not require invasive fertility preservation interventions.
- Some high-risk patients may proceed to haematopoietic stem cell transplant (HSCT), which may be associated with a high risk of infertility in birth assigned males and birth assigned females (>80%)[14]. Those deemed high risk of infertility should be offered fertility consultation, with fertility preservation procedures usually undertaken once remission is achieved, as per institutional guidelines.
- Around 48% will be treated on the standard/high risk arm with a CED of 4.7g/m2, which is expected to have a moderate risk of infertility for pre and post-pubertal birth assigned males and post-pubertal birth assigned females, and a low risk to infertility for pre-pubertal birth assigned females[14]. Those with standard/high risk disease not proceeding to HSCT require personalised counselling, as their fertility risk and impact is dependent on sex, age, pubertal status and family values.

TOTAL XVII treatment is divided into three phases for standard/high-risk patients:

- Remission induction (6 weeks): Treatment generally begins within 24-48 hours of diagnosis. Most

[33] Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clin Biochem. 2018 Dec;62:2-10.

patients are in complete remission after induction. Patients receive 1g/m2 of cyclophosphamide in remission induction

- Early Intensification (4 weeks)/Consolidation (8-16 weeks): Consolidate depth of remission and extra-medullary directed therapy (high dose methotrexate). Some children with B-ALL also receive immunotherapy. Patients receive a further 1g/m2 of cyclophosphamide during early intensification (total of 2g/m2 in first 4 months)
- Continuation (remainder of therapy): First 20 weeks involves intensified therapy e.g. re-induction blocks. Patients receive multiple low doses of cyclophosphamide during continuation therapy at approximately monthly intervals from week 20 to week 49 (9 doses of 300mg/m2).

This results in a total CED of 4.7g/m2 for standard/high-risk patients over the course of their therapy.

It is important to note that most patients who receive Reintensification II will proceed to transplant, and not complete continuation (so will not receive the additional 2.7g/m2 in Continuation). The CED from TOT17 in these patients prior to transplant will be 3.5g/m2 (low risk to fertility). The primary risk to fertility in these patients will be from HSCT conditioning.

All patients regardless of risk, would benefit from counselling about the impact of treatment on fertility. For reasons outlined below, the only feasible currently established fertility preservation procedure in patients with Leukaemia is cryopreservation of sperm. This is only possible prior to initiation of therapy, and cannot be performed after commencement of chemotherapy (and for at least 6 months following completion of chemotherapy) due to the possible fragmentation of gamete DNA associated with gonadal exposure to chemotherapy[24]. Sometimes collection after a 3 month window since chemotherapy is undertaken, or even sooner when there are no other options, as long as the family is warned about risks. For post-pubertal birth assigned males, the option of collecting a sperm sample before commencing treatment should therefore be discussed with the patient and family if it does not pose significant medical risk, even if they are low risk.

Where cryopreservation of sperm has not been undertaken, Oncofertility consultation to discuss other potential fertility preservation options may be offered after remission induction therapy, with the following considerations:

1. Almost half of patients will ultimately be classified as having low risk disease and therefore will receive only 1g/m2 of cyclophosphamide during their therapy. This CED carries a low risk to fertility and there is therefore no indication for invasive fertility preservation procedures in this group.
2. Stratification into high or low gonadotoxic risk groups occurs several weeks after initiation of treatment, which means that delayed fertility preservation strategies may need to be considered, making discussions more complex.
3. Due to the possible presence of Leukaemia cells, preserved gonadal tissue cannot be autografted in Australia, due to the risk of malignant reseeding. In Leukaemia patients, the potential for future successful implantation is predicated on the development of techniques for in vitro maturation of gametes (sperm or ova) from cryopreserved germ cells, which currently remain experimental.
4. In practice, there is a window for considering fertility preservation procedures after risk group assignment and before commencing continuation therapy, when standard and high-risk patients

would have received a CED of 2g/m2.

5. All patients regardless of risk would benefit from Oncofertility referral after treatment.

4.3 Fertility preservation Leukaemia pathways

4.3.1 The procedures apply to the Oncofertility team, who can include:

1. Oncology or other treating team: role is to undertake initial Oncofertility discussion and documentation, liaison with other teams including referral to surgery, attend Oncofertility huddles, relay sperm count results (see sperm guidelines or contact andrology for advice), refer to gynaecology and endo-oncology post treatment
2. Director of Oncofertility: role is provision of new protocols, overarching clinical guidance, clinical support, chairing MDMs, policies and procedures, managing Melbourne Oncofertility Registry, monitoring safety, handing complaints, reporting to executive
3. Endo-oncology consultant: role is consultation for birth assigned males, review histopathology results from surgery, follow-up after treatment, review of protocols
4. Gynaecology: role is consultation for birth assigned females, OTCP surgeries, review histopathology results from surgery, follow-up after treatment (menstrual management, fertility monitoring, interval FP, graft versus host, contraception, body image, liaison for reproductive laboratory)
5. Oncofertility Coordinator: support for clinicians and families, provision of written information, coordinating lab, summary of care letters to families
6. Surgical team: undertaking fertility procedures, postop care
7. Theatre staff: storage of tissue transport containers, specimen labelling, handover of gonadal tissue to laboratory team after collection, Zoladex® training
8. Reproductive Biology Unit/Andrology liaison: specimen processing, storage and reporting
9. Clinical ethics: review of ethics referrals, support ethically moral decision-making
10. Lines coordinator: coordinate with oncology and OC re lists at Thursday lines meeting.

4.3.2 Who do the procedures apply to: Eligible patients for fertility preservation procedures

Patient group	Action	Action in the future
Pre-pubertal female Leukaemia patients at low risk of infertility (<8g/m2 CED)	OTCP not routinely recommended	Consider oocyte collection in survivorship
Pre-pubertal female Leukaemia patients at moderate risk of infertility (8-<12g/m2 CED)	Individualised consultation	Refer gynaecology for Oncofertility consultation now and Consider oocyte collection in survivorship
Pre-pubertal female Leukaemia patients at high risk of infertility (≥12g/m2 CED)	OTCP can be considered prior to HSCT	Consider oocyte collection in survivorship
Post-pubertal female Leukaemia patients at low risk of infertility (<4g/m2)	• OTCP not routinely recommended • No time for oocyte collection • GnRH can be considered for menstrual management	Consider oocyte collection in survivorship
Post-pubertal female Leukaemia patients at moderate risk of infertility (≧4g-<8g/m2)	• Individualised consultation • Consider GnRH for menstrual management.	Refer gynaecology for Oncofertility consultation now and Consider oocyte collection in survivorship
Post-pubertal female Leukaemia patients at high risk of infertility (≥8g/m2 CED)	• OTCP can be considered prior to HSCT • Consider GnRH for menstrual management	Refer gynaecology for Oncofertility consultation now and Consider oocyte collection in survivorship
Pre-pubertal male Leukaemia patients at low risk of infertility (<4g/m2)	TTCP not routinely recommended	Refer endo oncology after treatment Sperm collection and storage in survivorship
Pre-pubertal male Leukaemia patients at moderate risk to high risk (≧4g/m2)	Individualised consultation, TTCP can be considered	Refer endo-oncology Sperm collection and storage in survivorship
Post-pubertal male Leukaemia patients at low risk of infertility (<4g/m2)	sperm collection before chemo starts	Refer endo-oncology Sperm collection and storage in survivorship
Post-pubertal male Leukaemia patients at moderate to high risk of infertility (≧4g/m2)	• sperm collection before chemotherapy starts • sperm collection contraindicated if chemo already started • testicular biopsy may be considered	Refer endo-oncology Sperm collection and storage in survivorship

5. Fertility preservation in patients with CNS tumours

5.1 Purpose

To ensure that consistent, evidence-based discussion regarding estimated infertility risk occurs with patients and their families, when they are receiving treatment for CNS tumours. This discussion should include options for fertility preservation procedures when indicated.

5.2 Background

There is limited knowledge of radiation dose delivered to reproductive organs from modern radiation therapy techniques. It is not routinely quantified in the treatment planning system (TPS) and is often 'out of field' with consequent uncertainty in TPS calculation. While scatter to the ovaries is likely to be limited, with expected low impact on fertility, it is unknown if cranio-spinal irradiation (CSI) has enough impact on oocyte DNA to significantly increase the risk of mutagenesis.

For post-pubertal patients if feasible, collection of sperm or eggs prior to the commencement of any chemoradiation is desirable. This needs to be balanced with the urgent need for surgery or other cancer treatments. Life-saving oncology care takes priority over invasive fertility measures. Furthermore collection of sperm and eggs requires physical and emotional maturity and oocyte collection requires a two week window. Quality of oocytes in young teenagers is unknown and oocyte yield may be variable.

Recommendations for Oncofertility care must be individualized, and the following approach may be permissible when it is medically safe, and the family places a high value on fertility:

- For pre-pubertal patients, consider OTCP or TTCP for those receiving moderate to high dose gonadotoxic treatment after surgery and in the window between radiation therapy and commencement of chemotherapy.
- For post-pubertal birth assigned males consider sperm collection prior to any therapy
- For older post-pubertal birth assigned females where it is medically safe consider oocyte collection after surgery and prior to radiation. Consideration must be given to the emotional impact of ovarian stimulation at this physical and emotionally vulnerable time. Oocyte collection may potentially be offered after CSI and prior to chemotherapy, but families would need to be fully informed about the theoretical risks of DNA damage to oocytes and mutagenic risk to the fetus. OTCP may still be offered in the window after radiation treatment and chemotherapy as collection of immature follicles, not fertilisable oocytes is being undertaken.
- Special consideration must be given to those patients with a ventriculoperitoneal shunt or advanced disease, where trendelenberg and laparoscopy may pose haemodynamic and infection risks. It is best to seek advice from neurosurgery prior to intervention.

6. Clinical ethics checklist for all fertility preservation procedures

This document refers to ethical principles[34] for surgical procedures to retrieve reproductive tissue from a child who has cancer, for the purpose of attempting to preserve fertility by freezing the tissue for future use. This refers to ovarian tissue from a birth assigned female, and testicular tissue from a birth assigned male.

6.1 Basic ethical requirements for a child of any age:

1. Informed consent of parents: In all cases where fertility preservation procedures are contemplated, parents should be provided with comprehensive written information, including clear and accurate information about the storage of reproductive tissue, including place costs of storage, what will be done with the tissue if the child does not survive, who has the right to access the tissue and for what purposes. It is crucial that parents understand that this procedure offers only a theoretical possibility of fertility preservation, for which there is not yet any evidence of success and is by no means a guarantee that the child will have fertility in adulthood. Parents must also be aware that the offer of a fertility preservation procedure does not imply that child's survival into adulthood is certain.

2. Assent of child (where child is old enough). The child should be given a developmentally-appropriate explanation of the procedure that will be done and its purpose. Ideally, the child should be in agreement with the procedure.

6.2 Formal clinical ethics review — when required

6.2.1 Clinical ethics review is NOT required in the following circumstances:

1. This procedure will not delay or interfere with the cancer treatment.
2. This procedure is itself of minimal risk, and will be performed under a GA which is required in any case for treatment for the cancer.
3. The treatment for cancer is being undertaken with the intent of cure or long-term survival.
4. Survival into adulthood is sufficiently probable that it is appropriate to undertake procedures aimed at promoting quality of life long-term.
5. There is risk of loss of fertility due to chemotherapy.
6. The procedure will leave one gonad intact, so that if the gonad from which tissue is taken ends up being damaged or completely removed, and the chemotherapy does not in fact cause loss of fertility, there is still one functioning gonad with good chance for natural fertility.

[34] McDougall R, Gillam L, Delany C, Jayasinghe Y. The ethics of fertility preservation for prepubertal children: should clinicians offer procedures where efficacy

7. There are none of the following complicating factors involved:
    a. The treatment for cancer is not being undertaken with the intent of cure or long-term survival.
    b. The child has an intellectual disability.
    c. The child or young person objects to having a fertility preservation procedure, but parents still want to go ahead.
    d. The parents are unwilling to inform the child about the procedure, when the child is at developmental stage where they would be able to understand at least the basic idea of the procedure.

Note - patients having OTCP do not require routine ethics review unless there are other complex medical or ethical factors to consider.

6.2.2 Clinical ethics review for a fertility preservation procedure IS REQUIRED if one or more of the following apply:

1. The risks of the FP procedure:
    a. The procedure will delay or interfere with the cancer treatment.
    b. The procedure is itself of greater than minimal risk (e.g. because of a co-morbidity which makes the procedure more risky than usual).
    c. The procedure has a significant risk of not leaving one gonad intact (e.g. if the child has only one gonad to begin with).
2. The potential benefits:
    a. The risk of loss of fertility due to chemotherapy is low.
    b. The potential for retrieving tissue that might be useable in the future is lower than usual, for any reason.
3. Other factors:
    a. The treatment for cancer is not being undertaken with the intent of cure or long-term survival.
    b. The child has an intellectual disability.
    c. The child is pre-pubertal and having TTCP
    d. The child or young person objects to having a fertility preservation procedure, but parents still want to go ahead.
    e. The parents are unwilling to inform the child about the procedure when the child is at developmental stage where they would be able to understand at least the basic idea of the procedure.
    f. Any treating clinician has an ethical question or concern about the procedure.

6.3 Clinical ethics checklist:

1. Pre-pubertal child having TTCP — use Referral Form 3A (FP Pre-pubertal).
2. Post-pubertal or pre-pubertal OTCP— use checklist below. If one or more items ticked below, clinical ethics meeting will be held—use Referral Form 3A for pre-pubertal and 3B (FP Post-pubertal
3. If no items ticked, no clinical ethics referral needed, no meeting required:

- ☐ The procedure will delay or interfere with the cancer treatment.
- ☐ The procedure itself is of greater than usual risk (e.g. because of a co-morbidity).
- ☐ The procedure has a significant risk of not leaving one gonad intact (e.g. if the child has only one gonad). The risk of loss of fertility due to chemotherapy is low.
- ☐ The potential for retrieving tissue that might be useable in the future is lower than usual, for any reason.
- ☐ The treatment for cancer is not being undertaken with the intent of cure or long-term survival.
- ☐ The child or adolescent is unlikely to be able to use any stored tissue for fertility purposes in the future, but parents still want the procedure done.
- ☐ The child or adolescent objects to having the fertility preservation procedure, but parents still want to go ahead.
- ☐ The parents are unwilling to inform the child or adolescent about the procedure (where developmentally appropriate to inform), but want the procedure done.
- ☐ Any treating clinician has an ethical question or concern about the procedure.

Clinical Ethics Referral Forms 3A and 3B can be found at the below links:

a. Pre-pubertal ethics referral (Intranet): Pre-pubertal form
b. Post-pubertal ethics referral (Intranet): Post-pubertal form

7. Ovarian tissue biopsy procedure

7.1 Ovarian tissue biopsy protocol: Many follicles are lost during processing and grafting. The laboratory has to cut away burnt tissue if diathermy is used and this may significantly reduce the potential of what is in storage.

7.2 It is recommended that the following surgical principles apply:

- At least ½ of the cortex of an entire ovary be collected in children and adolescents. Generous biopsies are especially important in adolescents who have significantly reduced follicle density. The biopsy may be taken by holding the antimesenteric border of ovary and raise a flap/s of cortex using scissors only. If there are physiological cysts please don't target those areas for biopsy if there are smooth areas of cortex available, as their inclusion reduces the follicle density of collected tissue. That is, try and collect tissue from a smooth surface if possible. Diathermy may be used for haemostasis after the ovarian biopsy is removed if this can be safely left until then. Cutting across medulla and bisecting the ovary has the potential to reduce the amount of tissue that can be stored, as diathermy is often required and ovarian medulla is not utilised for grafting.

- Oophorectomy occur for those having pelvic radiation, (usually of the irradiated side, as long as risk of malignant contamination from a solid tumour is low). For those receiving BMT with very high CEDs (>12g/m2 pre-pubertal; >8g/m2 post-pubertal) or TBI at high doses, or those who have had previous gonadotoxic therapy we would also consider oophorectomy as an individualised decision. The decision for oophorectomy versus biopsy will be discussed with the family and decided upon at the fertility consultation for every case.

7.3 Tissue biopsy QA: The laboratory can provide feedback to the treating surgeon and oncologist regarding biopsy quality after each surgery. Your team members may let us know if they would like to opt out of this feedback.

8. Deceased patients

8.1 Purpose

To ensure that the RCH can support families around decision making with respect to the stored tissue, and assist compliance with state legislation around tissue storage in the event that a patient becomes deceased.

8.2 Principles

Tissue from minors is required to be discarded by law for deceased patients and cannot be used by others for fertility purposes nor for research.[35,36] During working hours reproductive samples might be able to be released to funeral directors to be included for cremation or burial. Outside of hours, please speak directly to the applicable personnel to discuss if this can be accommodated. This may not be possible during lab closures.

8.2.1 Tissue/Oocytes collected prior to 1 July 2023

1. All gonadal tissue and eggs collected PRIOR to 1 July 2023 are now stored at Melbourne IVF (MIVF) in East Melbourne. The contact details are as follows:
   MIVF Fertility Preservation Nurse email: fertility.preservation@mivf.com.au
   MIVF Fertility Preservation phone (in hours): (03) 9473 4501/ +61 429 131 941 (ANUM)
   MIVF Fertility Preservation phone (out of hours): Heidi Jensen +61 417 626 055
2. For the release or disposal of tissue/oocytes MIVF require the following information to be provided: Pt name, D.O.B, Date of passing, declaration of passing, contact details for treating doctor, signed and completed MIVF Release of Tissue Form (RCH Intranet only) Melbourne IVF Consent to Removal of Ovarian or Testicular Tissue From Storage

8.2.2 Tissue/Oocytes collected after to 1 July 2023

1. All gonadal tissue and eggs collected AFTER 1 July 2023 are stored at the Reproductive Services Unit, The Royal Women's Hospital (RWH). The contact details are as follows:
   RSU laboratory supervisor email: rsuivflabsupervisors@thewomens.org.au
   RSU laboratory supervisor phone (in hours): 03 8345 3253
   RSU laboratory supervisor phone (out of hours): contact the on call reproductive fellow via RWH switch
2. For the release or disposal of tissue/oocytes RWH require a phone notification by the treating team. The following needs to be recorded in EMR: Pt name, D.O.B, Date of passing, declaration of passing, contact details for treating doctor. A signed and completed RWH Consent To Remove All

[35] Allan S, Gook D, Jayasinghe Y. The impact of the law in helping or hindering fertility preservation for children with cancer facing gonadotoxic therapies. Journal of Law and Medicine 2018 Dec;26(2):322–333

[36] Mr Michael Gorton AM. Helping Victorians create families with assisted reproductive treatment. Interim Report of the Independent Review of Assisted Reproductive Treatment October 2018.

Gonadal Tissue From Storage (located on RCH Intranet - temporary). The form needs to be uploaded into pt EMR so it can be viewed by both RCH and RWH.

8.2.3 Sperm

All sperm is stored at The RWH Andrology Unit & Sperm Bank.

The contact details are as follows:

Email: data.manager@thewomens.org.au Phone (03) 8345 3993

8.2.3 Families who do not want tissue/gametes released for burial/cremation

If families don't want to have the tissue for burial, the applicable lab may agree to continue the storage of the tissue for a short period of time. Families need to let the IVF centres know about the passing of their child. The decision to discard the tissue can be made by the storage center.

9. Monash Children's

9.1 Purpose

To provide support to Victorian children and families having treatment under the statewide Pediatric Integrated Cancer Service attending Monash Children's Hospital.

9.2 Principles:

1. The Pediatric Integrated Cancer Service is a statewide service endorsing fertility care for Victorian children in statewide guidance.[37,38]
2. Monash Children's offers FP onsite to children aged 13 years and above.
3. Until such time as the Monash Children's establishes laboratory, and clinical ethics governance for pre-pubertal children, The RCH team have provided support, by sharing of fertility protocols and guidance, advice to clinicians, and patient care.
4. The expected numbers of referrals are approximately 10 per annum are expected to increase.
5. In the event that a Monash clinician requests FP consultation and care:
   They will complete an RCH Fertility Referral Form, provide timelines for start date of cancer treatment and speak with Dr Leanne Super, Monash Liaison.
   The Oncofertility coordinator and the relevant RCH team (Gynaecology or Endo oncology or Surgery) will be notified and seek advice from executive.
6. RCH Executive will endeavor to provide an answer within 24 hours so as not to delay the onset of cancer treatment, or to allow time for review at another centre if feasible.

[37] Victorian Paediatric Integrated Cancer Service Victorian paediatric oncology care pathway: providing optimal care for children and adolescents—acute leukaemia. (Guidelines) 2017

[38] Victorian Paediatric Integrated Cancer Service Victorian paediatric oncology care pathway: providing optimal care for children and adolescents— CNS tumours (2018).

10. Tool kit

Information Support for families

A. Testicular Tissue Cryopreservation Information Sheet for families V7.2 15/6/2023
B. Testicular Tissue Cryopreservation Information Sheet **for Leukaemia Patients** V3 2/11/2023
C. Sperm Banking Information Sheet for families V2 15/6/2023
D. Ovarian Tissue Cryopreservation information Sheet for families V5 2/9/2022
E. Ovarian Tissue Cryopreservation Information Sheet **for Leukaemia Patients** V4 2/11/2023
F. Egg Freezing Information Sheet for families V1 1/9/2022
G. Zoladex Information Sheet for families V1 1/9/2022
H. Oestrogen Patch Information Sheet for families V1 27/10/2023
I. Adolescent & Young Men Undergoing Cancer Treatment Information Sheet for families V5 1/9/2023
J. Adolescent & Young Women Undergoing Cancer Treatment Information Sheet for families V5 1/9/2022

Information Support for clinicians

K. Sperm Banking (cheat sheet) Guidelines for an Inpatient V4.2 16/6/2023
L. Sperm Banking (cheat sheet) Guidelines for an Outpatient V4 16/6/2023
M. RWH Collection and Storage of Gonadal Tissue of a Minor Consent Form (Intranet only)
N. RWH RSU FPS Female Patient Referral (Intranet only)
O. RWH RSU FPS Male Patient Referral (Intranet only)
P. RWH Andrology Request for Sperm Storage in a Minor Consent Form (Intranet only)
Q. Melbourne IVF Consent to Remove all Gonadal Tissue From Storage (Intranet only)
R. Clinical Ethics Referral Form 3A (Pre-Pubertal) (Intranet only)
S. Clinical Ethics Referral Form 3B (Post-Pubertal) (Intranet only)
T. Fertility Preservation Procedures in Birth Assigned Males.
U. Impact of class of chemotherapeutic agent on ovarian function
V. Fertility Preservation Procedures Birth Assigned Females

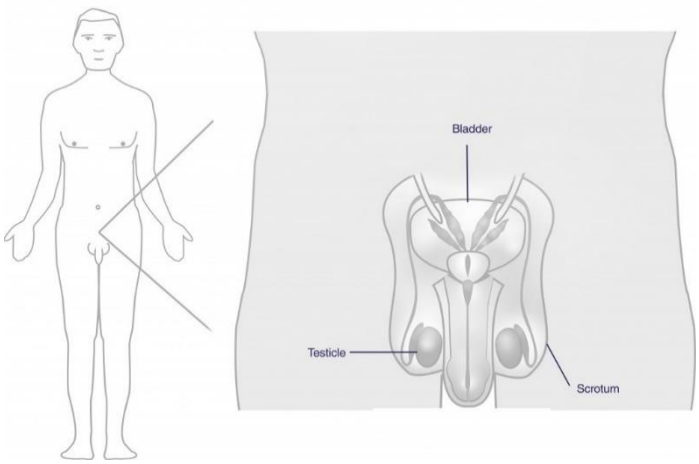
Information for Families

A.

The Royal Children's Hospital Fertility Preservation Service
Testicular Tissue Cryopreservation (TTCP) Information Sheet for Families

What Is Fertility Preservation?
Fertility preservation is a process that aims to give patients the opportunity to freeze sperm, eggs, or reproductive tissue. It is hoped that this may protect a person's ability to have a biological child in the future. Some of these procedures are proven to assist fertility with live births recorded, and others are considered experimental.

Reproduction in Biological Males
The mature testes contain 2 different types of cells, the Sertoli cells and the Leydig cells. The Sertoli cells are responsible for making sperm and the Leydig cells are responsible for producing testosterone. The testicles of a pre-pubertal child do not contain sperm, they contain germ cells. When puberty begins, usually between the ages of 9 & 15, the pituitary gland (located near the brain) secretes hormones (FSH sperm production & LH testosterone) that stimulate the testicles to produce testosterone and mature sperm.



Potential Impact on Fertility
Medical treatments such as chemotherapy and radiotherapy, or conditions in childhood such as genetic conditions, may damage the cells responsible for making sperm. Depending on the severity, this can permanently affect fertility. Your doctor will outline the estimated impact of your child's treatment on their fertility (low, medium or high risk). Unfortunately, it can be difficult to be precise about risk this due to limited data.

How Does Chemotherapy Affect Fertility?
Chemotherapy drugs enter the blood stream and travel around the body searching for cancer cells to destroy. It can also deplete Sertoli and Leydig cells along with sperm producing cells.

How Does Radiotherapy Affect Fertility?
Radiotherapy destroys cancer cells. If the testes are exposed to radiotherapy, then Sertoli and Leydig cells will be destroyed along with sperm producing cells. Total body radiation has a high risk of causing infertility. If radiotherapy is required to treat a brain tumour, the hormone messages from the brain to the testes can be disrupted or lost.

Testicular Tissue Cryopreservation (TTCP) - How Is This Procedure Done?
TTCP involves the collection of healthy testicular tissue, prior to starting treatment that may harm the testes. It is then preserved and frozen until your child is ready to think about starting a family. This is an experimental procedure. It is important to understand that there is no guarantee that the freezing of testicular tissue will lead to successful pregnancies and/or live births.

The tissue, which contains immature germ cells, is harvested via a small incision made in the scrotum, where part of the testicle is removed (approximately 30% of the testicle). The procedure takes approximately 20 minutes and is usually coordinated with another procedure. The incision will be closed with dissolving stitches and will have a small dressing. Recovery time is usually a few days.

Currently, scientists from the Reproductive Services Department at the Royal Women's Hospital (RWH) collect the tissue from theatre and process it at their centre. A small piece is sent for histopathology to see if there are any malignant cells in the tissue. It is then sliced, placed in liquid and frozen until required for future fertility treatment. Sometimes the tissue is dissected for mature sperm in children who are going through puberty.

Using This Tissue In The Future
In the future, it is hoped that the tissue might be utilised via two experimental options. Implanting the tissue back into the body or maturing the tissue outside the body in the IVF lab via a process called In Vitro Maturation (IVM).

Transplanting The Tissue Back Into The Body
Once thawed, the tissue containing the germ cells can be transplanted back onto the testes or another area. It is hoped that these germ cells will start to make sperm. Tissue that has been collected from patients who have been diagnosed with Leukaemia cannot be transplanted due to the risk of malignant cells being present and reintroducing Leukaemia back into the body. For children with Leukaemia we are hoping another technique (IVM) may be utilised.

Maturing The Tissue Via IVM
If the tissue is not suitable to be implanted into the body, we are hoping the tissue can be matured in the IVF lab. An IVF treatment would be necessary to use this sperm to create a pregnancy. IVM is currently experimental.

Who Is Eligible For TTCP?
Theoretically, there is no lower age limit for TTCP and it can be offered to patients of all ages. However, your child needs to be well enough for surgery. Bleeding disorders or serious immune deficiency may preclude your child from having the procedure done.

In a very young child, the testes will usually be very small and it is highly possible that one entire testicle may need to be removed. We cannot guarantee that the testicular tissue collected or the remaining testicle will be functional in the future.

Outcomes So Far
Currently, this procedure is deemed experimental as there are no live births to humans to date. Pregnancy has been achieved with implanted tissue in animal studies but not in humans. We would need Ethical approval for this procedure.

Risks and Benefits

The surgery (Testicular Biopsy, Testicular Tissue Cryopreservation, removal of one testicle) is not experimental as this procedure is performed routinely by surgeons for other indications.
Expected risks of the surgical procedure:

- Risk of a general anaesthetic.
- Infection
- Bleeding
- Haematoma (collection of blood)
- Risk of a second operation to address any of the above issues

What Other Options Are Available?

- If you decide not proceed with fertility preservation, your child can have their testicular function assessed later after treatment is finished.
- Sperm donation from father, brother, male relative or other donor in the future.
- Fostering or adoption.
- For post pubertal males, freezing of mature sperm is an option.

Other Issues to Consider

- Cost of tissue storage: currently the RWH does not charge for the storage of tissue until your child turns 21. After this, there will be an annual storage fee.
- Cost of IVF treatment if required.
- The tissue can only be used by your child and, in the unfortunate event of death, the tissue must be disposed of or may be released to you from the laboratory on request. The tissue cannot be donated to research or be utilised by anyone other than your child.

Who Do I Contact For Further Information?
For further information, please contact the Oncofertility team at RCH.

Oncofertility Team
The Royal Children's Hospital
50 Flemington Road
Parkville 3052
T: (03) 9345 5309
E: fertility@rch.org.au
W: www.rch.org.au/fertility

B.

The Royal Children's Hospital Fertility Preservation Service Testicular Tissue Cryopreservation (TTCP) Information Sheet for Leukaemia Patients

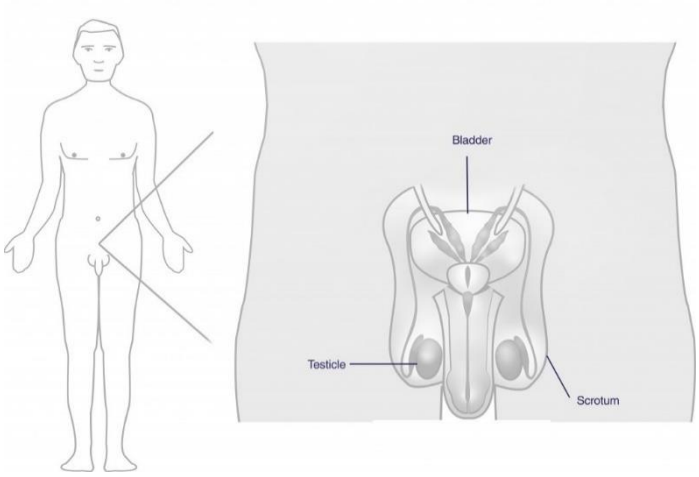
Impact of treatment on fertility
Some cancer treatments affect fertility. Children and adolescents who receive treatment for Leukaemia receive medication called alkylators which are known to affect fertility. Treatment can affect sperm count and the cells that make sperm. The risk to fertility can be low, medium or high risk, depending on many factors including the dose of treatment received, age and gender.

For a young biological male who has not reached puberty, we believe the risk to fertility becomes moderate after receiving 4g/m2 of Cyclophosphamide. Unfortunately, we can't be exact about the risk estimate due to insufficient data. Doses of around 5g/m2, and particularly doses exceeding 10g/m2, are strongly associated with a reduced likelihood of parenthood.

To many parents and young people, fertility is important to them, and many people ask about ways that fertility could potentially be protected.

What Is Fertility Preservation?
Fertility preservation is a process that aims to give patients the opportunity to freeze sperm, eggs or reproductive tissue. It is hoped that this may protect a person's ability to have a biological child in the future. Some of these procedures are proven to assist fertility with live births recorded, and others are considered experimental. Testicular Tissue Cryopreservation (TTCP) is the only fertility preservation procedure available to try and protect fertility for prepubertal males. However, this procedure is experimental.

Reproduction in Biological Males
The testicles of a pre-pubertal child do not contain sperm, they contain germ cells. When puberty begins, usually between the ages of 9 & 15, the pituitary gland (located near the brain) secretes hormones (FSH sperm production & LH testosterone) that stimulate the testicles to produce testosterone and mature sperm.



Testicular Tissue Cryopreservation (TTCP) – what is it?
TTCP involves the collection of healthy testicular tissue prior to starting treatment that may harm the testes. The tissue, which contains immature germ cells, is harvested via a small incision made in the scrotum, where part of the testicle is

removed (approximately 30% of the testicle). It is then preserved and frozen until your child is ready to think about starting a family.

This procedure is not routinely undertaken for those at low risk for infertility unless there are special circumstances. This is because:

1) It is an experimental procedure. It is important to understand that there is no guarantee that the freezing of testicular tissue will lead to successful pregnancies and/or live births. There are no live births to humans to date.
2) Furthermore, in someone receiving only low risk treatment, we would hope that there are other options for saving fertility down the track. For example, collecting a sperm sample later in life.
3) Sometimes people are too sick at the start of cancer treatment. In this situation, urgent chemotherapy without any delays can be lifesaving.
4) There are risks of the surgical procedure which may be made worse at the start of treatment when counts are low. These include:
    a. Risk of a general anaesthetic
    b. Infection
    c. Bleeding
    d. Haematoma (collection of blood)
    e. Risk of a second operation to address any of the above issues

Special Considerations

For patients with Leukaemia there are special considerations. There are only two ways to try and use the tissue.

- One way is to implant the tissue back into the body in the hope that it will produce sperm. Unfortunately, tissue that has been collected from patients who have been diagnosed with Leukaemia are not able to have this tissue reimplanted due to the risk of malignant cells being present and reintroducing Leukaemia back into the body.
- Another way is to try to mature the tissue outside the body in the IVF lab via a process called In-Vitro Maturation (IVM). Unfortunately, we do not know how to develop mature sperm from this tissue in humans.

Who Is Eligible For TTCP?

Theoretically, there is no lower age limit for TTCP and it can be offered to patients of all ages. However, your child needs to be well enough for surgery. Bleeding disorders or serious immune deficiency may preclude your child from having the procedure done.

In a very young child, the testes will usually be very small and it is highly possible that one entire testicle may need to be removed. We cannot guarantee that the testicular tissue collected or the remaining testicle will be functional in the future.

What Other Options Are Available?

- Your child can have their testicular function assessed later after treatment in follow-up clinic.
- Sperm donation from father, brother, male relative or other donor in the future.
- Fostering or adoption.
- For post pubertal males, freezing of mature sperm is an option.
- If the situation changes and the doses of treatment will become moderate or high risk to infertility, and surgery is deemed safe, then TTCP may be considered at a later date.

What does TTCP surgery involve?

The tissue, which contains immature germ cells, is harvested via a small incision made in the scrotum, where part of the testicle is removed (approximately 30% of the testicle). The procedure takes approximately 20 minutes and is usually coordinated with another procedure. The incision will be closed with dissolving stitches and may have a small dressing. Recovery time is usually a few days.

Currently, scientists from the Reproductive Services Unit at The Royal Women's Hospital (RWH) collect the tissue from theatre and process it at their centre. A small piece is sent for histopathology to see if there are any malignant cells in the tissue. It is then sliced, placed in liquid and frozen until required for future fertility treatment. Sometimes the tissue is dissected for mature sperm in children who are going through puberty.

Other Issues to Consider

- Cost of tissue storage: currently the RWH does not charge for the storage of tissue until your child turns 21. After this, there will be an annual storage fee.
- Cost of IVF treatment if required.
- The tissue can only be used by your child. In the unfortunate event of the death of your child, the tissue

cannot be donated to research or be utilised by anyone other than your child. Therefore, the tissue must be either:

- Disposed of
- Released to a nominated funeral director for burial/cremation with your child

Who Do I Contact For Further Information?
For further information, please contact the Oncofertility team at RCH.

Oncofertility Team
The Royal Children's Hospital
50 Flemington Road
Parkville 3052
T: (03) 9345 5309
E: fertility@rch.org.au
W: www.rch.org.au/fertility

C.

The Royal Children's Hospital Fertility Preservation Service
Sperm Banking Information Sheet

Male fertility

When a male is born, he has all the parts of his reproductive system in place, but it is not until puberty that he is able to reproduce. The testes contain 2 different types of cells, the Sertoli cells and the Leydig cells. The Sertoli cells are responsible for making sperm and the Leydig cells are responsible for producing testosterone. Until puberty, these cells are immature and inactive and do not produce sperm.

What is sperm banking?

Sperm banking is when you produce a sample of sperm via masturbation which is then frozen for future use. It is clearly labelled with your details and stored in a large tank of liquid nitrogen. Sperm can be stored for an indefinite amount of time.

Why do I need to consider freezing my sperm?

Chemotherapy drugs enter the blood stream and travel around the body searching for cancer cells to destroy. Unfortunately, this medication cannot differentiate between some healthy cells and cancerous cells, thus potentially destroying sperm and sperm producing cells in the process.

When would I need to consider freezing my sperm?

You will need to freeze your sperm before you start any chemotherapy or radiotherapy. This is because once you start this treatment, the damage to the sperm and sperm making cells is immediate and irreversible.

How do I do this?

The sample needs to be produced via masturbation. The entire sample needs to be collected in a jar that will be provided to you.

Where do I do this?

There are two options for you to produce your sample:

1. If you live within 45 mins of the Andrology Unit, you can produce your sample at home and then bring it in to the lab at your allocated time within 1 hour of producing. The laboratory staff will give you instructions and timing for this.
2. You may also produce your sample at the Andrology Unit. You will have an appointment time to attend the rooms. If you are a minor, you will need a parent to accompany you to this appointment. This can be awkward and embarrassing, but the staff at the Andrology Unit do this every day and will try to make you feel as comfortable as possible. You will be told step-by-step what to do and given as much time as you need.
3. You may be asked to give more than one sample, if there is enough time before you start your treatment, but not all in one go. The reason for this is that your sperm might not be of high quality because of the cancer. If time allows, you may be asked to wait 2-3 days between each collection to give the sperm time to build up again. This might not be possible though depending on your treatment protocol and how fast your doctor needs to start treatment.

What happens next?

Your sperm will be stored at the Andrology Unit for 10 years. Once this time limit is reached, you can apply for the storage to be extended. While this may not be a priority at diagnosis, it will be something you may

have to encounter down the track. It is important that you stay in contact with the sperm bank so that your yearly storage fees are paid and they know your contact details.

Who do I contact for further information?
If you would like any further information, please contact the Oncofertility team at RCH.

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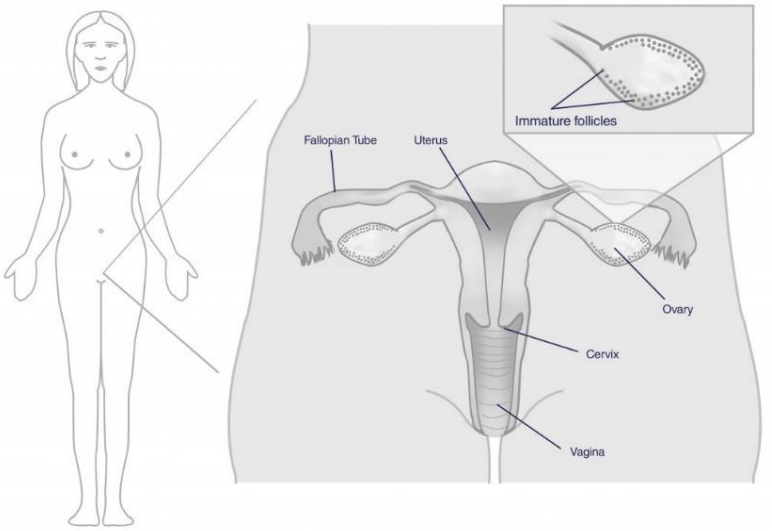
W: www.rch.org.au/fertility

D.

The Royal Children's Hospital Fertility Preservation Service
Ovarian Tissue Cryopreservation (OTCP) Information Sheet

What Is Fertility Preservation?
Fertility preservation is a process that has the potential to preserve a person's ability to have a biological child in the future. This includes the freezing of healthy ovarian tissue and mature eggs.

Reproductive System In Biological Females
When a biological female is born, the ovaries will contain hundreds of thousands of immature eggs (follicles). These are all the eggs required for life and they stay inactive until puberty. When puberty begins, usually between the ages of 8 & 14, the pituitary gland (located near the brain) starts making hormones that stimulate the ovaries to make hormones such as Oestrogen. Oestrogen causes breast development, and



periods. About once a month, during ovulation, an ovary sends a tiny egg into one of the fallopian tubes. Unless the egg is fertilised by a sperm, a period occurs 2 weeks later.

Potential Impact on Fertility
Medical treatments such as chemotherapy and radiotherapy, or conditions in childhood such as genetic conditions, may reduce the number of eggs in the ovaries. Depending on the severity, this can sometimes affect hormone production, puberty, periods and fertility. Your doctor will outline the estimated impact of your child's treatment on their fertility (low, medium or high risk). Unfortunately, it can be difficult to be precise about risk this due to limited data.

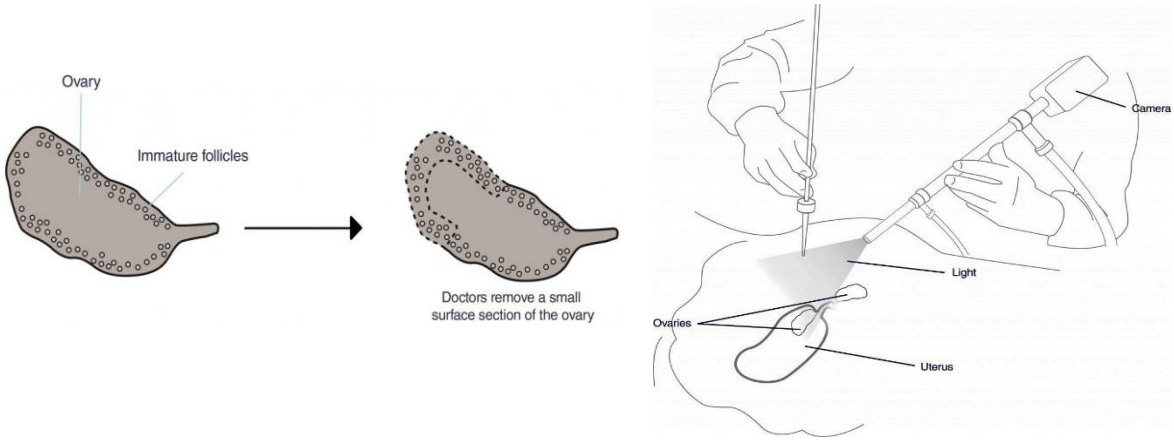
How Does Chemotherapy Affect Fertility?
Chemotherapy drugs enter the blood stream and travel around the body searching for cancer cells to destroy. Chemotherapy may reduce the number of eggs in the ovaries. If egg numbers are affected to a large extent there is a possibility that progression of puberty can be affected or menopause may start earlier, affecting fertility.

How Does Radiotherapy Affect Fertility?
Radiotherapy destroys cancer cells. If the ovaries are exposed to radiotherapy, then eggs can be destroyed. Total body radiation carries a high risk of causing infertility. If radiotherapy is required to treat a brain tumour, the hormone messages from the brain to the ovaries can be disrupted or lost causing the ovaries to

become inactive. However, the ovaries can be triggered into developing mature eggs via hormone stimulation (IVF) in the future.

Ovarian Tissue Cryopreservation (OTCP) - How Is This Procedure Done?
OTCP involves the collection of healthy ovarian tissue prior to starting treatment that may harm the ovaries. The tissue contains immature follicles. It is then preserved and frozen until your child is ready to think about starting a family. It is important to understand that there is no guarantee that the freezing of ovarian tissue will lead to successful pregnancies and/or live births.

The procedure is performed via laparoscopy (also known as 'keyhole' surgery), which involves a small incision in the belly button, along with 2-3 other small incisions in the abdomen, through which a camera and other surgical instruments are inserted. The surgeon will assess the ovary and then removes about 1/2 to one ovary. The whole ovary is removed if it is very small, or if the treatment is likely to cause a severe impact on future ovarian function. The procedure takes approximately 30 minutes and is usually coordinated with another procedure. Each of the incision sites will have a small dressing on them and recovery time is usually a few days.



Currently, scientists from the Reproductive Services Department at the Royal Women's Hospital (RWH) collect the tissue from theatre and process it at their centre. A small piece is tested for quality assurance to check for malignant cells in the tissue. The remainder is sliced, placed in liquid and frozen until required for future fertility treatment.

Using This Tissue In The Future
There are two techniques being developed to facilitate using this tissue to create a pregnancy. Implanting the tissue back into the body or maturing the tissue outside the body in the IVF lab via a process called In Vitro Maturation (IVM).

Transplanting the tissue back into the body
Once thawed, the tissue can be implanted into the body next to the ovary. If it develops a blood supply, the tissue will start to work again in response to the hormone messages sent from the brain. These hormones will mature the follicles in the tissue and there is then the potential for a natural pregnancy to occur.

The tissue can also be implanted elsewhere in the body, such as in the abdominal wall, but IVF treatment will be required to create a pregnancy. This would involve undergoing an IVF cycle where mature eggs are collected from the tissue. The eggs are then fertilised with a partner's sperm (or donor sperm) in the IVF lab. Once the egg is fertilised and grows into an embryo, this embryo will then be transferred into the uterus. Tissue that has been collected from patients who have been diagnosed with Leukaemia are not able to have this tissue implanted due to the risk of malignant cells being present and reintroducing Leukaemia back into the body. For these patients, maturing the tissue via IVM is being developed.

Maturing the eggs via IVM
If the tissue is not suitable to be implanted into the body, the eggs can be matured in the IVF lab, fertilised with sperm and the resulting embryo would be transferred into the uterus. IVM is considered an experimental technique.

Who Is Eligible For Ovarian Tissue Cryopreservation?
Theoretically, there is no lower age limit for Ovarian Tissue Cryopreservation and it can be offered to patients of all ages. However, your child needs to be well enough for surgery. Multiple abdominal scars, bleeding disorders or serious immune deficiency may preclude your child from having the procedure done.

In a very young child, the ovaries will usually be very small and it is highly possible that one entire ovary may need to be removed. We cannot guarantee that the ovarian tissue collected or the remaining ovary will be functional in the future.

Outcomes So Far
Approximatively 200 births have been reported worldwide using ovarian tissue cryopreservation technology. Three live births have been reported in women who have had their tissue stored in childhood.

Risks and Benefits
The surgery (Laparoscopy, Ovarian Tissue Cryopreservation, removal of one ovary) is not experimental as this procedure is performed routinely by gynaecologists and surgeons for other indications.

Expected risks of the surgical procedure:
- Risk of a general anaesthetic
- Infection
- Bleeding
- Damage to internal structures (bladder, bowel, blood vessels) which may occasionally require performing an open operation. These risks are likely to be higher during cancer therapy
- Risk of changing from keyhole surgery to a larger incision (laparotomy)

What Other Options Are Available?
- If you decide not proceed with fertility preservation, your child can have their ovarian function assessed later either after treatment in follow-up clinic.
- Egg donation from mother, sister, female relative or other donor in the future.
- Fostering or adoption.
- For post pubertal females, there is the option to have an injection called Zoladex® which is a hormone that suppresses ovarian function and may protect the ovary. Studies in adult women suggest that Zoladex® may have a small protective effect on fertility, but there are no studies in teenagers. Zoladex® is also used to suppress menstruation during chemotherapy.

Other Issues to Consider
- Cost of tissue storage: currently the RWH does not charge for the storage of tissue until your child turns 21. After this, there will be an annual storage fee.
- Cost of IVF treatment if required.
- The tissue may be stored at an alternate IVF centre: there may be storage and transport costs involved.
- The tissue can only be used by your child and, in the unfortunate event of death, the tissue must be disposed of. The tissue cannot be donated to research or be utilised by anyone other than your child.

Who Do I Contact For Further Information?
For further information, please contact the Oncofertility team at RCH.
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The Royal Children's Hospital
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W: www.rch.org.au/fertility

E.

The Royal Children's Hospital Fertility Preservation Service Ovarian Tissue Cryopreservation (OTCP) Information Sheet for Leukaemia Patients

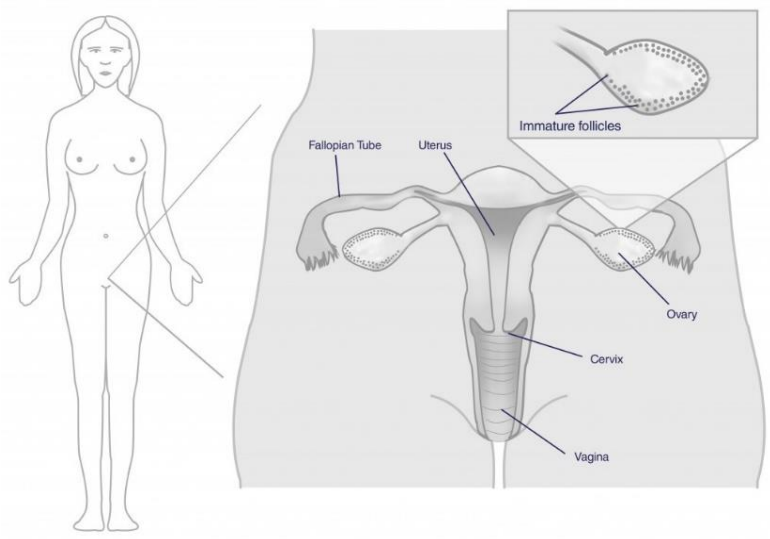
Impact of Treatment on Fertility
Some cancer treatments affect fertility. Children and adolescents who receive treatment for Leukaemia receive medication called alkylators which are known to affect fertility. Treatment can affect the number of eggs and follicles (containing immature eggs) in the ovary. The risk to fertility can be low, medium or high risk, depending on many factors including the dose of treatment received, age and gender.

For a young biological female who has not reached puberty, we believe the risk to fertility becomes moderate after receiving ≥8g/m2 of cyclophosphamide, and high after receiving ≥12g/m2. The impact on the ovary increases with age, so for a teenager who has gone through puberty, the risk to fertility becomes moderate after receiving ≥4g/m2 of cyclophosphamide and high after receiving ≥8 g/m2. Unfortunately, we can't be exact about these risk estimates due to insufficient data.

To many parents and young people, fertility is important to them, and many people ask about ways that fertility could potentially be protected.

What Is Fertility Preservation?
Fertility preservation is a process that aims to give patients the opportunity to freeze sperm, eggs or reproductive tissue. It is hoped that this may protect a person's ability to have a biological child in the future. Some of these procedures are proven to assist fertility with live births recorded, and others are considered experimental.

Reproductive System in Biological Females
When a biological female is born, the ovaries will contain hundreds of thousands of immature eggs (follicles). These are all the eggs required for life and they stay inactive until puberty. When puberty begins, usually between the ages of 8 & 14, the pituitary gland (located near the brain) starts making hormones that stimulate the ovaries to make hormones such as Oestrogen. Oestrogen causes breast development, and periods. About once a month, during ovulation in adults, an ovary sends a tiny egg into one of the fallopian tubes. Unless the egg is fertilised by a sperm, a period occurs 2 weeks later.



Ovarian Tissue Cryopreservation (OTCP) – what is it?
OTCP involves the collection of healthy ovarian tissue, often, prior to starting treatment that may harm the ovaries. The tissue contains immature follicles. It is then preserved and frozen until your child is ready to think about starting a family.

This procedure is not routinely undertaken for those at low risk for infertility unless there are special circumstances.
This is because:

1. It is an innovative procedure. It is important to understand that there is no guarantee that the freezing of ovarian tissue will lead to successful pregnancies and/or live births. Approximately 200 births have been reported worldwide using ovarian tissue cryopreservation technology. Three live births have been reported in women who have had their tissue stored in childhood.
2. Furthermore, in someone receiving only low risk treatment, we would hope that there are other options for protecting fertility down the track. For example, collecting mature eggs later in life.
3. Sometimes people are too sick at the start of cancer treatment. In this situation, urgent chemotherapy without any delays can be lifesaving.
4. The surgery (Laparoscopy, OTCP, removal of one ovary) is not experimental as this procedure is performed routinely by Gynaecologists and surgeons for other indications. But it does have risks. These include:
    - Risk of a general anaesthetic
    - Infection
    - Bleeding
    - Damage to internal structures (bladder, bowel, blood vessels) which may occasionally require performing an open operation. These risks are likely to be higher during cancer therapy
    - Risk of changing from keyhole surgery to a larger incision (laparotomy)

Special Considerations
For patients with Leukaemia there are special considerations. There are only two ways to try and use the tissue.

- One way is to implant the tissue back into the body in the hope that it will produce eggs. Unfortunately, tissue that has been collected from patients who have been diagnosed with Leukaemia, are not able to have this tissue reimplanted due to the risk of malignant cells being present and reintroducing Leukaemia back into the body.
- Another way is to try to mature the tissue outside the body in an IVF lab via a process called In-Vitro Maturation (IVM). In this scenario, we try to mature the eggs outside the body in the IVF lab. In the future, the eggs could potentially be fertilised with sperm and the resulting embryo would be transferred into the uterus. However, IVM is under development and in the very early phases of research, therefore it is currently considered an experimental technique

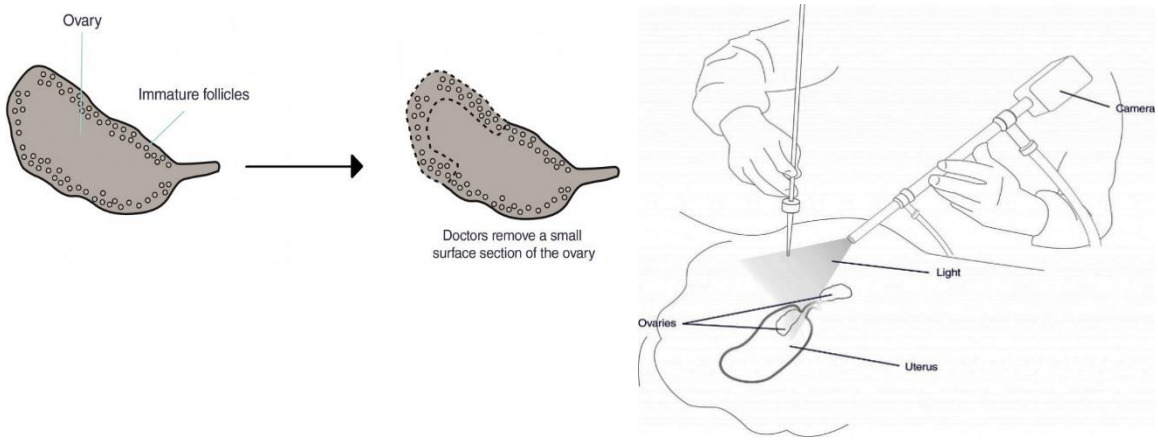
Who is Eligible for OTCP?
Theoretically, there is no lower age limit for OTCP and it can be offered to patients of all ages. However, your child needs to be well enough for surgery. Multiple abdominal scars, bleeding disorders or serious immune deficiency may preclude your child from having the procedure done.

In a very young child, the ovaries will usually be very small and it is highly possible that one entire ovary may need to be removed. We cannot guarantee that the ovarian tissue collected or the remaining ovary will be functional in the future.

What Other Options Are Available?

- Your child can have their ovarian function assessed later after treatment in follow-up clinic.
- Egg donation from mother, sister, female relative or other donor in the future.
- Fostering or adoption.
- For post pubertal females, there is the option to have an injection called Zoladex® which is a hormone that suppresses ovarian function and may protect the ovary. Studies in adult women suggest that Zoladex® may have a small protective effect on fertility, but there are no studies in teenagers. Zoladex® is also used to suppress menstruation during chemotherapy.
- If the situation changes and the doses of treatment will become moderate or high risk to infertility, and surgery is deemed safe, then OTCP may be considered at a later date.

What Does OTCP Surgery Involve?
The procedure is performed via laparoscopy (also known as 'keyhole' surgery), which involves a small incision in the belly button, along with 2-3 other small incisions in the abdomen, through which a camera and other surgical instruments are inserted. The surgeon will assess the ovary and then remove about 1/2 to one ovary. The whole ovary is removed if it is very small, or if the treatment is likely to cause a severe impact on future ovarian function. The procedure takes approximately 30 minutes and is usually coordinated with another procedure. Each of the incision sites will have a small dressing on them and recovery time is usually a few days.



Currently, scientists from the Reproductive Services Unit at The Royal Women's Hospital (RWH) collect the tissue from theatre and process it at their centre. A small piece is tested for quality assurance to check for infections and malignant cells in the tissue. The remainder is sliced, placed in liquid and frozen until required for future fertility treatment.

Other Issues to Consider

- Cost of tissue storage: currently the RWH does not charge for the storage of tissue until your child turns 21. After this, there will be an annual storage fee.
- Cost of IVF treatment if required.
- The tissue may be stored at an alternate IVF centre: there may be storage and transport costs involved.
- The tissue can only be used by your child. In the unfortunate event of the death of your child, the tissue cannot be donated to research or be utilised by anyone other than your child. Therefore, the tissue must be either:
  - Disposed of
  - Released to a nominated funeral director for burial/cremation with your child

Who Do I Contact For Further Information?

For further information, please contact the Oncofertility team at RCH.

Oncofertility Team
The Royal Children's Hospital
50 Flemington Road
Parkville 3052
T: (03) 9345 5309
E: fertility@rch.org.au
W: www.rch.org.au/fertility

F.

The Royal Children's Hospital Fertility Preservation Service
Egg Freezing Information Sheet

Female fertility

When a female is born, her ovaries will contain hundreds of thousands of eggs, which stay inactive until puberty begins. When puberty begins, usually between the ages of 8 & 14, the pituitary gland (located near the brain) starts making hormones that stimulate the ovaries to make female sex hormones (oestrogen and progesterone). These hormones assist with pubertal development and eventually the onset of periods. About once a month, during ovulation, an ovary sends a tiny egg into one of the fallopian tubes. For pregnancy to occur the egg needs to be fertilised by a sperm. If the egg is not fertilised by a sperm, a period will occur two weeks later.

What is egg freezing?

During the natural menstrual cycle, a group of eggs grow in fluid filled sacs (called follicles) in the ovary. Usually, only one egg will become fully mature and be released through ovulation. The other growing eggs will be reabsorbed. An egg freezing cycle stimulates the ovaries to grow a number of follicles and mature a number of eggs which can be collected and frozen.

Why do I need to consider freezing my eggs?

Chemotherapy drugs enter the blood stream and travel around the body searching for cancer cells to destroy. Unfortunately, this medication cannot differentiate between some healthy cells and cancerous cells, thus destroying the quickly dividing cells in the ovaries and reducing the number of eggs. If the number of eggs (ovarian reserve) decreases due to treatment, there is a possibility that menopause may start earlier. Progression through puberty, periods and fertility can sometimes be affected. The impact on fertility is variable and dependent on age and type of treatment.

When would I need to consider freezing my eggs?

Ideally, if time allows, you would have an egg freezing cycle before starting any chemotherapy or radiotherapy treatment. However, this is potentially an option from as early as 6 months after you finish your oncology treatment depending on your age and the dose of treatment you received.

How is this done?

You will need to take follicle stimulating hormone (FSH) injections for between 10-14 days to stimulate your ovaries to recruit and grow lots of follicles. This is an injection with a very fine needle into the abdomen daily. During this time, you will have ultrasounds to count and measure the follicles that are growing. Once the follicles measure the required size, you will need to take another injection to mature the eggs inside the follicles. This is called the trigger injection.

To collect the mature eggs, you will come into hospital for a short procedure that is done while you are asleep. This can take approximately 15-20 mins. Afterwards, you will wake up in recovery and we will be able to tell you how many eggs were collected. The scientists will check the eggs, selecting only the mature eggs, and then cryopreserve them for future use. Once you are comfortable, you will be able to go home, usually 1-2 hours after the procedure.

Risks involved with freezing your eggs

- There are risks associated with the procedure to retrieve the eggs

- While thousands of babies have been born using this technique, very few have been born to those who collected eggs as a teenager
- The ovaries may by hyperstimulated by the FSH injections resulting in a hospital admission
- There are costs involved for the storage of your eggs
- There are costs involved for future IVF cycles

Where do I have this done?
You will be referred to see an IVF specialist for your egg freezing cycle. We are happy to refer you to any IVF clinic of your choice.

What happens next?
Your eggs will be stored for 20 years. Once this time limit is reached, you can apply for the storage to be extended. While this may not be a priority at diagnosis, it will be something you may have to encounter down the track. It is important that you stay in contact with the IVF clinic where your eggs are stored.

Who do I contact for further information?
For further information, please contact the Oncofertility team at RCH.

Oncofertility Team
The Royal Children's Hospital
50 Flemington Road
Parkville 3052
T: (03) 9345 5309
E: fertility@rch.org.au
W: www.rch.org.au/fertility

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The Royal Children's Hospital Fertility Preservation Service Zoladex® 10.8mg Information Sheet

What is Zoladex®?
Zoladex® is a gonadotrophin releasing hormone agonist (GnRH agonist), also known as luteinising hormone releasing hormone agonist (LHRH agonist).

How does Zoladex® work?
Zoladex® suppresses ovarian function by reducing follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary (hormone centre in the brain). In women, Zoladex® stops eggs inside the follicles from maturing and quietens down the ovaries into a sleep like state. Therefore, production of oestrogen and progesterone from the ovaries is temporarily stopped. It takes approximately 3 weeks from administration of Zoladex® to see the effects of the medication. During this time, there may be some vaginal bleeding. However, after 3 weeks, periods should stop until the medication is discontinued.

Indication for use
Studies in adult women suggest that Zoladex® may have a small protective effect on fertility, but there are no studies in teenagers. Zoladex® can be used to suppress menstruation during chemotherapy.

How is Zoladex® given?
Zoladex® is an implant that will be injected into the skin of the abdomen every 3 months. The implant is a very small pellet that is given by a special needle and syringe known as SafeSystem. The pellet is designed to slowly release the medication into the body over 3 months.

Common side effects
The most common side effects seen while taking Zoladex® are:
· hot flushes or sweating
· headaches
· mood changes
· vaginal dryness

Please speak with your treating clinician if you have any concerns in regards to these side effects.

Who do I contact for further information?
If you would like any further information, please contact the Oncofertility team at RCH.

Oncofertility Team
The Royal Children's Hospital 50 Flemington Road
Parkville 3052
T: (03) 9345 5309
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W: www.rch.org.au/fertility

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The Royal Children's Hospital Fertility Preservation Service
Oestrogen Patch Information Sheet

What are Oestrogen Patches?

Oestrogen is a hormone made by the ovaries. Oestrogen levels can go down for a number of reasons during treatment with chemotherapy or radiation. These reasons include weight loss, a reduction in active egg numbers or due to administration of Zoladex® treatment which makes the ovary inactive. This drop in oestrogen levels causes periods to stop and cause uncomfortable symptoms such as hot flushes or vaginal dryness. Prolonged drops in oestrogen can affect the mineral content in bones (bone density). For these reasons your doctor may recommend the use of an oestrogen patch during treatment.

How do Oestrogen Patches Work?

Oestrogen patches works by releasing oestrogen through the skin into the bloodstream. Usually, a very low dose of oestrogen is used, much lower than the amount the body would normally produce.

Indication for use

1. After Zoladex® injections to protect bone density (the patches are only used for the duration of Zoladex® treatment).
2. To treat hot flushes or vaginal dryness during oncology treatment.
3. After chemotherapy or radiation treatment as hormone replacement therapy for those who need it.

How to Apply Oestrogen Patches

1. Patches come in a variety of doses, shapes and sizes. Each come with patient instructions. Please read and follow the instructions carefully. Ask your doctor if you have any questions.
2. Do not place the oestrogen patches on skin areas that have cuts, scrapes or burns. If it does get on these areas, rinse if off right away with water. The area of skin must be free of powder, oil or lotion for the patch to stick to your skin.
3. Wash your hands before and after application of the patch.
4. When you are ready to apply the oestrogen patch, carefully remove it from the protective pouch by tearing the package (do not use scissors as you may accidentally cut the patch).
5. The oestrogen patch is attached to an adhesive liner.
6. Some patches (for example Climara) have a silver foil sticker in the pouch. Do **not** remove this sticker from the pouch.
7. Peel off the backing from the patch and apply the patch to a clean, dry and hair free area of the skin between the abdomen and the upper thigh including the buttocks. Do **not** touch the sticky side of the patch. Try to avoid the waistline as clothing and belts may cause the patch to peel off.
8. Press on the patch firmly for at least 10 seconds and then rub along the edges to ensure that the patch is firmly in place.
9. You may bathe, shower or swim while wearing the patch. Contact with water may sometimes cause the patch to lift or fall off. To reduce this risk, you may reinforce it with Tegaderm® or another waterproof dressing. If the patch lifts off, try to reapply it on a new area of skin. If it does not stick completely, put on a new patch but follow the original schedule for changing the patches.
10. Change your patch as instructed by your doctor and place on a different area of your abdomen, buttock or thigh. It is important to use a different site each time you apply a new patch. If there is any sticky residue left on your skin, allow it to dry and then gently remove it with oil or lotion.
11. If you forget to replace your patch, apply a new one as soon as you remember.

Common side effects
The most common side effects seen while taking oestrogen patches are:

- A rash or local reaction to the site
- Nausea, headache, irregular bleeding (usually short lived)
- Oestrogen treatment can very rarely cause clots in the legs that can travel to the lungs. Oestrogen provided via a patch can minimise this risk as it is directly absorbed via the skin and therefore can be administered in very small doses that reduce the risk of these side effects.

The Gynaecology team will provide information about your personal risks and help to guide if the medication is safe for you or not. You must be under the care of a Gynaecologist for the duration of treatment. If it is deemed that hormone patches are to be used after oncology treatment as hormone replacement, then different preparations are used (which include the hormone progesterone). This is done to mimic the hormone production in a normal menstrual cycle (which produces oestrogen and progesterone). The progesterone keeps the lining of the uterus thin (so it does not overgrow or become abnormal).

Please speak with your treating clinician if you have any concerns in regards to these side effects.

Who do I contact for further information?
If you would like any further information, please contact the Oncofertility team at RCH.

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T: (03) 9345 5309
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W: www.rch.org.au/fertility

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The Royal Children's Hospital Fertility Preservation Service
Fertility Preservation Information Sheet for Adolescent and Young Men Undergoing Cancer Treatment

What Is Fertility Preservation?

Fertility preservation is a process that has the potential to preserve a person's ability to have a biological child in the future. This includes the freezing of healthy testicular tissue and mature sperm.

Why Do I Need to Think About Fertility Preservation?

Having children may not have been something that you have thought about. However, fertility preservation is something that we need to discuss before you start your cancer treatment due to the effects chemotherapy and/or radiotherapy have on fertility. You may be thinking that you don't want to have children but you may change your mind when you are older so it is important to keep your options open for the future.

Potential Impact of Cancer Treatment on Fertility

Cancer treatments such as chemotherapy and radiotherapy, may damage the cells responsible for making sperm. Depending on the severity, this can permanently affect fertility. Your Oncologist will outline the estimated impact of treatment on your fertility (low, medium or high risk). Unfortunately, it can be difficult to be precise about risk this due to limited data.

How Does Chemotherapy Affect Fertility?

Chemotherapy drugs enter the blood stream and travel around the body searching for cancer cells to destroy. Unfortunately, this medication may destroy sperm and the cells responsible for making sperm. After treatment, it can take many months for the affected sperm to be repaired and new healthy sperm to be produced.

How Does Radiotherapy Affect Fertility?

Radiotherapy destroys cancer cells. It can affect fertility directly through irradiation of the testis, or indirectly. Total body radiation has a high risk of causing infertility. If radiotherapy is required to treat a brain tumour, the hormone messages from the brain to the testes can be disrupted.

What Options Are Available to Me?

1. Sperm freezing: this is when you produce a sample of sperm via masturbation which is then frozen until you are ready to think about starting a family. It's not uncommon to need a few goes at collection of sperm and that's okay. Sometimes we don't achieve a sample or you may wish to try further and in that situation testicular tissue cryopreservation might be possible.
2. Testicular Tissue Cryopreservation (TTCP): this is the collection of a small piece of the testicle prior to starting treatment. In a mature teenager the tissue contains sperm as well as the cells that make sperm. In a young child who hasn't gone through puberty, the tissue will not contain any sperm and so is considered experimental. To collect the tissue a small incision is made in the scrotum, where part of the testicle is removed (approximately 20-30%). It is then preserved and frozen until you are ready to think about starting a family.
3. Sperm donation from a male relative or other donor in the future.
4. Fostering or adoption.

What About During and After Cancer Treatment?

Doctors at RCH are available to you for discussion about a range of topics. These include: relationships, fertility monitoring, return of hormone function after cancer treatment and any other concerns you may

have. After treatment, please ask your treating Oncologist to refer you to an Endocrinologist.

Who Do I Contact For Further Information?
For further information, please contact the Oncofertility team at RCH.

Oncofertility Team
The Royal Children's Hospital
50 Flemington Road
Parkville 3052
T: (03) 9345 5309
E: fertility@rch.org.au
W: www.rch.org.au/fertility

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The Royal Children's Hospital Fertility Preservation Service
Fertility Preservation Information Sheet for Adolescent and Young Women Undergoing Cancer Treatment

What Is Fertility Preservation?
Fertility preservation is a process that has the potential to preserve a person's ability to have a biological child in the future. This includes the freezing of healthy ovarian tissue and mature eggs.

Why Do I Need to Think About Fertility Preservation?
Having children may not have been something that you have thought about. However, many young people do feel that fertility preservation is something that should be discussed before starting chemotherapy and/or radiotherapy has they may affect fertility. You may be thinking that you don't want to have children but you may change your mind when you are older so it is important to keep your options open for the future.

Potential Impact of Cancer Treatment on Fertility
Cancer treatments such as chemotherapy and radiotherapy may reduce the number of eggs in the ovaries. Depending on the severity, this can sometimes affect hormone production, periods and fertility. Your Oncologist will outline the estimated impact of treatment on your fertility (low, medium or high risk). Unfortunately, it can be difficult to be precise about risk this due to limited data.

How Does Chemotherapy Affect Fertility?
Chemotherapy drugs enter the blood stream and travel around the body searching for cancer cells to destroy. Unfortunately, this medication can also target cells in the ovaries and reduce the number of eggs. Eggs produce a hormone called oestrogen which cause puberty and periods. After treatment, if egg numbers are reduced, there is a possibility that menopause may start earlier than other women and the opportunity to have a baby can be reduced.

How Does Radiotherapy Affect Fertility?
Radiotherapy destroys cancer cells (it stops cell division and cell repair). If the ovaries are exposed to radiotherapy, then eggs can be destroyed but the impact depends on the dose and where the therapy is directed. Total body radiation carries a high risk of causing infertility. If radiotherapy is required to treat a brain tumour, the hormone messages from the brain to the ovaries can be disrupted causing the ovaries to become inactive. However, the ovaries can be triggered into developing mature eggs via hormone stimulation (IVF) in the future.

What Options Are Available to Me?

1. Ovarian Tissue Cryopreservation (OTCP): this is the collection of healthy ovarian tissue, via laparoscopy (also known as 'keyhole' surgery), prior to starting cancer treatment. It involves removing at least 1/2 of the covering of the ovary (this is called the cortex, where the eggs are stored). The tissue is preserved and frozen until you are ready to think about starting a family. Approximatively 200 births have been reported worldwide using ovarian tissue cryopreservation technology.
2. Egg freezing: if there is time before you start your cancer treatment you may be able to complete an egg freezing cycle. An egg freezing cycle stimulates the ovaries to grow a number of follicles and mature a number of eggs which can be collected and frozen until you are ready to think about starting a family. Egg freezing can sometimes be done after treatment if the doses of treatment are not too high.
3. Zoladex®: this is a hormone injection that suppresses ovarian function and may protect the ovaries. There is some data in older women to suggest it may protect fertility but the protection is likely to

be small. Zoladex® is also used to suppress menstruation during chemotherapy. Zoladex may cause side effects such as hot flushes or dryness in the vagina. These symptoms can occur with cancer treatment alone. They can be easily treated.

4. Egg donation from a female relative or other donor in the future.
5. Fostering or adoption.

What About During and After Cancer Treatment?

Our Gynaecology team here at RCH are available to you for discussion about a range of topics. These include: periods, contraception, relationships, how you are feeling about your body, fertility monitoring and any other concerns you may have. All teenagers at the RCH are allowed to speak to doctors privately. Please ask your treating Oncologist to refer you if you would like to speak with a Gynaecologist.

Who Do I Contact For Further Information?

For further information, please contact the Oncofertility team at RCH.

Oncofertility Team
The Royal Children's Hospital
50 Flemington Road
Parkville 3052
T: (03) 9345 5309
E: fertility@rch.org.au
W: www.rch.org.au/fertility

K.

The Royal Children's Hospital Fertility Preservation Service
Sperm Banking Guidelines for an Inpatient

Referring to Andrology

Weekdays

1. Please contact the Andrology Unit on 8345 3991/3992 to speak with a team member to arrange a time for the patient to produce their sample. You must speak with the Andrology team **prior** to speaking with your patient.
2. Order the following tests on EMR:
   - Semen Analysis
   - Cryopreservation of Seminal Fluid/Spermatozoa
3. Give the patient/designated family member the following:
   - RWH Andrology Request for Sperm Storage in a Minor Consent Form (minors need a parent to consent) https://www.rch.org.au/fertility/health-prof/male/
   - Please ask the patient/designated family member to take their Medicare card & photo ID.
4. Give the patient a specimen cup (that has been clearly labelled with a patient label) and a paper bag.
5. Secure a private space e.g. single patient room and hang a "Stop Sign".
6. Ensure that all members of staff are aware not to enter the room.
7. Instruct patient to remove the sign when he is finished.
8. Once the patient has provided their sample, please check the following:
   - Specimen is in the cup and closed tightly
   - Cup is in the bag (please put paper bag inside a plastic biohazard specimen bag)
   - Sperm banking consent forms have been completed

Please ensure that the patient or family member delivers the specimen to the Andrology lab within **1 hour of collection and at the allocated time** to 321 Cardigan Street, Carlton 3053

After Hours

In the case of needing to commence emergency cancer treatment, when sperm must be collected and stored after hours, please contact the On Call Andrology Scientist in Charge via RCH or RWH switchboard. If you are unable to reach a member of the team, please contact Dr Gulfam Ahmad on 0470 332 923 (Scientist in Charge at Andrology).

Unable to collect a specimen

Upon completion of testing, it is important to discuss the results with the family. Scientists in the Andrology lab will be able to help you interpret the results. Sometimes patients may not be able to produce a sample due to a range of factors including distress, maturity and health. Sometimes a produced sample contains little or no viable sperm due to concurrent illness. If this is the case, please speak with the Oncofertility team to discuss this further.

Funding for sperm banking

The charity MyRoom will pay the fees for semen analysis and storage for 3 years for all oncology patients. After this period, they will be contacted by the Andrology lab. The yearly fee after the initial 3 years is $220 ($165 if patient has a concession card).

General principles

It is important to offer sperm banking prior to the start of gonadotoxic therapy (chemotherapy, radiation or TBI), where possible, for the following reasons:

1. Even low risk treatments may cause sperm DNA fragmentation which increase the risk of mutagenesis, which can persist for up to 2 years
2. Significant decline in sperm count and quality or even Azoospermia may occur by three months increasing the risk of unsuccessful semen collection
3. Medical and psychosocial factors

If sperm collection is being undertaken as an interval procedure (within one year of gonadotoxic therapy), a sample may be stored at the patients/family's request. However, documentation of the risks should occur and a waiver should be signed. They should also receive recommendations to collect a revised sample at 6, 12 or 24 months after treatment if possible. If the quality of semen is normal, the previous sample may be discarded. For those patients at very high risk of infertility who place a high value on fertility and have already received gonadotoxic treatment, seek advice to discuss the most appropriate management.

If the semen analysis is normal, it is recommended that the patient freeze 10 straws (each straw is 0.5ml of which half is cryoprotectant) and potentially 15-20 straws if there are atypical results. This means the patient should be given the opportunity to collect multiple sperm samples if medically safe to do so.

Normal semen analysis results are as follows:
Ph 7.2-8
Volume ≥ 1.5 to 6ml
Concentration ≥ 16M/ml or 39M/ejaculate
Motility 42%
Vitality 58%
Morphology 4%
Leukocytes <1M/ml

Who do I contact for further information?

If you would like any further information, please contact the Oncofertility team at RCH.

Oncofertility Team
The Royal Children's Hospital
50 Flemington Road
Parkville 3052
T: (03) 9345 5309 Spectra link: 52382
E: fertility@rch.org.au

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The Royal Children's Hospital Fertility Preservation Service
Sperm Banking Guidelines for an Outpatient

Referring to Andrology

Weekdays

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2. Order the following tests on EMR:

- Semen Analysis
- Cryopreservation of Seminal Fluid/Spermatozoa

3. Give the patient/designated family member the following:
    - RWH Andrology Request for Sperm Storage in a Minor Consent Form (minors need a parent to consent) https://www.rch.org.au/fertility/health-prof/male/
    - Please ask the patient/designated family member to take their Medicare card & photo ID.
4. They will be required to produce sample at:

Andrology Unit/Sperm Bank, The Royal Women's Hospital
321 Cardigan Street
Carlton Vic 3053
T: (03) 8345 3991/3992
Hours: Monday to Friday 8.30am – 5.30pm

Home Collection

If the patient plans to collect a sample at home, please provide:

- a large yellow top container (with a patient label attached)
- a paper bag and a biohazard specimen bag

Please ensure that the patient or family member delivers the specimen to the Andrology Unit within **1 hour of collection and at the allocated time** to 321 Cardigan Street, Carlton 3053

After Hours

In the case of emergency cancer treatment, when sperm must be collected and stored after hours, please contact the On Call Andrology Scientist in Charge via RCH or RWH switchboard. If you are unable to reach a member of the team, please contact Dr Gulfam Ahmad on 0470 332 923 (Scientist in Charge at Andrology).

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3. Medical and psychosocial factors

If sperm collection is being undertaken as an interval procedure (within one year of gonadotoxic therapy), a sample may be stored at the patients/family's request. However, documentation of the risks should occur and a waiver should be signed. They should also receive recommendations to collect a revised sample at 6, 12 or 24 months after treatment if possible. If the quality of semen is normal, the previous sample may be discarded. For those patients at very high risk of infertility who place a high value on fertility and have already received gonadotoxic treatment, seek advice to discuss the most appropriate management.

If the semen analysis is normal, it is recommended that the patient freeze 10 straws (each straw is 0.5ml of which half is cryoprotectant) and potentially 15-20 straws if there are atypical results. This means the patient should be given the opportunity to collect multiple sperm samples if medically safe to do so.

Normal semen analysis results are as follows:
Ph 7.2-8
Volume ≥ 1.5 to 6ml
Concentration ≥ 16M/ml or 39M/ejaculate
Motility 42%
Vitality 58%
Morphology 4%
Leukocytes <1M/ml

Who do I contact for further information?
If you would like any further information, please contact the Oncofertility team at RCH.

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T.

Fertility preservation procedure in biological males

Established methods							
Method	**Age**	**Description**	**Time**	**Advantages**	**Disadvantages**	**Efficacy**	**Approximate cost***
Freezing ejaculated sperm sample	During/ after puberty	Sample via masturbation	May need multiple collections	Proven Does not require a partner	Dependent on developmental maturity	High pregnancy rate Needs ICSI with IVF	$286 1st year, $220 pa Cost of ICSI and IVF
Freezing sperm extracted from testis surgically	After puberty	Surgical procedure under anaesthetic if unable to self-collect semen	Time to arrange procedure	Proven Does not require a partner	Anaesthetic Only a few sperm	High pregnancy rate Needs special technologies: ICSI with IVF	Cost of storage $286 per year Cost of ICSI and IVF
Donor sperm/ Adoption	N/A	Monitor sperm count after treatment Use alternative sperm source if necessary	N/A	No intervention to patient	Not biologically fathering a child	Successful methods	Some cost associated with donor sperm assisted reproduction
Experimental methods							
Testicular tissue freezing	Any age	Small sample of testicular tissue surgically removed	Time to arrange procedure	Only option for pre- pubertal boys	Anaesthetic Risk of malignant reseeding	Highly experimental in pre-pubertal boys Sperm seen in post-pubertal boys[12]	Free of charge in public hospitals Future costs uncertain

*Storage costs are determined by each individual IVF centres and they are subject to change.

U.

Impact of class of chemotherapeutic agent on ovarian function

Agent class	Risk category	Likelihood of livebirth[46]	Mechanism[42]
Alkylating agents[39,40,41,42]	High		The active metabolite form, cross-links with DNA with resultant inhibition of DNA synthesis and function. DNA double strand breaks and resultant P63-mediated apoptotic death in human primordial follicles. DNA inter-strand cross-linking drugs[43]
Cyclophosphamide ≥7.4 g/m^2	Pre-pubertal patients considered high risk ≥12 g/m^2 and moderate risk ≥8 g/m^2	HR 0.99[40]	
Ifosfamide ≥2.7 mg/m^2		HR 0.84[41]	
Busulfan <450 mg/m^2		HR 0.20[41]	
Busulfan ≥450 mg/m^2		HR 0.18[41]	
Chlorambucil		HR 1.0 [0.85–1.16] [41]	
Melphalan		HR 1.0 [0.85–1.16] [41]	
Nitrogen mustard		HR 1.0 [0.85–1.16] [41]	
Thiotepa		HR 1.0 [0.85–1.16] [41]	
Triazenes[44]	High		DNA inter-strand cross - linking
Procarbazine ≤3.4 mg/m^2		HR 0.87[41]	
Procarbazine ≥5.1 mg/m^2		HR 0.78[41]	
Dacarbazine		HR 1.0 [0.85–1.16] [41]	
Temozolamide		1.0 [0.85–1.16]	
Nitrosoureas	High		DNA inter-strand cross - linking
Carmustine		HR 1.0 [0.85–1.16] [41]	

[39] Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Future Oncol. 2016;12 (20):2333–2344.

[40] Chen XY, Xia HX, Guan HY, Li B, Zhang W. Follicle Loss and Apoptosis in Cyclophosphamide-Treated Mice: What's the Matter? Int J Mol Sci. 2016;17(6):836–843

[41] Meirow D, Biederman H, Anderson RA, Wallace WH. Toxicity of chemotherapy and radiation on female reproduction. Clin Obstet Gynecol. 2010;53(4):727–39.

[42] Oktay K, Moy F, Titus S, Stobezki R, Turan V, Dickler M, Goswami S. Age-related decline in DNA repair function explains diminished ovarian reserve, earlier menopause, and possible oocyte vulnerability to chemotherapy in women with BRCA mutations. J Clin Oncol. 2014; 32(10):1093–1094.

[43] Soleimani R, Heytens E, Darzynkiewicz Z, Oktay K. Mechanisms of chemotherapy induced human ovarian aging: double strand DNA breaks and microvascular compromise. Aging (Albany NY) 3(8), 782–793 (2011)

[44] van Dorp W, Mulder RL, Kremer LC, Hudson MM, et al. Recommendations for Premature Ovarian Insufficiency Surveillance for Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group in Collaboration With the PanCareSurFup Consortium. J Clin Oncol. 2016; 34(28):3440–3450.

Lomustine ≥411 mg/m^2		HR 0.60[41]	
Platin[42]	Medium	OR 1.77	Covalently binds to DNA to form intra- and interstrand DNA cross-links, leading to DNA breakage during replication. This inhibits DNA transcription, synthesis and function. Specific toxicity has not been shown in human primordial follicles
Cisplatin ≥488 mg/m^2		0.86	
Carboplatin		1.0 [0.85–1.16]	
Antimetabolites[42] (methotrexate, 5 fluorouracil, cytarabine)	Low		Inhibition of DNA, RNA, thymidylate and purine synthesis. No DNA damage in human follicles, hence, not gonadotoxic
Vinca alkaloids[42] (vincristine, vinblastine)	Low		Inhibition of tubulin polymerization and disruption of microtubule assembly during mitosis. This arrests mitosis during metaphase and leads to cell death. No DNA damage in human follicles, hence not gonadotoxic
Anthracyclin antibiotic[42,45] (doxorubicin, Adriamycin)	Low (apart from adriamycin: intermediate)		Inhibition of DNA synthesis and function. It interferes with DAN transcription. It inhibits topoisomerase II, which leads to DNA breaks. It also forms toxic oxygen-free radicals, which induce DNA strand breaks, thereby inhibiting DNA synthesis and function. Doxorubicin induces DNA double strand breaks P63-mediated apoptotic death in human primordial follicles

[45] Patel N, Joseph C, Corcoran GB, Ray SD. Silymarin modulates doxorubicin-induced oxidative stress, Bcl-xL and p53 expression while preventing apoptotic and necrotic cell death in the liver. Toxicol Appl Pharmacol. 2010;245(2):143–52.

V.

Fertility preservation procedures birth assigned females

Established methods							
Method	**Pubertal status**	**Description**	**Time needed**	**Advantages**	**Disadvantages**	**Efficacy**	**Approximate cost**
Oocyte (egg) freezing	In older teenagers	Stimulation of ovaries with daily hormone injections and surgical collection of mature eggs under anaesthetic	≥2 weeks	Proven Does not require a partner	Daily hormone injections Delay in start of treatment Requires emotional and physical maturity Poor yield <17 years of age	49% clinical pregnancy rate for women <34 years of age[46] 70% probability of live birth if at least 10 oocytes collected[47] ≥2000 births world wide	Yearly oocyte storage fee Future assisted reproduction (IVF) costs vary depending on clinic and private health insurance plan
Embryo freezing	After puberty	Stimulation of ovaries with daily hormone injections and surgical collection of eggs under anaesthetic, mixed with sperm in the lab to create embryos	≥2 weeks	Proven	Daily hormone injections Delay in start of treatment Requires emotional maturity Requires sperm	Pregnancy rates 30–37% per transfer Most established method	Yearly embryo storage fee Future assisted reproduction (IVF) costs vary depending on clinic and private health insurance plan
Donor oocytes/ embryo surrogacy adoption	N/A	Surrogacy if unable to carry pregnancy Consider adoption	N/A	No pre-treatment intervention to patient	Not biologically parenting child	Successful methods	Vary depending on choice
Ovarian pexy	Any	Laparoscopic surgery to move the ovaries outside field of radiation	Time to arrange procedure	May reduce risk of ovarian failure due to radiotherapy	Surgery under anaesthetic Risk of damage to ovary/blood supply Not considered superior to ovarian tissue preservation	Limited evidence	Free of charge in public hospitals

Table continued next page

[46] Ubaldi, F et al, Cumulative ongoing pregnancy rate achieved with oocyte vitrification and cleavage stage transfer without embryo selection in a standard infertility program, Hum Reprod, 2010 25 :1199–1205.

[47] Goldman et al, Predicting the likelihood of live birth for elective oocyte cryopreservation: a counseling tool for physicians and patients. Human Reproduction 2017, 32, 853–859.

Innovative							
Method	**Pubertal status**	**Description**	**Time needed**	**Advantages**	**Disadvantages**	**Efficacy**	**Approximate cost**
Oocyte freezing	In younger teenagers	Stimulation of ovaries with daily hormone injections and surgical collection of mature eggs under anaesthetic	≥2 weeks	Proven Does not require a partner	Daily hormone injections Delay in start of treatment Requires emotional and physical maturity Poor yield <17 years of age Only 1 birth from oocytes collected in teenagers	49% clinical pregnancy rate for women <34 years of age[26] 70% probability of live birth if at least 10 oocytes collected[27] ≥2000 births world wide	Yearly oocyte storage fee Future assisted reproduction (IVF) costs vary depending on clinic and private health insurance plan. For Residents in Victoria with a Medicare Card, public IVF offers 2 cycles free of charge
Ovarian tissue freezing	Any	Laparoscopic surgical removal of ovarian tissue/ whole ovary Freeze tissue for possible future reimplantation	Time to arrange procedure	Only option for pre- pubertal girls Minimal delay in treatment	Surgery under anaesthetic Concern re-implanted tissue may contain cancer cells[48]	Proof of concept[49] close to 200 pregnancies worldwide[50,51], two from tissue stored in childhood[52,53]	Free of charge in public hospitals and currently storage of tissue until adulthood is free though this may change in the future.
Ovarian suppression (GnRH agonist)	After puberty	Hormone injections to switch off ovaries. This may decrease ovarian damage from chemotherapy: data unclear	Immediate give prior to start of treatment	Effective for menstrual suppression	Monthly to 3 monthly injection No benefit with radiation Menopausal symptoms Needs gynaecology review with each dose and estrogen add back if no contra-indications	Conflicting results: probably overall benefit in adults but the benefit is likely small[54]. Not considered a replacement for other options	Approved pbs for those on alkylator Expenses covered via drug committee at RCH

[48] Gook D et al. Potential leukaemic contamination in cryopreserved ovarian tissue. Hum Reprod 2018:33: supp1:O81:i38.

[49] Stern C et al. First reported clinical pregnancy following heterotopic grafting Hum Reprod. 2013; 28: 2996–9.

[50] Donnez J et al. Fertility Preservation in Women. NEJM. 2017;377:1657–1665.

[51] Dolmanns M et al. Recent advances in fertility preservation. J Obstet Gynaecol Res. 2019; 45:266–279.

[52] Matthews S et al. successful pregnancy in a woman suffering from B-thalasemia following transplantation of ovarian tissue cryopreserved before puberty. Minerva Ginecological 2018; 70: 432.

[53] Demesteere et al. Live birth after autograft of ovarian tissue cryopreserved during childhood. Hum Reprod 2015;30 (9):2107-2109

[54] Jayasinghe Y, Wallace WH, Anderson RA. Ovarian function, fertility and reproductive lifespan in cancer patients. Expert Endocrinol Reviews (invited review) 2018; 13(3):125–136.

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