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Risks of Early Menopause – Cancer Patients

Alessandra Graziottin, MD
Director, Center of Gynaecology and Medical Sexology
H. San Raffaele Resnati, Milano, Italy
Consultant Professor, University of Florence, Italy
www.alessandragraziottin.it

Background

Women are never too young to get menopausal. By definition, **Premature Menopause (PM)** is defined as menopause at or before the age of 40. It can be **spontaneous**, and is defined as “Premature Ovarian Failure” (POF), or **iatrogenic**, after bilateral ovariectomy, chemotherapy or radiotherapy, either pelvic or total body irradiation. **Early Menopause (EM)**, encompasses the age range between 41 and 45. In the clinical conversation, “early” may encompass any menopause that appears before the age of 45.

Spontaneous PM may affect 1% and Iatrogenic PM may affect 3,4-4,5% of women before their 40s; with the latter figure currently raising thanks to the improvement in cancer treatment outcomes in young women. 11-15% of women are affected by spontaneous EM while another 12-18% of EM are iatrogenic. Early menopause is therefore a significant clinical issue, impacting women's life, health and relationships.

Objectives

To analyze risks factors for EM and key consequences on health, to empower physicians in the early diagnose and treatment of the many issues involved by EM, with special focus on cancer patients.

Method

Literature review plus Author's clinical observations.

Results

Risk factors for **Premature Ovarian Failure (POF)** are:

- **“idiopathic”**, when no cause is currently diagnosed;
- **genetic**, including Turner's syndrome, fragile X syndrome; mosaicism; deletion/inversion; galactosaemia; BRCA1 mutation;
- **autoimmune**: lupus erythematosus; rheumatoid arthritis. However every autoimmune disease, including the common autoimmune thyroiditis, should raise the issue of an impending autoimmune POF.

POF may as well be **associated with chronic diseases** such as chronic renal insufficiency and primary biliary cirrhosis.

Among **the iatrogenic PM and EM and for benign conditions** the clinician should consider endometriosis (specially after monolateral ovariectomy which immediately halves the ovarian reserve and/or when removal of bilateral cysts leaves minimal residual ovarian tissue), ovariectomy for bilateral dysgerminoma, or associated to hysterectomy.

PM and EM are as well **iatrogenic in women at risk of ovarian cancer**, in BRCA1 and/or BRCA2 carriers, and **in established malignant conditions** when bilateral oophorectomy, chemotherapy, pelvic radiotherapy, total body irradiation are required.

Factors modulating the impact of EM on health and psychosexual well being include:

age at EM and impact of the early loss of ovarian hormones, unless appropriate and timely HT is started, when oncologically appropriate if EM is secondary to cancer treatment;
impact of etiological heterogeneity of EM and associated co-morbidities on both general and sexual health;
the woman's current health status;

- psychosexual vulnerability to EM and associated infertility in POF and/or survivors of childhood, adolescent, adult (premenopausal) cancers;
- impact of EM on women's sexual identity, strongest in survivors of breast or gynaecologic cancers;

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- severity of the biological impairment of sexual function, in comorbidity with iatrogenic factors, with a specific impairing role of loss of ovarian testosterone after surgical menopause, and, to a variable extent, after chemotherapy and pelvic radiotherapy that may irreversibly damage the ovarian Leydig cells;
- sexual relationships issues and partner related factors.

Fertility issues are prominent in childless women, with a specific concern in preserving their ovarian fertility before initiating cancer treatment. Women at higher risk of negative general health and sexual outcome after Early Menopause are younger, single or in conflicting relationships, childless, with lower education and socioeconomic status.

Hormone therapy (HT) is indicated, when oncologically appropriate, but long-term safety data are lacking. The higher risk of second independent cancers – for genetic reasons and for the consequences of chemo and radiotherapy – should be discussed before starting HT. Androgen therapy, in estrogen depleted women, significantly improves all domain of sexual function after surgical menopause, with a specific antiaging effect on the brain. Further research is needed on fertility protection, quality of aging and sexuality, safety of long-term HT, and type of medical and psychosexual intervention to improve health and sexual outcome after Early Menopause.

Conclusion

EM is a significant issue that requires **a timely attention to risk factors, to early diagnosis and treatment** to minimize its complex impact on women's health and lives: a more complex task in cancer patients.