Female Gonadal Toxicity Surveillance Harmonization: Formulation of Recommendations

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Guideline

KNOWLEDGE/EVIDENCE

- Patient Concerns
- Best research evidence
- Clinical Expertise

EBM

RECOMMENDATION
Guideline development process

Steps:

1. Determine concordances and discordances among existing guidelines
2. Formulate clinical questions based on discordant guideline areas for the identification of the evidence (PICO)
3. Identify all available evidence for the formulated clinical questions
4. Summarize the evidence in evidence tables and appraise the quality of the evidence
5. Formulate recommendations according to the evidence, clinical considerations, and patient values
Summarising evidence

1. **PICO questions**
2. **Performing PubMed Search**
3. **Screening abstracts (inclusion)**
4. **If ? Screen full tekst papers for inclusion**
5. **REFs guidelines/experts/reviews**
6. **Evidence table of each paper (member)**
7. **Included papers to members**
8. **Check evidence tables (chairs/WG leaders)**
9. **Conclusion tables**
For the Evidence & Recommendation
Key issues that need to be addressed

WHO?  Who needs surveillance?

WHEN?  At what age or time from exposure should surveillance be initiated and finished?

HOW OFTEN?  At what frequency should surveillance be performed?

HOW?  What surveillance modality should be used?

ACTIONS?  What should be done when abnormalities are identified?
Definitions used in Harmonization Process

• Childhood cancer survivors: individuals treated for cancer up to age 18 years
• Primary ovarian insufficiency (POI): A clinical situation developing in any adult female <40 years of age with:
  - Absence of menses for at least 4 months
  - Two serum FSH levels (obtained at least 1 month apart) in the menopausal range
• Delayed puberty: absence of initiation of puberty (Tanner 2 breast) in girls 13 years
• Failure to progress in pubertal stage for 12 months

Definitions used in Harmonization Process

- Ovarian radiation: radiation treatment fields involving the ovaries (lumbar, sacral, whole spine, flank/hemiabdomen extending below iliac crest, whole abdomen, inverted Y, pelvic, vaginal, bladder, iliac, TLI, TBI)
Definitions used in Harmonization Process

CRITERIA FOR FORMULATING OVERALL CONCLUSIONS

Level A: If a risk factor is significantly associated with the outcome in 95-100% of the papers: ‘There is evidence that…’

Level B: If a risk factor is significantly associated with the outcome in ≥50% of the studies reporting on this risk factor, and in the remaining papers this association is not significant: ‘Evidence suggest…’

Level C: If 1 study reported on a risk factor which is significantly associated with the outcome: ‘Some evidence suggest….’

Level C: If a risk factor is significantly associated with the outcome in < 50% of the studies, while the others are not significantly associated: ‘Some evidence suggest…’

Level C: If a risk factor is significantly associated with the outcome in a positive direction in > 50% of the studies, while the risk factor is negatively associated with the outcome in other studies: ‘Some evidence suggest…’
Melissa:
I know that "significantly positively" is awkward, but "significantly positive associated" if not grammatically correct. Should we change this to:
O "If a risk factor is significantly associated with the outcome in a positive direction in > 50% of the studies...."

W. van Dorp; 3. 1. 2014
Definitions used in Harmonization Process

CRITERIA FOR FORMULATING OVERALL CONCLUSIONS

Conflicting evidence: If a risk factor is significantly associated with the outcome in a positive direction in the same number of studies of the same quality as the risk factor is negatively associated with the outcome: ‘There is conflicting evidence...’

No evidence: If no studies reported on a risk factor: ‘No studies reported on...’

Expert opinion: Expert opinion or standards of care: ‘Experts in the field report...’
What factors contribute to risk?

Level A evidence:
• Alkylating agents and procarbazine (dose-related risk)
• Radiation involving ovaries (dose-related risk)

Level B evidence:
• Combination of alkylating agents and radiation involving ovaries
• Older age at diagnosis

No evidence:
• Cisplatin/carboplatin
• Antimetabolites (methotrexate, cytarabine, 6MP)

Level C evidence for the risk of hypogonadotrophic hypogonadism:
• Pituitary-Hypothalamic region radiation
Cumulative incidence of nonsurgical menopause in female childhood cancer survivors demonstrating increasing incidence of menopause with advancing age and relationship to gonadotoxic cancer therapy. Treatment with both alkylating agents and abdominal-pelvic radiation were associated with highest incidence. Note: Study cohort does not include females who developed ovarian failure within first 5 years.
The effective (red, upper) and mean (blue, lower) sterilizing dose of radiation are illustrated for a known age at treatment. With increasing radiation dose, the predicted age of premature ovarian failure falls considerably.

Wallace et al, IJROBP, 2005
## WG 1 Step 1: Concordances/ Discordances

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<th>COG DCOG UKCCLG SIGN</th>
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<tr>
<td><strong>At risk</strong></td>
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<td>Alkylating agents</td>
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<tr>
<td>Carboplatin, cisplatin</td>
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<td>Non-classical alkylators</td>
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<td>RT involving ovaries</td>
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<td>RT involving brain</td>
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<tr>
<td>Oophorectomy</td>
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<td><strong>High risk</strong></td>
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<td>Higher doses alkylating agents</td>
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<td>Combination alkylating agents</td>
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<td>Alkylating agents + RT ovaries/brain</td>
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<td>≥40 Gy RT involving brain</td>
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<td>Prepubertal: ≥10 Gy RT ovaries</td>
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<td>Pubertal: ≥5 Gy RT ovaries</td>
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<td>≥18 Gy RT involving brain: precocious puberty</td>
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<tr>
<td>Unilateral oophorectomy</td>
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<tr>
<td><strong>Highest risk</strong></td>
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<tr>
<td>MOPP &gt;3 cycles</td>
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<td>Busulfan &gt;600 mg/m²</td>
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<td>Cyclophosphamide &gt;7.5 g/m²</td>
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<td>Cyclophosphamide for HCT</td>
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<td>Alkylating agents + pelvic RT/TBI</td>
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<td>Prepubertal: ≥15 Gy RT ovaries</td>
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<td>Pubertal: ≥10 Gy RT ovaries</td>
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<tr>
<td>Unilateral oophorectomy + pelvic RT/alkylating agents/TBI</td>
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<td>Bilateral oophorectomy</td>
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Discordant
Survivors treated with gonadotoxic chemotherapy* and/or ovarian radiation* and their providers should be aware of the risk of primary ovarian insufficiency and its implications for future fertility.

*Gonadotoxic chemotherapy: alkylating agents, procarbazine.
*Ovarian radiation: radiation treatment fields involving the ovaries (lumbar, sacral, whole spine, flank/hemiabdomen extending below iliac crest, whole abdomen, inverted Y, pelvic, vaginal, bladder, iliac, TLI, TBI)
What surveillance modality should be done?

Monitoring of growth and pubertal development (height, weight, Tanner stage) is recommended for pre-pubertal females treated with gonadotoxic chemotherapy* and/or ovarian radiation*#.

Counseling regarding the risk of primary ovarian insufficiency and its implications for future fertility is recommended for post-pubertal females treated with gonadotoxic chemotherapy* and/or ovarian radiation*.

*Gonadotoxic chemotherapy: alkylating agents, procarbazine; Ovarian radiation: radiation treatment fields involving the ovaries (lumbar, sacral, whole spine, flank/hemiabdomen extending below iliac crest, whole abdomen, inverted Y, pelvic, vaginal, bladder, iliac, TLI, TBI).

# Expert opinion: at least annually, with increasing frequency as clinically indicated based on growth and pubertal progress.
What surveillance modality should be done?

Laboratory evaluation with FSH and estradiol is recommended for prepubertal females who fail to initiate or progress through puberty*.

Laboratory evaluation with FSH and estradiol is recommended for post-pubertal females who present with menstrual cycle dysfunction suggesting POI or who desire assessment about potential for future fertility. Hormone replacement therapy or contraceptive pill should be discontinued prior to laboratory evaluation when applicable.

*Expert opinion: at least for girls of 11 years of age and older.

# Expert opinion: This assessment should be performed after ending HRT or OCP use, preferably after 4 months without OCPs (based on: amenorrhea = no menstrual cycle for at least 4 months).
Laboratory evaluation with AMH *may be reasonable* for female survivors 25 years or older who present with menstrual cycle dysfunction suggesting POI or who desire assessment about potential for future fertility.

Amenorrhea: >4 months (Nelson, New Engl J of Medicine 2009)
Irregular cycles: <21 days and >35 days (Munster et al, Br J Obstet Gyn 1992)
What should be done when abnormalities are identified?

Referral to pediatric endocrinology/gynecology *is recommended* for prepubertal females who fail to initiate or progress through puberty*.

Referral to gynecology/endocrinology/reproductive endocrinology *is recommended* for post-pubertal females who present with menstrual cycle dysfunction suggesting POI.

*Expert opinion: at least for girls of 11 years of age and older.*
What should be done when abnormalities are identified?

Treatment with sex steroid replacement therapy (transdermal or oral estrogens plus progestin) is recommended in prepubertal and postpubertal females diagnosed with POI.
What should be done when potential for future fertility is questioned?

Referral to gynecology/endocrinology/reproductive endocrinology and laboratory evaluation is recommended for post-pubertal females treated with gonadotoxic chemotherapy* and ovarian radiation* without signs and symptoms of primary ovarian insufficiency who desire assessment about potential for future fertility.

*Gonadotoxic chemotherapy: alkylating agents, procarbazine; Ovarian radiation: radiation treatment fields involving the ovaries (lumbar, sacral, whole spine, flank/hemiabdomen extending below iliac crest, whole abdomen, inverted Y, pelvic, vaginal, bladder, iliac, TLI, TBI).