Provincial Clinical Knowledge Topic
Fertility Preservation, – Pediatric - Inpatient
V 1.0

Revision History

Version	Date of Revision	Description of Revision	Revised By
1.0	September 2018	Topic completed	See Acknowledgements

Important Information Before you Begin

The recommendations contained in this knowledge topic have been provincially adjudicated and are based on best practice and available evidence. Clinicians applying these recommendations should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. This knowledge topic will be reviewed periodically and updated as best practice evidence and practice change.

The information in this topic strives to adhere to Institute for Safe Medication Practices (ISMP) safety standards and align with Quality and Safety initiatives and accreditation requirements such as the Required Organizational Practices. Some examples of these initiatives or groups are: Health Quality Council Alberta (HQCA), Choosing Wisely campaign, Safer Healthcare Now campaign etc.

This topic is based on the following guidance:

1. Loren A, Mangu P, Nohr, L et al. Fertility Preservation for Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology. 2013; 31(19):2500-2510.
2. American College of Obstetricians and Gynecologists. Committee opinion no. 607: gynecologic concerns in children and adolescents with cancer. *Obstet Gynecol*. 2014;124:403.
3. The Ethics Committee of the American Society for Reproductive Medicine Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion. Fertility and Sterility 100:1224-1231.
4. Lambertini M, Del Mastro L, Pescio MC, Andersen CY, Azim HA, Peccatori FA et al. Cancer and fertility preservation: International recommendations from an expert meeting. *BMC Medicine*. 2016 Jan 4;14(1). doi: 10.1186/s12916-015-0545-7
5. Rodriguez-Wallberg KA, Oktay K. Fertility preservation during cancer treatment: clinical guidelines. Cancer Management and Research. 2014;6:105-117. doi:10.2147/CMAR.S32380.
6. AYA cancer fertility preservation guidance working group. Fertility preservation for AYAs diagnosed with cancer: Guidance for health professionals. 2014. Sydney: Cancer Council Australia.
7. Mintziori G, Lambrinoudaki I, Ceausu I et al. EMAS position statement: Fertility preservation. 2017.

Rationale

With overall cure rates for childhood cancer exceeding 80%, long term survivorship is the expectation for most children at the time of a cancer diagnosis. Many of the therapies used in the treatment of childhood cancers may produce long-term health effects months to years after the cancer treatment is complete. Chemotherapy, radiation therapy (RT) and surgery can each adversely affect a child's future fertility. Cancer treatment related infertility can result in significant distress for both male and female survivors. Assessment of fertility risk related to cancer treatment and the discussion of fertility preservation options if risk exists has become an expected standard of care for our patients.

Goals of Management

Goals of Fertility Preservation for Children and Adolescents with Cancer:

1. Discuss fertility risk and established preservation options if infertility is a potential risk of cancer or therapy with all patients and with parents or legal guardians of children.
2. Address fertility preservation as early as possible, ideally before treatment starts and again with every change in therapy.
3. Document fertility preservation discussions in the medical record.
4. Refer patients who express an interest in fertility preservation to reproductive specialists.
5. Refer patients to psychosocial providers if they experience distress about potential infertility.
6. Encourage patients to participate in registries and clinical studies regarding fertility preservation when available.

Figure 1. Patient diagnosed with new malignancy, relapse or change in therapy

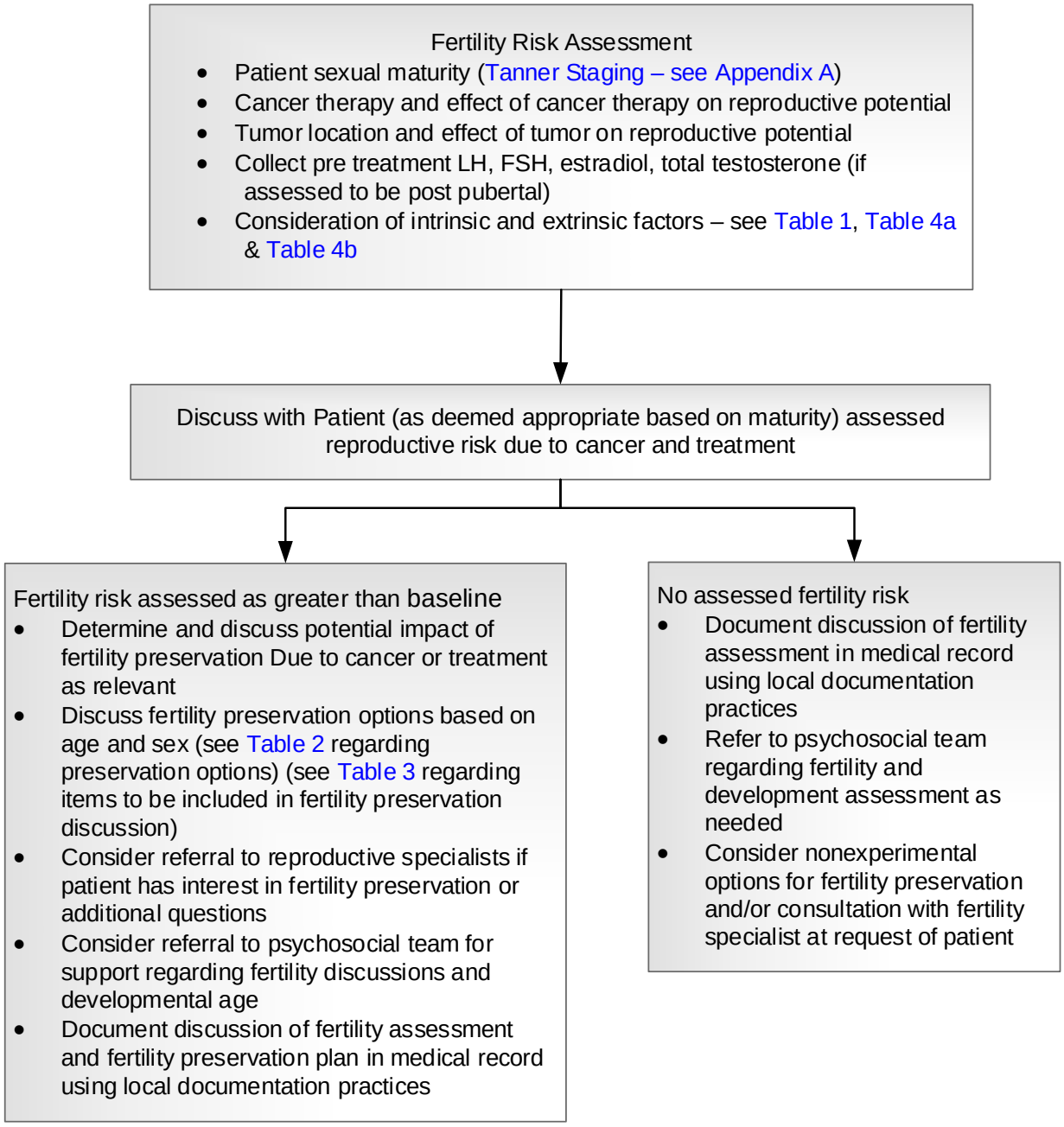

Table 1. Intrinsic and extrinsic factors for fertility preservation strategies in children and young adults[3,4,5]

Intrinsic factors	Extrinsic factors
• Health status of patient • Psychosocial factors • Consent/Assent (patient and/or parent) • Assessment of pubertal status • Assessment of ovarian reserve (female patients) • Tumor type, stage and location • Performance Status • Ability to undergo fertility sparing procedures	• Risk of predicted treatment (high, medium, low, or uncertain risk) • Time available for fertility preservation procedure (urgency to start cancer treatment) • Expertise and standard technical options available • Costs of procedures • Experimental Options available

Table 2. Fertility Preservation (FP) methods and additional options for parenthood[3,4,6]

	Standard Practice	Investigational Methods
Male	• Sperm Cryopreservation (self-stimulation or alternative collection methods) (see order set Male Fertility Preservation Pediatrics) • Gonadal Shielding (for RT) • Testicular Sperm Extraction (post treatment) Additional parenthood options: • Donor Sperm • Adoption	• Cryopreservation of testicular tissue
Female	• Oocyte or Embryo Cryopreservation • Ovarian Transposition (for RT) • Ovarian Shielding (for RT) • Fertility Sparing Procedures Additional parenthood options: • Donor oocyte • Donor embryos • Surrogacy • Adoption	• Cryopreservation of ovarian tissue • Ovarian Suppression (should not be relied on for fertility preservation in isolation)

Table 3. Discussion of Fertility Preservation (FP) options to include[7]:

1. Risk of cancer treatment on future fertility potential
2. Description of standard FP options available
3. Available experimental FP options
4. Risk of delaying cancer treatment or risk of treatment required for FP based on the cancer diagnosis.
5. Realistic likelihood of successful FP with available options
6. Risks of the FP procedure including estimated costs
7. The possible disposition of human reproductive materials[a]
8. Posthumous reproduction
9. Alternative options for parenthood.

[a] Assisted Human Reproduction Act http://laws-lois.justice.gc.ca/eng/acts/a-13.4/

Table 4a. Known risk of effects on male fertility based on cancer therapies[6,8]

Notes:
1. Prepubertal status does not protect from gonadal injury in males
2. Germ Cell function (spermatogenesis) is impaired at lower doses compared to Leydig cell (testosterone production) function

High Risk	Intermediate Risk	Lower Risk	Very Low/ No Risk	Unknown
• Alkylating agent +TBI • Alkylating agent +pelvic or testicular radiation • Total cyclophosphamide >7.5 g/m2 • procarbazine containing regimens (MOPP >3 cycles, BEACOPP >6 cycles) • Protocols with temozolomide or BCNU + cranial radiation • Testicular radiation (>2.5 Gy post pubertal, >6 Gy prepubertal) • TBI • Cranial Radiation >40 Gy	• Heavy metal containing regimens • Total cisplatin >400mg/m2 • Total carboplatin >2g/m2	• Multiagent protocols containing non alkylating agents (e.g. ABVD, CHOP, COP, multiagent regimens for leukemia) • Testicular Radiation (0.2-0.7 Gy) • Anthracycline +cytarabine regimen	• Multiagent therapy protocols using vincristine (leukemia/ lymphoma) • Radioactive iodine • Testicular radiation scatter (<0.2Gy)	• Monoclonal antibodies • Tyrosine kinase inhibitors

Alkylating Agents:
busulfan
carmustine (BCNU)
chlorambucil
cyclophosphamide
ifosphamide
lomustine (CCNU)
mechlorethamine
melphalan
procarbazine
thiotepa

Non-Classical Alkylators:
dacarbazine (DTIC)
temozolomide

Heavy Metals:
carboplatin
cisplatin

Table 4b. Known risk of effects on female fertility based on cancer therapies[6,8]

Note:

1. Doses that cause gonadal dysfunction show individual variation

High Risk	Intermediate Risk	Lower Risk	Very Low/ No Risk	Unknown
• Any alkylating agent + TBI • Any alkylating agent + Pelvic Radiation or lumbar sacral spine radiation (ovarian scatter) • Total cyclophosphamide >7.5 g/m2 • Regimens with procarbazine (>3 MOPP or >6 BEACOPP) • Regimens including temozolomide or BCNU + cranial radiation • Whole Abdomen or pelvis radiation (>6 Gy in adult women, >10 Gy in post pubertal girls, >15 Gy in post pubertal girls). • TBI • Cranial Radiation >40 Gy	• bevacizumab • Regimen including heavy metals • Partial abdominal/pelvic radiation (>10-15 Gy in prepubertal and >5-10 Gy in post pubertal)	• Regimens containing non alkylating agents or lower levels of alkylating agents (e.g. ABVD, CHOP, COP, multiagent therapies for leukemia • Anthracycline + cytarabine regimens	• Multiagent therapies using vincristine (leukemia/lymphoma) • Radioactive iodine • methotrexate • fluorouracil	• Monoclonal antibodies • Tyrosine kinase inhibitors • irinotecan • Taxanes • oxaliplatin

Alkylating Agents:
busulfan
carmustine (BCNU)
chlorambucil
cyclophosphamide
ifosphamide
lomustine (CCNU)
mechlorethamine
melphalan
procarbazine
thiotepa

Non-Classical Alkylators:
dacarbazine (DTIC)
temozolomide

Heavy Metals:
carboplatin
cisplatin

Name of Order Set: Male Fertility Preservation Pediatric Order Set

Order Set Restrictions: Male pediatric patients greater or equal to 12 years of age or Tanner Stage greater or equal to 3
Order Set Keywords: Sperm banking
Risk Assessment / Scoring Tools / Screening: Tanner Staging

Laboratory Investigations

Baseline Screening (optional)

- ☐ Follicle Stimulation Hormone (FSH)
- ☐ Luteinizing Hormone (LH)
- ☐ Total Testosterone (T)

Microbiology

- ☐ HBsAg
- ☐ Hepatitis C Antibody
- ☐ HIV Serology (Mixed Ag/Ab detection)- (HIV Antibody)
- ☐ HTLV I and II
- ☐ Syphilis Antibody Test (Syphilis EIA)

Referrals/ Consults

- ☐ Social Work Referral

No formal referral is required for sperm banking and patients may self-refer in Calgary. Referral is required in Edmonton. Semi-private appointments are available at clinics in Edmonton and Calgary.

- ☐ Clinical Communication: Arrange appointment for sperm banking as per patient/ family request
- ☐ MD Consult - Pediatric Psychology Consult
- ☐ MD Consult - Pediatric Urology Consult

Consider referral if patient or family wishes to discuss future options prior to sperm banking.

- ☐ MD Consult – Infertility Consult. Fax completed referral form to fertility clinic, indicating “Urgent New Cancer Diagnosis.”

Discharge

- ☐ Discharge Instructions. Patient to attend follow up appointment at sperm bank. Provide patient/family appointment time.

Alberta Health Services

Name of Order Set: Female Fertility Preservation Pediatric Order Set

Order Set Restrictions: Female pediatric patients greater or equal to 12 years of age or Tanner Stage greater or equal to 3
Order Set Keywords: Fertility preservation, female, egg, oocyte, embryo, ovary
Risk Assessment / Scoring Tools / Screening: Tanner Staging

Laboratory Investigations

Baseline Screening (optional)

- ☐ Day 3 Follicle-stimulating hormone (FSH)
- ☐ Day 3 Estradiol (E2)
- ☐ Day 3 Luteinizing hormone (LH)
- ☐ Anti-Mullerian hormone (AMH)

Microbiology

- ☐ HBsAg
- ☐ Hepatitis C Antibody
- ☐ HIV Serology (Mixed Ag/Ab detection)- (HIV Antibody)
- ☐ HTLV I and II Antibody
- ☐ Syphilis Antibody Test (Syphilis EIA)

Referrals/ Consults

- ☐ Social Work Referral
- ☐ MD Consult - Pediatric Psychology Consult
- ☐ MD Consult – Infertility Consult. Fax completed referral form to fertility clinic, indicating “Urgent New Cancer Diagnosis”.

Discharge

- ☐ Discharge Instructions. Patient to attend follow up appointment with fertility specialist. Provide patient/family appointment time.

Disposition Planning

Patient and Family education/discharge instructions

- MyHealth Alberta Fertility and Cancer Treatments
  - Video Fertility Options for Young Male Cancer Patients
  - Video Fertility Options for Young Female Cancer Patients

Analytics

1. Frequency fertility assessment risk is completed on pediatric patients with new malignancy, relapse or change in therapy.

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1. Marshall WA, Tanner JM. "Variations in pattern of pubertal changes in girls". Arch. Dis. Child. 1969; 44 (235): 291–303.
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8. Children's Oncology Group. (2013, October). Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer. Retrieved from http://www.survivorshipguidelines.org/.

Additional Reading and General References

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Appendix A - Tanner Staging

Table 5. Tanner Staging

Stage	Females		Males	
	Breasts	**Pubic hair**	**Genitalia**	**Pubic Hair**
1	Pre-adolescent; elevation of papilla only.	No pubic hair.	Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.	No pubic hair.
2	Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.	Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly along the labia.	The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin.	Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly at the base of the penis.
3	Further enlargement of breast and areola, with no separation of their contours.	Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.	Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.	Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.
4	Projection of areola and papilla to form a secondary mound above the level of the breast.	Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.	Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin.	Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.
5	Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.	Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs, but not up the linea alba or elsewhere above the base of the inverse triangle.	Genitalia adult in size and shape.	Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern. Spread to the medial surface of the thighs but not up the linea alba or elsewhere above the base of the inverse triangle.

Adapted from:

1. Marshall W, Tanner J. Variations in pattern of pubertal changes in girls. *Archives of Disease in Childhood*. 1969;44(235):291-303. doi:10.1136/adc.44.235.291.
2. Marshall W, Tanner J. Variations in the Pattern of Pubertal Changes in Boys. *Archives of Disease in Childhood*. 1970;45(239):13-23. doi:10.1136/adc.45.239.13.

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Name	Title	Zone
Knowledge Lead		
Tony Truong	Physician, Pediatric Oncology	Provincial
Sunil Desai	Physician, Pediatric Oncology	Provincial
Topic Lead		
Sarah McKillop	Physician, Pediatric Oncology	Edmonton
Working Group Members		
Kathleen Reynolds	Physician, Medical Lead, Long Term Survivor Clinic, Calgary	Calgary Zone
Shu Foong	Physician, Obstetrics & Gynecology	Calgary Zone
Peter Metcalfe	Physician, Pediatric Urology	Edmonton Zone
Clinical Support Services		
Frances Cusano	Pharmacy Information Management Governance Committee (PIM-GC) *on behalf of* Pharmacy Services	Provincial
James Wesenberg	*on behalf of* Laboratory Services - Provincial Networks	Provincial
Bernice Lau	*on behalf of* Diagnostic Imaging Services	Provincial
Carlota Basualdo-Hammond & Kim Brunet Wood	*on behalf of* Nutrition & Food Services	Provincial
Clinical Informatics Lead		
Sarah Searle & Sarah McNeill	Registered Nurse	Provincial

Additional Contributors

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For questions or feedback please contact ClinicalKnowledgeTopics@ahs.ca