Clinical Practice Subcommittee Concept Submission Cover Page

Pediatric and Adolescent Committee of the Oncofertility Consortium

Date: February 15, 2021

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Proposed title of study:

Current Practices in the use of Anti-Mullerian Hormone for Surveillance of Ovarian Function in Childhood Cancer Survivors

Please attach a document with the following information:

1. Title of project
2. Proposed author list/working group: please include disciplines and contact information (e-mail)
3. Background/rationale: Please include at least 2-3 paragraphs outlining the clinical problem you are trying to address and relevant information published on this subject. Please include references. This may be incorporated into your future introduction.
4. Specific aims/objectives: What question are you trying to answer? You must include at least one.
5. Analytic plan: Briefly describe how will you accomplish this? Please include what resources are needed, proposed location for any statistical analysis, etc.

    - Who are you studying? (provide clear and concise inclusion/exclusion criteria)
    - What information are you collecting? (outcomes, demographics, exploratory variables, etc.)
    - Consider what and how many tables/figures you may need to include. Attach shell tables to concept proposal.

6. Special considerations: (is there anything else we need to know to consider your concept?)

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Date initial submission received: 2/15/21
Date sent to PAC Leadership: 5/14/21
Final approval: Yes ◉ No ○
Final Decision Date: 8/24/21

Notes:

Attached draft of survey.

Title: Current Practices in the Use of Anti-Mullerian Hormone for Surveillance of Ovarian Function in Childhood Cancer Survivors

Committee: Clinical Practice

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Background:

Five-year survival rates for childhood cancers have increased to over 80%[1], resulting in an increasing population of adult survivors experiencing long-term effects from their cancer and its treatment. In females, these long-term sequelae include effects on the reproductive system and fertility. Compared to sibling controls, female survivors of childhood cancers in the Childhood Cancer Survivor Study (CCSS) had a decreased likelihood of pregnancy[2], and an increased risk of infertility compared to a sibling control group. This was associated with increasing doses of both radiation to the uterus, and alkylating agent chemotherapy.[3] These therapies are thought to deplete the primordial follicle pool, resulting in diminished ovarian reserve, and leading to increased risk of premature menopause (menopause prior to the age of 40). Childhood cancer survivors have commonly cited fertility and reproductive concerns as a

concern and an often unmet need in survivorship,[4,5] and want to know their fertility status after therapy.[6]

Previously, estimating reproductive potential relied on menstrual history, antral follicle count and measurement of estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH). However, alterations in these measurements were a late marker of reduced ovarian reserve[7] and once identified, left individuals with limited options for biologic children. An earlier, more direct measure of ovarian reserve was desired for use in female cancer survivors, to assist with appropriate counseling of patients about their reproductive future, and options available for fertility preservation or family building. Anti-Mullerian hormone (AMH) is a hormone that is produced by ovarian granulosa cells surrounding antral follicles[8] and has been shown to be a measure of ovarian reserve[9]. It has been shown to also be a measure of ovarian reserve in female childhood cancer survivors[10] and has been shown to be decreased among survivors receiving gonadotoxic therapies regardless of pubertal status[11].

While AMH screening can be used for assessing ovarian reserve in the female childhood cancer population, there are few to no guidelines regarding when to obtain AMH, and whether repeated screening is useful, and if so, at what interval. In fact, the International Guideline Harmonization Group (IGHG) does not recommend routing AMH screening in childhood cancer survivors because there is, to date, little evidence supporting routine AMH assessment for identifying premature ovarian insufficiency[12]. Understanding the risk factors for infertility, and the natural history of reproductive concerns is necessary for appropriate counseling of childhood cancer survivors, but also for decision making regarding fertility preservation or fertility treatments.

In this study, we plan a two-pronged approach. First, we plan to conduct a systematic review of the current evidence supporting AMH screening of female childhood cancer survivors, and second, to survey members of the of the Oncofertility Consortium, an international, interdisciplinary network of clinicians and researchers, to inquire about current practices of AMH screening in the female childhood cancer survivor population. The consortium is comprised of practitioners in multiple disciplines, including oncology, endocrinology, urology, obstetrics and gynecology, psychology and the basic sciences. The goal of this study will be to understand AMH surveillance practices across disciplines and identify gaps in the literature needing further study to allow for future data-driven recommendations.

Aims:

1. Examine the literature through a systematic review to elucidate current recommendations and existing evidence for timing and frequency of AMH screening in female pediatric cancer survivors.
2. Evaluate current practices of AMH screening in female pediatric cancer survivors among a multidisciplinary group of oncofertility practitioners who care for and order testing for evaluation of fertility in this population.

Methods:

To determine the landscape of the current literature for AMH surveillance in pediatric cancer survivors, we will undertake a systematic review, utilizing the library services at Anschutz Medical Campus of University of Colorado. We will use search terms including “anti-mullerian hormone”, “oncofertility”, “cancer”, “ovarian reserve”, and will utilize multiple databases, including Medline, Embase, and the Cochrane library. We will include original research articles from any year that have ≥20 female childhood cancer survivors in the study population. We plan to exclude studies that do not include pediatric oncology survivors (≤18 years of age) and that do not include raw AMH values. We will also exclude studies with a mixed pediatric/young adult population that do not have a majority of pediatric patients, or that do not separate the pediatric AMH data from the adult females.

The authors, as a panel of experts in the field of oncofertility, were involved in survey development. The survey addresses provider demographics and ordering habits for AMH and other measures of fertility/ovarian reserve in a female childhood cancer population and does not ask for any patient data. We plan for assessing face validity, content validity as well as pilot testing with experts in the field who are not a part of the Oncofertility Consortium, prior to sending out the survey. We will utilize REDCap for data collection from the web-based survey.

Descriptive statistics will be provided (tables and/or graphs) for each question in the survey. These statistics include but are not limited to, respondent distributions, proportion, and its confidence interval (CI) per question. Further one can analyze the association of respondent count with the responder characteristic using test/Fisher exact test if it will be needed. The proportion of respondents per question will be described in a frequency table. Further, one may evaluate differences in responses based on demographic categories using Fisher’s exact or test depending on the sample size.

The survey will not require a response to move forward to the next question to allow for increased participant response. As we will allow non-response to questions, we may experience missing data. And though we believe it will likely be missing at random, we will first check the percentage of missing in each question as well as the missingness pattern in the whole survey, if the percentage is high enough that it may cause some bias in the analysis, we’ll use multiple imputation (MI) approach for handling nonresponse in the sample survey

References

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Table 1: Participant Demographics

	N	%
Profession		
Physician		
Nurse (RN, BSN, MSN)		
Advanced Practice Provider (NP, PA)		
PhD/Researcher		
Other		
Primary Specialty		
Medical Oncology		
Pediatric Oncology		
AYA oncology		
REI		
Adult Endocrinology		
Pediatric Endocrinology		
OB/GYN		
Ped/Adolescent gynecology		
Psychology/behavioral health		
Pediatric surgery		
Urology		
Other		
Years in primary specialty practice		
≤5 years		
6-10 years		
11-15 years		
>15 years		
Are you part of your institution's oncofertility clinic/team?		
Yes		
No		
Unsure		
Are you part of your institution's survivorship clinic/team?		
Yes		
No		

Table 2: Institutional demographics

	N	%
Institution type		
Academic Hospital/university affiliated		
Private hospital/private practice		
Public hospital		
Freestanding children's hospital		
Other		
Dedicated oncofertility team		
Yes		
No		
Unsure		
Dedicated survivorship program		
Yes		
No		
Unsure		
When do majority of patients enter survivorship program at your institution?		
2 years after treatment		
5 years after treatment		
10 years after treatment		
Other		
Unsure		
No survivorship program		

Table 3: Use of AMH in female childhood cancer survivors by specialty

	Total		Oncology		Endocrinology		REI		OB/GYN		Other		p
	N	%	N	%	N	%	N	%	N	%	N	%	
Frequency of AMH levels in cancer survivors													
More frequently than every 12 mo													
Every 12 mo													
every 2 year													
Every 5 years													
Only recheck if initial AMH low													
Recheck until 2 or 3 values stable													
Once and if normal do not check again													
Individualize frequency by patient													
I do not routinely follow AMH													
How do you use AMH in your practice?													
As a measure of ovarian reserve													
Predict response to ovarian stimulation for oocyte harvest													
Support likelihood of developing POI (if DOR is present)													
Assess likelihood of current or future infertility													
Track ovarian reserve over time to identify declines and offer fertility preservation													
Assist with decision to refer to REI or fertility team													
I do not think that we should use AMH													
Other													

AMH Survey for Oncofertility Consortium Pediatric and Adolescent Committee

*must provide value

*Name: _____
*Institution: _____

***Are you a member of the Pediatric Initiative Group within the Oncofertility Consortium?**
- **a. Yes**
- **b. No**

***Do you provide clinical care to genetically female patients?**
- **a. Yes**
- **b. No**

PERSONAL DEMOGRAPHICS

1) *What is your job description/role?
   a) Physician
   b) Nurse (RN, BSN, MSN)
   c) Advanced Practice Provider (Nurse practitioner, physician assistant)
   d) PhD/Researcher
   e) Other _____

2) *What age group do you primarily care for?
   a) Mostly pediatric patients (under the age of 21 years)
   b) Mostly adolescent and young adult patients (12-29 years)
   c) Mostly adult patients (21 years and up)
   d) Approximately 50/50 split between pediatric and adult
   e) Other_____

3) *What is your primary specialty?
   a) Medical oncology
   b) Pediatric oncology
   c) Adolescent and Young Adult oncology
   d) Reproductive Endocrinology and Infertility (REI)
   e) Adult endocrinology
   f) Pediatric endocrinology
   g) General obstetrics/gynecology
   h) Pediatric/adolescent gynecology
   i) Psychology/behavioral health
   j) Pediatric surgery
   k) Urology
   l) Other _____

4) How many years have you practiced your primary specialty?
   a) ≤5 years
   b) 5-10 years
   c) 11-15 years
   d) >15 years

5) What role do you play in oncofertility? (choose all that apply)
   a) fertility preservation consults **pre**-treatment
   b) fertility preservation consults **post**-treatment
   c) fertility status assessment

d) provide assisted reproductive technology
e) perform surgeries for fertility preservation
f) survivor care provider
g) other
h) none

6) How many years have you worked in fertility preservation/fertility status assessment?
   a) ≤5 years
   b) 5-10 years
   c) 11-15 years
   d) >15 years

INSTITUTIONAL DEMOGRAPHICS

7) How would you describe your institution? (choose all that apply)
   a) Academic Hospital/University affiliated
   b) Private hospital/private practice
   c) Public hospital
   d) Freestanding children's hospital
   e) Other _____

8) Does your institution have a dedicated oncofertility clinic/team? If no, skip to question 10.
   a) Yes
   b) No
   c) Unsure

9) Are you a part of your institution's dedicated oncofertility clinic/team?
   a) Yes
   b) No
   c) Unsure

10) Does your institution have a dedicated survivorship program? If no, skip to question 13.
    a) Yes
    b) No
    c) Unsure
    d)

11) Are you a part of your institution's dedicated survivorship program?
    a) Yes
    b) No
    c) Unsure

12) When do the **majority** of patients at your institution enter into a survivorship program, on average?
    a) 2 years after treatment
    b) 5 years after treatment
    c) 10 years after treatment
    d) Other_____ years after treatment
    e) Unsure

SPECIFIC USE OF AMH

13) Have you ever ordered an AMH level for a childhood cancer patient/survivor at your institution? If no or unsure, skip to question 16
    a) Yes
    b) No

c) Unsure

14) If you routinely follow AMH levels in cancer survivors, how frequently do you typically obtain levels (Choose all that apply)?
   a) More frequently than every 12 months
   b) Every 12 months
   c) Every 2 years
   d) Every 5 years
   e) I only recheck AMH if the initial value was low
   f) I recheck AMH until 2 or 3 values are stable
   g) I do not routinely follow AMH levels
   h) Once, and if normal do not check again
   i) I individualize

15) How do you use AMH in your practice? (choose all that apply)
   a) As a measure of ovarian reserve
   b) Predict response to ovarian stimulation for oocyte harvest
   c) Support the likelihood of developing primary ovarian insufficiency (if diminished ovarian reserve is present)
   d) Assess the likelihood of current infertility
   e) Assess the likelihood of future infertility
   f) Track ovarian reserve over time to identify declines and offer fertility preservation
   g) Assist with decision to refer to reproductive endocrinology and infertility (REI) or fertility team
   h) I do not think that we should use AMH
   i) Other_____

16) In your opinion, what is the **best** use of AMH? (**rank top 3 choices, in order**)

	Choice 1	Choice 2	Choice 3
a) As a measure of diminished ovarian reserve			
b) As a measure of normal ovarian reserve			
c) Predict response to ovarian stimulation for oocyte harvest			
d) Predict likelihood of developing primary ovarian insufficiency (if DOR is present)			
e) Assess the likelihood of current infertility			
f) Predict the chances of future fertility			
g) Tract ovarian reserve over time to identity declines and offer fertility preservation			
h) Assist with decision to refer to REI or fertility team			
i) I do not think that we should use AMH			
j) Other_____			

17) **In an ideal world, when do you think** we should obtain AMH levels in female childhood cancer patients? (choose all that apply)
   a) At diagnosis
   b) During therapy
   c) Once off therapy
   d) At entry into survivorship if old/mature enough to be referred for post-treatment oocyte harvest
   e) At entry into survivorship regardless of ae/development
   f) During survivorship/long-term follow-up if oldmature enough for post-treatment oocyte harvest
   g) During survivorship/long-term follow-up regardless of age/development

h) No standard, check on case-by-case basis
i) Do not check AMH

18) **In an ideal world,** when is the earliest timepoint off-therapy that you will start checking AMH levels?
a) <6 months off therapy
b) 6-11 months off therapy
c) 12-23 months off therapy
d) 2 years off therapy
e) Entry into survivorship
f) During survivorship
g) At transition to adult care

19) If you are not obtaining AMH levels as often as you would ***in an ideal world***, why? (choose all that apply)
a) Availability of AMH testing
b) Cost/insurance coverage of AMH testing
c) Lack of time to counsel patients about AMH routinely
d) Patient distress over possible results
e) Lack of guidance over when to act on AMH results
f) I do not believe routine use of AMH testing is helpful
g) Other _____
h) N/A I do check as often as I would like

20) What are your perceived limitations of AMH? (choose all that apply)
a) Variability of results due to other factors (i.e. patient, reproductive or lifestyle factors)
b) Poor predictor of pregnancy
c) Insurance coverage/cost
d) Lack of standardization
e) Time delay in receipt of results
f) Other_____

21) In your opinion, do you think the benefits of AMH testing outweigh the limitations?
a) Yes
b) No
c) Unsure

GENERAL APPROACH TO TESTING OVARIAN RESERVE

Ovarian reserve testing refers to the assessment of the primordial follicle pool through laboratory and/or ultrasound measures with the goal of informing reproductive potential in pediatric, adolescent and young adult cancer survivors

22) **In your current practice, when do you** typically evaluate ovarian reserve in female childhood cancer patients? (choose all that apply)
a) At diagnosis
b) During therapy
c) Once off therapy
d) <6 months off therapy
e) At entry into survivorship if old/mature enough to be referred for post-treatment oocyte harvest
f) At entry into survivorship regardless of ae/development
g) During survivorship/long-term follow-up if oldmature enough for post-treatment oocyte harvest
h) During survivorship/long-term follow-up regardless of age/development
i) No standard, check on case-by-case basis

j) Do not check ovarian reserve

23) When is the earliest timepoint off-therapy that you will start checking ovarian reserve levels?
   a) <6 months off therapy
   b) 6-11 months off therapy
   c) 12-23 months off therapy
   d) 2 years off therapy
   e) Entry into survivorship
   f) During survivorship
   g) At transition to adult care

24) Which test(s) do you typically use in your practice to evaluate ovarian reserve in **pre-pubertal** patients? (Check all that apply)
   a) Anti-Mullerian hormone (AMH)
   b) Ultrasound/Antral follicle count
   c) Follicle stimulating hormone (FSH)
   d) Estradiol
   e) Luteinizing hormone (LH)
   f) Other
   g) None of the above

25) Which test do you think is **best** for evaluating ovarian reserve in **pre-pubertal** patients?
   a) AMH
   b) Ultrasound/Antral follicle count
   c) FSH
   d) Estradiol
   e) LH
   f) Other
   g) None of the above

26) Which test(s) do you typically use in your practice to evaluate ovarian reserve in **post-pubertal** patients? (Check all that apply)
   a) Anti-Mullerian hormone (AMH)
   b) Ultrasound/Antral follicle count
   c) Follicle stimulating hormone (FSH)
   d) Estradiol
   e) Luteinizing hormone (LH)
   f) Other
   g) None of the above

27) Which test do you think is **best** for evaluating ovarian reserve in **post-pubertal** patients?
   a) AMH
   b) Ultrasound/Antral follicle count
   c) FSH
   d) Estradiol
   e) LH
   f) Other
   g) None of the above

28) How do the following affect your **likelihood** of assessing ovarian reserve in childhood cancer **survivors**?

	Less likely to order	Does not affect my decision to order	More likely to order
Prepubertal at time of diagnosis			
Post-pubertal (onset of breast development) at the time of diagnosis			
Too young/immature to refer for post-treatment oocyte harvest at time of visit			
Old enough/mature enough to refer for post-treatment oocyte harvest at time of visit			
Patient/family request			
Patient expressed desire for biologic children			
Previously normal ovarian reserve markers			
Previously Low ovarian reserve markers			
Current regular menses			
Current irregular menses/amenorrhea			

29) How do the following factors affect your **likelihood** of completing an assessment of ovarian reserve in female cancer survivors who have been treated with the following modalities?

	Less likely to order	Does not affect my decision to order	More likely to order
History of total body irradiation			
History of bone marrow transplant			
Pelvic radiation at a **pre-**pubertal age < 15 gy			
Pelvic radiation at a **pre-**pubertal age > 15 gy			
Pelvic radiation at a **post-**pubertal age < 10 gy			
Pelvic radiation at a **post--**pubertal age > 10 gy			
CED exposure at a **pre-**pubertal age, CED < 8 g/m2			
CED exposure at a **pre-**pubertal age, CED 8-12 g/m2			
CED exposure at a **pre-**pubertal age, CED > 12 g/m2			
CED exposure at a **post-**pubertal age, CED < 4 g/m2			
CED exposure at a **post-**pubertal age, CED 4-8 g/m2			
CED exposure at a **post-**pubertal age, CED > 8 g/m2			
Heavy metal exposure			
Immunotherapy			

*CED = Cyclophosphamide equivalent dosing

30) In post-pubertal patients, do you typically time the labs you obtain to evaluate ovarian reserve for days 3-5 of the menstrual cycle?
    a) Yes
    b) No
    c) I don't know

31) **Before** obtaining measures of ovarian reserve, do you counsel patients that they may receive news about possible subfertility or infertility?
    a) Yes
    b) No
    c) I don't typically assess ovarian reserve

32) Any other comments or questions