Fertility Preservation Service

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

For health professionals to use when helping newly diagnosed patients and families make choices about fertility preservation

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Introduction letter

Dear Colleagues,

Families report that information about fertility is one of their highest unmet needs at the time of cancer diagnosis. Suboptimal discussions and/or those occurring 'too late' (after onset of treatment) lead to regret.[1] It is an international standard of care to inform families about the risks of infertility due to gonadotoxic treatment in a timely manner.[2,3] **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**.[4]

Fertility preservation (FP) is not considered standard practice in children. FP is now approved as a novel technology at The Royal Children's Hospital (RCH), with research governance for data collection and clinical ethics approval for individual cases (including for all pre-pubertal patients).[5] This provides a governance framework within which clinicians can practice safely.

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. It is hoped that these resources may reduce disparities in clinical practice and assist all families to receive good quality care irrespective of gender, culture, education and socioeconomic status. 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. Where there is discord around these decisions, clinical ethics pathways can be activated by any team member so that consensus decisions can be made.

Further information and clinical pathways and forms can be found on http://www.rch.org.au/fertility/health-prof/

These pathways are under continuous renewal, informed by research as well as consumer and clinician voices. The Fertility Preservation Steering Committee is happy to provide information and advice to clinicians at the point of clinical care.

The oncofertility coordinators Rafael Serrano Real and Paula Spain can be contacted via Tel: (03) 9345 5896 Ext: 55896 Pager: 7047, and for non-urgent matters emailed on fertility@rch.org.au.

1. 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 pediatric and adolescent cancer population. JARG Accepted 16th July 2019.
2. Anazado A, Ataman L, Jayasinghe Y, Woodruff T. Oncofertility — An Emerging Discipline Rather Than a Special Consideration. Ped Blood and Cancer 2018; 65 (11):e27297.
3. Oktay, K et al. Fertility Preservation in patients with cancer: ASCO practice guideline update. JCO 2018;36:1994-2001.
4. 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.
5. Jayasinghe Y, Gillam L, Orme L, Zacharin M, McCarthy M, Sullivan M, Heloury Y. RCH Novel Technologies submission 2014.

1. Talking to families about fertility risks

The following points will help prepare you for a discussion.

1.1 Prepare

We have included talking points below; a series of tables on risk of infertility based on treatment, potential recommendations according to risk of infertility, and fertility preservation options and their pros and cons. 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 summary. It is not perfect and we endeavour to update it annually. We are aiming to provide this information in a more streamlined electronic format soon, integrated into the electronic medical record.

1.2 Who should be there?

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.[6] 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.[7] If you are uncomfortable or unsure about discussion of this topic, you may find it helpful to contact the 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 for the discussion if possible.

Give some thought to the age and gender of the young person, and whether it is appropriate for them to attend the discussion or 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.[8,9]

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.[10] Be sure to ask mature adolescents and/or families who they would like involved in this conversation. Pubertal males may feel most comfortable discussing fertility matters and sperm preservation privately with a parent or a health professional. They may prefer a male staff member.

1.3 Timing and documentation

There is so much information to give to families at this distressing and overwhelming time. If you are discussing the details of the cancer diagnosis at the same time, consider taking a break and having a separate 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 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.[7]

6. 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.
7. 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.
8. 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.
9. 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.
10. 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.

1.4 Discussion points

1.4.1 Risk:

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

1.4.2 Options:

1. Introduce potential options available for preserving fertility based on gender, pubertal stage, cancer, treatment plan 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.

Discussions regarding experimental procedures should be measured and made with consideration: the final decision for experimental procedures will rest with the clinical teams and family, and depend on comorbidities. The surgical teams will ultimately decide upon the decision to proceed to surgery.

1.5 Research

RCH is undertaking one of the largest studies on the safety and efficacy of paediatric fertility preservation (HREC 33064). 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.

1.6 What to remember:

1. All patients and families have the right to know if their fertility is at risk, even if:
   a. There is no time to do anything about it.
   b. There is nothing that can be done.
   c. Prognosis is poor.
   d. We do not think it is a good idea or necessary to preserve fertility.
2. When it is judged to be medically and ethically safe (by all relevant teams), with our information and support, the decision then rests with the patient and family.
3. Document discussions in the medical record.
4. Provide written resources to families.
5. Provide information sheet about the fertility audit (HREC 33064).

2. RCH fertility preservation principles for biological 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 Endocrinology, RCH Immunology, RCH Nephrology, RCH Rheumatology, RCH Surgery, RWH or Monash Andrology and RWH or Monash Reproductive Biology Units will work collaboratively to:

1. Provide education and consultation to all 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.
3. Infertility risk can be based on risk stratification tables, but all situations are to be considered individually.
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 HREC 33064 prospective fertility audit 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. Oncofertility coordinator.
2. Oncology or other treating team.
3. Endocrine consultant/fellow.
4. Surgical team.
5. Reproductive Biology Unit/Andrology liaison.
6. Oncology liaison.
7. Clinical ethics.
8. Lines coordinator.

2.4 Eligibility for the discussion

All new male patients having gonadotoxic treatment with curative intent should have a discussion about the impact of cancer treatment on fertility.

2.5 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.
6. Invitation and consent for participation in the FP audit (which also includes consent for linkage to RWH FP database, consent to linkage with Register of Births, consent for contact for future research).

2.6 When to consider referral in biological males

2.6.1 Sperm collection

All post-pubertal male patients at any risk of infertility (can be referred directly to Andrology for sperm collection).

2.6.2 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.
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.

2.6.3 Fertility consultations also occur at other times in response to:

1. Males with relapsed disease and a new gonadotoxic treatment plan.
2. Referrals from any provider (nephrology, rheumatology, immunology, other).
3. At request of patients or families.
4. Males who have completed treatment and having long term follow-up who require surveillance.

2.7 Referral for sperm collection

2.7.1 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.
3. A referral to Surgery or Endocrinology can be made to explore other options, such as testicular biopsy.

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

1. Contact oncofertility coordinator.
2. Give the patient/designated family member the following materials:
   a. Sperm preservation instructions.
   b. Male fertility preservation handouts:
      i. *Having Children After Cancer* (RCH handout for teens developed by psycho-oncology group).
      ii. *Can I Still Have Children? Information for Men Having Chemotherapy and Radiotherapy* (MIVF brochure for mature males).
      iii. *Maybe Later Baby? A Guide to Relationships, Sex and Fertility for Young People With Cancer* (CANTEEN).
   c. Sperm banking consent:
      i. If using Andrology Services — Andrology Unit Request for Sperm Storage.
      ii. If using Monash Medical Centre — Semen Storage Consent.
      iii. For Andrology Services complete Andrology Request Form and fax to: (03) 8345 3990.
      iv. Call the Andrology Laboratory on (03) 8345 3992 to report that request slip and consent are on the way.
3. Give the patient a specimen cup and a paper bag.
4. Secure a private space e.g. single patient room and hang 'Stop Sign'. Instruct patient to remove sign when finished.
5. When the stop sign is removed, check with the patient to ensure:
   a. Specimen is in the cup with a tightly closed lid, and the cup is in a bag.
   b. Sperm banking consent forms completed.
   c. Payment method determined (the first two years are funded by My Room Children's Cancer Charity).
6. Arrange a timely delivery of the specimen to the Andrology Lab.
7. The referring team is responsible for relaying results to the family. Please seek advice from Andrology or Endocrinology if you cannot interpret the results. If the specimen is inadequate, recollection may need to be attempted, or consider referral for TTCP. Including the oncofertility coordinator can facilitate these discussions and follow-up.
8. Arrange follow-up with Endocrinology to discuss results formally after treatment.
9. Invite the patient to participate in the Fertility Preservation Research Audit. Patients can be invited whether they decide to pursue fertility preservation or not.
   a. 33064 Parent Information and Consent Form if the child is <18 years.
   b. 33064 Patient Information and Consent Form if the young person is ≥18 years.
10. Document notes in the EMR.

2.7.1.2 After hours sperm collection

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.

2.7.2 Outpatient procedures for sperm preservation

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

1. Contact oncofertility coordinator.
2. Give the patient/designated family member the following materials:
   a. Sperm preservation instructions.
   b. Male fertility preservation handouts:
      i. *Having Children After Cancer* (RCH handout for teens developed by psycho-oncology group).
      ii. *Can I Still Have Children? Information for Men Having Chemotherapy and Radiotherapy* (MIVF brochure for mature males).
      iii. *Maybe Later Baby? A Guide to Relationships, Sex and Fertility for Young People With Cancer* (CANTEEN).
   c. Sperm banking consent:
      i. If using Andrology Services — Andrology Unit Request for Sperm Storage.
      ii. If using Monash Medical Centre — Semen Storage Consent.
3. Invite the patient to participate in the Fertility Preservation Research Audit. Patients can be invited whether they decide to pursue fertility preservation or not:
   a. 33064 Parent Information and Consent Form if child is <18 years.
   b. 33064 Patient Information and Consent Form if young person is ≥18 years.
4. If using Andrology Services:
   a. Complete Andrology request form and fax to (03) 8345 3990.
   b. Call the Andrology Laboratory on (03) 8345 3992 to say that request slip and consent are on the way, and the family will be making an appointment.
   c. 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 3992 Hours: Monday–Friday 9am–5pm
5. Please follow-up the results prior to cancer treatment. If the count is low, then organize a repeat collection or consider referral for TTCP. The oncofertility coordinator can assist with this if notified and can provide a summary of fertility care letter.
6. Arrange follow-up with Endocrinology to discuss results at an appropriate time.
7. If the patient plans to collect a sample at home, provide container and paper bag and ensure sample will arrive at Andrology Lab within one hour of collection.
8. Document notes in the EMR.

2.8 Testicular Tissue Cryopreservation (TTCP) guidance for biological males

2.8.1 Eligible population for referral to Endocrinology for a TTCP consultation:

1. Pre-pubertal patients at moderate to high risk of infertility (defined as ≥20% risk).
2. Peri-pubertal or post-pubertal patient with inability to ejaculate or poor quality of sperm.
3. At request of patient/family.
4. At discretion of treating team.

Patients may include:

1. Oncology (potential number: 20–30/year).
2. Nephrology (nephrotic syndrome, lupus — 2 to 4/year).
3. Others may include rheumatology, immunology, neurology.

2.8.2 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 possible fertility preservation options as appropriate.
3. 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.
4. Determine requirements for other co-existent operative procedures (CVL, LP, BMA).
5. Provide written resources to patient/family depending on age and type of FP procedure.
   a. *Having Children After Cancer* (RCH handout for teens developed by psycho-oncology group).
   b. *Can I Still Have Children? Information for Men Having Chemotherapy and Radiotherapy* (MIVF Brochure for mature males).
   c. *Maybe Later Baby? A Guide to Relationships, Sex and Fertility for Young People With Cancer* (published by CANTEEN for mature adolescent patient).
   d. Male TTCP Information Sheet and Pre-consent Form (for TTCP candidates).
6. Contact the oncofertility coordinator who can invite the patient to participate in the Fertility Preservation Research Audit. Patients can be invited whether they decide to pursue fertility preservation or not. The parent may consent on their behalf, however if the patient is 18 or above, they may complete their own consent form.
   a. 33064 Parent Information and Consent Form if child is <18 years.
   b. 33064 Patient Information and Consent Form if young person is ≥18 years.
7. If a referral is required, contact the oncofertility coordinator and endocrinology team via phone. Use the fertility referral form, which assists with FP decision-making. This should include:
   a. Brief history.
   b. Developmental maturity of patient (tanner stage testicular volume).
   c. Planned treatment, urgency (with clear indication of acceptable timeframe), prognosis, indication of infertility risk (high >80%/medium/low <20%).
   d. Handover of patient/family's understanding of the diagnosis, prognosis, FP options/response to introductory discussion.
   e. Other procedures planned.
   f. Other factors pertinent to cancer/reproductive potential (e.g. prognosis, likelihood of RT, likelihood of relapse).
   g. Factors that may specifically increase surgical risk such a mediastinal mass, significant immunosuppression, bleeding disorder.
   h. Social concerns within the family such as custody issues and parental disagreement.
   i. The level of complexity of the young patient's situation that would necessitate consultant review.
   j. Any specific concerns the treating oncologist has with respect to proceeding with an FP procedure.
   k. Indicate intended date of gonadotoxic treatment and acceptable timeframe for FP.
8. If the referring clinician feels the patient/family should not yet be approached, they will let the endocrinologist know how and when it is best to see the patient. The oncology team should always have introduced the fertility discussion before the endocrine team sees the family for consultation.

2.8.3 Endocrinology consultation for TTCP:

1. Referrals will be made by oncology staff, sometimes other departments (e.g. Renal, Immunology), often at short notice before chemotherapy because they discuss life and death prior to FP. Endocrinology 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.
2. Patients may be seen a) in the ward or b) brought to endocrine clinic by a CCC staff member or c) sent there by oncology staff or d) at the Day Cancer Centre.

   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 http://www.rch.org.au/fertility/health-prof/.
3. An endocrinologist needs to discuss issues which differ depending on:
   a. If the boy is pre-pubertal.
   b. Peri-pubertal (e.g. testes 10 ml, pubic hair stage 3).
   c. Post-pubertal.
4. The endocrinology consultation is as follows:
   a. Explanation of role as endocrinologist and purpose of visit.
   b. Assess and discuss young person's level of infertility risk based upon age, pubertal stage diagnosis and treatment plan.
   c. Explain the level of risk to fertility if no action is taken.
   d. Introduce potential options for preserving fertility.
   e. Clearly describe what is experimental and what is considered standard, and pros and cons of the most appropriate FP plan for the individual.
   f. Details of testicular biopsy and the procedure.[11]
   g. 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.
   h. 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. 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. Therefore,

11. 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.

if in future the young man might wish to use the stored tissue to try to propagate sperm, this can only be attempted ex vivo if the technology has advanced enough to allow this to happen. Testicular tissue preservation may be contraindicated in acute lymphoblastic leukemia and lymphoblastic lymphoma and it is best to seek advice from the treating haematologist.

i. Freezing immature testicular tissues is free until 21 years of age at this time if undertaken with RWH. After this time the boy may decide whether to keep the tissue or not — can be a difficult decision at that time due to immaturity — storage may not be required if fertility is proven in the future by semen analysis.

j. For boys 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).[12] This incurs the same cost as per sperm storage.

k. Please provide information to families as appropriate — available on the intranet under: www.rch.org.au/fertility/health-prof/.

   i. *Having Children After Cancer* (RCH handout for teens developed by psycho-oncology group).

   ii. *Can I Still Have Children? Information for Men Having Chemotherapy and Radiotherapy* (MIVF Brochure for mature males).

   iii. *Maybe Later Baby? A Guide to Relationships, Sex and Fertility for Young People With Cancer* (CANTEEN).

   iv. Male TTCP Information Sheet and Pre-consent Form (for TTCP candidates).

2.8.4 If TTCP is to proceed:

1. Please document in the notes that parent has read and understood the Male Fertility Preservation Information Sheet and Pre-Consent Form (as suggested by RCH Legal). This form goes through the experimental nature of the procedure. Please provide this to families to keep.
2. FP surgical team will obtain surgical consent for FP procedure, which should clearly state its experimental nature.
   a. Consent from patient if patient ≥18.
   b. Consent from parent and assent from patient of sufficient maturity to understand concepts <18.
3. MIVF Testicular Tissue Cryopreservation Form and FPS Database forms to be completed.
4. FP oncology team with assistance of oncofertility coordinator will liaise with family, endocrinology team, lines coordinator, IVF Andrology scientists (RWH (03) 8345 3232 or lab.supervisors@mivf.com.au; Monash (03) 9420 8218) and clinical ethics regarding logistics and booking.
5. Lines coordinator will coordinate with surgeons, theatre and anaesthetists, and endeavor to book cases for the morning as each biopsy takes hours to process by the scientists. There is no reproductive lab service after 3 pm, on weekends or holidays.
6. Oncology and Endocrinology 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.
7. The oncofertility coordinator will assist with review of histology (for example to ensure no malignancy on the tissue) and discussion with families, however it is the responsibility of the referring clinician to ensure this has been completed.

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

2.8.5 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.
3. If a clinical ethics meeting is held, the expected invitees include a representative from Oncology, Endocrinology and special experts where appropriate (e.g. Haematology/Genetics).
4. If the sole issue is that the child is pre-pubertal then an expedited review may occur upon written referral.

2.8.6 Follow-up:

1. The patient/family should be referred after treatment to Paediatric Endocrine Oncology Clinic for further discussion, confirmation of storage arrangements and discussion of the evolving technology. This provides an opportunity to answer questions and manage expectations.
2. Timing of follow-up by Endocrinology is at the discretion of oncologist (around 12 months).
3. The oncofertility coordinator will provide a follow-up summary of fertility care letter to the family and copy to referring oncologist, and local doctor. Transition to an adult facility for discussion with an andrologist is recommended when appropriate.

Figure 1. Testicular tissue cryopreservation pathway biological males

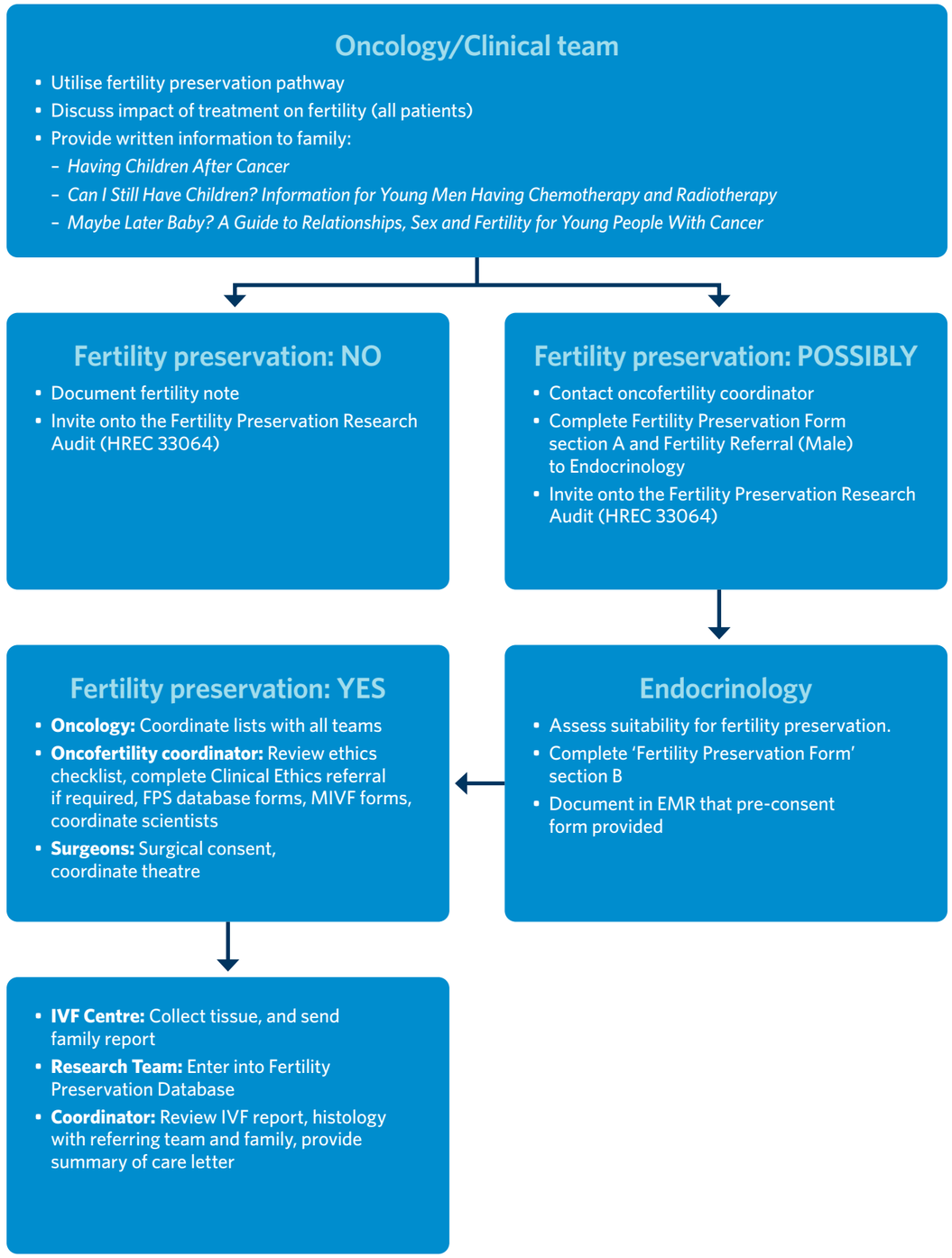

Table 1. Comparison of biological male fertility compromise guidelines

Risk	Stern et al. 2013[13]	COSA guidelines	Green et al. 2014[14]
Low	HL — ABVD, OEPA, NOVP, CHOP, COP NHL — COP/COPDAM/CYM (+/- R) RCHoP ***3.3*** Testicular radiation <0.7Gy RCHOP ALL — AALL0331 ***2.0*** ***Temporary azoospermia post treatment***	HL, NHL — Lower dose alkylating chemotherapy: ABVD (8% risk), OEPA, NOVP, CHOP, COP	Spermatogenesis less likely when ced >4000mg/m^2 No cumulative dose below which azoospermia didn't occur and above which azoospermia did occur
Medium	NHL — COP/COPDAM/CYVE (+/- R) ***4.8*** NHL — Abdo/pelvic radiation (1–6Gy) with testicular radiation dose= scatter GCT — BEP (2/4) ***200.0/400.0*** ALL — AALL0331 ***4.0***	Wilms, NB — Testicular radiation dose 1–6 Gy (as a result of scatter from abdominal/ pelvic radiation	
High	***Prolonged azoospermia*** HL — BEACOPP ***7.5*** escBEACOPP, ChIVPP/ EVA, COPP/ABV (4/6), MOPP/ABV, OEPA/COPP (4) NHL — HyperCVAD (8) NHL testicular radiation >2.5Gy men and >6Gy boys BMT — HSCT containing TBI/alkylator, cyclo/ busulfan/melphalan BT — SJMB96 (96-03) ***16.0, 300*** Cranial radiation >40Gy ALL — craniospinal radiation	HSCT — TBI GC, ALL, NHL sarcoma — ≥6Gy radiation to testes HL — Protocols containing procarbazine: COPP, MOPP (83% risk), MVPP (97% risk), ChIVPP, ChIVPP/EVA, MOPP/ABVD, COPP/ABVD (62% risk) BMT/ SCT — Alkylating chemotherapy for transplantation conditioning (cyclophosphamide, busulfan, melphalan) (70% risk)	
High	OS — MAP, MAPIE ***240*** ES — EuroEwings 99 VIDE (6)/VAI (8) ***102.0*** AEWS0031 interval VDC/IE/VC ***8.4 63.0*** RMS IRS III VAC ***23.4***, IRS IV VAC ***26.4***, D9803 VAC ***30.8***, ARST 0531 vac ***16.8***, ARST 0531 VAC/VI ***8.4***, ARST 0431 VDC/IE/Vi ***9.6, 45.0***	Testicular cancer, BMT/SCT, ALL, NHL, sarcoma, NB, HL- Any alkylating agent (eg, procarbazine, nitrogen mustard, cyclophosphamide) + TBI (80–90% risk), pelvic/testicular radiation, HL — BEACOPP (67–80% risk) Sarcoma, NHL, NB, ALL — Cyclophosphamide > 7.5 g/m^2 BT — Cranial/brain radiation ≥ 40 Gy	

13. Stern C et al. reproductive concerns of children and adolescents with cancer: challenges and potential solutions. COAYA. 2013;3:63–78.
14. Green DM 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.

Table 2. Infertility risk and potential recommendations in biological males

Age	Risk category	Potential to recommend FP
Pre-pubertal	Low	No
	Mod >20 risk	May consider experimental options
	High >80% risk	May consider experimental options
	Uncertain	No
	Contraindication ALL LBL	No
Pubertal	Low	Preserve sperm if able
	Mod	Yes. Consider testicular tissue cryopreservation if unable to produce sample
	High	Yes. Consider testicular tissue cryopreservation if unable to produce sample
	Uncertain	Discuss or consider possible biopsy Preserve sperm if able
	ALL LBL	Preserve sperm if able

Table 3. Male level of risk for gonadal failure/infertility above that for the general population (Paediatric Initiative Network)[15]

		Minimally increased risk	Significantly increased risk	High level of increased risk
Alkylators CED* gm/m²		CED <4		CED ≥4
Hematopoietic stem cell transplant				Alkylator +/- total body irradiation 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; ^RPLND = Retroperitoneal Lymph Node Dissection

The Cyclophosphamide Equivalent Dose is calculated using the following equation:
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])

15. Meacham, L., et al. JAYAO 2020 (in press)

Table 4. 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

3. RCH fertility preservation principles for biological 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 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 newly diagnosed female patients/families where the patient is to receive any chemotherapy, radiation or surgical procedure that could impair fertility (Table 8):
    a. Pubertal females (>12y and ≥Tanner 3):
        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 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.
4. Involve Clinical Ethics as appropriate.
5. Provide age appropriate discussions with patients when fertility preservation procedure is being considered.
6. Document fertility discussions and use of resources in medical record.
7. Discuss participation in HREC 33064 prospective fertility audit and database (DB 044) for all patients.
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. Oncofertility coordinator.
2. Paediatric Gynaecology (PAG) fellow.
3. PAG consultant.
4. Reproductive Biology Unit liaison.
5. Oncology liaison.
6. Clinical Ethics.
7. Lines coordinator.
8. Surgical team as required.

3.4 Eligibility for fertility discussion

Female patients are to be identified by the Children's Cancer Centre or treating team staff. The eligible population includes all new female patients with a proven cancer diagnosis with intent to cure.

FP team will also provide consultation at other times in response to:

1. Females with relapsed disease and a new gonadotoxic treatment plan.
2. Referrals from any provider.
3. At request of patients or families.
4. Females who have completed treatment and are having ovarian reserve surveillance.

3.5 Initial discussion by appropriate oncology team 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.
2. If there is intent to cure, Section A of Female Fertility Preservation Form can be completed electronically through EPIC (in notes search 'fertility').
3. Written resources may be distributed to the patient and her family, providing an overview of fertility preservation.
    a. *Having Children After Cancer Young Women* (RCH Handout for teens developed by psych-oncology group).
    b. *Can I Still Have Children? Information for young Women Having Chemotherapy and Radiotherapy* (MIVF Brochure).
    c. *Maybe Later Baby? A Guide to Relationships, Sex and Fertility for Young People With Cancer* (published by CANTEEN for mature adolescent patient).
4. Discussion of possible fertility preservation options as appropriate. The table outlining female fertility preservation procedures may be used to guide discussion.
5. FP consultation can be formally documented in EMR using a template or just use your own notes.
6. Invite the patient to participate in the Fertility Preservation Research Audit. Patients can be invited whether they decide to pursue fertility preservation or not. If the patient is under 18, the parent may consent on their behalf, however if the patient is 18 or above, they may complete their own consent form.
    a. Parent Information and Consent Form if child is <18 years or
    b. Patient Information and Consent Form if young person is ≥18 years.

3.6 Potential indications for FP referrals to Gynaecology:

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

3.7 Procedures for fertility preservation referral biological females

Make a referral to the Paediatric Gynaecology Service at The Royal Children's Hospital using the Female Oncofertility Referral Form in the EMR. Also please call the oncofertility coordinator and speak directly to the gynaecology fellow or gynaecologist.

3.8 Handover from Oncology or referring team to Gynaecology team:

1. The referring clinician needs to relay details relevant to making an FP decision including:
    a. Brief history.
    b. Developmental maturity of patient.
    c. Planned treatment, urgency (with clear indication of acceptable timeframe), prognosis.
    d. Handover of patient/family's understanding of the diagnosis, prognosis, FP options/response to introductory discussion.
    e. Other procedures planned.
    f. Requirement for menstrual suppression.
    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, battle scarred abdomen, significant immunosuppression, bleeding disorder, presence of a malignant abdominal/retroperitoneal mass.
    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 gynaecology consultant review.
    k. Any specific concerns the treating oncologist has with respect to proceeding with an FP procedure.
    l. 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.
2. 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.

3.9 Paediatric adolescent gynaecology FP consultation:

1. PAG FP team 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. The gynaecology fellow in association with the oncofertility coordinator and gynaecology consultant will 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. Where the Oncology team has not been able to do so, the FP guidance can be utilized. Be aware of considerations for oophorectomy (see appendix).
4. Pre-op bloods may be considered 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.
5. The consultant and/or fellow can make their own notes in the EMR or use the special 'fertility' templates which assist with fertility decision-making.
6. FP gynaecology team can offer potentially beneficial FP options to:
    a. **All referred pubertal females (>12y ≥Tanner 3)** and their families when patient is planned to receive any chemotherapy, radiation or surgery that could possibly impair fertility where it is felt that the FP is beneficial to the patient and the risk is acceptable.
    b. **Referred pre-pubertal female patients** in whom the risk of infertility is moderate or high according to treatment regimen/cumulative drug doses where it is felt that the FP is beneficial to the patient and the risk is acceptable.
    c. Other referred patients where it is felt that the FP is beneficial to the patient and the risk is acceptable.
7. The PAG FP team are to provide age appropriate education and logistical information to the young patient on fertility preservation options. The team is also to address any issues around menstrual management and sexual health.
8. The PAG FP team including oncofertility coordinator will arrange any further consultations if required.
9. PAG FP team will communicate back to the oncology clinician and reproductive team the plan, particularly any impact on the start of treatment.

3.10 Clinical ethics:

1. Clinical ethics must be carefully considered according to the clinical ethics checklist.
2. If a clinical ethics opinion is needed, Clinical Ethics Service, 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.
3. Expected invitees: a representative from Oncology, Gynaecology, and special experts where appropriate e.g. Haematology/Genetics.

3.11 Fertility preservation procedure to proceed:

1. If OTCP is to proceed, please document in the notes that parent has read and understood RCH information sheet Ovarian Tissue Pre-Consent Form (as suggested by RCH Legal). This form goes through the experimental nature of the procedure. Please provide this to families to keep.
2. Offer storage at any IVF centre of the family's choice. Both Monash and MIVF documents are on the RCH website.
3. Many families choose RWH as storage which is free until 21 years of age at this time. If so, please complete the MIVF Consent to Ovarian Tissue Storage for Minors.
4. FP gynaecology or surgery team will obtain surgical consent for the fertility preservation procedure which should clearly state its experimental nature.
   a. Consent from patient if patient ≥18.
   b. Consent from parent and assent from patient of sufficient maturity to understand concepts <18.
5. Oncology coordinator will liaise with family, Gynaecology team, lines coordinator, Clinical Ethics and reproductive laboratories.
6. 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 3 p.m. on weekends or holidays.
7. 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.
8. The oncofertility coordinator will assist with review of histology (for example to ensure no malignancy on the tissue) and discuss reproductive findings with family postoperatively, however it is the responsibility of the referring clinician to ensure this has been completed.

3.12 Follow-up:

1. The oncofertility coordinator will provide a summary of fertility care letter to the family and copy to referring oncologist and local doctor.
2. 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.
3. Timing of follow-up by gynaecology is at the discretion of oncologist (around 12 months) or from around nine years of age.
4. Transition to an adult facility is recommended when appropriate.

Figure 2. Ovarian tissue cryopreservation pathway biological females

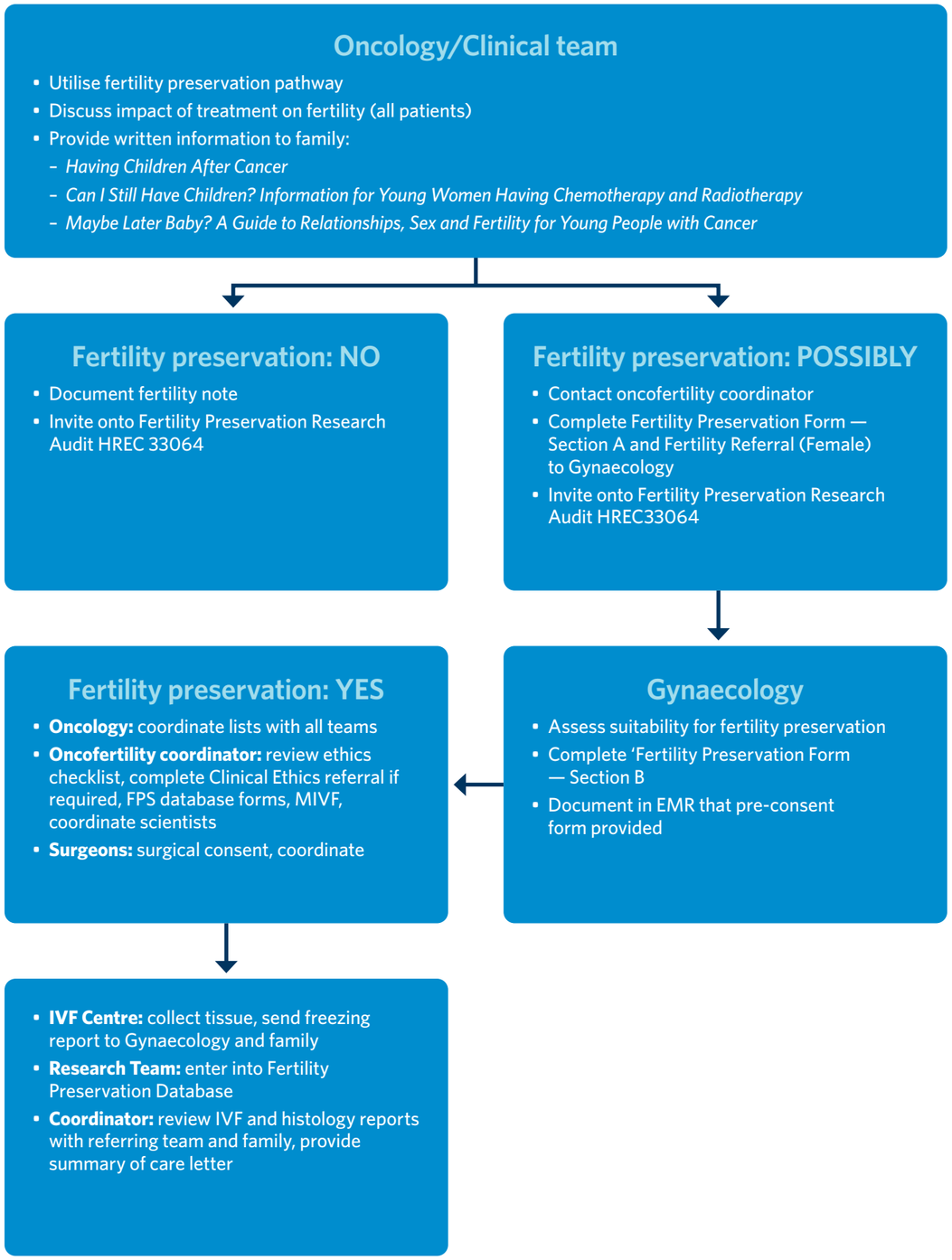

Table 5. Comparison of fertility compromise guidelines biological females

Risk	Stern et al. 2013[13]	Jadoul et al. 2012[16]	COSA (likelihood of POI)	COSA guidelines (development amenorrhea)	Wallace et al. 2005 [17]
Low	HL — ABVD, OEPA, NOVP, CHOP, COP NHL — COP/ COPADM/CYM (+/- R) RCHOP ***3.3*** ALL — AALL0331 ***2.0***	HL — ABVD, younger patients NHL ALL AML	Sarcoma — <10–40% HL — U5% unless intensive (later onset POF ~19%) Leukaemias — <10%	HL + NHL — ABVD (5%), CHOP(q21), COP (in women 30–35) AML — anthracycline, cytarabine ALL — multiagent therapies ***V low risk (negligible)*** Leukaemia, HL, NHL, NB, RMS, Wilms, Kaposis — vincristine	***<20% risk of subfertility*** ALL WT Soft tissue sarcoma stage 1 GCT with no RTx Retinoblastoma BT — cranial radiation <24Gy
Medium	NHL — COP/ COPADM/CYVE (+/- R) ***4.8*** GCT — BEP (2/4) ***200.0/400.0***		HL — 40–60% if escalated therapy NHL — 10–40%	HL — BEACOPP Wilms, NB — whole abdo/pelvic RTx 10<15Gy pre-pubertal Spinal tumour, BT, NB, relapsed ALL, NHL — whole abdo/ pelvic Rtx 5–10Gy post-pubertal girls, spinal ≥ 25Gy	AML — difficult to quantify Hepatoblastoma ES — nonmet STS — stage II or III NB NHL HD — alternating rx BT — craniospinal radiatiotherapy, cranial irradiation >24Gy
High	HL — BEACOPP, escBEACOPP, ChIVPP/EVA, COPP/ ABV (4/6), MOPP/ ABV, OEPA/COPP (4) ***7.5*** HL + NHL — external beam rtx to field incl ovaries NHL — hyper CVAD (8) ***14.4*** BMT — TBI/alkylator or cyclo/busulfan/ melphalan BT — SJBM96 (96-03) ***16.0/300*** + cranial radiation ***>40Gy*** ALL — craniospinal radiation OS — MAP ***240.0***, MAPIE ***27.0*** ES — EuroEwings 99 VIDE (6)/VAI (8) ***102.0*** AEWS0031 interval VDC/IE/VC ***8.4***, ***63.0*** RMS — IRS III VAC ***23.4***, IRS IV VAC ***26.4***, D9803 VAC ***30.8***, ARST 0531 vac ***16.8***, ARST 0531 VAC/VI ***8.4***, ARST 0431 VDC/IE/Vi ***9.6***	HL — MOPP, CHOP, BEACOPP, older patients, HSCT refractory disease ALL — if undergoing HSCT	HSCT or high dose rx — >70–90%	Wilms, NB, sarcoma, HL — whole abdo/ pelvic Rtx ≥15Gy in prepubertal and ≥1–0Gy in post-pubertal TBI NHL, NB, ALL, sarcoma — CY 7.5g/ m^2 in women <20 BMT/SCT = alkylating chemo for conditioning BMT/SCT, ovarian sarcoma, NB, HL — alkylating agent+ TBI or pelvic radiation HL — protocols involving procarbazine (51% risk), MOPP, mVPP, COPP, CHiVPP, ChIVPP/EVA, MOPP/ ABVD, COPP/ABVD BT — cranial/brain radiation ≥40Gy	Whole body radiation Localised radio pelvic or testicular Chemo conditioning HD — rx alkylators STS — stage IV disease ES — metastatic

Table 5 continued next page

16. Jadoul P and Kim S. Fertility considerations in young women with hematological malignancies. Journal of Assisted reproduction and Genetics 2012 29(6):479–498.

17. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol 2005a;6:209–218.

Table 6. Infertility risk and potential recommendations biological females

Age	Risk category	Pre-treatment FP recommendation
Pre-pubertal	Low	No
	Mod >20 risk	Yes, for consideration
	High >80% risk	Yes, for consideration
	Uncertain	No
	Contraindication ALL LBL	No, unless high risk
Pubertal	Low	No, but up to patient/family
	Mod	Yes. Consider oocyte harvest if time Consider experimental options
	High	Yes. Consider oocyte harvest if time Consider experimental options
	Uncertain	Up to patient if >16
	Contraindication ALL LBL	No unless high risk

Table 7. Female level of risk for gonadal failure / infertility above that for the general population (Paediatric Initiative Network)[15]

			Minimally increased risk	Significantly increased risk	High level of increased risk
Alkylators CED* gm/m²		**Prepubertal**	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**	**Prepubertal**		<15 Gy	≥15 Gy
		Pubertal		<10 Gy	≥10 Gy
	Hypothalamus		22–29.9 Gy	>30–39.9 Gy	>40 Gy

*CED = Cyclophosphamide Equivalent Dose

For the CED equation, please see page 15

18. Chow EJ 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;17(5):567–576.

    Longterm followup study of almost 11000 childhood cancer survivors compared to sibling controls showing that male sur- viviors had a high risk of infertility after exposure to alkylators, while female survivors were at risk after exposure to the highest quartile dose.

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20. 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.

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

22. 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.

23. 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.

24. Blumenfeld Z. Chemotherapy and fertility. Best Pract Res Clin Obstet Gynaecol. 2012; 26(3):379–390.

25. 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.

Table 8. Impact of class of chemotherapeutic agent on ovarian function

Agent class	Risk category	Likelihood of livebirth[18]	Mechanism
Alkylating agents[19,20,21,22]	High		DNA inter-strand cross-linking drugs
Cyclophosphamide ≥7.4 g/m²	Pre-pubertal patients considered high risk ≥12 g/m² and moderate risk ≥8 g/m²	HR 0.99[18]	
Ifosfamide ≥2.7 mg/m²		HR 0.84[18]	
Busulfan <450 mg/m²		HR 0.20[18]	
Busulfan ≥450 mg/m²		HR 0.18[18]	
Chlorambucil		HR 1.0 [0.85–1.16][18]	
Melphalan		HR 1.0 [0.85–1.16][18]	
Nitrogen mustard		HR 1.0 [0.85–1.16][18]	
Thiotepa		HR 1.0 [0.85–1.16][18]	
Triazenes[23]	High		DNA inter-strand cross-linking
Procarbazine ≤3.4 mg/m²		HR 0.87[18]	
Procarbazine ≥5.1 mg/m²		HR 0.78[18]	
Dacarbazine		HR 1.0 [0.85–1.16][18]	
Temozolamide		1.0 [0.85–1.16]	
Nitrosoureas	High		DNA inter-strand cross-linking
Carmustine		HR 1.0 [0.85–1.16][18]	
Lomustine ≥411 mg/m²		HR 0.60[18]	
Platin[19]	Medium	OR 1.77	DNA inter-strand cross-linking
Cisplatin ≥488 mg/m²		0.86	
Carboplatin		1.0 [0.85–1.16]	
Antimetabolites[19] (methotrexate, 5 fluorouracil, cytarabine)	Low		No DNA damage in human follicles, not gonadotoxic
Vinca alkaloids[19] (vincristine, vinblastine)	Low		No DNA damage in human follicles, not gonadotoxic
Anthracyclin antibiotic[19,25] (doxorubicin, Adriamycin)	Low (apart from adriamycin: intermediate)		Inhibit DNA synthesis, create DNA breaks

Table 9. Fertility preservation procedures biological females

Established methods							
Method	**Pubertal status**	**Description**	**Time needed**	**Advantages**	**Disadvantages**	**Efficacy**	**Approximate cost**
Oocyte (egg) freezing	After puberty	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[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
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 suppression (GnRH agonist)	After puberty	Hormone injections to switch off ovaries. This may decrease ovarian damage from chemotherapy	Immediate give prior to start of treatment	May stop or decrease menstruation during treatment	Monthly to 3 monthly injection No benefit with radiation Menopausal symptoms	May decrease oocyte loss by 40% Conflicting results: probably overall benefit in adults but the benefit is likely small.[28] Not considered a replacement for other options	$340/ monthly injection Partially covered through some drug plans Expenses covered via drug committee at RCH
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
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[29]	Proof of concept[30] About 150 pregnancies worldwide[31,32] from tissue stored in childhood[33]	Free of charge in public hospitals and currently storage of tissue until 21 years is free though this may change in the future

Table 9 continued next page

26. 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.
27. 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.
28. 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.
29. Gook D et al. Potential leukaemic contamination in cryopreserved ovarian tissue. Hum Reprod 2018:33: supp1:O81:i38.
30. Stern C et al. First reported clinical pregnancy following heterotopic grafting Hum Reprod. 2013; 28: 2996–9.
31. Donnez J et al. Fertility Preservation in Women. NEJM. 2017;377:1657–1665.
32. Dolmanns M et al. Recent advances in fertility preservation. J Obstet Gynaecol Res. 2019; 45:266–279.
33. Matthews S et al. succesful pregnancy in a woman suffering from B-thalasemia following transplantation of ovarian tissue cryopreserved before puberty. Minerva Ginecological 2018; 70: 432.

4. Clinical ethics checklist for all fertility preservation procedures[34]

This document refers to 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 girl, and testicular tissue from a boy.

4.1 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.

4.2 Formal clinical ethics review — when required

4.2.1 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.
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.

34. McDougall R, Gillam L, Delany C, Jayasinghe Y. The ethics of fertility preservation for prepubertal children: should clinicians offer procedures where efficacy is largely unproven? J Med Ethics 2018;44 (1):27–31.

4.2.2 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.
   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.

4.3 Clinical ethics checklist:

1. Pre-pubertal child — use Referral Form 3A (FP Pre-pubertal).
2. Post-pubertal — use checklist below. If one or more items ticked below, clinical ethics meeting will be held — use Referral Form 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 is itself 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 on the clinical ethics website: http://www.rch.org.au/bioethics/clinical_ethics_service/.

5. Deceased patients

5.1 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.

5.2 Principles

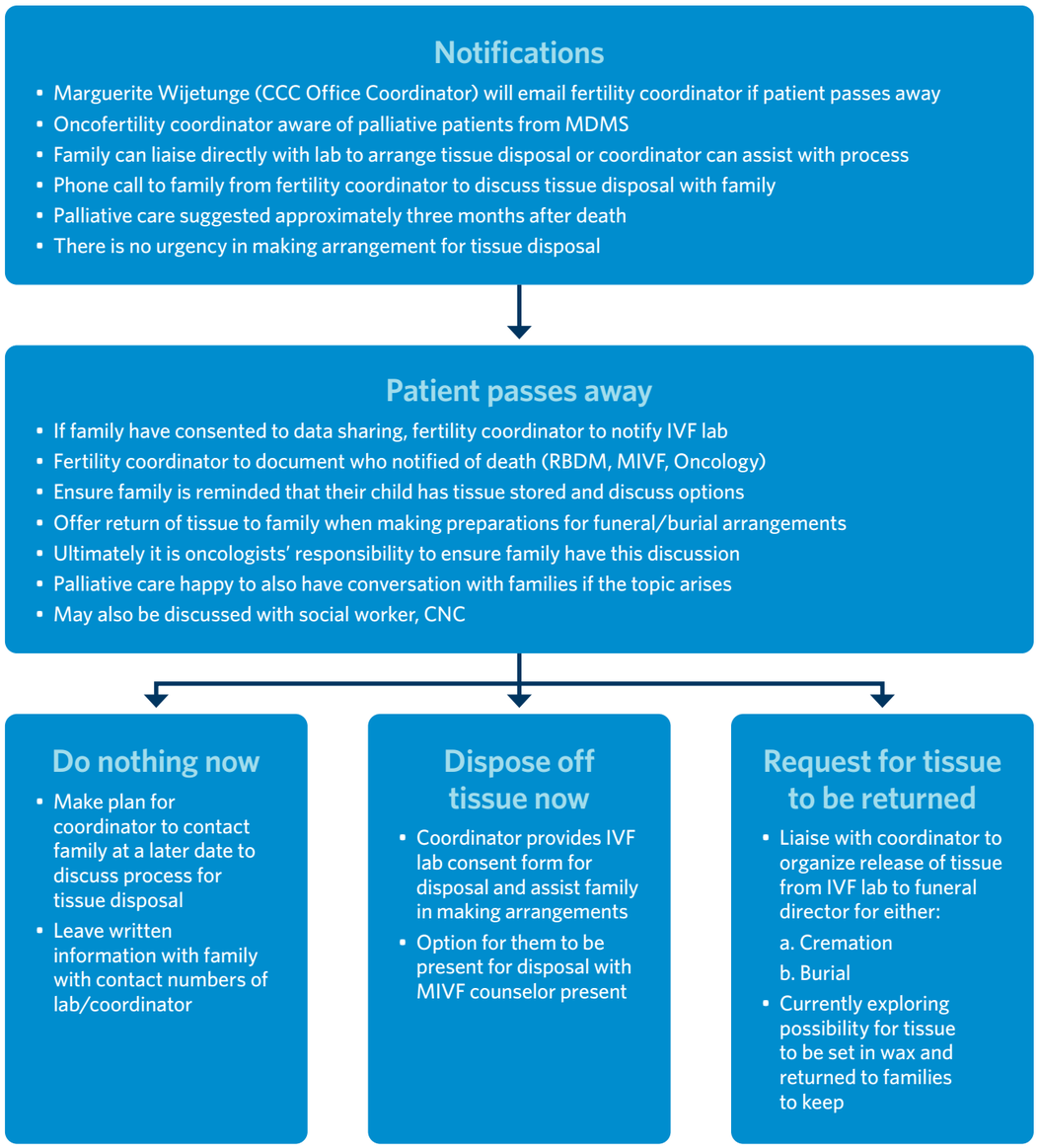
Tissue from minors is required to be discarded by law for deceased patients and cannot be used by others for fertility purposes nor for research.[35,36] We have developed a pathway for notification to the Women's laboratory and a stepped care protocol for discussion with families who may opt to cremate or bury the tissue if they desire. Ultimately this pathway is the responsibility of the oncology consultant.

Principles for data sharing with the Reproductive Services laboratory:

1. When patients store tissue, they become a patient of the RCH and the adult institution.
2. Families have to let the IVF centres know about the passing of their child but this does not always occur.
3. Eventually we will have a shared EMR so clinicians from all sites can access information as required for seamless integration of care.
4. Until then we will provide this information to the adult storage centre for those who have signed consent for data linkage.
5. We have also modified the IVF forms to let families know that we may notify the laboratories in the event of their child's passing. For those who sign this new form we will share this data.
6. Families have to sign a consent to disposal form before the tissue is discarded. This does not occur if the family is lost to follow up and the storage period of 20 years is exceeded in which case the decision to discard the tissue is made at an executive level at The Royal Women's Hospital.
7. The Women's laboratory will notify the RCH prior to disposal of any tissue of RCH patients who are lost to follow up.

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.

Figure 3. Deceased patient tissue pathway



6. Monash Children's

6.1 Purpose

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

6.2 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. In the past three years clinicians have referred five families for onsite fertility consultation and care at the RCH. In 2019, five referrals were received of whom one proceeded to FP. These numbers are expected to increase with a projection of 10 referrals per year to the RCH for consultation.
5. In the event that a Monash clinician requests FP consultation and care:
    i. They will complete an RCH Fertility Referral Form, provide timelines for start date of cancer treatment and speak with Dr Leanne Super, Monash Liaison.
    ii. The oncofertility coordinator and the relevant RCH team (Gynaecology or Endocrinology or Surgery) will be notified who will seek advice from executive.
    iii. 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 e.g. with IVF specialists at the Women's.

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).

Appendix

Attachments: revised or new documents

A. Information sheet on TTCP for RCH patients
B. Information sheet on OTCP for RCH patients
C. Summary of care of letters
D. COVID-19 (Coronavirus) — Advice to children and families

The Royal Children's Hospital Melbourne

The Royal Children's Hospital Fertility Preservation Service

Information sheet — Testicular tissue harvest for possible fertility preservation

The impact of a boy's cancer treatment on his testis and prospects for fatherhood

Treatment with chemotherapy or radiation can affect male fertility by damaging sperm production. Sperm banking prior to commencing cancer treatment is the only reliable option to preserve and protect the chance of fatherhood for males. However, this is only possible when sperm are being produced after puberty.

Sperm production

Sperm are produced in the testes. During a boy's journey from infancy to pre-puberty, there is no active sperm production in the testes. Instead, the testis contains immature cells called germ cells. Once puberty starts, the testis increases in size because it starts producing sperm. The testes also produce testosterone the hormone which creates the physical changes that distinguish men from boys.

Mature sperms are produced from mature germ cells. Banking mature sperms therefore becomes possible only from about the age of fourteen, although the exact time varies between boys.

In boys too young to make sperm

In boys that are too young to make sperm there are experimental options available to collect fragments of the testis by biopsy and storing the tissue containing germ cells by freezing it. The cells are immature. It is hoped that in the future, procedures may be developed to allow development of sperm from the germ cells, to allow the young man to father a child. It is hoped that this might be done via two experimental options:

1. Returning the tissue to the body at a later date (transplantation) or
2. Trying to grow sperm outside the body (in vitro spermatogenesis).

Transplantation would take some of the stored tissue containing germ cells and inject it into the testis during adulthood, in the hope that the germ cells settle in the testis and start to make sperm. Similar procedures have been performed in some animals but so far no procedures have ever been effective in humans. Transplantation also has the risk of transplanting some cancer cells.

In vitro spermatogenesis involves growing sperm in the laboratory but so far no such reliable methods have been developed. It is also unknown how testicular tissue from biopsies should be stored and, if this storage is not suitable, sperm production may not be possible.

Testicular biopsy for fertility preservation is experimental, and is only undertaken at The RCH under special approvals. The only situations at the RCH where we may find it acceptable to store germ cells in a child, is if the surgical procedure is going to be low surgical risk, and if the chemotherapy or radiotherapy has a significant risk of infertility. Right now the tissue cannot be used for fertility purposes. Some hope that the technology may advance by the time your child is ready to attempt parenthood, however there is no guarantee of future fertility. Therefore the procedure (testicular tissue cryopreservation) is not considered standard practice. For some young boys from the age of around 12 onwards, we have found a small number of mature sperm in the biopsy material, which is also saved.

About the procedure

During the procedure a small part of one testicle is removed and frozen. It is important to understand that there is no guarantee that the banking of testicular tissue will lead to successful sperm production.

The surgery is performed under a general anaesthetic, preferably at the same time that another procedure is required. After removing part of a testicle, the scrotum may be painful for a few days. The tissue is collected by IVF scientists and stored at IVF laboratories. Currently the scientists from the Reproductive Services Department at The Royal Women's Hospital (RWH) are able to collect the tissue at surgery and process it at their centre. You do not have to have tissue stored at this centre if you don't want to, in which case we will do everything possible to arrange storage at another IVF centre of your choice and to inform you of any costs involved. If your child's tissue is stored at RWH, it does not mean that he will be required to have future fertility care at that centre (Melbourne IVF, RWH). He may go wherever he chooses. Currently there is no storage fee for the tissue up until your child turns 21. However, a storage charge may be introduced by Melbourne IVF at any point. If the tissue also contains mature sperm an annual storage fee may be requested. Doctors at The Royal Children's Hospital have nothing to do with the tissue storage after it is collected by the scientists, and all future dealings regarding the stored tissue would be between yourself and the IVF centre.

Who is eligible

Theoretically there is no lower age limit for testicular tissue biopsy. We may advise against the procedure in certain situations such as cancers where there may be a risk of reintroducing the cancer back into the body from transplantation in the future. For example, in leukemia if tissue is collected it is currently deemed too dangerous to put back into the body and cannot be currently used for fertility purposes.

We also need to determine that your child is well enough for surgery and to ensure that the procedure does not delay cancer treatment. Bleeding disorders or serious immune deficiency may prevent your child from having the procedure done. We also take into account differing views within a family about such procedures. Sometimes we consult with the Clinical Ethics Committee to assist the decision making for the procedure in the event that the decision is not so clear cut. This is undertaken urgently so as not to delay treatment.

Risks and benefits

It remains experimental to collect testicular tissue from boys to be stored frozen in the hope of future fertility. The surgery for the biopsy itself is not experimental as this procedure is performed routinely by surgeons for other indications.

Fertility Preservation is not necessarily offered only if your child has an excellent chance of survival. It can still be offered when the oncology doctors are hoping for cure, regardless of the chance of survival.

Expected risks of the surgical procedure:

1. Risk of a general anaesthetic. There may be situations where your child's medical situation may present specific increases in the risk of anaesthesia. In these situations you the anaesthetist and the other treating teams will need to discuss the risk versus benefit issues. The safety of your child in the short term is a very important factor. Mostly the risk relating to the anaesthesia for the extra fertility procedure for your child will be so small it would be difficult to estimate. The anaesthetist can clarify if your child has any special aspects of their condition that could influence the risk of surgery.
2. Risk of surgery: infection, bleeding and damage to internal structures. In the rare instance that there is a complication such a haematoma (collection of blood) a second surgery to manage a complication might be required. These risks are likely to be higher during cancer therapy.
3. Delay to treatment: the procedure will usually be timed with other operative procedures necessary for treatment of the disease. As far as possible the surgery is performed within a few days of diagnosis, and if so should not impact prognosis. We will try and find the earliest date to undertake the procedure, however we will defer to your treating doctor (e.g. oncologist) if he or she deems that it is too unsafe to wait for this date. In this event the fertility procedure will need to be cancelled, as safety is our priority.

4. The biopsied testis may not develop fully as a result of the biopsy so may remain smaller than the non-biopsied testis. This is additional to the damage that chemotherapy or radiation treatment produce to reduce the size of the testes by damaging sperm production.

Other options:

1. Delay intervention until fertility is required. Sperm may still develop in the boy as an adult. But if not, it is possible to have a biopsy or similar procedure as an adult to collect or mature sperm. In some boys, although the chemo- or radiotherapy may be damaging to the testis, sperm production may still develop in adulthood. Even if this is at lower levels than normal, there may be sufficient sperm produced to allow for fatherhood either naturally or with IVF assistance. The degree of testicular damage depends on the extent of cancer treatment, which is usually not known for any boy before treatment starts.
2. Sperm donation in future.
3. Adoption.

Other issues to consider:

1. Cost of procedure: this is currently free but it may change in future.
2. Storage of tissue: occurs for at least 20 years after which time you have to renew the request. This is an arrangement between you and the IVF centre and does not involve The Royal Children's Hospital.
3. Costs of future IVF treatment and tissue storage.
4. The tissue can only be used by your child and in the unfortunate event of death the tissue must be disposed of. In this instance a member of the team would contact you to discuss arrangements.
5. Due to current legal restrictions, the tissue cannot be donated for research. The tissue may never be utilized by anyone other than your child.

The Royal Children's Hospital Melbourne

The Royal Children's Hospital Fertility Preservation Service

Information sheet — Ovarian tissue harvest for possible fertility preservation

Background

Medical treatments or conditions in childhood (such as chemotherapy, radiotherapy, hormone conditions) may reduce the number of eggs in the ovaries. Depending on severity, this can sometimes affect hormone production, puberty, periods or fertility. Your health providers will outline the estimated impact of your child's treatment on fertility. Unfortunately it can be difficult to be precise about this due to limited data. The banking of mature eggs (egg collection) prior to commencing cancer treatment is still the best guarantee of preserving long-term fertility for females, but this is only possible after puberty, and can cause delays to cancer treatment so is not always possible.

When there is little time before cancer treatment, or in pre-pubertal girls, we can offer storage of tissue from the ovary which contains immature follicles (ovarian tissue freezing). This is experimental, and is only undertaken at the RCH under special approvals.

The procedure and logistics

Ovarian tissue freezing requires collection of healthy ovarian tissue, via a key-hole operation (a laparoscopy) prior to starting treatments that may harm the ovary and preserved for a future time when fertility may be required. It is hoped this may be done via two experimental options:

1. Returning the tissue to the body at a later date (transplantation).
2. Maturing the cells outside the body and using mature eggs derived from that technique.

It is important to understand that there is no guarantee that the banking of ovarian tissue will lead to successful pregnancies and live births.

The surgery is performed by the Gynaecology team or the Surgery team at The Royal Children's Hospital. The procedure is performed by laparoscopy ('key hole' surgery), which involves a small incision in the belly button through which a camera is introduced. One to three other small incisions are made in the abdomen and about one third of the covering of the ovary (the cortex, where the eggs are stored) is removed. Sometimes the whole ovary is removed if it is very small, or if the treatments are likely to cause a severe impact on future ovarian function. The procedure takes about 30 minutes but is usually coordinated with other operations so the total time asleep may be longer. By the next day your child should be walking and eating. Recovery time is usually a few days.

The tissue is collected by IVF scientists and stored at IVF laboratories. Currently scientists from the Reproductive Services Department at The Royal Women's Hospital (RWH) are able to collect the tissue at surgery and process it at their centre. You do not have to have tissue stored at this centre if you don't want to, in which case we will do everything possible to arrange storage at another IVF centre of your choice and inform you of any costs involved. If your child's tissue is stored at RWH, it does not mean that they have to have future fertility care at that centre (Melbourne IVF, RWH). Currently there is no storage charge for the tissue until your child turns 21 at RWH. However, a storage charge may be introduced by Melbourne IVF at any point. Doctors at The Royal Children's Hospital are not involved with the storage after the tissue is collected, and all future dealings regarding the stored tissue would be between yourself and the IVF centre.

Outcomes so far

Only around 140 pregnancies have been reported worldwide using ovarian harvest technology so it is considered experimental. Two live births have been reported in women who have had their tissue stored in childhood. The ovaries of young people, especially children contain immature eggs. It is difficult to mature the eggs after they are thawed. Furthermore there are high rates of loss of eggs during the freezing and thawing process. The procedure is offered in the hope that by the time your child has achieved adulthood and wishes to have a baby, the procedures may be more successful. There have been isolated case reports in children of the replanted tissue being hormonally active again. If your child has a diagnosis of cancer, there is a risk that the tissue might contain cancer cells which could be reintroduced back into the body when the tissue is implanted.

Who is eligible

Theoretically there is no lower age limit for ovarian tissue harvest. We may advise against the procedure in certain situations such as certain cancers where there may be a risk of reintroducing the cancer back into the body in the future. For example, in leukemia if tissue is collected it is deemed too dangerous to put back into the body at this stage. Technology may advance to allow the tissue to be matured outside the body so that mature eggs can be collected from that tissue for IVF, however the technology is in very early stages.

We need to also determine that your child is well enough for surgery. Multiple abdominal scars, bleeding disorders or serious immune deficiency may preclude your child from having the procedure done. We also take into account the differing views within a family about such procedures. Sometimes we consult with the Clinical Ethics Committee to assist the decision making in the event that the decision is not so clear cut. This is undertaken urgently so as not to delay treatment.

Risks and benefits

The surgery (laparoscopy and ovarian tissue harvest or removal of one ovary) is not experimental as this procedure is performed routinely by gynaecologists and surgeons for other indications. However, the use of immature ovarian tissue to attempt pregnancy in the future is considered experimental.

Fertility Preservation is offered where there is a hope of cure, irrespective of the chance of survival.

Expected risks of the surgical procedure:

1. Risk of a general anaesthetic. There may be situations where your child's medical situation may present specific increases in the risk of anaesthesia, for example age less than one year. In these situations yourself, the anaesthetist and the other treating teams will need to discuss the risk versus benefit issues. The safety of your child in the short term is the very important factor. Mostly the risk relating to the anaesthesia for the extra fertility procedure for your child will be so small it would be difficult to estimate. The anaesthetist can clarify if your child has any special aspects of their condition that could influence the risk of surgery.
2. Risk of laparoscopy in general are: infection (around 7%), bleeding, damage to internal structures (bladder, bowel, blood vessels, 1-3/1000) which may occasionally require performing an open operation. These risks are likely to be higher during cancer therapy.
3. Risk of changing from keyhole surgery to a larger incision (laparotomy) 0.5–2%.
4. Death 4/100 000.
5. In the event of young age: The ovaries will usually be very small, it is highly possible that one entire ovary may need to be removed. We are not sure if the removed ovarian tissue or the remaining ovarian tissue will be functional in the future.
6. Delay to treatment: the procedure will usually be timed with other operative procedures necessary for treatment of the disease. As far as possible the surgery is performed within a few days of diagnosis, and if so should not impact prognosis. We will try and find the earliest date to undertake the procedure, however we will defer to your treating doctor (e.g. oncologist) if he or she deems that it is too unsafe to wait for this date. In this event the fertility procedure will need to be cancelled, as safety is our priority.

Other options:

1. Monitoring of ovarian function when your child is older occurs regardless of whether they have fertility preservation now or not, with a view to having egg freezing. However, if there is a high chance of ovarian failure we may not have the opportunity to undertake this.
2. Oocyte retrieval now if age appropriate and time permitting.
3. Egg donation from mother, sibling or other donor in the future.
4. Adoption.
5. Use of a hormone which suppresses ovarian function (Zoladex) and may protect the ovary, however studies on this are very conflicting in terms of success. This is only offered to girls who have already gone through puberty.
6. None of the above.

Other issues to consider:

1. Cost of procedure: this is currently free but it may change.
2. Storage of tissue: occurs for 20 years after which time you have to renew the request. This is an arrangement between you and the IVF centre and does not involve The Royal Children's Hospital.
3. Costs of future IVF treatment and tissue storage costs.
4. The tissue can only be used by your child and in the unfortunate event of death the tissue must be disposed of. In this instance a member of the team will contact you to discuss arrangements.
5. The tissue cannot be donated to research or be utilized by anyone other than your child.

The Royal **Children's** Hospital Melbourne

Date:

MRN:

Dear

We are writing to you as a follow-up of our discussion on the [date] where we spoke about whether there were any fertility optimisation procedures available for [child's name] during chemotherapy or radiation treatment. During this conversation, we explored the potential impact of treatment on fertility, the required timelines for treatment, the risks of the fertility procedures, and the current and potential future success and limitations of reproductive technologies. We made a shared decision to not proceed with the fertility intervention. We understand that these decisions can be very difficult to make in the context of cancer treatment, and that they are made with a lot of thought and care. There is no right or wrong decision. The best decision is one that is medically safe and aligned with your values at the time.

After treatment is over, members of the Oncofertility team can answer questions about growth development and fertility if required. Your oncologist can organise a referral to the Oncofertility team when you and your child are ready.

For any questions related to the fertility preservation service, please do not hesitate to contact the Oncofertility Coordinator.

RCH fertility preservation contact: **Rafael Serrano Real**

RCH fertility preservation contact email address: fertility@rch.org.au

Kind regards,

Rafael Serrano Real

Oncofertility Coordinator

The Royal **Children's** Hospital Melbourne

Date:

MRN:

Dear Parent/Guardian of:

Date of birth:

Fertility preservation procedure: **OVARIAN TISSUE FREEZE**

Date of procedure:

Number of slices frozen:

Location where ovarian tissue is being stored: **The Royal Women's Hospital/Melbourne IVF (Reproductive Services Unit)**

Contact telephone number: **(03) 8345 3242**

Storage facility email address: **lab.supervisors@mivf.com.au**

RCH fertility preservation contact: **Rafael Serrano**

RCH fertility preservation contact email address: **fertility@rch.org.au**

Please remember that at the time of this letter, the fees for storage of the ovarian tissue from your child have been waived until the age of 21, however the IVF centre may change this in the future. According to Victorian Law, your child will take ownership of the frozen ovarian tissue once she reaches the age of 18.

It is important that you contact either the facility where your child's ovarian tissue is stored or the RCH contact person if the following circumstances happen:

- Change of address or telephone number.
- Your child turns 21 years of age.
- If the tissue is not going to be used or no longer required.

After treatment is over, members of the Oncofertility team can answer questions about growth development and fertility. Your oncologist can organise a referral to the Oncofertility team when you and your child are ready.

Kind regards,

Rafael Serrano Real

Oncofertility Coordinator

The Royal **Children's** Hospital Melbourne

Date:

MRN:

Date of birth:

Dear Parent/Guardian of:

Fertility preservation procedure: **SPERM BANKING**

Date of procedure:

Number of straws frozen:

Location where sperm is stored: **Andrology Unit/The Royal Women's Hospital**

Andrology Contact number: **(03) 8345 3992**

RCH fertility preservation contact: **Rafael Serrano**

RCH fertility preservation contact email address: **fertility@rch.org.au**

Please be advised that the fee for the storage of the sperm samples in the Andrology department will be covered by the charity My Room for the first two years. You will be contacted by the Andrology department after this period.

It is important that you contact either the facility where your child's sperm sample is stored or the RCH contact person if the following circumstances happen:

- Change of address or telephone number.
- Your child turns 21 years of age.
- If the sperm sample is not going to be used or no longer required.

After treatment is over, members of the Oncofertility team can answer questions about growth development and fertility. Your oncologist can organise a referral to the Oncofertility team when you and your child are ready.

Kind regards,

Rafael Serrano Real

Oncofertility Coordinator

The Royal **Children's** Hospital Melbourne

Date:

MRN:

Date of birth:

Dear Parent/Guardian of:

Fertility preservation procedure: **TESTICULAR TISSUE FREEZE**

Date of procedure:

Number of vials frozen:

Location where testicular tissue is being stored: **The Royal Women's Hospital/Melbourne IVF (Reproductive Services Unit)**

Contact telephone number: **(03) 8345 3232**

Storage facility email address: **lab.supervisors@mivf.com.au**

RCH fertility preservation contact: **Rafael Serrano**

RCH fertility preservation contact email address: **fertility@rch.org.au**

Please remember that at the time of this letter, the fees for storage of the testicular tissue from your child have been waived until the age of 21, however the IVF centre may change this in the future. According to Victorian Law, your child will take ownership of the frozen testicular tissue once he reaches the age of 18.

It is important that you contact either the facility where your child's testicular tissue is stored or the RCH contact person if the following circumstances happen:

- Change of address or telephone number.
- Your child turns 21 years of age.
- If the tissue is not going to be used or no longer required.

After treatment is over, members of the Oncofertility team can answer questions about growth development and fertility. Your oncologist can organise a referral to the Oncofertility team when you and your child are ready.

Kind regards,

Rafael Serrano Real

Oncofertility Coordinator

The Royal Children's Hospital Melbourne

Date:

MRN:

To the Parent/Guardian of:

Fertility preservation procedure:

Date of injection:

The medication your child has received is a long-acting injection usually given every three months. It works by shutting down the activity of the ovaries. Some research on adults suggests these medications might have a slight protective effect on fertility, but the results are not consistent. It can also be prescribed to suppress menstruation, which can be advantageous during chemotherapy treatment, in order to reduce heavy periods.

Some of the side effects of the Zoladex® injection include hot flushes and mood changes if they used for over six months. Your doctor will let you know if you have to use it for longer.

Date for the next Zoladex® injections (if needed):

After treatment is over, members of the Oncofertility or Gynaecology team can answer questions about growth development and fertility if required. Your oncologist can organise a referral to the Oncofertility team when you and your child are ready.

For any questions related to this medication or to the fertility preservation service, please do not hesitate to contact the Oncofertility Coordinator.

RCH fertility preservation contact: **Rafael Serrano Real**

RCH fertility preservation contact email address: **fertility@rch.org.au**

Kind regards,

Rafael Serrano Real

Oncofertility Coordinator

The Royal Children's Hospital Melbourne

The Royal Children's Hospital Fertility Preservation Service

COVID-19 (Coronavirus) — Advice to children and families update number four 25th May 2020

Disclaimer

All the information provided below is intended for oncology patients and those receiving gonadotoxic therapy and may not be relevant to your child's treatment for their diagnosis. It is specific to fertility preservation procedures only. Please speak to your doctor to ensure this is applicable to you.

Could COVID-19 affect fertility care for my child?

Some cancer treatments can affect fertility. The impact on fertility is different for each person. Fertility preservation refers to freezing eggs, sperm or tissue from the ovary or testis to try to protect fertility. Some of these procedures have proven benefit (freezing eggs and sperm). Others, like freezing ovarian or testicular tissue, are in the very early stages of development for children.

Fertility preservation that involves surgery (collection of ovarian or testicular tissue) has traditionally been offered when cancer treatment might significantly affect fertility and only when healthcare teams and families think it is safe. For example, when it won't delay cancer treatment when a child is well enough to have surgery, and when surgery won't increase risks for a child.

During this uncertain and unprecedented time, The RCH Fertility Preservation Service is working together with the global fertility community of clinicians to provide up-to-date fertility preservation information to families. We are not sure if COVID-19 is present in frozen fertility tissue or sperm and eggs in infected patients. Should we receive further information from the relevant authorities we will update our guidelines immediately.

During the COVID-19 pandemic, we wish to continue to provide safe care. This means:

1. The RCH will try to provide counselling to all families about risks to fertility and potential fertility preservation options available. Most consultations will be online and/or over the phone.
2. At this point in time we are making careful decisions about offering fertility preservation procedures for safety or logistical reasons. The RCH Management, the Reproductive Laboratory and the Children's Cancer Centre will provide regular updates on whether the fertility surgeries can continue.
3. For children who are COVID positive, have symptoms or have travelled overseas in the last 14 days, we advise that they not undertake a surgical procedure for fertility purposes. When treatment is over, your child will be referred for another fertility consultation where they will be offered monitoring of reproductive function and further options discussed at that point.
4. If a surgical procedure is undertaken and ovarian or testicular tissue is collected after 2pm it will be stored and processed the next day. This could affect the quality of the tissue. However, overnight storage is normal procedure at other international centres.
5. For families considering sperm collection, you will be asked screening questions about your son at The RCH and also over the phone by the RWH Andrology Laboratory. However, they will not be allowed to provide a specimen if they are unwell at the time (COVID-19 positive or suspected case), unless this sample is required for urgent fertility preservation prior to gonadotoxic chemotherapy or radiotherapy treatment. If is not urgent,

an appointment can be booked again when they are well, with no less than 14 days from onset of illness or upon advice from the Fertility Preservation team.

6. Sperm collection should not be undertaken at the Andrology Laboratory at this time. We will provide guidance on how to self-collect the semen sample at home/hospital. Specimens must be delivered to the Andrology Lab in person or by courier within 60 minutes of collection, and those delivering samples to the laboratory must call them on arrival for further instructions (phone 03 8345 3992). Please call the Andrology Lab if you live more than 60 minutes from the laboratory.
7. Patients may be able to collect a sperm sample closer at home and keep it stored at another laboratory. We will try and facilitate that for you.
8. The fertility coordinator can be contacted on fertility@rch.org.au. The team are here to help you and your family during this time and after treatment is over.

Fertility Preservation Service

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50 Flemington Road
Parkville Victoria 3052
RCH SWITCHBOARD +61 3 9345 5522
EMAIL fertility@rch.org.au
www.rch.org.au/fertility/

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