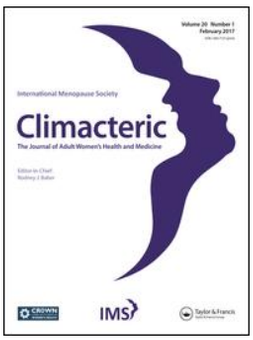

Climacteric

ISSN: 1369-7137 (Print) 1473-0804 (Online) Journal homepage: https://www.tandfonline.com/loi/icmt20

Sexuality in premature ovarian insufficiency

R. E. Nappi, L. Cucinella, E. Martini, M. Rossi, L. Tiranini, S. Martella, D. Bosoni & C. Cassani

To cite this article: R. E. Nappi, L. Cucinella, E. Martini, M. Rossi, L. Tiranini, S. Martella, D. Bosoni & C. Cassani (2019): Sexuality in premature ovarian insufficiency, Climacteric, DOI: 10.1080/13697137.2019.1575356

To link to this article: https://doi.org/10.1080/13697137.2019.1575356

Published online: 22 Mar 2019.

CLIMACTERIC
https://doi.org/10.1080/13697137.2019.1575356

Taylor & Francis
Taylor & Francis Group

REVIEW

Sexuality in premature ovarian insufficiency

R. E. Nappi, L. Cucinella, E. Martini, M. Rossi, L. Tiranini, S. Martella, D. Bosoni and C. Cassani

Research Center for Reproductive Medicine, Gynecological Endocrinology and Menopause, Obstetrics and Gynecology Unit, IRCCS S. Matteo Foundation, Department of Clinical, Surgical, Diagnostic and Paediatric Sciences, University of Pavia, Pavia, Italy

ABSTRACT

Sexuality in women with spontaneous premature ovarian insufficiency (POI) deserves attention because of the young age and the distressing impact of such a life-changing diagnosis. Biomedical and psychosocial factors work in concert to determine significant changes of sexual function. Early hormonal deprivation gives origin to symptomatic vulvovaginal atrophy and contributes to hypoactive sexual desire disorder modulating central and peripheral circuitries, which regulate sexual response. Emotional and cognitive adjustment to the short-term and long-term consequences of POI may further determine negative attitudes toward sexuality. It is essential to counsel POI women on every aspect of their life, from menopausal symptoms to fertility concerns, from health risks to potential therapeutic solutions. The biopsychosocial perspective is the best approach to manage sexual symptoms, including tailored hormone therapy and focused counseling. Pharmacotherapies specifically investigated in spontaneous POI conditions are lacking and clinical judgment has to guide the choice of treatment, which must be continued at least until the average age at natural menopause according to the most recent guidelines. Further studies are needed to better characterize POI women and to understand the effective role of novel therapeutic strategies, including androgens and cognitive-behavioral and sexual interventions.

ARTICLE HISTORY
Received 7 November 2018
Revised 8 January 2019
Accepted 22 January 2019
Published online 22 February 2019

KEYWORDS
Premature ovarian insufficiency; female sexual function; female sexual dysfunction; estrogens; androgens; counseling; psychosexual therapy

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[1]. 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[2]. POI prevalence appears to vary by ethnicity, being higher in women from African and Latin American countries[3]. 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[4]. 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[5]. Spontaneous early menopause affects approximately another 5% of women between ages 40 and 45 years[6]. 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[7]. 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[8]. 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[9,10]. Importantly, these consequences may include the burden of infertility and the management of fertility preservation[11].

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[12]. 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[13] and the increased risk of overall mortality in women with early experience of menopause[14]. On the other hand, POI requires adequate counseling at multiple levels, including psychosocial and sexual consequences, because there is an acceleration of the aging process. Indeed, hormonal replacement is not always entirely able to relieve the multitude of implications for women who have to move forward with their own lives in a POI state[15].

Here, we will summarize the complex interplay of biomedical and psychosocial factors significantly affecting sexual

CONTACT R. E. Nappi renappi@tin.it Research Centre for Reproductive Medicine, Obstetrics and Gynecology Unit, IRCCS Policlinico San Matteo, Piazzale Golgi 2, 27100 Pavia, Italy

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[16]. 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[17]. 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)[18]. In young estrogen-replete women with spontaneous 46,XX POI, the Derogatis Interview for Sexual Function Self-Report (DISF-SR) indicated that scores were lower, but still in the normal range, in comparison with regularly menstruating controls[19]. van der Stege *et al.*[20] 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 $\leq$ 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[21]. In another cross-sectional study with 80 women with POI, matched by age to 80 women with normal gonadal function, Benetti-Pinto *et al.*[22] 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[23].

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[24].

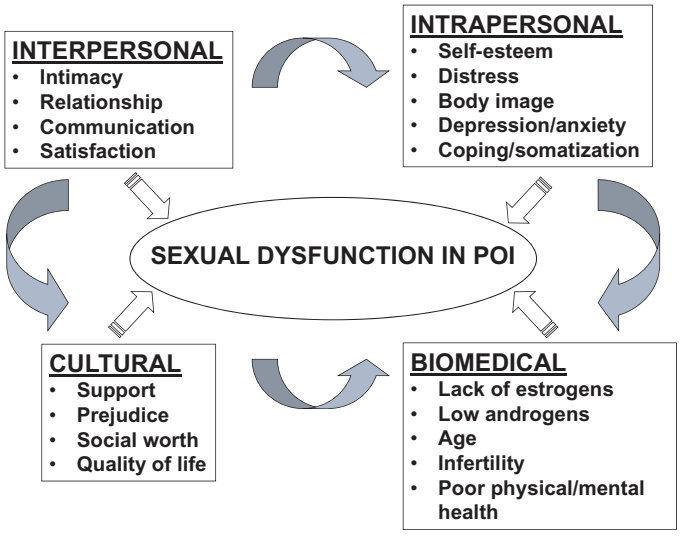

Figure 1. Multitude of biomedical and psychosocial variables contributing to sexual dysfunction in women with premature ovarian insufficiency (POI).

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[25].

Estrogens

Changes of circulating levels

Hypoestrogenism can occur suddenly or progressively at different life stages depending on the etiology of POI[1,6,8]. 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[26].

Brain effect

Estrogens target brain areas critical to emotional and cognitive well-being[27], and sexual symptoms are likely to be the result of the domino effect of menopausal complaints[28]. 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[27,29].

Peripheral effect

Estrogens target peripheral tissues to translate sexual clues into physical arousal[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)[30], recently renamed genitourinary syndrome of menopause (GSM) to include also the effect of aging and androgen deprivation[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[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[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[34–36], the mechanisms behind lower ovarian production of androgens in spontaneous POI women remain to be elucidated. Ovarian autoimmunity and concomitant adrenal autoimmunity[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[38]. Moreover, surgical menopausal women are at risk for low testosterone concentration and report a high rate of hypoactive sexual desire disorder[39].

Peripheral effects

Androgens target peripheral tissues and diminished testosterone levels contribute to symptoms and health risks traditionally attributed to premature low concentration of estrogens[40]. Several lines of evidence corroborate the idea that androgens cooperate with estrogens in human genitourinary 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[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[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[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[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[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[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[45,46]. Spontaneous POI women also perceive lower levels of social support[47] and there is a positive correlation between functional and spiritual well-being[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[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[50]. In another study, psychological distress measured by validated scales was lower in POI women irrespective of their androgen levels[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[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.*[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[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[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[53].

Psychosexual counseling in women with premature ovarian insufficiency

Basic counseling is an integral part of treating the psychosexual consequences of menopause[54] and it seems even more important for POI women according to several investigations[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 had discussed these issues with their HCPs[18]. Given the traumatic nature of a POI diagnosis, it is essential to proactively offer psychosocial support in addition to brief psychosexual interventions to relieve the complex impact of entering menopause earlier. POI women are emotionally unprepared for the diagnosis and in need of sensible information in order to understand the reasons, the consequences, and the solutions[55]. Unfortunately, as outlined by expert working groups and editorials in the field[53,56–59], a well-established psychosexual management is lacking because there is still a strong need for longitudinal research on large samples of women with POI with different etiologies. A community formed around this condition to raise awareness, remove barriers to care, and stimulate research is mandatory for effective management in daily practice[1,53].

The best approach for assessing and treating POI women with sexual dysfunction has to follow the general principles that every caring health provider should know to promote sexual well-being in menopause practice[16,60]. However, it is likely that sexual symptoms in POI women are strongly associated with distress because age is crucial for personal and relational impact[61]. Combining elements of cognitive behavioral therapy with sexual health education to address psychosexual concerns is a promising intervention in POI women. A pilot single-arm trial conducted in 37 women undergoing risk-reducing salpingo-oophorectomy after age 35 years or completion of childbearing showed a significant improvement in several domains of sexual function (desire, arousal, satisfaction, and pain), including FSFI total score, with a significant decline of somatization and anxiety scores[62]. Participants were assessed at baseline and 2 months post intervention, which included a one-time, half-day educational session comprised of targeted sexual health education, body awareness and relaxation training, and mindfulness-based cognitive therapy strategies, followed by two sessions of tailored telephone counseling. Women were highly satisfied with the intervention content and reported utilizing new skills to manage sexual dysfunction[62].

Treatments of sexual dysfunction in premature ovarian insufficiency

General principles

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[63]. 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[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–progestin contraception may be considered to avoid the pregnancy risk, which is, however, very low[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[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

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.

Treatment	*Evidence in postmenopausal women*	*Evidence in women with spontaneous POI*
Menopause hormone therapy (estrogens/progestogens)	+	+
Tibolone	+	−
Transdermal testosterone	+	−
Oral DHEA	−	−
Lubricants/moisturizers	+	−
Local estrogen therapy	+	−
Local testosterone cream	+	−
Local DHEA pessary	+	−
Laser therapy	+	−
Psychosexual therapy	+	−
Pelvic floor/physical therapy	+	−

DHEA, dehydroepiandrosterone; POI, premature ovarian insufficiency; +, yes; −, no.

of exogenous hormones should guide clinical decisions[71]. Then, transdermal estradiol may be preferable over oral estrogen therapy because of less effect on sex hormone-binding globulin and free testosterone levels[72] and modest improvement of sexual function in early postmenopausal women[73]. Similarly, the use of a natural estradiol-containing contraceptive pill should be preferred over ethinylestradiol. Even androgenicity of progestogens has some value[74]. Tibolone, a special form of HT with weak androgenic properties, was investigated in postmenopausal women with low desire and poor arousal, showing positive results[75]. 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[64,76].

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/norepinephrine reuptake inhibitors/psychoactive agents may be used to relieve menopausal symptoms, including mood disorders[77]. However, HCPs should consider that selective serotonin reuptake inhibitors are associated with secondary sexual dysfunction in 35–70% of users[78].

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[79].

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[80]. 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[16]. 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[63,67,80]. 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[81]. In women with autoimmune ovarian failure and coexisting adrenal insufficiency, adrenal androgen therapy with oral dehydroepiandrosterone (DHEA) may be beneficial[82].

Local androgens, such as DHEA pessaries and testosterone cream, deserve future consideration to improve sexual function in POI women[38,71,83]. 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[84]. 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[85].

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.

Source of funding Nil.

ORCID

R. E. Nappi http://orcid.org/0000-0002-5216-9882

References

1. Maclaran K, Panay N. Current concepts in premature ovarian insufficiency. *Womens Health (Lond Engl)* 2015;11:169–82
2. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. *Obstet Gynecol* 1986;67:604–6

3. Luborsky JL, Meyer P, Sowers MF, *et al.* Premature menopause in a multi-ethnic population study of the menopause transition. *Hum Reprod* 2003;18:199–206
4. Nelson LM. Clinical practice. Primary ovarian insufficiency. *N Engl J Med* 2009;360:606–14
5. Cox L, Liu JH. Primary ovarian insufficiency: an update. *Int J Womens Health* 2014;6:235–43
6. Santoro N. Mechanisms of premature ovarian failure. *Ann Endocrinol (Paris)* 2003;64:87–92
7. Sarrel PM, Sullivan SD, Nelson LM. Hormone replacement therapy in young women with surgical primary ovarian insufficiency. *Fertil Steril* 2016;106:1580–7
8. De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. *Lancet* 2010;376:911–21
9. Allshouse AA, Semple AL, Santoro NF. Evidence for prolonged and unique amenorrhea-related symptoms in women with premature ovarian failure/primary ovarian insufficiency. *Menopause* 2015;22: 166–74
10. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric* 2015;18:483–91
11. Ben-Nagi J, Panay N. Premature ovarian insufficiency: how to improve reproductive outcome? *Climacteric* 2014;17:242–6
12. Panay N, Kalu E. Management of premature ovarian failure. *Best Pract Res Clin Obstet Gynaecol* 2009;23:129–40
13. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. *Fertil Steril* 2016;106:1588–99
14. Muka T, Oliver-Williams C, Kunutsor S. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol* 2016;1: 767–76
15. Graziottin A. Menopause and sexuality: key issues in premature menopause and beyond. *Ann N Y Acad Sci* 2010;1205:254–61
16. Simon JA, Davis SR, Althof SE. Sexual well-being after menopause: an International Menopause Society White Paper. *Climacteric* 2018; 21:415–27
17. Mann E, Singer D, Pitkin J, *et al.* Psychosocial adjustment in women with premature menopause: a cross-sectional survey. *Climacteric* 2012;15:481–9
18. Singer D, Mann E, Hunter MS, *et al.* The silent grief: psychosocial aspects of premature ovarian failure. *Climacteric* 2011;14:428–37
19. Kalantaridou SN, Vanderhoof VH, Calis KA, *et al.* Sexual function in young women with spontaneous 46,XX primary ovarian insufficiency. *Fertil Steril* 2008;90:1805–11
20. van der Stege JG, Groen H, van Zadelhoff SJ, *et al.* Decreased androgen concentrations and diminished general and sexual well-being in women with premature ovarian failure. *Menopause* 2008; 15:23–31
21. De Almeida DM, Benetti-Pinto CL, Makuch MY. Sexual function of women with premature ovarian failure. *Menopause* 2011;18:262–6
22. Benetti-Pinto CL, Soares PM, Giraldo HP, *et al.* Role of the different sexuality domains on the sexual function of women with premature ovarian failure. *J Sex Med* 2015;12:685–9
23. Pacello PC, Yela DA, Rabelo S, *et al.* Dyspareunia and lubrication in premature ovarian failure using hormonal therapy and vaginal health. *Climacteric* 2014;17:342–7
24. Althof SE, Meston CM, Perelman MA, *et al.* Opinion paper: on the diagnosis/classification of sexual arousal concerns in women. *J Sex Med* 2017;14:1365–71
25. Graziottin A, Basson R. Sexual dysfunction in women with premature menopause. *Menopause* 2004;11:766–77
26. Nappi RE, Polatti F. The use of estrogen therapy in women's sexual functioning (CME). *J Sex Med* 2009;6:603–16
27. Nappi RE, Domoney C. Pharmacogenomics and sexuality: a vision. *Climacteric* 2013;16:25–30
28. Nappi RE, Verde JB, Polatti F, *et al.* Self-reported sexual symptoms in women attending menopause clinics. *Gynecol Obstet Invest* 2002;53:181–7
29. Nappi RE, Albani F, Santamaria V, *et al.* Hormonal and psycho-relational aspects of sexual function during menopausal transition and at early menopause. *Maturitas* 2010;67:78–83
30. Lachowsky M, Nappi RE. The effects of oestrogen on urogenital health. *Maturitas* 2009;63:149–51
31. Portman DJ, Gass MLS. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Climacteric* 2014;17:557–63
32. Janse F, Tanahatoe SJ, Eijkemans MJ, Fauser BC. Testosterone concentrations, using different assays, in different types of ovarian insufficiency: a systematic review and meta-analysis. *Hum Reprod Update* 2012;18:405–19
33. Soman M, Huang L-C, Cai W-H, *et al.* Serum androgen profiles in women with premature ovarian insufficiency: a systematic review and meta-analysis. *Menopause* 2019;26:78–93
34. Simon JA. Estrogen replacement therapy: effects on the endogenous androgen milieu. *Fertil Steril* 2002;77:77–82
35. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. *Hum Reprod Update* 2001;7:535–43
36. Meirow D, Dor J, Kaufman B, *et al.* Cortical fibrosis and blood-vessels damage in human ovaries exposed to chemotherapy. Potential mechanisms of ovarian injury. *Hum Reprod* 2007;22: 1626–33
37. Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. *Endocr Rev* 1997;18:107–34
38. Davis SR, Worsley R, Miller KK, *et al.* Androgens and female sexual function and dysfunction-findings from the Fourth International Consultation of Sexual Medicine. *J Sex Med* 2016;13:168–78
39. Nappi RE, Wawra K, Schmitt S. Hypoactive sexual desire disorder in postmenopausal women. *Gynecol Endocrinol* 2006;22:318–23
40. Davis SR, Wahlin-Jacobsen S. Testosterone in women-the clinical significance. *Lancet Diabetes Endocrinol* 2015;3:980–92
41. Simon JA, Goldstein I, Kim NN, *et al.* The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Menopause* 2018;25: 837–47
42. Traish AM, Vignozzi L, Simon JA, *et al.* Role of androgens in female genitourinary tissue structure and function: implications in the genitourinary syndrome of menopause. *Sex Med Rev* 2018;6: 558–71
43. Nappi RE. To be or not to be in sexual desire: the androgen dilemma. *Climacteric* 2015;18:672–4
44. Aydin S, Ateş S, Arioğlu Aydin Ç, *et al.* The role of premature ovarian failure awareness in female sexual functions and distress. *J Sex Marital Ther* 2017;43:354–60
45. Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. *J Psychosom Obstet Gynaecol* 2000;21:167–74
46. Schmidt PJ, Luff JA, Haq NA, *et al*. Depression in women with spontaneous 46, XX primary ovarian insufficiency. *J Clin Endocrinol Metab* 2011;96:E278–87
47. Orshan SA, Ventura JL, Covington SN, *et al.* Women with spontaneous 46,XX primary ovarian insufficiency (hypergonadotropic hypogonadism) have lower perceived social support than control women. *Fertil Steril* 2009;92:688–93
48. Ventura JL, Fitzgerald OR, Koziol DE, *et al.* Functional well-being is positively correlated with spiritual well-being in women who have spontaneous premature ovarian failure. *Fertil Steril* 2007;87:584–90
49. Deeks AA, Gibson-Helm M, Teede H, *et al.* Premature menopause: a comprehensive understanding of psychosocial aspects. *Climacteric* 2011;14:565–72
50. Schmidt PJ, Cardoso GM, Ross JL, *et al.* Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. *JAMA* 2006;295:1374–6
51. Guerrieri GM, Martinez PE, Klug SP, *et al.* Effects of physiological testosterone therapy on quality of life, self-esteem, and mood in women with primary ovarian insufficiency. *Menopause* 2014;21: 952–61

52. Driscoll MA, Davis MC, Aiken LS, *et al.* Psychosocial vulnerability, resilience resources, and coping with infertility: a longitudinal model of adjustment to primary ovarian insufficiency. *Ann Behav Med* 2016;50:272–84
53. Rafique S, Sterling EW, Nelson LM. A new approach to primary ovarian insufficiency. *Obstet Gynecol Clin North Am* 2012;39:567–86
54. Al-Azzawi F, Bitzer J, Brandenburg U, *et al.* Therapeutic options for postmenopausal female sexual dysfunction. *Climacteric* 2010;13: 103–20
55. Groff AA, Covington SN, Halverson LR, *et al.* Assessing the emotional needs of women with spontaneous premature ovarian failure. *Fertil Steril* 2005;83:1734–41
56. Cooper AR, Baker VL, Sterling EW, *et al.* The time is now for a new approach to primary ovarian insufficiency. *Fertil Steril* 2011;95: 1890–97
57. Panay N, Fenton A. Premature ovarian failure: a growing concern. *Climacteric* 2008;11:1–3
58. Panay N, Fenton A. Premature ovarian insufficiency: working towards an international database. *Climacteric* 2012;15:295–6
59. Panay N, Fenton A. Iatrogenic menopause following gynecological malignancy: time for action!. *Climacteric* 2016;19:1–2
60. Kingsberg SA, Althof S, Simon JA, *et al.* Female sexual dysfunction-medical and psychological treatments, Committee 14. *J Sex Med* 2017;14:1463–91
61. Nappi RE, Cucinella L, Martella S, *et al.* Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). *Maturitas* 2016;94:87–91
62. Bober SL, Recklitis CJ, Bakan J, *et al.* Addressing sexual dysfunction after risk-reducing salpingo-oophorectomy: effects of a brief, psychosexual intervention. *J Sex Med* 2015;12:189–97
63. Hamoda H, British Menopause Society Women's Health Concern. The British Menopause Society and Women's Health Concern recommendations on the management of women with premature ovarian insufficiency. *Post Reprod Health* 2017;23:22–35
64. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause* 2017;24:728–53
65. Committee on Gynecologic Practice. Committee opinion no. 698: hormone therapy in primary ovarian insufficiency. *Obstet Gynecol* 2017;129:e134–e141
66. Webber L, Davies M, Anderson R, *et al.* European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod* 2016;31:926–37
67. Baber RJ, Panay N, Fenton A. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. *Climacteric* 2016;19:109–50
68. Vujovic S, Brincat M, Erel T, *et al.* European Menopause and Andropause Society. EMAS position statement: Managing women with premature ovarian failure. *Maturitas* 2010;67:91–3
69. Popat VB, Vanderhoof VH, Calis KA, *et al.* Normalization of serum luteinizing hormone levels in women with 46,XX spontaneous primary ovarian insufficiency. *Fertil Steril* 2008;89:429–33
70. Popat VB, Calis KA, Kalantaridou SN, *et al.* Bone mineral density in young women with primary ovarian insufficiency: results of a three-year randomized controlled trial of physiological transdermal estradiol and testosterone replacement. *J Clin Endocrinol Metab* 2014;99:3418–26
71. Nappi RE, Cucinella L. Advances in pharmacotherapy for treating female sexual dysfunction. *Expert Opin Pharmacother* 2015;16: 875–87
72. Shifren JL, Desindes S, McIlwain M, *et al.* A randomized, open-label, crossover study comparing the effects of oral versus transdermal estrogen therapy on serum androgens, thyroid hormones, and adrenal hormones in naturally menopausal women. *Menopause* 2007;14:985–94
73. Taylor HS, Tal A, Pal L, *et al.* Effects of oral vs transdermal estrogen therapy on sexual function in early postmenopause: ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). *JAMA Intern Med* 2017;177:1471–9
74. Davis SR, Bitzer J, Giraldi A, *et al.* Change to either a nonandrogenic or androgenic progestin-containing oral contraceptive preparation is associated with improved sexual function in women with oral contraceptive-associated sexual dysfunction. *J Sex Med* 2013;10:3069–79
75. Biglia N, Maffei S, Lello S, *et al.* Tibolone in postmenopausal women: a review based on recent randomised controlled clinical trials. *Gynecol Endocrinol* 2010;26:804–14
76. Palacios S, Castelo-Branco C, Currie H, *et al.* Update on management of genitourinary syndrome of menopause: a practical guide. *Maturitas* 2015;82:308–13
77. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. *Menopause* 2015;22:1155–72
78. Fooladi E, Bell RJ, Davis SR. Management strategies in SSRI-associated sexual dysfunction in women at midlife. *Climacteric* 2012;15: 306–16
79. Faubion SS, Larkin LC, Stuenkel CA, *et al.* Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. *Menopause* 2018;25:596–608
80. Achilli C, Pundir J, Ramanathan P, *et al.* Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder: a systematic review and meta-analysis. *Fertil Steril* 2017;107:475–82.e15
81. Braunstein GD. Safety of testosterone treatment in postmenopausal women. *Fertil Steril* 2007;88:1–17
82. Davis SR, Panjari M, Stanczyk FZ. Clinical review: DHEA replacement for postmenopausal women. *J Clin Endocrinol Metab* 2011; 96:1642–53
83. Bell RJ, Rizvi F, Islam RM, *et al.* A systematic review of intravaginal testosterone for the treatment of vulvovaginal atrophy. *Menopause* 2018;25:704–9
84. Labrie F. Intracrinology and menopause: the science describing the cell-specific intracellular formation of estrogens and androgens from DHEA and their strictly local action and inactivation in peripheral tissues. *Menopause* 2019;26:220–4
85. Davis SR, Robinson PJ, Jane F, *et al.* Intravaginal testosterone improves sexual satisfaction and vaginal symptoms associated with aromatase inhibitors. *J Clin Endocrinol Metab* 2018;103: 4146–54