

Effect of premature menopause on sexuality

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Premature menopause, that is, menopause – spontaneous or iatrogenic – occurring at or before the age of 40 years, affects sexual identity, sexual function and sexual relationships. The woman's health, wellbeing and achievement of life's goals may be variably impaired. Factors modulating the individual's sexual outcome after premature menopause include: etiological heterogeneity of premature menopause and associated medical and sexual comorbidities; psychosexual vulnerability to premature menopause and associated infertility in survivors of childhood and adolescent cancers; impact of premature menopause on women's sexual identity, sexual function – particularly the biological basis of desire, arousal, orgasm and vaginal receptivity – and sexual relationships; partner-related factors; fertility issues; and preventive/therapeutic measures. Hormone therapy is indicated but long-term safety data are lacking. An interdisciplinary medical and psychosexual approach comprises appropriate counseling, fertility protection, when feasible, individualized hormone therapy and specific psychosexual treatment(s). Further research on fertility protection and the safety of long-term hormone therapy after premature menopause is needed.

Premature menopause (PM) refers to hypergonadotropic amenorrhea occurring at or before the age of 40 years [1–4]. It may be spontaneous, usually referred to as 'premature ovarian failure' (POF) [1,3,4], or iatrogenic, secondary to surgical removal of both ovaries (bilateral oophorectomy) or to the irreversible ovarian damage caused by chemotherapy or radiotherapy (systemic, i.e., total-body irradiation, or pelvic) [1–5]. The term POF currently encompasses all modalities of ovarian exhaustion when the ovaries remain *in situ*.

The incidence of POF is increasing, largely due to improved survival rates of cancer patients treated with radiation and chemotherapy [6]. Delayed diagnosis and management of POF leads to suboptimal outcomes [6,7]. Anticipation and early detection of this condition in high-risk women is a critical step towards prevention and effective treatment of associated psychosexual issues. This goal may be achieved by means of ovarian function testing, followed by early institution of appropriate management to improve health-related and sexual outcomes. Choice of strategies should vary depending on the age of onset, associated symptoms and fertility aspirations of the individual, and should change with the patient's advancing age [6,7].

PM is a major turning point in a woman's life: the younger the woman, the higher the risk of significant health and psychosexual impact [2,5,8–14].

Morbidity and mortality from cardiovascular disease, stroke, accelerated brain aging and osteoporosis present a greater risk in PM women compared with controls [1,3,4]. A higher frequency of psychosexual disorders and more significant personal distress are reported amongst PM women [2,8–14]. The woman's overall sense of wellbeing and achievements of life goals may be variably affected.

To prevent such negative outcome from premature loss of sex hormones, clinicians usually consider hormone therapy (HT). The three most credited international scientific associations on menopause currently recommend HT to be continued until the age of natural menopause, 51 years, with the exception of women with hormone-dependent cancers or obvious major contraindications [15–17]. However, scientific data regarding benefits and risks of long-term HT in this cohort of often very young women with PM of diverse etiology are minimal.

Therefore, 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. After reviewing the main factors modulating sexual issues after PM, the paper analyzes:

- Psychosexual development and sexual identity issues [2,5,8–11] in survivors of childhood and adolescent cancers [18,19];

Keywords: arousal disorders, cancer survivors, desire disorders, dyspareunia, estrogen, hormone therapy, infertility, premature menopause, sexual dysfunction, testosterone

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- Women's sexual identity after PM, with focus on femininity and fertility issues [1–6,12,18,19];
- Women's sexual function, with special attention given to the consequences of iatrogenic menopause in terms of sexual desire, arousal, orgasm and dyspareunia [2,5,13,14,18–24];
- Sexual relationships and main couple's vulnerabilities [2,10–13];
- Impact of ethnicity, both on prevalence and psychosexual outcome of PM [10,21,26,27];
- Options for fertility protection and ovidonation when feasible, accepted and legally available [2,6,7,28–33];
- Medical and psychosexual management of pre-existing or PM-associated female sexual disorders (FSD) [2,5,23,25,34–51].

Methods

A Medline search was carried out, with the search terms PM, premature ovarian failure, iatrogenic menopause, etiology, endometriosis, Turner's syndrome, fragile X syndrome, galactosemia, ethnicity, childhood cancer survivors, adolescent survivors, leukemia, Hodgkin's disease, breast cancer, gynecologic cancer, chemotherapy, radiotherapy, bone marrow transplantation, fertility protection, cryopreservation, sexual identity, sexual function, sexual relationships, desire disorders, arousal disorders, dyspareunia, orgasmic disorders, couple issues, HT, estrogen therapy, androgen therapy and psychosexual therapy.

Results

The evidence specifically analyzing the relationship between PM and sexual dysfunctions, and between PM and available treatment options is limited, with the exception of new randomized, controlled trial (RCT) data on the effect of testosterone patches on sexuality in surgically menopausal women (Level I) [47,52–54]. This review is based on these new studies, and on Level II-2 and Level III evidence (as per the US Preventative Services Task Force), along with the clinical experience of the author (implied when no data are referenced).

Prevalence of premature menopause & associated sexual disorders

Spontaneous POF affects on average 1% of women aged under 40 years [26], although percentages as high as 7.1% have recently been reported [27]. The Study of Women Across the Nation (SWAN) [26], indicates that POF was reported by 1.1% of women. By ethnicity, 1.0%

of Caucasian, 1.4% of African-American, 1.4% of Hispanic, 0.5% of Chinese and 0.1% of Japanese women experienced POF. The differences in frequency across ethnic groups were statistically significant ($p = 0.01$). Lifestyle-related sociocultural factors, besides genetic factors, may be important contributors to age at menopause, as well as modulators of its impact on sexuality. By convention, menopause that occurs at ages 40–45 years is considered 'early' and occurs in approximately 5% of women.

Iatrogenic PM, caused by benign and malignant conditions, affects 3.4–4.5% of women aged under 40 years [1,3,4,27]. The 5-year survival for all malignancies in childhood and adolescence is 72% (up to 90% for some cancers) [10,18,19,55], and an increasing number of survivors are facing the challenges of adulthood deprived of their gonadal hormones, unless an appropriate HT is prescribed. Some 25% of breast cancer patients are premenopausal at diagnosis, and 15% are younger than 45 years.

Systematic studies on the prevalence of FSD in women affected by PM are limited. A recent European survey of 2467 women (in France, UK, Germany and Italy) showed that in the age cohort from 20–49 years the percentage of women with low sexual desire is 19%, but is significantly higher (32%) in women who have undergone surgical menopause. This difference disappears when comparing naturally postmenopausal women (aged 50–70 years) and age-matched surgically menopausal women (46 and 48%, respectively). The percentage of women distressed by their loss of desire, and thus defined as having Hypoactive Sexual Desire Disorder (HSDD), was 27% in fertile women and 28% after surgical menopause in the age cohort 20–49 years, compared with 11% in women with natural menopause and 14% in those with surgical menopause in the age cohort 50–70 years [56]. Thus, although the probability of HSDD increases with age, the distress associated with the loss of desire is inversely correlated with age [57]. The data indicate that age at menopause is a critical factor: younger women undergoing a surgical PM have a significantly higher vulnerability to HSDD in comparison with older women with either natural or surgical menopause [56,57].

Etiology of premature menopause & associated health vulnerabilities

Heterogeneity is the hallmark of PM etiology. It can be idiopathic or can include genetic

causes [1,3,4,58–61] and autoimmune factors [62,63], or be associated with chronic diseases, such as primary biliary cirrhosis [65]. PM can also have iatrogenic causes, namely benign [66,67] or malignant disease [2,5,6,8–14,18–24,28,68] (Box 1).

The effect of PM on health and sexuality varies accordingly. It may be limited in women affected by POF who already have a family and who are receiving optimal HT. It may be dramatic when the consequences of PM are superimposed onto a serious medical condition, such as chronic autoimmune disease or cancer, more so if the latter is hormone dependent and contraindicates HT.

Therefore, the diagnosis and treatment of sexual dysfunctions associated with PM require an interdisciplinary medical and psychosexual approach. If unaddressed, the many sexual fears and complaints of women with PM can contribute to feelings of helplessness and hopelessness, adding to the distress associated with PM [56,57].

According to the etiology, both symptoms of menopause and sexual problems may have appeared before the clinical diagnosis of PM. Key factors to be considered in the clinical practice may be summarized as follows:

- In POF, premenopausal symptoms – polymenorrhea and/or menstrual variability, worsening of premenstrual symptoms, hot flushes or night sweats, night tachycardia, insomnia, mood imbalance, irritability, arthralgias – usually not

recognized as signs of imminent menopause, may have already challenged the woman's equilibrium, self-confidence and sense of control [2,35]. Clinicians should alert themselves to this diagnostic possibility, independently of the woman's fertile age, as an early diagnosis is the first step to minimizing PM consequences on both general and sexual health;

- Turner's syndrome requires a timely diagnosis in order to start treatment in the early peripubertal years and minimize the impact of the missed production of sexual hormones on growth [58,59];
- Fragile X syndrome and other genetic conditions may be associated with a variable degree of mental retardation [61], which may delay the diagnosis of PM and affect its consequences on general health and sexuality;
- In galactosemia, an inherited inborn error of the major galactose assimilation pathway, long-term complications, such as cognitive and motor abnormalities and hypergonadotropic hypogonadism in female patients, are still unavoidable [61]. Clinical management of ovarian failure relies on hormonal treatment;
- In autoimmune conditions, such as systemic lupus erythematosus (SLE) [63,64], the impact on sexuality depends on the age of onset, rate of progression, severity of disease, duration of treatment with cortisone and immunosuppressants, and their impact on general health, body shape and body image. In SLE patients treated with cyclophosphamide, 60% suffered from POF and hypergonadotropic amenorrhea [64]. In SLE-affected women, PM may be the latest trauma of a challenging disease or a devastating new problem in an otherwise controlled situation;
- Endometriosis [69] may compound prior sexual dysfunction due to deep dyspareunia [39] and/or chronic pelvic pain and low sexual confidence associated with impaired fertility. Relationship issues related both to sexual difficulties and infertility further increase the vulnerability for problematic sexuality [39];
- Iatrogenic PM associated with cancer treatments may be the most challenging form of PM. Key variables include: type of cancer, stage and prognosis [5]; age at diagnosis [5,8–10,18,19,22,23,55,68]; the surgery involved; conservative versus radical treatment [12–14]; adjuvant chemo- and/or radio-therapy and associated side effects [5,8,18–21,55,68]; and presence and severity of recurrences. The impact

Box 1. Etiology of premature menopause.

Premature ovarian failure

- Idiopathic [1,3,4]
- Genetic: Turner's syndrome [58,59], fragile X syndrome [58,60], mosaicism [1,3,4,58], deletion/inversion [1,3,4,58], galactosemia [61]
- Autoimmune: lupus erythematosus [63,64], rheumatoid arthritis [62]
- Associated with chronic disease: chronic renal insufficiency [1,3,4], primary biliary cirrhosis [65]

Iatrogenic: benign conditions

- Endometriosis [69]
- Bilateral dysgerminoma or cystoadenoma [1,3,4,87]
- Ovarian hyperstimulation in infertility (?) [66]
- Oophorectomy concomitant to hysterectomy [1,3,4,87]

Iatrogenic: women at risk of ovarian cancer

- Breast cancer-associated genes (*BRCA1* and/or *BRCA2*) [87]

Iatrogenic: established malignant conditions

- Bilateral oophorectomy [1,3,4,87,101]
- Chemotherapy [5,9,13,14,18,28,55,68,83,87]
- Pelvic radiotherapy [18,22,23,55,87]
- Total body irradiation [70,87]

Modified from [2].

of bone marrow transplantation, either allogenic or autologous, on overall health is a further complicating issue [70]. Depending on etiology, menopausal symptoms appear shortly after surgical PM, while there may be a variable lag time between medical oncological treatment and onset of PM [18,19,55,68]. This is true for PM subsequent to chemotherapy or radiation and varies according to different drug regimens, radiation doses and the woman's age [5,8,18,19,55,68].

It follows that PM has a different impact according to whether it is 'isolated' in an otherwise healthy woman, or associated with other genetic or acquired medical and psychological problems.

Factors modulating sexual issues associated with premature menopause

Etiology of PM is the single most powerful biological factor affecting the psychosexual outcome. Age at PM and stage in life cycle, factors personal to the woman, and contextual factors – both relational and sociocultural – that interact and partly overlap, further contribute to modulate the final impact of PM on the individual woman and couple (Box 2).

Etiology of premature menopause & psychosexual issues in adolescents

In a lifespan perspective, the earlier the PM, the more complex the impact on all dimensions of sexuality. Sexual identity is particularly vulnerable when PM disrupts the process of psychosexual maturity [2,5–10], both in women with POE, especially those with Turner's syndrome [59], and in iatrogenic conditions, such as childhood and adolescent cancers [2,5,8–10]. In these cases, the psychosexual impact of the primary disease is added to the consequences of PM. Chemotherapy and/or radiotherapy, particularly in hematological cancers, may irreversibly damage the ovaries. Pubertal changes may not occur unless timely HT is started [2,5,8,55,68]. Attachment needs may be very disturbed in children and adolescents, due to repeated hospitalization, separation from parents, friends, school and playtime, invasive and painful tests and treatments, long hours of loneliness, anxiety, fear regarding the future and possibly the absolute isolation required in bone marrow transplantation [2,5,8,9]. The average time involved in treatment and close follow-up in hematological cancers is 3 years: this critical suspension from normal life and the shift to emergency survival may disrupt the basic

process of psychosexual maturity [2,5,8,9]. Achievement of autonomy is delayed, compromising self confidence and the timing of normative psychosexual events, with variably increasing age at first kiss, first dating, first masturbation, first foreplay and sexual intimacy. The impact of cancer at a young age on self-perception, plus the need for invasive treatments, may further affect body image, and self-confidence and intimacy issues – both physically and emotionally [5]. Different coping strategies at the time of cancer treatment may shape future relationships, including sexual relationships [2,5,8,9].

Research focusing on sexuality in young women surviving leukemia involving 31 survivors (mean age 20.1 years) and 50 healthy controls, confirms this complex psychosexual vulnerability [9]. Women in this study were similar when considering age at initiation of dating and sexual activity, frequency of sexual intercourse, and opinions on sexual behavior, but significantly different in specific domains:

- Less feminine in sexual identity and more infantile ($p < 0.002$)
- More restrictive, passive and submissive images of sexuality ($p < 0.001$)
- Lower confidence with masturbation ($p < 0.001$)
- Less experience of sexual intercourse ($p < 0.03$)
- Less initiative in sexual intercourse ($p < 0.003$)
- Minor ability to express personal sexual desires to the partner ($p < 0.001$)
- Less enjoyment of sexual intercourse ($p < 0.01$)

These data suggest that:

- Successful psychosexual development is a prerequisite for a satisfactory sexual function;
- Psychosexual consequences of childhood/adolescent cancers may overlap the consequences of iatrogenic menopause;
- The scenario is complex and needs to be addressed with a combined medical and psychosexual approach [2,5].

Age at premature menopause, stage in lifecycle & fertility

Approximately 1/1000 adults is a cancer survivor, and most are of reproductive age [6]. Radiation therapy may irreversibly damage fertility. The degree and persistence of damage depends on three factors: dose of radiation; intensity of the irradiation field; and the patient's age [6]. The

Box 2. Factors affecting sexual outcome after premature menopause.**Biological factors**

- Age at PM [1–5,9,10,12,14,23,27,35,55,63,68,69,82]
- Etiology of PM [1–5,8–14,18–24,28,58–67,87,88,108]
- Premature ovarian failure versus PM associated with chronic disease [1–6,8–14,18–25,28,47,53,56,58–67,88]
- Iatrogenic: benign versus malignant causes [1–6,8–14,18,19,22,23,58–65,87,108]
- Debility from associated medical conditions [2,5,20,21]
- Reactive depression [1–5,8–14,18,19,22,23,58–65,87,108]
- Severity of the residual chronic pelvic pain and deep dyspareunia in endometriosis [39,69,95]
- Type of cancer, stage and prognosis, conservative versus radical surgery [2,5,8–14,18–23,28,55,68,82,83,108]
- Adjuvant chemo/radiotherapy/bone marrow transplant [2,5,8–14,18–23,28,55,68,70,82,83,108]
- Hormone therapy: feasibility, type and length [2,5,15–17,23,34–36,39,42,47–54,68,69,75,93,95,102,106–108]
- Fertility protection [2,6,28–33,55]

Psychosexual factors

- Psychosexual stage at PM: the younger the woman the higher the impact [2,5,9–12,68,82]
- Fulfilment of life goals prior to diagnosis [2,5,9–12,25,87]
- Coping strategies [2,5,8,11,13,14,23–25,57,82,84,98,101]
- Previous erotic self-perception, sexual self-confidence [2,5,9–12,68,82]
- Premenopausal sexual experiences and quality [2,5,12,13,23]
- Premorbid personality and psychiatric status [1–5,8–14,18,19,22,23,58–65,87,108]
- Social/professional role [2,11,83]

Contextual factors

- Family dynamics (attachment vs autonomy in peripubertal children and adolescents) [2,5,9–12,68,82]
- Couple dynamics and marital status [2,5,10,84]
- Partner-related issues: his acceptance of PM-induced infertility [2,5,6,84]
- Support network (family, friends, colleagues and self-help groups) [2,5,8]
- Quality of medical and psychosexual care [2,5,6,14,23,68]
- Ethnicity and sociocultural issues [26,27]

PM: Premature menopause. Modified from [5].

two most important factors affecting fertility following cancer chemotherapy are a woman's age and the agent used [6]. Fertility is a critical issue affecting sexual adjustment; the younger the woman the higher her vulnerability to personal and couple's consequences of iatrogenic POF.

The loss of cycling periods deprives the young woman of a biological clock, of biorhythms that make her feel part of the community of fertile women, with their sharing of dreams and projects regarding present and future family and children [5].

Already having children or not at the time of PM is a critical factor modulating the overall psychosexual outcome. While some women, especially those with higher education and career

focus, are seen to be making a choice to delay permanent relationships and children, PM removes such options, often at a very early stage [1,2,5]. The loss of reproductive potential may specifically impair the motivation to initiate or accept intercourse in women highly distressed by their loss of fertility. 'It's worthless now', is frequently a dominant theme.

Reproductive function is a particularly vulnerable dimension of sexual self-image in young PM women [2,5,12,14]. After PM, biological maternity becomes impossible, unless ovidonation is feasible, accepted and legally available. Sexual reproduction requires three types of differentiation [71]: gonadal, for the production of gametes; genital, for the conveyance of gametes to the point of fertilization; and behavioral, for the urge to behave sexually. PM may variably impair all three: gametes are depleted [1–5]; estrogen loss leads to genital atrophy [72,73]; estrogen and androgen loss may impair sexual pleasure, response and desire [34–37,74,75]. PM-related biological and psychosexual factors do variably interact in the individual woman, with infertility becoming the paradigm of all the losses the woman has to cope with. Prevention of infertility, when feasible, is a critical part of the medical approach (see section on protection of fertility) [6,28–33,68].

Woman-related factors

These include biological, psychosexual and sociocultural factors.

Biological factors

PM may affect body image. Physical and psychosexual consequences of both the specific condition causing PM and PM itself may impair body image with a complex mechanism, more so when the etiology, for example, hormone-dependent cancer, contraindicates HT. Skin and hair texture and her scent (pheromone secretion is hormonally modulated) may all change [35,37]. The skin is a key sexual organ [37]: subtle changes of increased wrinkles, mucosal and skin dryness and loss of elasticity, hair loss and nail fragility diminish the young woman's sense of attractiveness [37,76]. Some speak of their sense of 'sexual invisibility' and difficulties of dating. Change of body shape and tendency to gain weight [77–79] is of special concern to women who care most regarding their fitness. Many complain that they need much more exercise to maintain the same muscle tone and strength – a more demanding goal when fatigued.

Psychosexual factors

The coping attitudes a woman has, her personality, mental wellbeing and quality of sexuality before PM, may further modulate the psychosexual outcome after PM. Denial, anger, an overwhelming sense of loss and/or a catastrophizing approach increase the severity of consequent sexual dysfunctions [2,5,14,24,25]. The quality of premenopausal sexual experiences is an independent predictor, in PM as well as in normal menopause. Premorbid personality and psychiatric status further modulate coping strategies, affecting the final outcome. Affective disorders, depression and anxiety, frequently secondary to the diagnosis of PM and the underlying medical condition, especially if chronic pain is involved, may further modulate the sexual outcome [2,23,39,80,81].

Eroticism may be impaired by both the reduced sense of femininity and sensuality and the specific sexual dysfunctions [37]. Loss of sexual desire [2,5,9–12,14,34,35,37,74,75], mental and genital arousal impairment [22,23], orgasmic difficulties [12,13,22,23], dyspareunia [2,5,22,23,39] and physical sexual dissatisfaction may all affect erotic self-perception and sexual self-confidence.

Sociocultural factors

The level of education a woman has reached before PM, a satisfying professional/social role – another dimension of female sexual identity that is increasingly important in high-income societies – and her socioeconomic status may further modulate the impact of PM. The network of supportive relationships, personal income and likelihood of accessing good medical and psychosexual support may all be relevant [2,5,14,82]. A solid social role may minimize the impact of PM and its associated conditions as it offers other life-goals than maternity. Indeed, the subsets of women more vulnerable to the consequences of PM, as seen in young breast cancer patients with PM [12,82], include those who are younger, single and in conflicting relationships, and those with a low socio-economic status and/or unemployed. However, even social role and professional ability may be biologically impaired by the impact of chemotherapy on the brain [83]. Cognitive impairment following chemotherapy included reduced attention, mental flexibility, speed of information processing, visual memory and motor function. The impairment was apparently unaffected by anxiety, depression, fatigue and time since treatment, and not related to the self-reported complaints of cognitive

dysfunction [83]. The combination of chemotherapy and loss of sexual hormones on cognition needs to be investigated.

Contextual factors

Partner-related factors

The partner's reaction to the associated infertility, his/her personal and sexual health, the quality of intimacy and of the relationship before and after PM further modulate the individual and couple's coping attitudes, the need for help and the clinical outcome [2,5,35,84].

PM, particularly when associated with a cancer diagnosis, can be a tremendous strain on the couple's relationship and on the family. Younger women experience more emotional distress compared with older women [82]. Younger husbands report more problems carrying out domestic roles ($p < 0.001$) and more vulnerability to life stressors ($p < 0.01$) in comparison with older husbands [82]. PM may lead to male sexual dysfunction [2,5,14]. Vaginal dryness makes penetration unpleasant or difficult [14,23], precipitating erectile dysfunction or great delay in reaching ejaculation, especially if the man believes the lack of lubrication to imply rejection. His partner's lack of sexual excitement may also lead to situational erectile dysfunction. Men who cannot accept the loss of reproductive potential may end the relationship. Multiple psychosexual losses, on personal goals achievement, love and relationship commitment, may further worsen the impact of PM on women's sexual wellbeing.

Ethnicity

The ethnic background of the affected woman may also be important. A cohort of 10,425 survivors of cancer, diagnosed between 1970 and 1986 and treated in childhood or adolescence (<20 years), of whom 46.3% were female, were followed at 25 oncology centers in the USA and Canada, participating in the Childhood Cancer Survivor Study [10]. Self-reported data on marriage, living as married and divorce were compared with the US population according to age-specific cohorts. Overall, 32% of survivors were married or common-law (much less than the US population); 6% divorced or separated (women less and men more than the US population); 0.07% widowed (less than the US population); 62% never married (significantly more than the US population in each cohort). Black survivors were more likely to have married, although they were more likely to divorce/separate once married compared with white or

Hispanic survivors. Younger black survivors were also more likely to divorce than black people without cancer [10]. Ethnicity may prove to be an important variable modulating adaptation to cancer, chronic disease, loss of fertility and PM.

Pathophysiology of sexual dysfunction after premature menopause

Reduced androgen production

In women, the serum levels of testosterone and proandrogens exceed that of estradiol, even during peak reproductive years, by several-fold to several thousand-fold [34,75,85]. This often-overlooked biological fact highlights the importance of androgens for a woman's wellbeing. In women, approximately half of circulating testosterone is secreted directly by the ovarian stroma and adrenal zona fasciculata in roughly equal quantities; the other half is derived from conversion of the proandrogen androstenedione, which is secreted by the same tissues. The proandrogen dehydroepiandrosterone sulfate (DHEAS) is produced entirely in the adrenal zona reticularis; conversion of DHEAS accounts for approximately 30% of circulating dehydroepiandrosterone (DHEA), with the remaining DHEA secreted by the adrenal zona reticularis and the ovarian theca [85]. In contrast with the relatively sharp decline in circulating estrogens during natural menopause, androgen levels tend to peak when women are in their twenties and drop gradually with age; typical serum levels of testosterone and androstenedione at age 40 years are approximately half those at age 20 years, and at age 60 years are further reduced [85].

Ovarian androgen production ceases with surgical PM and is often minimal after radiation- or chemotherapy-induced PM. Despite having ovaries *in situ*, such therapies may irreversibly destroy not only follicles, but also the Leydig cells that are responsible for ovarian androgen production, leading to characteristic symptoms of androgen deficiency. These women constitute an often-unrecognized subgroup of iatrogenic menopause patients [2,5,87].

The situation in POF is variable. Recent work suggests reduced production of both ovarian and adrenal androgens in some women with POF, especially those with organ-specific antibodies [57].

Androgen loss undermines the neurobiology of sexual drive and central/subjective sexual arousal, given androgen's biological 'initiating' role on the seeking–appetitive pathway in the brain [89,90]. Complaints of lack of energy, decreased muscle strength and tone, and reduced

assertiveness may be due to androgen loss [34,35,91]. Thus, androgen loss may play a role in changes in body shape and body image [34]. It may also contribute to genital arousal disorder given androgen's enhancement of nitric oxide activity in cavernosal tissues [92].

The impact of testosterone loss on sexual desire and overall sexual wellbeing of women after natural and surgical menopause has been recently reviewed in *Women's Health* by Alexander and colleagues, with a solid body of evidence to support its role in improving women's sexuality and psychological wellbeing [34]. The positive impact of testosterone on all domains of sexual function has also been reviewed in the last Cochrane review [93]. However, a more cautious approach to the diagnosis of 'androgen deficiency' has been recently published by Wierman and colleagues [75].

Reduced estrogen activity

For some women with POE, ovarian androgen production continues, allowing estrogen synthesis from adrenal and ovarian sources, particularly when the woman has an elevated body mass index. When ovarian androgen activity is absent, estrogen production will be limited to estrone derived from conversion of adrenal androgens.

Loss of estrogens may lead to genital arousal disorder, contributing to vaginal dryness and dyspareunia [2,5,42,72,73,92]. There is high clinical comorbidity of urinary tract symptoms, genital arousal disorder and sexual pain disorders [39,94,95]. Of note, urinary tract symptoms were associated with arousal disorders and sexual pain disorders (relative risk [RR]: 4.02 [2.75–5.89] and 7.61 [4.06–14.26], respectively), according to an epidemiological survey by Laumann and colleagues [94]. This has a plausible pathophysiological background given the role of progressive urogenital atrophy [72,73], reduced vascular congestion around the vagina and the urethra [92], where an extension of the equivalent to the male corpus spongiosum has been histologically demonstrated [96], and reflex hypertonicity of the pelvic floor [39]. Sexual symptoms associated with estrogenic loss include vaginal dryness, dyspareunia (both superficial and deeper) and sexual avoidance due to pain and/or postcoital cystitis [35,39]. The marked clinical association of sexual pain disorders with urogenital dysfunction requires further research. Particularly when PM overlaps with cancer treatments for breast or gynecologic cancers, genital arousal disorder and dyspareunia tend to worsen over time, making early intervention urgent [12–14,22,23].

It is possible that estrogen loss may be involved in the reduced arousability and desire from PM. Although traditionally androgen rather than estrogen has been considered to be the relevant sex hormone [34–37,52–54,74], both hormones may contribute to optimal desire and mental and genital arousability. Loss of sexual hormones may synergize in causing FSD after PM.

Medical comorbidities associated with premature menopause

The psychosexual consequences secondary to sexual hormone loss may be further worsened by concomitant medical comorbidities associated with or consequent to the different etiologies of PM. Asthenia and depression may contribute to loss of desire and difficulties in mental arousability. Radical surgery and pelvic radiotherapy may cause vaginal shortening and vascular damage, and impair the genital arousal response, leading to vaginal dryness, introital and deep dyspareunia and orgasmic difficulties [22,23]. Associated bladder problems may further complicate the clinical picture. Clinicians should be aware that a comprehensive medical evaluation of women affected by PM, and appropriate management of their menopausal symptoms, is a prerequisite for both optimal health outcomes and psychosexual management. Unfortunately, this comprehensive approach is still too often neglected, even in recent years, particularly in cancer survivors [68].

Diagnosis of female sexual disorders associated with premature menopause

FSD may be antecedent to PM, concomitant to PM, and/or specifically caused and/or maintained by PM [87]. Early diagnosis of PM is key: alerting symptoms, even in adolescents, include cycle irregularities, such as polymenorrhea and/or skipping periods not due to other obvious causes [97], worsening of the premenstrual syndrome, transient and recurrent hot flashes and sweats, night tachycardia and/or sleep disorders (more frequent in the menstrual phase, when estrogens are at the lowest level) and/or sexual complaints. The etiology of PM, accompanying symptoms (cycle-related, menopausal and/or sexual), time since PM diagnosis, ongoing treatments (for the disease causing PM, if any, or HT) and her current health may all deeply modulate the physical and psychosexual scenario that the woman is experiencing.

A comprehensive diagnosis of sexual dysfunctions associated with PM should therefore investigate both the health context and

outcome related to PM and the specific psychosexual complaint, focusing on the following factors.

Etiology of the female sexual disorder

PM may act as a specific biological precipitating factor in a context of a variable individual and/or couple psychosexual vulnerability [97–100]. Coherently with the pathophysiology of PM, the healthcare provider should evaluate:

- Biological factors, such as age at PM and modality of loss of sexual hormones (sudden in surgical menopause vs gradual in POF of various etiologies). Menstrual irregularities and/or menopausal symptoms should alert the clinician to an impending PM, independently of the woman's age: the earlier the diagnosis, the higher the possibility of more effective interventions to protect fertility and sexual function [2,5,35,28–33]. Potential contributing factors, such as pelvic floor disorders, urological issues (e.g., recurrent cystitis or urinary incontinence), neurological conditions (particularly pain-related), depression and anxiety (either pre-existing, associated with or caused by PM), should be assessed [98–100]. All the medical conditions that may directly or indirectly affect sexuality, through their multi-systemic impact and/or the consequences of pharmacologic, surgical and/or radiotherapeutic treatment, should be considered in the differential diagnosis of potential contributors to FSD [87]. If the woman is already receiving HT after PM and complains of persisting FSD, diagnosis should consider if and why HT could be inadequate, to offer a better HT tailoring. Clinicians should reconsider other contributors, biological, psychosexual or context-dependent, not previously evaluated or more recently appeared.
- Psychosexual factors: diagnosis should include predisposing psychosexual factors (such as prolonged attachment dynamic and/or sexual identity issues secondary to childhood or adolescent cancers) [2,5,9,10,35,98]; body image concerns, more frequent in women treated for breast or gynecologic cancer [12,14,23,99] or receiving long-lasting corticosteroids for SLE; loss of self-esteem and self-confidence, which may also modulate the level of trust in the relationship, the intensity of the commitment and the confidence in loving and long-standing attitudes toward affective and erotic intimacy after the disrupting effect of PM [82,84]; and

previous maternity or desire for having children [2,5]. Diagnostic attention should carefully record the leading sexual symptoms the woman is reporting and the associated FSD.

- Contextual factors: diagnosis should consider if the woman is single or in a significant relationship, current interpersonal difficulties [82,84], partner's general health issues and/or sexual dysfunctions, his concerns regarding future fertility, and sexual, emotional and/or sociocultural contexts [98].

It is important to determine whether the disorder is generalized (with every partner and in every situation) or situational (specifically precipitated or worsened by partner-related or contextual factors, which should be specified [100]): the former is more likely rooted in the biological etiology of PM and related FSD, while the latter is more likely to involve psychodynamic/relational factors. For example, loss of desire consequent to POF and associated infertility may be precipitated by the partner's inacceptance to remain childless, but may be relieved in a relationship with a partner who already has children.

It should be noted whether the disorder has been lifelong (from the very first sexual experience) or acquired after PM, after months or years of satisfying sexual interaction.

In addition, it should be recorded whether the level of distress consequent to PM and its etiology, and FSD, and its impact on personal life is an important factor. Sexual distress should be distinguished from nonsexual distress and from depression [57,101]. The degree of reported distress may have implications for prognosis and for the woman's motivation for therapy [101].

The woman's perception of the relative weight of different factors contributing to her current complaint should be noted, as well as her (and her partner's) motivation to comply with treatment recommendations [2,38]. In a stable relationship, counseling for both partners could help the couple understand the compounding effects of:

- The woman's impaired physical response from androgen deficiency and reduced sexual self-image from the prematurity of the menopause – both of which reduce her sexual arousability;
- Lack of reward from sexual experiences, resulting in little motivation to repeat them;
- Decreased emotional intimacy due to negative sexual outcomes.

On the positive side, couples should be informed of the possibility of regaining a satisfactory sexual intimacy if appropriate HT, when indicated, and psychosexual support are integrated in the therapeutic approach [2].

Physical examination

Given the importance of the biological disruption associated with PM, the diagnosis of FSD should be made in the context of a rigorous medical assessment [2,5,38,39,102]. Accurate physical examination of the woman, particularly her external genitalia, vagina – including end vaginal pH – and pelvic floor should be carried out, with special attention paid to recording the 'pain map' [39,95] for dyspareunia. Iatrogenic consequences of surgery and/or pelvic radiotherapy (cosmetic and functional) should be recorded [87]. Assessment of vaginal tropism and pH is preliminary to topical estrogenic therapy, when oncologically appropriate, to normalize both the vaginal ecosystem, thus reducing the vulnerability to recurrent vaginitis and cystitis, and vaginal lubrication [2,5,35,39,48–51,102]. The physical examination may also contribute to the assessment of acquired desire disorders, given that they are frequently secondary to sexual pain disorders [39,95].

Clinical approach to psychosexual consequences of premature menopause

Psychosexual impact of premature menopause in adolescents

Psychosexual support should be offered to adolescents who face POF, either spontaneous or iatrogenic [2,5,8–10]. Well-tailored HT, when oncologically appropriate, should be recommended. Bioidentical hormones (i.e., estradiol and natural progesterone) may be appropriate as they 'mimic' the normal cycle. However, many young women prefer the estroprogestinic contraceptive choice (pill, patch or vaginal ring) to feel 'normal' like their fertile friends.

Prevention of infertility in women facing impending premature ovarian failure

Fertility normally peaks in the early twenties. Results from studies on women treated with donor sperm demonstrate that the monthly probability of conception leading to a live birth remains optimal until age 31 years, and decreases progressively thereafter. However, at age 38 years, the monthly probability of conception has already dropped to a quarter of that in women aged below 30 years [7]. This probability of conception is likely to be significantly further

reduced in women facing an earlier menopausal transition, and this should be clearly discussed with the woman/couple when diagnosing impending PM. However, fertility is not definitely excluded in POF and cases of spontaneous pregnancies having been reported 2 years after a confirmed diagnosis of PM [1,2–4].

Protection of fertility in these women is therefore a key issue [2,6]. It may be indicated in young, single women facing a diagnosis of spontaneous POF, or in young couples who cannot commit to/afford a pregnancy in that period of life and yet would like to maintain an open door for the future. It may reduce the emotional and psychosexual impact of ongoing cancer treatment and help to maintain hope in a better future. However, an honest disclosure of current limits of all these techniques should be clearly acknowledged in counseling with patients [6,28–33].

Protection of fertility can be surgical, with transposition of the ovaries away from the radiation field to protect them from the toxic effect of radiotherapy; pharmacologic (with oral contraceptive pills, medroxyprogesterone acetate, gonadotropin-releasing hormone agonists [GnRH-a]); and/or involve assisted reproductive technologies [6].

Three lines of research are currently raising new hopes in the pursuit of ovarian and fertility protection in young women: cryopreservation, temporary ovarian suppression and oocyte protection.

Cryopreservation

Cryopreservation is an option in women with impending POF, either spontaneous (when family history suggests a high risk of it) or in women who have to undergo chemo- and/or radiotherapy for cancer [6]. Oocyte cryopreservation can be considered for single adult women who understand that pregnancy rates are low with this experimental strategy. However, this approach, similar to embryo freezing, needs several weeks of ovarian stimulation.

Women of reproductive age and their partners can undergo a cycle of IVF to cryopreserve their embryos before chemotherapy [29,30]. Unfortunately, most cancer patients do not have sufficient time to complete the necessary ovarian stimulation for IVF, a choice that may also be risky in patients with hormone-dependent cancers. This option is also not acceptable for single women who do not want to use donor sperm for their children [6].

An experimental ovarian cryopreservation and autotransplantation technique has been developed. Cryopreserved ovarian tissue, obtained

from a 30-year-old woman with breast cancer before chemotherapy-induced menopause, was successfully subcutaneously transplanted 6 years later [30]. Ovarian function resumed and 20 oocytes were retrieved. Of the eight oocytes suitable for IVF experiments, one fertilized normally and developed into a four-cell embryo [30]. However, hematological and solid tumors that may spread to the ovary are contraindications to any consideration of grafting.

Temporary ovarian suppression

Experimental temporary ovarian suppression versus chemotherapy for adjuvant therapy in breast cancer has recently been evaluated. The efficacy and tolerability of goserelin (3.6 mg every 28 days for 2 years; $n = 817$) versus cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy (six 28-day cycles; $n = 823$) for adjuvant therapy in premenopausal patients with node-positive breast cancer was tested [28]. Analysis was performed when 684 events had been achieved and the median follow-up was 6 years. A significant interaction between treatment and estrogen status was found ($p = 0.016$). In estrogen receptor (ER)-positive patients (approximately 74%), but not in ER-negative patients, goserelin was equivalent to CMF for disease-free survival (hazard ratio [HR]: 1.01; 95% confidence interval [CI]: 0.84–1.20). Amenorrhea occurred in more than 95% of patients by 6 months versus 58.6% of CMF patients. Menses returned in most goserelin patients after therapy had finished, whereas amenorrhea was generally permanent in CMF patients (22.6 vs 76.9% amenorrheic at 3 years).

Despite these and other positive reports, the long-term effects and benefits of cotreatment with GnRH-a are still unclear. This treatment should therefore be offered as an investigational protocol, with institutional board review, and appropriate informed consent, to young women (and couples) of childbearing age with ER-positive breast cancer who would like to consider maternity after completion of breast cancer therapy.

Oocyte protection

The mechanism mediating the undesirable ovarian toxicity of cancer therapies has only recently been explored. Some important, although very preliminary, insights into the role of ceramide and sphingosine-1-phosphate as a mediator and suppressor, respectively, of cancer therapy-induced oocyte apoptosis have emerged over the

past few years [32]. A better understanding of how radiation and chemotherapy destroy this irreplaceable population of ovarian cells may allow future development of novel lipid-based strategies to prevent infertility and PM. However, this approach is currently only experimental [6].

Management of sexual dysfunction associated with premature menopause

The most important sexual issues are related to:

- Age and psychological impact of the diagnosis of PM *per se*
- Effects of estrogen and androgen loss
- Severity of menopausal symptoms
- Loss of fertility and its meaning to both partners

Early diagnosis of PM is key to effective management. HT is the hormonal etiological answer, when no contraindications exist [15–17]. HT-positive effects on both menopausal symptoms and acquired FSD after PM may be sufficient to normalize sexuality in women with spontaneous POF or after surgical menopause [2,5,34–36,41,42,47–54,74,93,102]. HT is also a prerequisite for the specific treatment of other contributors to sexual dysfunctions after PM. Management of FSD is more difficult in female survivors of breast cancer or genital adenocarcinoma [14,23]. Current contraindications to HT in such patients complicate the treatment of both the menopausal symptoms and concomitant sexual disorders. Optimal management of sexual dysfunction associated with menopause has been recently well discussed [36]. Here the focus is on special issues arising from the prematurity.

Sexual interest/desire disorders

PM may exacerbate lifelong or acquired hypoactive desire/interest disorder, usually comorbid with subjective arousal disorder. Both may benefit from medical and psychosexual approaches.

Medical approach

Hormonal

Androgen treatment, although still considered investigational in many countries, including the USA, may be indicated when the neurobiology of sexual desire is impaired by the androgen loss typical of surgical menopause [34–36,41,47,52–54,74,93]. RCTs indicate the positive effect of androgens, namely testosterone, on different domains of female sexual function [34–36,41,52–54,74,93]. The use of androgens locally for vulvar dystrophy and clitoral insensitivity is often overlooked, but is a very

efficacious treatment for genital sexual dysfunction. A recently published RCT was conducted in surgically menopausal women (aged 24–70) who developed stressful hypoactive sexual desire disorder [47]. Treatment with 300 µg/day testosterone patches in women receiving estrogen therapy increased sexual desire and frequency of satisfying sexual activity and were well tolerated [47]. Secondary outcomes indicate a significant improvement of arousal and orgasm, self-image and self-esteem, and a significant reduction in anxiety and concerns. The testosterone patch treatment was approved by the European Agency for the Evaluation of Medicinal Products in July 2006. Most studies to date have involved women with surgical menopause for benign disease. Androgen treatment attempting to achieve high physiological androgen levels rather than markedly supraphysiological levels is now beginning. Awareness that androgens may be important for sexual arousability and response, as well as possibly increasing sexual thinking and desire, is another important advance [34]. Caution remains regarding hormone-dependent cancers, with different opinions among experts [103]. Hormonal therapy with estradiol and norethisterone [104] has shown a significant improvement in muscle strength, tone and performance in a controlled study in postmenopausal women. This finding is of special interest for women complaining of PM associated with low sexual drive and somatic symptoms, such as reduced muscle competence, who are concerned regarding their fitness and physical shape. Tibolone, available in Europe but not in the USA, via its androgenic metabolite and its ability to significantly reduce sex-hormone binding globulin, has been shown to increase sexual desire/interest and subjective sexual arousal [48]. Long-term safety data for the use of androgens or tibolone regarding cardiovascular or metabolic outcomes are lacking. Careful ongoing follow-up is necessary, in addition to explaining that androgen therapy for sexual dysfunction is still deemed investigational in many countries, even for women with known sudden reduced production.

Nonhormonal

There are no approved nonhormonal pharmacological treatments for low arousability or low desire, but a recent placebo-controlled study of bupropion for nondepressed women with low desire showed increased sexual arousability and response in those receiving active drug [46]. However, changes in 'sexual desire', defined as sexual thoughts and fantasies, were not significantly different from placebo.

Psychosexual approach

Individual psychosexual [44,45] or behavioral therapy [45] should be considered, especially when psychosexual immaturity, attachment issues, sexual inhibitions, poor erotic skills, poor body image, low self-confidence or previous abuse are involved. Any comorbid depression and anxiety should be addressed with a combined pharmacological and psychotherapeutic approach [45]. Associated sexual dysfunction in the partner contributing to the woman's low desire must also be addressed. Similarly, nonsexual couple issues, such as conflicts, poor erotic skills or communication inadequacies, need to be addressed first with couple psychotherapy [44,45].

Arousal disorders

Subjective and combined arousal disorders, either lifelong or acquired, usually comorbid with sexual desire disorders, should be treated as mentioned above [92,100]. Combination of medical and psychosexual therapy is most beneficial.

Medical

Vaginal dryness is the most frequently reported symptom of genital arousal disorders [38,9,42,72,73,92]. It can be treated at least with local estrogen [49–51,102]. The Million Women Study, within the limits of an observational study, is reassuring regarding breast cancer risk when topical vaginal treatments are prescribed, the RR being 0.67 for any type of vaginal estrogen [105]. Its safety in breast cancer patients was recently confirmed in the cohort study of Dew and colleagues [102]. In terms of compliance, one head-to-head study suggested vaginal treatment with tablets of 17- β -estradiol is preferred to topical conjugated equine estrogens [49]. Vaginal estrogenic treatment is key when the genital arousal disorder causes and/or is associated with dyspareunia [2,23,39,50,87,92], postcoital cystitis, urogenital atrophy or urinary incontinence [50,87]. Early treatment, during pelvic or vaginal radiotherapy, may minimize the impact of radiotherapy on vaginal tissue [23].

While women with prior breast cancer, SLE or other known contraindications to exogenous estrogen are prescribed local vaginal estrogen only, the question of systemic estrogen for other women after PM, over and beyond short-term management of menopausal symptoms, remains open. Guidelines from the American College of Obstetrics and Gynecology and the Canadian Society of Obstetrics and Gynecology endorse the careful prescription of systemic estrogen treatment

(ET) for some of these women for ongoing sexual problems. Recommendations from the European Menopause and Andropause Society, the International Society of Menopause and the North American Menopause Society include PM being treated with HT until the age of natural menopause (51 years of age), unless a specific contraindication is diagnosed [15–17]. In iatrogenic PM caused by benign conditions, such as endometriosis when the uterus is preserved, individually tailored continuous combined estrogen plus progesterone is the first choice. Caution regarding systemic HT in breast cancer patients continues after the publication of the Hormonal replacement therapy After Breast cancer diagnosis – Is it Safe? (HABITS) study [106,107], which reduces the optimism from previous studies. Although RCTs of tibolone have shown a positive effect of the drug on both subjective and genital arousal [48], these studies have not focused on women diagnosed with sexual dysfunction. The randomized, prospective, controlled Livial International Study in sexual Arousal disorders (LISA) trial of tibolone in women with breast cancer has been completed. Data should be available in 2007–2008.

Radical hysterectomy accompanying bilateral salpingo-oophorectomy in the young woman may or may not damage the autonomic nerve fibers subserving vaginal and vulval engorgement. Surgeries minimizing damage to autonomic fibers in the uterosacral and cardinal ligaments may minimally impair the urogenic vasodilation [108]. It is possible that phosphodiesterase inhibitors may prove to be beneficial for women with autonomic nerve damage. Early rehabilitation, with topical estrogen (except in women having had an adenocarcinoma) soon after surgery, pelvic floor stretching and vaginal moulds to maintain vaginal elasticity, optimal length and 'habitability', is to be recommended to guarantee the possibility of satisfying intercourse [23].

Psychosexual

Counseling to address the complex psychosexual issues that may inhibit mental arousal and worsen the desire disorder is a key part of the treatment [2,5,38]. Couple support, in stable couples, may also help to address the partner's issues, such as an acquired functional erectile deficit, when vaginal dryness may precipitate it.

Orgasmic disorders

Comorbidity of FSD is frequent; more so in PM women, especially after surgical menopause, as the loss of testosterone may impair both the

central and peripheral mechanisms leading to orgasm [109]. Orgasmic difficulties after PM may also be treated with a combined medical and psychosexual approach.

Medical

True orgasmic disorder acquired subsequent to PM may benefit from HT. Failure to orgasm may be the result of unsatisfactory stimulation of estrogen-depleted vulval and/or vaginal tissues, with pain and soreness distracting from sexual sensations. Topical or systemic estrogen may restore orgasmic potential. However, not uncommonly, there is difficulty in reaching orgasm despite ET and any orgasm is muted. As previously mentioned, androgen's ability to restore orgasmic response is now under more intense investigation, with an increasing body of evidence supporting a positive restorative role of testosterone [34–36,47,52–54]. Pelvic floor rehabilitation is indicated when hypotonia is diagnosed as contributing to reduced orgasmic sensations [109]. Comorbid urge or stress incontinence with fear of leakage with orgasm should be appropriately addressed [109].

Psychosexual

Lifelong 'isolated' orgasmic disorders may benefit from a behavioral educational treatment, encouraging self-knowledge and eroticism with the experience of higher arousal sensations, possibly with use of vibrators [109]. However, more often, lack of orgasm is associated with poor arousal [92], the latter being the focus of treatment.

Lack of orgasm may result from intrapersonal psychological issues related to the PM or to its etiology. Fear of premature aging and loss of sexual attractiveness is a common theme. Emotional distancing between the partners from the outcome and meaning of PM may similarly contribute. Psychological help for the couple or the woman may be needed in addition to a medical approach [109].

Sexual pain disorders

Pain is (almost) never psychogenic. Sexual pain is no exception [39,87]. Attention to biological etiologies of dyspareunia is mandatory also in PM patients, when loss of sexual hormones may be complicated by factors more related to a specific PM etiology, such as vaginal shortening after radical surgery for cervical cancer and/or vaginal narrowing after pelvic or vaginal radiotherapy [22,23,109]. Again, the clinical approach should consider the two, usually interacting, components.

Medical

Dyspareunia may have a prominent endocrine etiology, secondary to sexual hormone loss, in women undergoing spontaneous POF or after surgical menopause for benign conditions. Restoring the hormonal balance through appropriate HT may be sufficient for the woman to enjoy a normalization of her sexual response and a pleasurable intercourse [36,41,42,81,87,95]. Dyspareunia may be variably complicated by different iatrogenic factors, when PM is secondary to medical treatment of cancer [87,95]. Urogenital atrophy may cause painful vaginal entry, a friction type of dyspareunia associated with reduced lubrication, reflexive pelvic muscle tightening or embarrassment from repeated vaginal or urinary tract infections [39,95]. Pelvic radiation may cause painful or impossible vaginal entry. It may also cause distress from the partner's complaint of minimal depth of penetration due to vaginal foreshortening.

The stress of PM may be associated with exacerbation or onset of localized vulvar dysesthesia (formerly known as vulvar vestibulitis syndrome) [43]. There may be pre-existing chronic deep dyspareunia from the underlying disease, for example, endometriosis. Whatever the nature of the initial medical problems, the mechanisms of chronic pain, with its associated central and peripheral sensitization, may be similar [39,95].

Reflexive pelvic muscle tightening ('hyperactivity of the elevator ani') may benefit from self-massage and stretching, electromyographic biofeedback and/or physiotherapy [39,95]. If vulvodinia is present, comprehensive treatment should include pain modulation with predominantly centrally acting drugs, such as pregabalin, gabapentin [43] or amitriptyline, which seems to work both at central and peripheral levels, and peripherally acting analgesic techniques, such as electroanalgesia and/or the ganglion impar block [110]. Reducing the complex biological components of pain is preliminary to the psychosexual support.

Psychosexual

Ongoing sexual symptoms, such as dyspareunia, can contribute to the avoidance of all physical intimacy. Affectionate sharing may partially replace former erotic experiences such that overall emotional satisfaction remains high [39,95]. However, the price of survival – the progressive loss of the erotic life and physical satisfaction – can be high, especially in young women (and couples) where PM is secondary to iatrogenic treatment for malignant conditions [11–14].

Management needs to be both general and specific. Generally the couple can be encouraged to capitalize on nonpenetrative sex – expanding, possibly for the first time, the full range of sexual expression over and beyond intercourse [2]. A brief explanation of the nature of chronic pain and its detrimental effect on the rest of the woman's sexual response cycle should be given to both partners [2]. Specific therapies include behavioral therapy, especially when there is phobic avoidance, vaginal inserts, progressive rehabilitation of the pelvic floor and, if necessary, pharmacological treatment for any intense phobic avoidance [111].

Multidisciplinary teams

Sexual dysfunctions associated with PM need a multidisciplinary approach, given the heterogeneity of etiological factors and the variety of co-morbidity, both in the medical and psychosexual domain. One individual clinician could become skilled in all areas but often appropriate referral is required [2,38] (Box 3).

The gynecologist is usually the first physician to be asked for help for FSD after PM. His/her role is key to prescribe a well-tailored HT, when no contraindications exist, and to address FSD itself, if he/she has special interest in sexual

dysfunction. This approach can be carried out by an internist or family physician with a special interest in sexual medicine, for sexual dysfunctions in either partner. The oncologist is a necessary decision-making partner when HT is considered for cancer survivors. The urologist is another referral resource, when the partner has erectile or ejaculatory dysfunction that is assessed to require medical intervention. The psychiatrist's help is indicated when depression and anxiety are precipitated by PM and do not normalize after HT. Given the increasing awareness of pelvic floor dysfunctions as predisposing, precipitating and/or maintaining factors in the etiology of FSD, before and after PM, the physical therapist is a key figure of the multidisciplinary FSD team, specifically when hyper- or hypo-tonicity of pelvic floor is contributory [2,38].

Physicians may need to specifically refer to psychotherapists with different specializations: to a sex therapist, to address the need for different and more intense sexual stimulation in view of the altered hormonal status, situational erectile dysfunction, either partner's orgasmic difficulties and loss of sexual motivation in either partner; to a couple therapist, when relationship issues are a primary contributor to the sexual dysfunction; to an individual psychotherapist, when personal psychodynamic issues are inhibiting sexual function [2,38,44,45,112].

Before referral, the clinician should establish that the woman has one or more treatable sexual dysfunctions and has tried a first-line hormonal approach if indicated. Medical, lifestyle and relationship issues need to be addressed before specific sexual referral. The sexual symptoms as described by the patient can be summarized in the referral letter, along with the provisional diagnoses. Other medical problems, medications, past relevant medical and surgical interventions, and important psychological and relationship issues should be included. The clinician should also detail management to date, plus outcome. It is helpful to end with expectations (e.g., treat, advise, educate and operate) of the specialist and of the patient. Such transfer of information gives the patient/couple the feeling of coordinated care, and confirms the legitimacy of their sexual complaints and the healthcare providers' commitment to address them with an integrated approach [38].

Conclusion

PM is a heterogeneous condition comprising widely different etiologies. Early assessment of the individual's risk of developing POE, development

Box 3. Referral resources.

- Gynecologist: when premature menopause (PM) requires a well tailored hormone treatment (HT) and/or diagnosis of pelvic comorbidities.
- Gynecologist with special interest in sexual dysfunction: when sexual dysfunction requires specialized evaluation and/or treatment.
- Reproductive endocrinologist: when fertility protection and/or fertility assisted technology is an issue.
- Urologist: when the partner has erectile or ejaculatory dysfunction that is assessed to require medical intervention.
- Internist or family physician with special interest in sexual medicine: for sexual dysfunctions in either partner and/or metabolic comorbidities (e.g., diabetes).
- Oncologist: when HT is considered for cancer survivors; and/or recurrences are present.
- Psychiatrist: when depression and anxiety are precipitated by PM.
- Sex therapist: to address the need for different and more intense sexual stimulation in view of the altered hormonal status, situational erectile dysfunction, either partner's orgasmic difficulties, as well as loss of sexual motivation in either partner.
- Couple therapist: when relationship issues are a primary contributor to the sexual dysfunction.
- Individual psychotherapist: when personal psychodynamic issues are inhibiting sexual function.
- Physical therapist: when hyper- or hypo-tonicity of pelvic floor is contributory.

Modified from [38].

of a strategic management plan, and timely commencement of infertility and hormone deficiency treatment, together with counseling, in an integrated management plan should improve both the short- and long-term health of those with POF.

The impact of PM on women's sexuality is modulated by its etiology, the lifecycle stage, factors personal to the woman, as well as those related to relationship, family and society. Age is a critical factor: the earlier the PM, the higher the likelihood of complex impairment of many aspects of sexuality. PM may be associated with delay in reaching psychosexual maturity, impairment of the sense of sexual identity, onset or exacerbation of sexual dysfunction, and emotional distancing of partners. When appropriate HT is prescribed, and the woman and her partner have worked through the real and symbolic losses of PM, the sexual outcome is generally positive. Sexual adjustment can be increasingly difficult when women are younger, single or in troubled relationships, when childlessness is a major loss, when the partner cannot accept a childless future, and when the socioeconomic status is low. Improvement of the sexual outcome requires a comprehensive assessment of the predisposing, precipitating and maintaining factors using a combined medical and psychosexual approach. Appropriate counseling, medical and psychosexual, is a critical component of the relationship between the woman and her healthcare provider(s) on such a sensitive issue. In the case of a stable relationship, listening to and counseling the couple may be critical, more so when infertility is a core issue and/or specific sexual disorders are complained of.

Future perspective

The incidence of POF is increasing, largely due to improved survival rates of cancer patients treated with radiation and chemotherapy. The two major determinants of ovarian damage following cancer

therapy are the woman's age and the class of chemotherapeutic agents used. As delayed diagnosis and management of POF leads to suboptimal outcomes, anticipation and early detection of this condition in high-risk women by means of ovarian function testing, followed by early institution of appropriate management, should become a routine part of cancer patients' follow-up, to increase their quality of life and sexual life. Choice of strategies should vary depending on the age of onset, associated symptoms and fertility aspirations of the individual, and should change with the patient's advancing age.

A strong educational effort is needed, both among healthcare providers and women, to increase their awareness of PM and the need for early diagnosis and treatment.

Counseling on sexual issues after spontaneous or iatrogenic POF should be increasingly offered in every menopausal clinic and in oncology centers.

Given the current controversy on the 'real' androgen deficiency [34,74,75], further research on the specific role of PM in the etiology of sexual dysfunction and safety data for long-term estrogen and androgen therapy in young women with PM are needed.

The most promising area of PM research involves fertility preservation: prevention of gonadal toxicity in all conditions requiring chemotherapy (either malignant or benign, such as SLE) is rapidly improving and future studies will design different treatment options.

Development of better freezing, thawing and maturation techniques is expected to improve pregnancy rates following oocytes cryopreservation in PM patients.

Gynecologists, reproductive endocrinologists, oncologists and family physicians should become increasingly familiar with the options available to preserve fertility in young cancer survivors. Options should be discussed before starting treatment.

Executive summary

Definition of premature menopause & key features

- Premature menopause (PM) refers to menopause occurring at or before the age of 40 years.
- PM may be spontaneous, which is referred to as premature ovarian failure (POF).
- PM may be iatrogenic: secondary to surgical removal of both ovaries (bilateral oophorectomy), or to the irreversible ovarian damage caused by chemotherapy or radiotherapy.
- Surgical menopause suddenly deprives the woman of the total ovarian hormone production.
- POF, either spontaneous or iatrogenic, has a gradual, insidious evolution over 2 or more years.
- Occasional ovulation is possible for 2–3 years after POF diagnosis, defined as follicle-stimulating hormone elevation above 40 International Units (IU)/l in two consecutive samples, 1-month apart.
- A variable ovarian testosterone production is maintained after POF.
- The POF acronym currently encompasses all modalities of ovarian exhaustion when the ovaries remain *in situ*.

Executive summary (cont.)

Prevalence of premature menopause

- Spontaneous POF affects, on average, 1% of women aged under 40 years, although percentages as high as 7.1% have been reported.
- Iatrogenic menopause, caused by benign and malignant conditions, affects 3.4–4.5% of women aged under 40 years.

Prevalence of female sexual disorders after premature menopause

- 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 increases with age, while the distress associated with the loss of desire is inversely correlated with age.

Etiology of premature menopause & health vulnerabilities

- Heterogeneity is the hallmark of the PM etiology.
- Etiology can be genetic, autoimmune, associated with chronic diseases or iatrogenic in the context of benign or malignant disease.
- PM should be considered in the differential diagnosis when, independent of the fertile age of the woman, premenopausal symptoms are complained of.

Factors modulating sexual issues associated with premature menopause

- 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.
- Stage in life cycle may contribute to FSD, fertility being a major issue in childless women and couples.
- The woman's coping attitude, personality, mental wellbeing and quality of sexuality before PM may all affect the sexual outcome after PM.
- Education, socioeconomic status, professional role and access to qualified medical care affect PM and FSD outcome.
- The partner's reaction to the associated infertility, his/her personal and sexual health, the quality of intimacy and of the relationship 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 premature menopause

- Estrogens and androgens modulate the neurobiology of sexual desire and mental arousal, and the neurovascular cascade of events leading to genital arousal, lubrication and orgasm.
- Estrogen is thought to be a modulator of sexual response, and a permitting factor for the vasoactive intestinal polypeptide, which translates desire and central arousal into vaginal congestion and lubrication.
- Testosterone is thought to have an initiating role in desire and central arousal, acting on the dopaminergic appetitive pathway, and a modulator role in the peripheral response as a permitting factor for nitric oxide, the key mediator of clitoral and cavernosal body congestion.
- Estrogen and androgen loss combine to reduce desire and central and peripheral arousal, with vaginal dryness, and cause/worsen orgasmic difficulties and dyspareunia, causing loss of self-confidence and self-esteem, and increase in anxiety and concerns.
- Comorbidity of FSD is frequent.
- Concomitant medical comorbidities associated with or consequent to different etiologies of PM may contribute to FSD.

Diagnosis of premature menopause

- Impending PM is hypothesized when menopausal symptoms appear in women younger than age 40 years, leading to POF.
- Definite diagnosis is based on follicle-stimulating hormone levels above 40 IU/l in two consecutive samples, 1-month apart.
- Ecography may show small ovaries for the age, with no residual oocytes.
- PM is implicit when bilateral oophorectomy is performed in women younger than age 40 years.

Diagnosis of female sexual disorders after premature menopause

- FSD may be antecedent to PM, concomitant to PM, and/or specifically caused and/or maintained by PM.
- Early diagnosis is key to minimize health and sexual consequences.
- Biological, psychosexual and contextual factors, including having a partner and his/her attitude, may modulate the scenario of the individual FSD experience.
- Diagnosis should consider etiology of FSD, the disorder being generalized or situational, lifelong or acquired, and the level of distress it causes.
- In stable relationships, counseling for both partners is a crucial part of the diagnosis and management.
- Accurate physical examination is mandatory, given the importance of biological disruptions associated with PM, with focus on tropism of external genitalia, vagina and vaginal pH, pelvic floor tonicity and 'pain map', in the case of dyspareunia.

Executive summary (cont.)**Treatment of premature menopause**

- Tailored HT is the treatment of choice in POF (when noncontraindicated, i.e., in survivors of breast cancer or genital adenocarcinoma, or after thromboembolic disease and acute hepatitis).
- Systemic estrogen therapy (ET) is the choice in women who underwent hysterectomy besides oophorectomy.
- Topical vaginal ET may address vaginal atrophy and bladder symptoms when system ET is not suitable or not considered.
- Recommendations from the European Menopause and Andropause Society, the International Society of Menopause and the North American Menopause Society include PM being treated with HT until the age of natural menopausal (51 years) unless a specific contraindication is diagnosed.

Management of female sexual disorders associated with premature ovarian failure

- The most important sexual issues are related to: age and psychological impact of the diagnosis of PM *per se*; effects of estrogen and androgen loss; severity of menopausal symptoms; and loss of fertility and its meaning to both partners.

Management of desire disorders

- Randomized, controlled trials (RCTs) indicate the positive effect of testosterone in estrogen-replenished women after surgical menopause, when etiology appears to be hormone dependent.
- RCT treatment with 300 µg/day testosterone patches in estrogen-replenished women increased sexual desire and frequency of satisfying sexual activity, and was well tolerated.
- 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 was approved by the European Agency for the Evaluation of Medicinal Products in July 2006.
- Tibolone and HT with estradiol and norethisterone are other options to improve sexual desire.
- Bupropion is a nonhormonal drug that may improve sexual desire.
- Psychosexual support includes individual behavioral therapy; psychotherapy to cope with the many losses PM and its etiology have caused; and couple's therapy to address nonsexual couple issues, such as conflicts, poor erotic skills or communication inadequacies.

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, leading complaint of genital arousal disorders, can be treated with vaginal estrogens.
- Safety of vaginal estrogen therapy has been documented in RCT and in observational studies such as the Million Women Study, the relative risk of breast cancer being of 0.67 for whatever type of vaginal estrogen used.
- Vaginal estrogenic treatment is key when the genital arousal disorder causes and/or is associated with dyspareunia, postcoital cystitis, urogenital atrophy or urinary incontinence.
- Psychosexual counseling is synergic in desire and arousal disorders.

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.
- When lack of orgasm is associated with poor arousal, the latter is the focus of psychosexual treatment.

Management of sexual pain disorders such as dyspareunia

- Pain is (almost) never psychogenic. Sexual pain is no exception.
- 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 present, treatment should include pain modulation with drugs, such as pregabalin, gabapentin and/or amitriptyline, and peripherally acting analgesic techniques, such as electroanalgesia and/or the ganglion impar block.
- Psychosexual therapy includes behavioral therapy, vaginal inserts/moulds, progressive rehabilitation of the pelvic floor and, if necessary, pharmacological treatment for any intense phobic avoidance.

Conclusions

- PM, and FSD reporting after PM, is increasing.
- FSD increases with age. However, the distress associated to FSD is inversely correlated with age. Women with PM are at higher risk for distressing sexual disorders.
- Positive outcomes of a RCT of 300 µg testosterone patches in treating desire disorders (and associated FSD) in surgically menopausal women will fuel new interest in addressing FSD in PM women.
- Awareness of the impact of PM on general and sexual health will increase in the next few years.
- More studies are needed to improve fertility protection in women undergoing POF and to assess long-term safety of HT.

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