International Guideline Harmonization Group
for Late Effects of Childhood Cancer

IGHG Premature ovarian insufficiency surveillance recommendations 2016

General recommendation
Survivors treated with one or more potentially gonadotoxic treatments[†], and their providers, should be aware of the risk of premature ovarian insufficiency and its implications for future fertility (level A and level C evidence).
Who needs surveillance?
Counselling regarding the risk of premature ovarian insufficiency and its implications for future fertility *is recommended* for survivors treated with: • Alkylating agents in general (level A evidence) • Cyclophosphamide and procarbazine (level C evidence) • Radiotherapy potentially exposing the ovaries (level A evidence)
What surveillance modality should be used for pre- and peri-pubertal survivors?
Monitoring of growth (height) and pubertal development and progression (Tanner stage) *is recommended* for pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion and no literature search).[†‡] FSH and oestradiol *are recommended* for evaluation of premature ovarian insufficiency in pre-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] who fail to initiate or progress through puberty (expert opinion and no literature search).[¶#]
What surveillance modality should be used for post-pubertal survivors?
A detailed history and physical examination with specific attention for premature ovarian insufficiency symptoms, e.g. amenorrhoea and irregular cycles *is recommended* for post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries (expert opinion and no literature search).[†] FSH and oestradiol *are recommended* for evaluation of premature ovarian insufficiency in post-pubertal survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility. Hormone replacement therapy should be discontinued prior to laboratory evaluation when applicable (expert opinion and no studies).[#§]
AMH *is not recommended* as the *primary surveillance modality* for evaluation of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] who desire assessment about potential future fertility (expert opinion and no studies).
AMH *may be reasonable* in conjunction with FSH and oestradiol for identification of premature ovarian insufficiency in survivors treated with potentially gonadotoxic chemotherapy and/or radiotherapy potentially exposing the ovaries[†] aged ≥25 years who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency or who desire assessment about potential for future fertility (expert opinion and no studies).
When should pre- and peri-pubertal survivors be referred?
Referral to paediatric endocrinology or gynaecology *is recommended* for any survivor who has • No signs of puberty by 13 years of age; • Primary amenorrhoea by 16 years of age; • Failure of pubertal progression[‖] (expert opinion and no literature search).
When should post-pubertal survivors be referred?
Referral to gynaecology, reproductive medicine or endocrinology (according to local referral pathways) *is recommended* for post-pubertal survivors treated with potentially gonadotoxic chemotherapy

and/or radiotherapy potentially exposing the ovaries[†] who present with menstrual cycle dysfunction suggesting premature ovarian insufficiency (expert opinion and no literature search).
What should be done when abnormalities are identified in pre-, peri- and post-pubertal survivors?
Consideration of sex steroid replacement therapy *is recommended* for pre-, peri- and post-pubertal survivors diagnosed with premature ovarian insufficiency *by referral to gynaecology or endocrinology* (expert opinion and no literature search).
What should be done when potential for future fertility is questioned?
Referral to gynaecology, reproductive medicine or endocrinology (according to local referral pathways) *is recommended* for post-pubertal females treated with potentially gonadotoxic chemotherapy and/or ovarian irradiation[†] without signs and symptoms of premature ovarian insufficiency who desire assessment about potential for future fertility (expert opinion and no literature search).

Definition POI: a clinical condition developing in any adult female before 40 years of age, characterized by: (1) absence of menses for at least 4 months, and (2) two elevated serum follicle-stimulating hormone (FSH) levels in the menopausal range (based on the maximum threshold of the laboratory assay used)

* Green, class I = strong recommendations to do; orange, class IIb = weak recommendation to do; red, class III = recommendation not to do.
[†] Treatments with evidence for causing premature ovarian insufficiency include alkylating agents in general (level A evidence), cyclophosphamide, procarbazine (level C evidence), and radiotherapy potentially exposing the ovaries (level A evidence)
[‡] At least annually, with increasing frequency as clinically indicated based on growth and pubertal progression.
[¶] At least for girls of 11 years of age and older, and for girls with primary amenorrhoea (age 16).
[#] If amenorrhoea, measure FSH and oestradiol randomly; if oligomenorrhoea, measure during early follicular phase (day 2-5).
[§] This assessment should be performed after ending oral contraceptive pill/sex steroid replacement therapy use, ideally after two months without oral contraceptive pills.
[‖] The absence of initiation of puberty (Tanner stage 2 breast development) in girls 13 years or older or failure to progress in pubertal stage for ≥12 months.

Publication

van Dorp W, Mulder RL, Kremer LC, Hudson MM, van den Heuvel-Eibrink MM, van den Berg MH, Levine JM, van Dulmen-den Broeder E, di Iorgi N, Albanese A, Armenian SH, Bhatia S, Constine LS, Corrias A, Deans R, Dirksen U, Gracia CR, Hjorth L, Kroon L, Lambalk CB, Landier W, Levitt G, Leiper A, Meacham L, Mussa A, Neggers SJ, Oeffinger KC, Revelli A, van Santen HM, Skinner R, Toogood A, Wallace WH, Haupt R. 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. Journal of Clinical Oncology 2016;34:3440-3450.