Innersense
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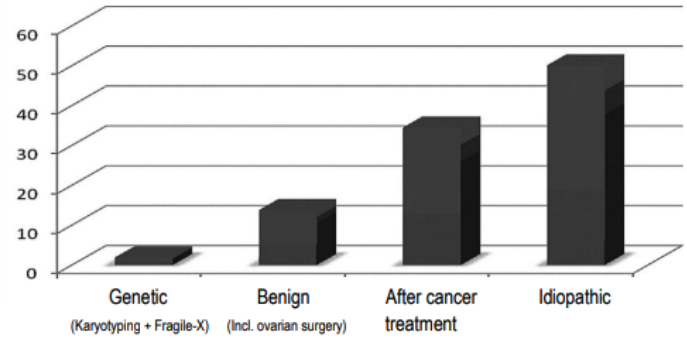
SRL Global Knowledge Forum
Expanding Horizons

Premature Ovarian Insufficiency in Cancer Survivors

Premature ovarian insufficiency (POI) also known as premature ovarian failure or hypergonadotropic ovarian failure or menopausa precoce is defined as an ovarian defect, characterized by an absent menarche (primary amenorrhea) or premature loss of ovarian follicles before 40 years of age (secondary amenorrhea). Characteristic features include amenorrhoea (cessation of ovulation) for 4 months or more, hypoestrogenism (estradiol levels <50 pg/ml) and high serum gonadotropin levels, especially two serum follicle-stimulating hormone (FSH) levels (>4 weeks apart) in menopausal range (>40 IU/l).

Approximately one in 50 women have a diagnosis of cancer below 40 years of age and modern cancer therapies have led to increasing survival for young women with cancer. The 5-year survival rate for childhood, adolescent, and young adult cancer currently exceeds 80%. However of current concern is the increasing incidence of spontaneous-onset POI in childhood cancer survivors (CCS). The surging success rates of cancer treatments such as chemotherapy, radiation therapy and surgery can lead to detrimental impact on woman's fertility resulting in a rising prevalence of iatrogenic POI.



Aetiology of POI cases managed at the West London Menopause and PMS Centre, London, UK (Maclaran and Panay, 2011)

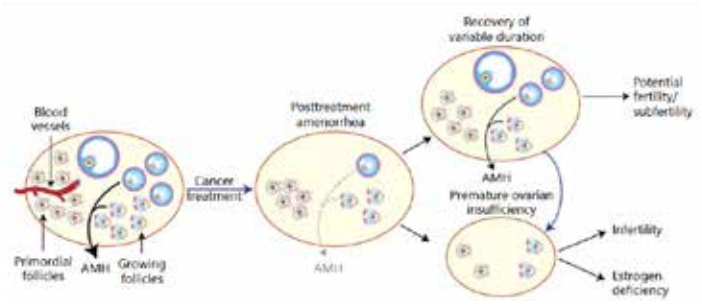
The risk of developing POI after radiotherapy is dependent on the radiation therapy field (abdominal pelvic, total body irradiation) and on dose and age. Oocyte is highly radiosensitive and responds to even 2 Gray dose of radiotherapy.

Chemotherapuetic agents and class known to cause gonadotoxicity and premature ovarian insufficiency risk[7]	Radiation dose and age at exposure as determinants of permanent ovarian damage and premature ovarian insufficiency risk[8,9]
Alkylating agent	20.3 Gy at birth
Nitrogen mustard	18.4 Gy at age 10 years
Chlorambucil	16.5 Gy at age 20 years
Cyclophosphamide	14.3 Gy at age 30 years
Busulfan	6.0 Gy at age 40 or more years
Melphalan	
Dacarbazine	
Anthracycline	
Doxorubicin	
Substituted hydrazine	
Procarbazine	

Chemotherapy & radiation exposure and risk for POI

Incidence of POI in CCS

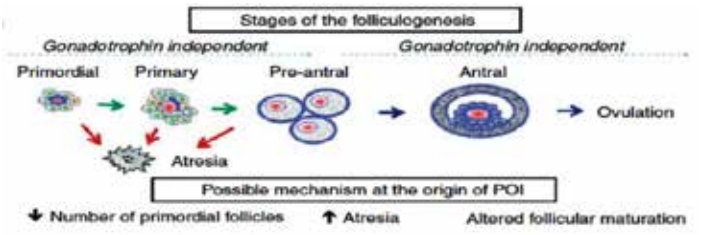
Overall, CCS have an estimated nonsurgical cumulative risk to develop POI by age 40 of approximately 8%. Radiotherapy to the abdomen, pelvis or spine can affect ovarian function even in low doses. Many chemotherapy regimens are also toxic to ovarian follicles, particularly the alkylating agents. Combination therapy (chemo and radio therapy) and a diagnosis of Hodgkin's lymphoma are associated with the highest risk of ovarian insufficiency. Gynaecological cancers (most commonly cervical and ovarian) requiring surgical treatment account for approximately 25% of iatrogenic cases of POI.



Effects of gonadotoxic treatment on the ovary (some patients show recovery allowing fertility, although their reproductive lifespan may be shortened)

Pathogenesis

The exact mechanism for development of POI in CCS is not known. Chemotherapy affect granulosa cell functions and oocytes inducing apoptosis of mature ovarian follicles, and histological studies have shown fibrosis, vascular damage, and reduced follicle numbers. Furthermore, accelerated follicular atresia can be because of changed apoptosis rate, defective follicle maturation blocking and abnormalities in primordial follicle activation ultimately causing ovarian insufficiency.



Mechanism of Origin of POI

Diagnosis of POI in CCS

Screening for POI in at risk survivors of cancer has been recommended by the International Guideline Harmonization Group (IGHG). Clinical assessment for POI in pre- and peripubertal survivors should be carried out by measuring height and calculating height velocity in conjunction with clinical examination of pubertal stage. As a rise in the concentration of serum FSH is a quite specific and sensitive tool to diagnose POI, determination of FSH level is the recommended screening tool in girls at risk for POI age 12 or up. For fertility counselling, determination of serum anti-Mullerian hormone (AMH) levels and antral follicle count have been proposed.

AMH, produced by secondary, preantral and early antral follicles, is considered the best currently available biomarker of the ovarian reserve, although it only reflects this indirectly. That AMH is readily detectable in prepubertal girls makes it a potential useful marker. The most established clinical use of AMH is prediction of ovarian response to ovarian stimulation in assisted reproductive technology, predicting oocyte quantity.

Effects of Chemotherapy, Radiotherapy and Surgery on Ovarian Function and AMH

A decrease in ovarian reserve with a fall in AMH can occur after treatments including chemotherapy, radiotherapy and ovarian surgery. In some women, depending on age, preexisting ovarian reserve/AMH and treatment administered, POI may result with undetectable AMH after treatment and without recovery.

The potential use of AMH to detect a detrimental effect of chemotherapy on ovarian function is well established in CCS. By the end of six cycles of chemotherapy treatment for breast cancer, AMH is almost undetectable in most women. Pretreatment AMH predicts post-treatment recovery of ovarian function and AMH levels, which in turn indicate remaining ovarian lifespan.

CCS who received radiotherapy to the abdomen, pelvis, sacrum and total body have lower AMH than survivors with irradiation to other parts of the body. Women treated with TBI for stem cell transplant all developed POI with undetectable AMH. Also, there is reduction in the ovarian reserve after ovarian cystectomy as evidenced by a fall in AMH.

In all female cancer survivors with elevated FSH levels, although the likelihood of previous treatment being the causative factor is high, the broader differential diagnosis of gonadal insufficiency should be considered, such as X-linked genetic defects, Turner syndrome or auto-immune ovarian failure. For this reason, physical and laboratory examination should at least include evaluation of Turner stigmata such as short stature, webbed neck, low set ears, cardiac abnormalities and a peripheral blood karyotype. It must be realized however, that in girls following allogeneic stem cell transplantation, the karyotype may have changed after undergoing the transplantation. In this case, the original karyotype should be requested at the oncology department.

Test of General Health

Given the well-characterized cardiometabolic and bone impact of POI, optimal management of this condition should involve a baseline assessment of insulin resistance (e.g. HbA1c, a lipid profile, and a dual-energy X-ray absorptiometry [DXA] scan). The importance of these tests and the frequency with which they are repeated in each individual will depend on risk factors, premorbid personal and family history.

Laboratory tests	Rationale
Human Chorionic gonadotropins	Exclude pregnancy
Follicle-stimulating hormone Estradiol	Assess hypothalamic-pituitary-ovarian axis
Anti-mullerian hormone	Assess ovarian reserve
Karyotype, fragile X mental retardation 1 (FMR1) premutation	Evaluate for genetic etiology
Thyroid-stimulating hormone Thyroid peroxidase antibody 21-hydroxylase antibody	Evaluate for thyroid function Quantify risk for thyroid and adrenal dysfunction
Radiologic tests	**Rationale**
Transvaginal ultrasound	Evaluate antral follicle count to assess ovarian reserve
Dual-energy x-ray absorptiometry scan	Assess bone density

Diagnostic consideration in evaluation of POI

Conclusion

It is of great importance that clinicians involved in childhood cancer follow-up clinics are aware of the risk factors for hypogonadism, so that patients and parents are adequately counselled and survivors of pubertal age are appropriately assessed. This will avoid delay in sex steroid replacement therapy and may subsequently prevent growth failure or psychological distress in teenagers.

Fertility preservation should be offered to those women who are at risk of irreversible ovarian damage with no recovery of AMH before they undergo gonadotoxic treatment such as TBI and high-risk chemotherapy.

References

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2. van Santen H.M. Horm Res Paediatr 2019; 91:93-103
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4. Curr Opin Endocrinol Diabetes Obes. 2018 Dec; 25(6): 391–398
5. QHY Wong. Kumar N. Women Health Open J 2017; 3(2): 45-58
6. ESHRE 2016. Information for women with iatrogenic POI
7. ESHRE 2015. Management of women with premature ovarian insufficiency
8. Torrealday S. F1000Research 2017; 6(F1000 Faculty Rev):2069

Tests Offered at SRL

Test	Method	Test Code
AMH (Anti-Müllerian Hormone)/ Müllerian Inhibiting Substance (MIS)	CLIA	1705R
Fertility Panel, Female, Endocrine (TSH3G UL, Prolactin, Progesterone, Estradiol, LH, FSH)	ECLIA	1578
Menopausal Diagnostic Panel (FSH, TSH, FT4, ESTRADIOL)	Chemiluminescence	1006
Menuposal Monitoring Panel (Estradiol, FSH, Lipid Profile, Calcium, Phosphorus)	Spectophotometry/ Chemiluiminecence	1008
Menopause Plus Profile (Estradiol, Estrone, Estriol, Progesterone, & Testosterone)	LIA, EIA	7002
Vital Care Menopause (FSH, TSH, fT4, Estradiol, Calcium, Phosphorus, 25-OH Vitamin D)	Biochemistry	CMP94

Contact the nearest SRL laboratory for details on related diagnostic tests and panels.