

# Premature Menopause – the challenge of accelerated sexual aging

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## Abstract

### Objectives

To analyze the impact of Premature Menopause (PM) (defined as menopause, spontaneous or iatrogenic, at or before the age of 40) on women's sexual aging, with special attention to sexual identity, function and relationship.

### Method

Literature review plus clinical observations

### Results

PM may be spontaneous or iatrogenic, following bilateral ovariectomy, chemotherapy or radiotherapy, either pelvic or total body irradiation. Factors modulating the impact of PM on health and psychosexual well being include: age at PM; impact of etiological heterogeneity of PM and associated co-morbidities on both general and sexual health; the woman's current health status; psychosexual vulnerability to PM and associated infertility in survivors of childhood and adolescent cancers; impact of PM on women's sexual identity which is

strongest in survivors of breast or gynaecologic cancers; severity of the biological impairment of sexual function, together with iatrogenic factors, specifically the role of loss of ovarian testosterone after surgical menopause; sexual relationships issues and partner related factors. Fertility issues are prominent in childless women. Women at higher risk of negative general health and sexual outcome after Premature Menopause are younger, single or in conflicting relationships, childless, with lower education and socioeconomic status.

Hormone therapy (HT) is indicated but long-term safety data is lacking. Androgen therapy, in estrogen depleted women, significantly improves all domains of sexual function after surgical menopause. 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 Premature Menopause.

**Key words:** *aging; androgens; hormone therapy; infertility; premature menopause; sexual dysfunction; cancer survivors*

## Introduction

The prolonged survival of children, adolescents and young women successfully treated for cancer increases the number of women facing Premature Menopause (PM)<sup>[1-3]</sup>. The complexity of their clinical picture, their increased vulnerability to accelerated aging due to the combined effect of PM and side effects of chemo and/or radiotherapy, and their expectations for a better quality of life (QoL), both general and sexual, challenges the physician's ability to tailor the appropriate medical and psychosexual treatment<sup>[4,5]</sup>.

By definition, PM refers to menopause occurring at or before the age of 40. It may be spontaneous and is then referred to as "premature ovarian failure" (POF)<sup>[6-8]</sup>. PM may be iatrogenic, i.e. secondary to surgical removal of both ovaries (bilateral oophorectomy), or to the irreversible ovarian damage caused by chemotherapy or radiotherapy, either pelvic or total body irradiation<sup>[1-8]</sup>. The POF acronym currently encompasses all modalities of ovarian exhaustion when the ovaries remain in situ.

Surgical menopause suddenly deprives the woman of total ovarian hormone production. POF, either spontaneous or iatrogenic, has a gradual, insidious evolution over two or more years. Occasional ovulation is possible for 2-3 years after POF diagnosis, i.e. FSH elevation above 40 IU/L in two consecutive samples at a one month interval<sup>[7]</sup>.

Given the trophic role of sexual hormones on body tissues, PM is associated with an increased risk of

accelerated aging – the younger the woman the higher the risk – unless appropriate Hormonal Treatment (HT), when feasible, is initiated and adequately maintained at appropriate doses<sup>[4,5,9]</sup>. Morbidity and mortality from cardiovascular disease, stroke, accelerated brain aging and osteoporosis present a greater risk in PM women compared to controls. In particular, the recent research of Rocca et al on the effect of uni- or bilateral oophorectomy indicates an OR of 1.46 of accelerated aging in women who underwent this surgery whilst still fertile. The younger the woman, the more vulnerable the brain to cognitive impairment and dementia<sup>[9]</sup>.

Sexual dysfunction is reported with higher frequency and with more significant personal distress after surgical menopause<sup>[10]</sup>. Overall sense of well-being and achievement of life's goals; specifically having a partner, getting married, having a satisfying sexual life and having children; may be variably affected<sup>[4,5,11]</sup>. Fertility is a major issue in childless women facing PM<sup>[1-3]</sup>.

The presentation will focus on main characteristics of PM and its impact on accelerated aging, both general and sexual, with a specific focus on sexual identity, sexual function, and sexual relationships<sup>[1-15]</sup>.

## Prevalence of PM and associated FSD

Spontaneous POF affects on average 1% of women under 40 years of age<sup>[7,9]</sup>. Ethnicity is a contributor. The highest figure of POF is reported among African

American and Hispanic (both 1,4%); the lowest in Japanese (0,1%)<sup>[16]</sup>. Iatrogenic menopause, secondary to benign and malignant conditions, affects 3.4-4.5% of women under 40<sup>[1-5,17]</sup>

Systematic studies on prevalence of Female Sexual Disorders (FSD) in women affected by PM are limited. The prevalence of low desire for younger surgically menopausal women is significantly higher (32%) than that found for premenopausal women of the same age (19%). The probability of Hypo-active Sexual Desire Disorder (HSDD) increases with age, while the distress associated with the loss of desire is inversely correlated with age<sup>[18]</sup>.

### Etiology and diagnosis and impact of PM

The hallmark of the etiology of PM is its heterogeneity. It can be genetic, auto-immune, associated with chronic diseases, or iatrogenic in the context of benign or malignant disease<sup>[1-9]</sup> [Tab 1]. The impact of PM on health and sexuality varies accordingly. It may be limited in women affected by POF who have a family and are on optimal HT. It may be dramatic when the consequences of PM are superimposed on a serious medical condition such as breast cancer where HT is currently contra-indicated, and/or in a childless younger woman or couple<sup>[5,19,20]</sup>. Multiple pathologies (and their associated treatments) further increase the risk of accelerated aging as exemplified when PM is associated with cancer or autoimmune diseases.

Impending PM is hypothesised when menopausal symptoms appear in women younger than 40 yrs of age, leading to POF. Predictors of PM include both poor response to ovarian stimulation and raised basal FSH. Definite diagnosis is based on FSH levels above 40 IU/L in two consecutive samples at one month intervals<sup>[7,9]</sup>. Ecography may show small ovaries for age, with no or a few residual oocytes. PM is implicit when bilateral oophorectomy is performed in women younger than 40 yrs of age.

### Factors Modulating Aging and Sexual Issues after PM

The etiology of PM is the single most powerful biological factor affecting quality of aging and psychosexual outcome. Age at PM is critical. The earlier the PM, the more complex the impact on general health and sexuality<sup>[4,5]</sup>.

Sexual identity is more affected when PM disrupts the process of psychosexual maturity such as after peripubertal spontaneous POF, or after iatrogenic POF secondary to childhood or adolescent cancers<sup>[4,5]</sup>. Stage in life cycle may contribute to FSD, fertility being a major issue in childless women and couples<sup>[1-3,5,11]</sup>.

Body image concerns, skin changes, changes in body shape and tendency to weight gain and central adiposity may impair the sense of personal attractiveness, contributing to loss of self-confidence and self-esteem, and a general sense of "feeling and looking older"<sup>[4,5,19-21]</sup>. The risk of dysmetabolic diseases, particularly diabetes, is greater in overweight PM women. Corticosteroids, when needed to treat the leading auto-immune pathol-

ogy, such as Lupus Erythematosus Systemicus (LES) or Rheumatoid Arthritis (RA), further increase this risk. Body image issues may become prominent in women who underwent breast or gynaecologic oncological surgery and associated treatments causing PM<sup>[5,19-21]</sup>.

The woman's overall health, ability to cope and quality of sexuality before PM may all affect the sexual outcome after PM. Women at higher risk of negative sexual outcome after Premature Menopause are younger, single or in conflicting relationships, childless, with lower education and socio-economic status<sup>[5,19-22]</sup>.

The partner's reaction to the associated infertility and the quality of the relationship before and after PM further modulate the individual's and the couple's ability to cope. Contextual factors – both in the relationship and socio-cultural such as ethnicity – contribute further<sup>[11]</sup>.

### Pathophysiology of Sexual Dysfunction after PM

Estrogens and androgens modulate the neurobiology of brain aging. There is increasing evidence for their trophic role in neuronal membrane repair, in promoting neuronal sprouting and interneuronal connectivity, and on neurotransmitter levels. They also modulate sexual desire and mental arousal, and the neurovascular cascade of events leading to genital arousal, lubrication and orgasm. Estrogens are modulators of sexual response, and "permitting" factors for the Vasoactive Intestinal Polypeptide (VIP), which "translates" desire and central arousal into vaginal congestion and lubrication.

Testosterone has an initiating role on desire and central arousal, acting on the dopaminergic appetitive-seeking pathway, and is a modulator of the peripheral response, acting as a "permitting" factor for Nitric Oxide (NO), the main mediator of clitoral and cavernosal body congestion.<sup>[4,5,23]</sup>

The loss of estrogens and androgens contributes to impaired brain aging, as exemplified by increased and anticipated neurovegetative, affective and cognitive disorders in PM women. It reduces sexual desire, central and peripheral arousal, and with vaginal dryness, causes or exacerbates orgasmic difficulties and dyspareunia. This results in loss of self-confidence and self-esteem and increases anxiety. Sexual hormone loss may also contribute to the neurobiological etiology of depressed mood that is so often a comorbid factor with acquired



**Table 1. Etiology of Premature Menopause**

- Premature Ovarian Failure (POF)
  - idiopathic
  - genetic: Turner's syndrome  
fragile X syndrome  
mosaicism  
deletion/inversion  
galactosaemia  
BRCA1 mutation
  - auto-immune:
    - lupus erythematosus
    - rheumatoid arthritis
  - associated with chronic disease:
    - chronic renal insufficiency
    - primary biliary cirrhosis
- Iatrogenic for benign conditions:
  - endometriosis
  - bilateral dysgerminoma
  - ovariectomy concomitant to hysterectomy
- Iatrogenic in women at risk of ovarian cancer:
  - BRCA1 and/or BRCA2 carrier
- Iatrogenic for established malignant conditions:
  - bilateral oophorectomy
  - chemotherapy
  - pelvic radiotherapy
  - total body irradiation

*Modified from Graziottin & Basson, 2004<sup>[5]</sup>*

loss of desire, and may potentiate the depressive state that is often the consequence of PM<sup>[24]</sup>.

Comorbidity of FSD is frequent. The issue of FSD cannot be separated from the impact on sexuality of concomitant medical comorbidities associated with or consequent to different etiologies of PM.<sup>[5]</sup>

### Diagnosis of FSD after PM

FSD may antecede PM, be concomitant with PM, and/or specifically caused and/or maintained by PM. Diagnosis should take into account the multifactorial etiology of FSD (with special attention to biological and psychosexual predisposing, precipitating and maintaining factors) as well as whether the disorder is generalised or situational, lifelong or acquired and also the level of distress it causes.

In stable relationships, counselling of both partners plays a crucial part of diagnosis and management. Accurate physical examination is mandatory given the importance of the biological disruption associated with PM, with focus on degree of atrophy of external genitalia and vagina, vaginal pH, pelvic floor tonicity and a "pain map" if there is dyspareunia<sup>[5,25]</sup>. A poor quality of genital sexual feed-back is usually an under evaluated contributor of loss of sexual desire in young PM women.

Laboratory investigations may include a plasma hormone sample, when POF diagnosis has not yet been established, and vaginal pH. Specific investigations should be considered according to the clinical history and etiology of PM.

### Treatment of PM and associated fertility issues

Tailored HT is the treatment of choice in POF (when non contra-indicated such as in survivors of breast cancer or genital adenocarcinoma, or after thromboembolic disease, acute hepatitis etc). Systemic estrogen treatment (ET) is the treatment of choice in women who have undergone hysterectomy as well as oophorectomy. Topical vaginal ET may address vaginal atrophy and bladder symptoms when systemic ET is not suitable or desired.

Recommendations from the European Menopause

and Andropause Society (EMAS)<sup>[26]</sup> and the International Menopause Society (IMS)<sup>[27]</sup> include PM being treated with HT, up until the age of natural menopause (51 years of age), unless a specific contra-indication is diagnosed.

Prevention of infertility in women facing impending POF is critical in childless women. Three lines of research are currently raising new hopes in the pursuit of fertility protection in young women. Cryopreservation: a) of oocytes is an option in women with impending POF; b) of embryos is feasible, but requires a cycle of in vitro fertilisation (IVF)- time before cancer treatment may be a key limiting factor<sup>[28]</sup>; c) of ovarian tissue is promising<sup>[1]</sup>.

Temporary ovarian suppression with goserelin may be an option for women with ER positive breast cancer<sup>[29]</sup>.

However, with an impending PM the current possibility of having a child is very rare. An honest disclosure of current limits of all these techniques should be clearly acknowledged in counseling with patients and their partner.

### Management of general health and sexual issues associated with PM

The most important sexual issues are related to:

- 1) age- physical and psychological impact of PM;
- 2) effects of estrogen and androgen loss on general and sexual health;
- 3) severity of menopausal symptoms;
- 4) loss of fertility and its meaning to both partners<sup>[5]</sup>.

An interdisciplinary approach offers the best opportunity to tailor treatment according to the needs of the woman and couple.

When feasible, HT is the treatment that may minimise the impact of PM on general health and menopausal symptoms and signs. The focus here will be on treatment of FSD associated with PM.

### Medical Management of FSD

#### • Desire and central arousal disorders

Desire and central arousal overlap. RCT's indicate the positive effect of testosterone in estrogen repleted women after surgical menopause when etiology appears to be hormone dependent. RCT treatment with 300-µg/d testosterone patches on estrogen repleted women significantly increased sexual desire, frequency of satisfying sexual activity, reduced sexual distress and was well tolerated<sup>[12-15]</sup>. Two systematic reviews of RCT's indicate a positive effect of testosterone on all dimensions of sexual function as well as providing some psychological benefits.<sup>[24,30]</sup>

Secondary outcomes indicate a significant improvement in arousal and orgasm, in self-image and self-esteem, and a significant reduction in anxiety and concerns. The testosterone patch treatment has been approved by the European Agency for the Evaluation of Medicinal Products (EMA) on July 2006. However, controversy still exists on the indication for androgen therapy in women<sup>[31]</sup>.

Tibolone and HT with estradiol and noretisterone are other options for improving sexual desire. Bupropion is a non hormonal drug that may have a beneficial effect on sexual desire.

#### • Genital arousal disorders

Vaginal dryness, the leading complaint in genital arousal disorders, can be treated with vaginal estrogens<sup>[32]</sup>. Safety of vaginal estrogen therapy has been documented in RCT's and in observational studies such as the Million Women Study, the RR of breast cancer was 0.67 whatever the type of vaginal estrogen used.

Vaginal estrogen treatment is indicated when the gen-

ital arousal disorder causes and/or is associated with vaginal dryness, dyspareunia, post-coital cystitis, urogenital atrophy and/or urinary incontinence, mostly of the urge type<sup>[5,25]</sup>. Accelerated urogynaecological comorbidity will be delayed with appropriate HT. Early vaginal estrogenic treatment, pelvic floor stretching and vaginal moulds, to maintain vaginal elasticity, optimal length and "habitability" during pelvic or vaginal radiotherapy for squamous cervical cancer, may minimise the impact of radiotherapy on vaginal tissue.

Anecdotally, testosterone cream (2% in vaseline jelly or petrolatum) applied in minimal quantity daily to the vulva may improve vulval atrophy and clitoral sensitivity, genital arousal and erotic response. It may therefore improve the genital feed-back that may contribute to maintaining sexual desire and central arousal. Controlled studies are however lacking.

#### • **Orgasmic disorders**

True orgasmic disorder acquired subsequent to PM may benefit from HT. Increasing evidence supports a positive role of testosterone in restoring orgasmic potential<sup>[12-15, 24,30]</sup>. Pelvic floor rehabilitation is indicated when hypotonia is diagnosed as contributing to reduced orgasmic sensations. Comorbid urge or stress incontinence with fear of leakage with orgasm needs to be addressed appropriately<sup>[5]</sup>.

#### • **Sexual pain disorders, i.e. dyspareunia**

Dyspareunia requires a careful pathophysiological understanding of its complex biological etiology (muscular, endocrine, vascular, nervous, immunological, iatrogenic...) and meaning in order to design an effective treatment programme<sup>[25]</sup>. Frictional introital dyspareunia, secondary to vaginal dryness, may benefit from vaginal ET. Reflexive pelvic muscle tightening ("hyperactivity of the levator ani" secondary to pain), may benefit from self massage and stretching, electromyographic biofeedback and/or physiotherapy.

#### **Psychosexual management**

Psychosexual support to improve FSD includes individual behavioural therapy; psychotherapy to cope with the

many losses PM and its etiology have caused on health and sexuality; couple therapy to address nonsexual couple issues, such as conflicts, poor erotic skills or communication inadequacies. When lack of orgasm is associated with poor arousal, the latter is the first focus of psychosexual treatment.

In case of dyspareunia, psychosexual therapy includes behavioural therapy, vaginal inserts/moulds, progressive rehabilitation of the pelvic floor and, if necessary, pharmacological treatment for any intense phobic avoidance.

#### **Conclusions**

PM accelerates general health and sexual aging unless appropriate HT, when not contra-indicated, is initiated and maintained over time. Reports of FSD increase after PM. Women with PM are at higher risk for distressing sexual disorders. RCT's indicate that HT, with estrogen and testosterone, may have positive effects on all domains of sexual function, specially after surgical PM.

Positive outcomes of RCT's on 300 microgram testosterone patches in treating desire disorders (and associated FSD) in surgically menopausal women may offer more effective pharmacologic options for women complaining of FSD after PM. However, women and partners should be informed about the "lag time" (up to two or three months) between onset of treatment with testosterone patches and sexual improvement. This "waiting time" could be constructively used to address concomitant psychosexual issues (personal and/or partner related) and to (re)explore the sexual map after the difficult period of PM diagnosis.

More studies are needed to improve fertility protection in women undergoing POF, to evaluate long-term safety of HT and its efficacy in reducing the accelerated aging associated with PM, and to assess the more effective treatment strategies to address women's (and couple's) sexual complaints after PM. ◆

*References on request*

