Premature menopause and women's sexuality

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Introduction

Premature menopause (PM) refers to menopause occurring at or before the age of 40. It may be spontaneous, and is referred to as "premature ovarian failure" (POF) (Fassnacht et al., 2006; Meskhi & Seif, 2006; Laml et al., 2000). PM may be iatrogenic; that is, 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. The POF acronym currently encompasses all modalities of ovarian exhaustion, when the ovaries remain on site.
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 two to three years after POF diagnosis; i.e., FSH elevation above 40 IU/L in two consecutive samples at one month distance (Meskhi and Seif, 2006). A variable ovarian testosterone production is maintained after POF.
PM is a major turning point in a woman's life and the younger the woman, the higher the risk of significant health and psychosexual impact (Graziottin, 2003; Graziottin & Basson, 2004). Morbidity and mortality from cardiovascular disease, stroke, accelerated brain ageing and osteoporosis present a greater risk in PM women compared to controls. Sexual dysfunctions are reported with higher frequency and more significant personal distress after surgical menopause (Dennerstein et al., 2007). Overall sense of well-being and achievements of life's goals, specifically having a partner, getting married, having a satisfying sexual life and having children, may be variably affected (Rauck et al., 1999; Graziottin, 2003; Graziottin & Basson, 2004). Fertility is a major issue in childless women facing PM (Thomson et al., 2002; Larsen et al., 2003; Abdullah & Muasher, 2006).
This review focuses on the main characteristics of PM and its impact on the three major dimensions of human sexuality: sexual identity, sexual function, and sexual relationships, with special attention to options for fertility protection.

Results

The evidence specifically analysing the relationship between PM and sexual dysfunctions is scanty. Only recently RCT have focused on sexual outcomes of women undergoing surgical menopause, not specifically premature, treated with oestrogen and testosterone (Shifren et al., 2000; Buster et al., 2005; Simon et al., 2005 Davis et al., 2006). This review relies mainly on level II-2 and level III evidence and the author's clinical observations.

Prevalence of PM

Spontaneous POF affects on average 1% of women under 40 years of age (Meskhi & Seif, 2006; Laml et al., 2000). 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%) (Luborsky et al., 2003). Iatrogenic menopause, for benign and malignant conditions, affects 3.4 to 4.5% of women under 40. Survivors of childhood and adolescent malignancies are a growing subset of PM patients, with specific psychosexual issues deserving special attention and care (Puukko et al., 1997; Graziottin, 2003; Graziottin & Basson, 2004).

Prevalence of FSD after PM

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 Hypoactive Sexual Desire Disorder (HSDD) increases with age, while the distress associated with the loss of desire is inversely correlated with age (Graziottin, 2007).

Aetiology of PM and health vulnerabilities

Heterogeneity is the hallmark of the PM aetiology. It can be genetic, autoimmune, associated with chronic diseases, or iatrogenic in the context of benign or malignant disease (Meskhi & Seif, 2006; Laml et al., 2000) (table 1). Impacts of PM on health and sexuality vary 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 onto a serious medical condition which currently contraindicates HT, such as breast cancer, and/or in a childless woman and couple (Graziottin & Basson, 2004). Onset of symptoms, menopausal and sexual, is usually insidious in POF, either spontaneous or after chemo- and/or radiotherapy. It is usually rapid after surgical menopause.

Alerting symptoms of impending PM and associated FSD

Thinking of PM should be considered in the differential diagnosis when, independently of the woman's fertile age, premenopausal symptoms are complained of. Polymenorrhea and/or menstrual variability, skipping periods, worsening of premenstrual symptoms, hot flushes or night sweats, night tachycardia, insomnia, mood imbalance, anxiety, irritability, arthralgias and sexual symptoms should be understood in their meaning and not generically attributed to "life stressors" when they appear in young women (Meskhi & Seif, 2006; Laml et al. 2000, Graziottin & Basson, 2004).
Desire disorders and arousal difficulties with vaginal dryness are what FSD women complain about most frequently (Dennerstein et al., 2007). These disorders may anticipate or be concomitant to the diagnosis of PM, with orgasmic disorders appearing later.
Comorbidity between acquired desire, arousal and orgasmic disorders is more frequently reported after surgical menopause, as the sudden androgen loss, besides oestrogen, may contemporarily impair all the domains of sexual response.

Factors modulating sexual issues associated with PM

Etiology of PM is the single most powerful biological factor affecting the psychosexual outcome. Age at PM is critical; the earlier the PM, the more complex the impact on all dimensions of sexuality (Graziottin & Basson, 2004).
Sexual identity is more vulnerable when PM disrupts the process of psychosexual maturity, after peripubertal spontaneous POF or iatrogenic POF, after childhood or adolescent cancers (Puukko et al., 1997, Graziottin, 2003). The stage in the life cycle may contribute to FSD, fertility being a major issue in childless women and couples. Factors personal to the woman, biological, psychosexual and sociocultural, may modulate the FSD perception, meaning, impact and also possibility of disclosure in the clinical setting.
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. Body image issues are specifically important, and may become prominent in women who have undergone breast or gynaecologic oncological surgery and associated treatments causing PM (Schover, 1994; Graziottin & Castoldi, 2000).
The woman's coping attitude, personality, mental well-being and quality of sexuality before PM may all affect the sexual outcome after PM. Other variables that may contribute to further modulate women's sexuality include education and socioeconomic status, professional role and access to qualified medical care (Graziottin & Basson, 2004).
The partner's reaction to the associated infertility, his or her personal and sexual health, the quality of intimacy and of the relationships before and after PM further modulate the individual and couple's coping attitudes. Contextual factors – both relational and sociocultural, such as ethnicity – further contribute.

Pathophysiology of sexual dysfunction after PM

Oestrogens and androgens modulate the neurobiology of sexual desire and mental arousal, and the neurovascular cascade of events leading to genital arousal, lubrication and orgasm. Oestrogens are credited to be 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 is credited with having an initiating role on desire and central arousal, acting on the dopaminergic appetitive-seeking pathway, and a modulator role of the peripheral response, as permitting factor for nitric oxide (NO), the key mediators of clitoral and cavernosal bodies' congestion (Bachmann et al., 2002).
The loss of oestrogens and androgens contributes to reduce sexual desire, central and peripheral arousal, with vaginal dryness, and causes or worsens orgasmic difficulties and dyspareunia, causing loss of self-confidence and self-esteem, and an increase in anxiety and concerns. It may well contribute to the neurobiological aetiology of depressed mood that is so often comorbid with acquired loss of desire, and potentiates the depressive feelings consequent to the many losses PM implies (Alexander et al., 2006).
Comorbidity of FSD is frequent, given the interdependence of different phases of sexual function and the shared pathophysiology, particularly endocrine, neurobiological and psychosexual. The specific role of each hormone loss in contributing to FSD is still under investigation.
The issue of FSD cannot be separated from the impact on sexuality of concomitant medical comorbidities associated with or consequent to different aetiologies of PM. They may contribute to FSD through asthenia and depression, body image concerns, vaginal shortening and/or vascular/autonomic nervous damages secondary to genital surgery or radiotherapy, or associated bladder problems (Graziottin & Basson, 2004).

Diagnosis of PM

Impending PM is hypothesised when menopausal symptoms appear in women younger than 40 years 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 distance (Meskhi and Seif, 2006; Laml et al., 2000). Ecography may show small ovaries for the age, with no or a few residual oocytes. PM is implicit when bilateral oophorectomy is performed in women younger than 40 years of age.

Diagnosis of FSD after PM

FSD may be antecedent to PM, concomitant to PM, and/or specifically caused and/or maintained by PM. Early diagnosis is the key to minimising health and sexual consequences. Aetiology of FSD associated to PM is multifactorial. Biological, psychosexual and contextual factors, including having a partner and his or her attitude, may modulate the scenario of the individual FSD experience.
Diagnosis should consider aetiology of FSD (with special attention to predisposing, precipitating and maintaining factors, biological and psychosexual); the disorder being generalised or situational, lifelong or acquired and the level of distress it causes.
In stable relationships, counselling to both partners is a crucial part of the diagnosis and management. Accurate physical examination is mandatory, given the importance of biological disruptions associated to PM, with focus on trophism of external genitalia, vagina and vaginal pH, pelvic floor tonicity and "pain map", in case of dyspareunia (Graziottin & Basson, 2004). A poor quality of genital sexual feed-backs is usually an underevaluated contributor of the loss of sexual desire in women.
Exams may include plasmatic hormone sample, when POF diagnosis has not yet been established, and vaginal pH. Specific exams should be considered according to the clinical history and aetiology of PM.

Treatment of PM

Tailored HT is the treatment of choice in POF (when non contraindicated; i.e., in survivors of breast cancer or genital adenocarcinoma, or after thromboembolic disease, acute hepatitis, etc). Systemic ET (oestrogen treatment) is the choice in women who have undergone hysterectomy besides oophorectomy. Topical vaginal ET may address vaginal atrophy and bladder symptoms when systemic ET is not suitable or desirable.
Recommendations from the European Menopause and Andropause Society (EMAS) (Skouby et al., 2004) and the International Society of Menopause (ISM) (Burger et al., 2004) include PM being HT treated up until the age of natural menopausal (51 years of age), unless a specific contraindication is diagnosed.

Prevention of infertility in women facing impending POF

Three lines of research are currently raising new hopes in the pursuit of ovarian and fertility protection in young women. Cryopreservation (1) of oocytes is an option in women with impending POF, (2) of embryos is feasible, but requires a cycle of in-vitro fertilisation (IVF) – time before cancer treatment may be a key limiting factor (Oktay et al., 2003), and (3) of ovarian tissue is promising (Abdullah & Muasher, 2006).
Temporary ovarian suppression with goserelin is an option for women with ER positive breast cancer (Jonat et al., 2003). New perspectives include substances such as sphingosine-1-posphate and ceramide to protect oocytes from iatrogenic treatment-related toxicity.
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 counselling with patients and their partner. Discussing the possibility of having a child and the most appropriate fertility-protecting choice for the individual patient could have two precious positive effects: instilling a pragmatic approach to fertility issues, which might otherwise become the core of later depressive feelings and regrets, and maintaining the right to hope. This is of special importance in the oncological setting when discussing ovarian side effects of chemo or radiotherapy with young, childless women.

Management of FSD associated to PM

The most important sexual issues are related to (1) age and psychological impact of the diagnosis of PM per se, (2) effects of oestrogen and androgen loss, (3) severity of menopausal symptoms, and (4) loss of fertility and its meaning to both partners (Graziottin & Basson, 2004).

Management of desire disorders

RCT indicate the positive effect of testosterone in oestrogen-repleted women after surgical menopause, when aetiology appears to be hormone dependent. RCT treatment with 300-µg/d testosterone patches on oestrogen-repleted women significantly increased sexual desire and frequency of satisfying sexual activity, reduced sexual distress, and was well tolerated (Shifren et al., 2000; Buster et al., 2005; Simon et al., 2005 Davis et al., 2006).
Secondary outcomes indicate a significant improvement of arousal and orgasm, of 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 (EMEA) on July 2006. However, controversy still exists on the indication of androgen therapy in women (Somboonporn et al., 2006; Wierman et al., 2006).
Testosterone cream (2% in vaseline jelly or petrolatum) applied to the genitals may anecdotically improve vulvar trophism and clitoral sensitivity, thus improving the genital feed-backs that may contribute to maintaining sexual desire. However, controlled studies are lacking.
Tibolone and HT with estradiol and noretisterone are other options to improve sexual desire. Bupropion is a non-hormonal drug that may improve it as well.
Psychosexual support includes individual behavioural therapy, psychotherapy to cope with the many losses PM and its aetiology have caused, and couple therapy to address nonsexual couple issues, such as conflicts, poor erotic skills or communication inadequacies (Graziottin & Basson, 2004).

Management of arousal disorders

Subjective and combined arousal disorders, either lifelong or acquired, usually comorbid with sexual desire disorders, should be treated as mentioned above. Vaginal dryness, the leading complaint of genital arousal disorders, can be treated with vaginal oestrogens (Goldstein & Alexander, 2005). Safety of vaginal oestrogen therapy has been documented in RCT and in observational studies such as the Million Women Study, the RR of breast cancer being of 0.67 for whatever type of vaginal oestrogen used.
Vaginal oestrogenic treatment is indicated when the genital 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 (Graziottin & Basson, 2004; Graziottin, 2006).
Early vaginal oestrogenic 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.
Psychosexual counselling is synergic in desire and arousal disorders and should be offered to patients and partners.

Management of 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. 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 is to be appropriately addressed (Graziottin & Basson, 2004).
Lifelong "isolated" orgasmic disorders, concomitant to PM, may benefit from a behavioural educational treatment, encouraging self-knowledge and eroticism with the experience of higher arousal sensations, possibly with use of vibrators. When lack of orgasm is associated with poor arousal, the latter is the first focus of psychosexual treatment.

Management of sexual pain disorders – dyspareunia

Pain is (almost) never psychogenic. Sexual pain is no exception. It requires careful pathophysiologic understanding of its complex biological aetiology (muscular, endocrine, vascular, nervous, immunitary, iatrogenic ...) and meaning to design an effective treatment (Graziottin, 2006). Friction introital dyspareunia, secondary to vaginal dryness, may benefit from vaginal ET. Reflexive pelvic muscle tightening ("hyperactivity of the elevator ani", secondary to pain), may benefit from self-massage and stretching, electromyographic biofeedback and/or physiotherapy.
If vulvodynia is complained of, treatment should include pain modulation, with drugs, such as pregabalin, gabapentin and/or amitryptiline, and peripherally acting anthalgic techniques, such as electroanalgesia and/or the ganglion impar block (Graziottin, 2006).
Psychosexual therapy includes behavioural therapy, vaginal inserts/moulds, progressive rehabilitation of the pelvic floor and, if necessary, pharmacological treatment for any intense phobic avoidance.

The multidisciplinary team and appropriate referral

Sexual dysfunctions associated with PM need a multidisciplinary approach, given the heterogeneity of aetiological factors and the variety of co-morbidities, both in the medical and psychosexual domain.
The gynaecologist or the family physician is usually the first to diagnose PM, and to initiate HT, and is asked for help for FSD after PM. Appropriate referral includes an oncologist for HT in cancer patients with PM, a urologist for concomitant partner's problem, a psychiatrist to address affective disorders, a physiotherapist, for the pelvic floor-related issues, and a psychotherapist and sex therapist.
Appropriate referral gives the patient/couple the feeling of coordinated caring and confirms the legitimacy of their sexual complaints (Graziottin & Basson, 2004).

Conclusions

PM and FSD, reporting after PM, is increasing. The most important contributing factor is the increasing cohort of women surviving childhood or adolescent cancers. FSD increases with age. However, the distress associated with FSD is inversely correlated with age. Women with PM are at higher risk for distressing sexual disorders.
RCT indicate that HT, with oestrogen and testosterone, may have positive effects on all domains of sexual function, especially after PM.
Positive outcomes of RCT 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, 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 to assess the more effective treatment strategies to address their sexual complaints after PM.

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Table 1: Aetiology of premature menopause

Premature ovarian failure (POF)

- idiopathic
- genetic:
  - Turner's syndrome
  - fragile X syndrome
  - mosaicism
  - deletion/inversion
  - galactosaemia
  - BRCA1 mutation
- autoimmune:
  - lupus erythematosus
  - rheumatoid arthritis
- associated with chronic disease:
  - chronic renal insufficiency
  - primary biliary cirrhosis
- iatrogenic for benign conditions:
  - endometriosis
  - bilateral disgerminoma or cystoadenoma
  - ovarian hyperstimulation in infertility (?)
  - 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)