Sexuality in premature ovarian insufficiency

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Introduction

Premature ovarian insufficiency (POI) is an early event in the reproductive life span with a significant impact on several dimensions of women’s well-being and general health. It affects 1% of women under age 40 years, 0.1% of women under age 30 years, and 0.01% of women under 20 years of age. POI prevalence appears to vary by ethnicity, being higher in women from African and Latin American countries. Such terminology describes the spectrum of conditions associated with the loss of ovarian function prior to the natural age of menopause. It includes both spontaneous POI and those situations in which POI derives from iatrogenic interventions such as radiation therapy, chemotherapy, or surgery. Women with POI may display established premature menopause or present with intermittent residual ovarian function. The premature hormonal deficiency may be of unknown origin or may be the result of several etiologies, including genetic, autoimmune, metabolic, and infective causes, which lead to ovarian follicular dysfunction or depletion of functional primordial follicles. Spontaneous early menopause affects approximately another 5% of women between ages 40 and 45 years. Moreover, even though the rate of bilateral oophorectomies routinely performed at the time of hysterectomy is declining, a significantly high number of women still enter menopause earlier due to bilateral oophorectomy performed for treatment of ovarian pathology or for prophylactic purpose in women genetically predisposed to breast and ovarian cancer. The percentage of cancer survivors has also increased over time because of improved success in the treatment of cancer in children, adolescents, and reproductive-age women. Therefore, early hormonal deprivation occurs in a large number of women and the short-term and long-term consequences are variable, depending mainly on age at onset and type of POI. Importantly, these consequences may include the burden of infertility and the management of fertility preservation.

POI is usually diagnosed when two follicle stimulating hormone levels in the menopausal range (>30 U/l), at least 1 month apart in the setting of 4–6 months of amenorrhea, are documented. A timely diagnosis and a tailored hormonal treatment at least until the average age at natural menopause occurring around 50 years are mandatory to relieve menopausal symptoms, and to prevent osteoporosis, cardiovascular risks, and neurocognitive disorders and the increased risk of overall mortality in women with early experience of menopause. On the other hand, POI requires adequate counseling at multiple levels, including psychosexual therapy and counseling; androgens; counseling; androgens and cognitive-behavioral and sexual interventions.
function in women with POI, focusing mainly on spontaneous conditions. In addition, we will point to the need for further research in the area of sexual dysfunction in order to manage POI women effectively and with a comprehensive biopsychosocial approach.

Sexual function in relation to premature ovarian insufficiency

Biomedical and psychosocial variables contribute to sexual dysfunction in women with POI (Figure 1), exactly as in every postmenopausal woman. The efforts of health-care providers (HCPs) should be to recognize the impact, to diagnose the condition, and to establish the most effective treatment plan. There is a paucity of well-designed research on sexual function in women with spontaneous POI and many studies address sexual concerns generally as part of the climacteric syndrome. The Women’s Health Questionnaire sexual behavior score was lower in women entering menopause earlier compared to women of typical peri/postmenopausal age. Using the Short Personal Experiences Questionnaire, 50% of POI women reported sexual dysfunction, in spite of the high proportion (69%) currently taking hormone therapy (HT). In young estrogen-replete women with spontaneous 46,XX POI, the Derogatis Interview for Sexual Function Self-Report (DISFSR) indicated that scores were lower, but still in the normal range, in comparison with regularly menstruating controls. van der Stege et al. investigated sexual function using the Questionnaire for Screening Sexual Dysfunctions in 81 women with POI and 68 controls, demonstrating that POI women had diminished general and sexual well-being and were less satisfied with their sexual lives. In addition, they had fewer sexual fantasies and masturbated less frequently. Sexual contact was associated with less sexual arousal, reduced lubrication, and increased genital pain. The experience of sexual symptoms was associated with significant distress. However, the frequency of actual sexual contact with the partner, as well as the frequency of desire to have sexual contact, did not differ between women with POI and control women. Women having a partner and wishing to have (more) children displayed a higher frequency of desire for sexual contact. A cross-sectional study including 58 women with a diagnosis of POI compared with a control group composed of 58 women of reproductive age with normal ovarian function, paired for age (±2 years), indicated 62.1% of sexual dysfunction (total Female Sexual Function Index [FSFI] score ≤ 26.55) in the POI group compared with 37.8% (n = 22) in the control group (p = 0.0093). Belonging to the POI group increased a woman’s likelihood of having sexual dysfunction by 2.8-fold (odds ratio = 2.78, 95% confidence interval 1.29–5.98, p < 0.05) and the only FSFI domain in which no statistically significant difference was found between the two groups was desire. In another cross-sectional study with 80 women with POI, matched by age to 80 women with normal gonadal function, Benetti-Pinto et al. explored the proportional influence of each domain on the composition of the total FSFI score. Exploratory factor analysis of sexual function showed that the domain with greater influence in the total FSFI score was arousal, followed by desire. Of interest, even after 12 months of systemic HT, women with POI displayed significantly lower FSFI domain scores in comparison with age-matched women with normal gonadal function, despite having similar tropism and vaginal flora.

Collectively, these data suggest an overall impact of POI on sexual function and point to the need to further explore the desire domain, which seems highly sensitive to both hormonal and intimacy-based stimuli and partially linked to subjective arousal.

Premature ovarian insufficiency as an endocrine challenge for sexuality

Early hormonal deprivation is a major challenge for women with POI and may explain the occurrence of sexual symptoms from a biomedical perspective (Figure 1). Poor physical and mental health associated with early menopause may be an additional factor significantly contributing to the impairment of sexual function in POI women.

Estrogens

Changes of circulating levels

Hypoestrogenism can occur suddenly or progressively at different life stages depending on the etiology of POI. Sharp decline in or fluctuations of estrogens may affect neuroendocrine circuitries and neurovascular/neuromuscular pathways mediating sexual response within the brain and at various peripheral tissues.

Brain effect

Estrogens target brain areas critical to emotional and cognitive well-being, and sexual symptoms are likely to be the result of the domino effect of menopausal complaints. Indeed, most of the neurotransmitters and neuromodulators contributing to the mental component of sexual response
are involved in other central nervous system adjustments influencing mood and behavioral responses to menopause\textsuperscript{27,29}.

**Peripheral effect**

Estrogens target peripheral tissues to translate sexual clues into physical arousal\textsuperscript{27}. Estrogens are also vital for the functional anatomy of urogenital tissues, favoring congestion and lubrication with arousal and preventing signs and symptoms of vulvovaginal atrophy (VVA)\textsuperscript{30}, recently renamed genitourinary syndrome of menopause (GSM) to include also the effect of aging and androgen deprivation\textsuperscript{31}.

**Androgens**

**Changes in circulating levels**

A systematic review and meta-analysis of controlled observational studies demonstrated that total testosterone concentrations are decreased in women with spontaneous POI or iatrogenic menopause controlling for age and body mass index\textsuperscript{32}. Another similar study investigating serum androgen profiles in women with POI confirmed the risk for decreased concentrations of testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione. However, DHEAS levels are lower in postmenopausal controls when compared with POI cases, because of their different age\textsuperscript{33}. Whereas the lack of ovarian contribution to circulating androgens is overt in young women with iatrogenic menopause due to surgery or gonadal disruption due to chemotherapy or radiotherapy\textsuperscript{34–36}, the mechanisms behind lower ovarian production of androgens in spontaneous POI women remain to be elucidated. Ovarian autoimmunity and concomitant adrenal autoimmunity\textsuperscript{37} may be one of the possible explanations for lower androgen secretion from steroidogenic cells together with other unknown mechanisms associated with POI.

**Brain effects**

Androgens target brain areas critical to motivation and sexual satisfaction. The cluster of signs and symptoms associated with the so-called androgen insufficiency syndrome is an indirect evidence of androgen action because it includes sexual dysfunction and other central nervous system symptoms\textsuperscript{38}. Moreover, surgical menopausal women are at risk for low testosterone concentration and report a high rate of hypoactive sexual desire disorder\textsuperscript{19}.

**Peripheral effects**

Androgens target peripheral tissues and diminished testosterone levels contribute to symptoms and health risks traditionally attributed to premature low concentration of estrogens\textsuperscript{40}. Several lines of evidence corroborate the idea that androgens cooperate with estrogens in human genital-urinary physiology, preventing reduced collagen and elastin, thinning epithelium, altered function of smooth muscle, loss of elasticity and flexibility, diminished blood supply, and changes of nerve activity, as a consequence of hormonal deprivation\textsuperscript{41}. Such an effect is evident not only in vaginal tissues, but also in labia majora and labia minora, vestibule, clitoris, urethra, and bladder, explaining in part the high rate of sexual dysfunction in women with low androgens\textsuperscript{42}.

**Conflicting evidence of androgen levels and sexual response in clinical studies**

Establishing a clear link between circulating androgens and sexual response in women is difficult\textsuperscript{43} and POI is no exception. One of the few studies linking androgen milieu to sexuality indicated that women with premature ovarian failure did not show an important independent role for androgens in various aspects of sexual functioning, in spite of having lower androgen levels\textsuperscript{20}. A similar result was obtained correlating total testosterone levels to a validated sexual self-report interview in young women who had spontaneous 46,XX primary ovarian insufficiency and were receiving physiologic estradiol replacement\textsuperscript{19}.

**Premature ovarian insufficiency as a psychosocial challenge for sexuality**

Intrapersonal and interpersonal factors (Figure 1) may also be important to explain sexual consequences of POI, as indicated by the lack of difference between sexual function and distress in women who are unaware that they have POI and age-matched women with normal gonadal function\textsuperscript{44}. Following diagnosis, psychological difficulties are present in POI women, including high levels of depression and perceived stress, and low levels of self-esteem and life satisfaction\textsuperscript{45,46}. Spontaneous POI women also perceive lower levels of social support\textsuperscript{47} and there is a positive correlation between functional and spiritual well-being\textsuperscript{48}. In an Australian observational study including 25 women with spontaneous POI, 17 women with surgically induced menopause, 12 women with chemically induced menopause, and 23 controls, depression, anxiety, body image, and self-confidence are compromised for women across different groups of POI\textsuperscript{49}. A cross-sectional study exploring measures of psychosocial distress in women with Turner syndrome, early menopausal women with normal karyotype, and healthy controls showed that hormonal deficiency is not the sole factor explaining the psychological burden of these dissimilar groups of POI women. Indeed, the majority of menopausal women were taking HT and had similar psychosocial profiles, with increased shyness, social anxiety, and depression, and decreased self-esteem compared with women with healthy ovarian function\textsuperscript{50}. In another study, psychological distress measured by validated scales was lower in POI women irrespective of their androgen levels\textsuperscript{20}. Moreover, the evidence that augmentation of standard HT with physiologic testosterone replacement (150 μg) in young women with POI neither aggravates nor improves baseline reports of quality of life (QoL), or self-esteem, and has minimal effect on mood against placebo following 12 months\textsuperscript{51} further reinforces the idea that POI is a distressing condition by itself. However, these data do not exclude that androgens can make a difference in modulating emotional and sexual well-being in young POI women, depending on type, dose, and timing of use.
Singer et al.\textsuperscript{18} explored concerns and needs of POI women in the UK with qualitative and quantitative measures, demonstrating that infertility is the most disturbing aspect of entering an early menopause followed by other dimensions of physical and mental well-being. In particular, women with POI had an impairment of QoL, reporting significantly more emotional role limitation and poorer social functioning, vitality, and mental health than women of typical menopausal age. Experiencing hot flushes and/or night sweats, having less satisfaction with medical services, and being younger were associated with poorer psychosocial functioning\textsuperscript{17}. Avoidance to acknowledge stress deriving from infertility, regardless of parity status, seems to be the most important factor to cope with POI in a negative manner\textsuperscript{52}. However, concerns regarding long-term health are also very important, as well as sexual and relational aspects. Thus, apart from the achievement of reproductive goals, POI is a life-altering diagnosis encompassing multiple dimensions of womanhood\textsuperscript{49}.

**Psychosexual counseling in women with premature ovarian insufficiency**

Basic counseling is an integral part of treating the psychosexual consequences of menopause\textsuperscript{54} and it seems even more important for POI women according to several investigations\textsuperscript{17,18,52}. Professional help to assist in coping with this highly distressing condition should be provided. Indeed, the majority of POI women felt that they had been offered inadequate information on their own condition and when they identified specific sexual symptoms, such as vaginal dryness and poor sexual desire, only about half of the study sample identified specific sexual symptoms, such as vaginal dryness and equate information on their own condition and when they identified specific sexual symptoms, such as vaginal dryness and poor sexual desire. Avoidance to acknowledge stress deriving from infertility, regardless of parity status, seems to be the most important factor to cope with POI in a negative manner\textsuperscript{52}. However, concerns regarding long-term health are also very important, as well as sexual and relational aspects. Thus, apart from the achievement of reproductive goals, POI is a life-altering diagnosis encompassing multiple dimensions of womanhood\textsuperscript{49}.

Medical treatments should be part of a multidisciplinary management of POI taking into account that this is a special cohort of women who have natural menopause beyond the age of 50 years\textsuperscript{53}. HT is a real replacement, even though little evidence is specifically available in POI women in order to establish the more appropriate treatment for them\textsuperscript{1,13}. Unless there is an absolute contraindication to taking estrogen therapy, guidelines and recommendations all agree on the need to prescribe it for women with POI to reduce the risk of osteoporosis, cardiovascular disease, and symptomatic VVA and to maintain sexual health and QoL. A progestin needs to be added for those with an intact uterus, whereas in the case of spontaneous ovarian activity combined estrogen–progesterin contraception may be considered to avoid the pregnancy risk, which is, however, very low\textsuperscript{63–68}. Transdermal estradiol in higher doses with adequate endometrial protection seems to be the best choice to control symptoms and to obtain bone protection\textsuperscript{69,70}.

**Considerations in managing sexual symptoms with hormonal therapies**

There is a knowledge gap in the management of sexual symptoms specifically in POI women (Table 1). The principle of avoiding androgen insufficiency induced by administration of androgen therapy, guidelines and recommendations all agree on the need to prescribe it for women with POI to reduce the risk of osteoporosis, cardiovascular disease, and symptomatic VVA and to maintain sexual health and QoL. A progestin needs to be added for those with an intact uterus, whereas in the case of spontaneous ovarian activity combined estrogen–progesterin contraception may be considered to avoid the pregnancy risk, which is, however, very low\textsuperscript{63–68}. Transdermal estradiol in higher doses with adequate endometrial protection seems to be the best choice to control symptoms and to obtain bone protection\textsuperscript{69,70}.

### Table 1. Treatments for sexual function problems with some evidence in postmenopausal women and whether they have been evaluated specifically in women with spontaneous POI.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence in postmenopausal women</th>
<th>Evidence in women with spontaneous POI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause hormone therapy (estrogens/progestogens)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tibolone</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Transdermal testosterone Oral DHEA</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Lubricants/moisturizers</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Local estrogen therapy</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Local testosterone cream</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Local DHEA pessary</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Laser therapy</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Psychossexual therapy</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Pelvic floor/physical therapy</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

DHEA, dehydroepiandrosterone; POI, premature ovarian insufficiency; +, yes; –, no.
of exogenous hormones should guide clinical decisions. Then, transdermal estradiol may be preferable over oral estrogen therapy because of less effect on sex hormone-binding globulin and free testosterone levels and modest improvement of sexual function in early postmenopausal women. Similarly, the use of a natural estradiol-containing contraceptive pill should be preferred over ethinylestradiol. Even androgenicity of progestogens has some value. Tibolone, a special form of HT with weak androgenic properties, was investigated in postmenopausal women with low desire and poor arousal, showing positive results. Various local estrogen treatments are equally effective in reversing VVA/GSM symptoms, including dyspareunia and other associated sexual dysfunctions, alone or even combined with systemic HT. They have a good safety profile because low doses result in minimal systemic absorption.

**Non-hormonal alternatives**

Women with contraindications to hormonal medications are candidates for alternative non-hormonal strategies to manage short-term and long-term consequences of POI. Lifestyle changes, mind–body techniques, dietary management and supplements, prescription therapies, and other strategies are available. Paroxetine salt, approved by the US Food and Drug Administration for the management of vasomotor symptoms, and other selective serotonin reuptake inhibitors/psychoactive agents may be used to relieve menopausal symptoms, including mood disorders. However, HCPs should consider that selective serotonin reuptake inhibitors are associated with secondary sexual dysfunction in 35–70% of users.

Lubricants and vaginal moisturizers are the first-line treatments for isolated VVA/GSM symptoms. Lubricants are short-acting substances (water, silicone, or oil based) that are useful to reduce friction during sexual activity, whereas moisturizers are longer acting than lubricants and their efficacy has been tested in clinical studies. Even 4% aqueous lidocaine versus saline showed efficacy for insertional dyspareunia. Other strategies include psychosexual therapy and pelvic floor/physical therapies. Increasing evidence supports efficacy of the microablative fractional carbon dioxide laser or the non-ablative vaginal erbium YAG laser in alleviating VVA/GSM symptoms, but long-term efficacy and safety data are warranted.

**Androgens**

The role of systemic androgen therapy in women with spontaneous POI is presently still controversial, even though high physiologic doses of transdermal testosterone for the treatment of hypoactive sexual desire disorder in postmenopausal women and women in their late reproductive years showed effectiveness and safety. Until data are available in POI women, androgen replacement therapy should not be given routinely, but the decision-making process has to follow the standard process of care for postmenopausal women presenting with sexual problems. If androgen therapy is commenced, treatment effect should be evaluated after 3–6 months and women with POI should be informed that limited data on long-term safety are available. Androgenic side-effects (acne, hirsutism, deepening of the voice, and androgenic alopecia) are rare with doses below 300 µg of testosterone per day. Pregnancy is uncommon in young women with POI and, in case they are using androgens, the virilization risk to the fetus is minimal and occurs in a very high hyperandrogenic state. In women with autoimmune ovarian failure and coexisting adrenal insufficiency, adrenal androgen therapy with oral dehydroepiandrosterone (DHEA) may be beneficial.

Local androgens, such as DHEA pessaries and testosterone cream, deserve future consideration to improve sexual function in POI women. A series of studies based on the science of intracrinology demonstrated that daily intravaginal administration of 0.50% (6.5 mg) DHEA (prasterone) has local beneficial effects on VVA/GSM symptoms, including moderate to severe dyspareunia or pain at sexual activity. On the other hand, a recent double-blind, randomized, placebo-controlled trial showed that intravaginal testosterone cream (300 µg per dose), self-administered daily for 2 weeks and then thrice weekly for 24 weeks, significantly improved sexual satisfaction and reduced dyspareunia in postmenopausal women on aromatase inhibitor therapy.

**Conclusion**

Women with POI deserve special care because the early onset of hormonal deficiency brings a multitude of short-term and long-term consequences, including sexual dysfunction. Accurate diagnosis, sensitive counseling, and tailored treatment are key factors for effective management in a biopsychosocial perspective. However, more research is needed in order to understand the complexity of factors involved in the occurrence of sexual symptoms in POI women. At present, HT is the mainstay, but psychosexual counseling is essential to overcome the burden of the condition and invest in the life goals and expectations of young women and, eventually, of their partners.

**Conflict of interest**

R. E. Nappi had past financial relationships (lecturer, member of advisory boards, and/or consultant) with Boehringer Ingelheim, Ely Lilly, Gedeon Richter, HRA Pharma, Pfizer Inc., Procter & Gamble Co., TEVA Women’s Health Inc, and Zambon SpA. At present, she has an ongoing relationship with Bayer HealthCare AG, Endoceutics, Exceltis, Merck Sharpe & Dohme, Novo Nordisk, Palatin Technologies, Shionogi Limited, and Theramex. The other authors do not declare any conflict of interest.

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