Hormonal contraception and vulvodynia: an update

Leen Aerts, Nicola Pluchino

Geneva University Hospitals, Dept. Gynaecology, 30 Boulevard de la Cluse, Switzerland

ABSTRACT

Introduction: Vulvodynia is likely a multifactorial disorder, with multiple potential psychosocial and medical pathways leading to the development and persistence of pain. Sex steroid hormones and, in particular, hormonal changes secondary to intake of hormonal contraception, have been considered among the medical factors suggested to play a role in the initiation and/or persistence of vulvodynia.

Aim: To provide an update on the topic of steroid hormones and pain regulation, both in general and more specifically in the domain of vulvodynia.

Methods: Literature for this review was obtained from PubMed searches and from relevant text books.

Main outcome measures: A comprehensive review on the impact of hormonal contraception on pain in general and on vulvodynia.

Results: Hormonal contraception may change vulvovaginal morphology by increasing vascular resistance and causing atrophy, reduced elasticity and hypolubrication. In addition, reduction of the levels of the neuroactive steroids in the brain may alter sexual motivation and behavior. Finally, sex steroids are implicated in nociception at peripheral, spinal and supra-spinal levels.

Conclusions: Hormonal contraception and the associated decrease in neuroactive steroids may interfere with nociceptive pain regulation. Future research into the impact of hormonal contraceptives on pain and sexual function is needed. The findings will help women make informed choices about their contraception and will help optimize the care of women with vulvodynia.

KEYWORDS

Hormonal contraception, vulvodynia, pain, sexual function.

Introduction

Hormonal contraception is currently one of the world's most prescribed drug treatments. Although the advent of hormonal contraception allowed women to separate their sexual and reproductive lives, some women decline the use of hormonal contraception because of health concerns or fear of side effects. Recent studies have shown that hormonal contraception may increase the risk of depression and other mental health issues [1,2]. More recently a statement from the European Society of Sexual Medicine (ESSM) has put under scrutiny potential effects of hormonal contraception on sexual function [3]. Meanwhile the debate on the impact of hormonal contraception on the development of vulvodynia is still ongoing.

In the 2015 Classification of Persistent Vulvar Pain and Vulvodynia, vulvodynia is defined as vulvar pain of at least 3 months' duration and of unknown origin [4]. Prevalence studies have estimated that 8% of women under the age of 40 have a history of chronic vulvar pain that limited sexual intercourse [5]. Vulvodynia is likely multifactorial in nature with physiological, psychological and interpersonal factors leading to the appearance of the vulvar pain. In addition, controlled studies have shown that vulvodynia itself can negatively impact a couple's psychological, sexual and relational well-being [6], contributing to the persistence of pain.

Although we strongly believe that a multimodal approach to the assessment and care of women with vulvodynia is warranted, in the current review we focus on the role of hormonal contraception in the development of vulvodynia. First, a brief overview on the influence of sex steroid hormones on sexual function is provided, and then the effect of hormonal contraception on the sexual response is explored. Finally, the existing literature on steroidal hormone regulation of pain in general, and more specifically in the domain of vulvodynia, is discussed.

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Contact
Leen Aerts; leen.aerts@hcuge.ch
Geneva University Hospitals, Dept. Gynaecology
30 Boulevard de la Cluse, Switzerland

Sex steroid hormones and sexual function

It is commonly acknowledged that the sexual response results from an interplay between psychological, interpersonal and physiological factors, including hormonal factors. Sex hormones influence both the central nervous system and genital tissues, thereby modifying sexual function and sexual experiences.

First, estrogen and androgens are critical in preserving vaginal and vulvar sensation, and thus in preventing dyspareunia. Steroid hormones influence vaginal blood flow, smooth muscle contraction and vulvar and vaginal lubrication [7]. In the absence of adequate levels of sex steroids, for example in menopause or during lactation, the mucosa of the vagina and vestibule can atrophy. The atrophic mucosa becomes friable and more sensitive to contact and friction. Furthermore, due to a loss of lactobacilli the vaginal pH becomes less acidic, making the vagina more prone to infection [8]. In addition to their peripheral effects, steroid hormones influence sexual motivation and behavior [9,10]. Previous research has shown that sexual fantasies, sexual desire, and the initiation of sexual activity by women peak around the time of ovulation [11]. Second, sexual activity in premenopausal women has been shown to be associated with increased sex hormone levels [12]. Finally, it has generally been assumed that androgens are important for female sexual interest and arousal [13]. However, studies on the association between androgen levels and female sexual function have shown inconsistent findings [14], probably the result of the variation in study designs and the lack of assays that precisely measure low testosterone levels.

Impact of hormonal contraception on sexual response

The ESSM recently stated that the effects of hormonal contraception on sexual response have been understudied and remain to date controversial [3]. Combined oral contraceptives suppress the hypothalamic-pituitary-ovarian axis, resulting in decreased levels of sex hormones. In addition, hormonal contraception increases hepatic production of sex hormone-biding globulin (SHBG), resulting in a decline in circulating free and biologically active testosterone [15]. Finally, some hormonal contraceptives contain progestins that may act as antagonists at the androgen receptor [16].

The decline in estrogen and androgen levels leads to reduced activation of sex steroid receptors in peripheral tissues, resulting in increased vascular resistance of the vulvar and vaginal arteries [17], decreased pelvic blood flow, increased vaginal and vestibular atrophy, and vulvovaginal hypolubrication. Furthermore, it has been shown that combined hormonal contraceptives change the morphology of the vestibular mucosa. Compared with vestibular biopsies of women without hormonal contraception, vestibular tissue of women on hormonal contraception showed more shallow and sparse dermal papillae, making the mucosa "more vulnerable to mechanical strain" [18] and thereby increasing the risk of pain during sexual contact. In addition to peripheral effects, intake of hormonal contraception and the associated decrease in levels of circulating allopregnanolone negatively influence several aspects of brain function, including mood, cognition and concentration [9,10,19]. Keeping in mind the biopsychosocial model of sexual function, changes in psychological well-being may influence sexual function and sexual experiences. Research has shown that allopregnanolone is involved in psychiatric disorders such as anxiety and depression [20]. Furthermore, recent findings have shown that hormonal contraception intake was associated with the use of psychotropic drugs, suicide attempts and suicides [1,2].

Previous research focusing specifically on hormonal contraception and sexual well-being showed mixed results [3]. Some studies showed an improvement in sexual function and experiences with hormonal contraception intake [21,22]. This is likely the consequence of a reduced risk of unwanted pregnancy and a reduction of troublesome gynecological symptoms such as heavy menstrual bleeding and dysmenorrhea. Others studies reported a negative impact of hormonal contraception on sexuality, including a decrease in libido, sexual arousal and lubrication, and a decrease in frequency of sexual activities [17,23-27]. Although the exact mechanism by which hormonal contraception influences sexual behavior and function is not completely understood, it is suggested that the decrease in delta-4 androgens, progesterone and allopregnanolone levels induced by the intake of hormonal contraception contributes to the negative changes in sexual well-being in some women. It has been shown that decreased brain allopregnanolone concentrations induced by a combination of ethinylestradiol (EE) and levonorgestrel is associated with a reduction in sexual motivation in female rats [28], and that testosterone replacement in ovariectomized rats is associated with increased concentration of allopregnanolone in selective brain areas [29].

Sex steroids and the regulation of pain

To understand how changes in the sex steroid hormone milieu may be related to chronic sexual pain, and more particularly vulvodynia, knowledge on the influence of sex steroids on pain regulation is needed. Numerous studies have found that sex steroids can regulate pain perception by binding to receptors on nerve endings in the pelvic region, the lumbosacral dorsal root ganglia and the brain. First, binding of steroid hormones to their peripheral receptors may regulate nociception of the pelvic region. Nociceptors are free nerve endings that detect mechanical (e.g., pressure and distension), thermal and chemical stimuli. Nociceptors are activated by potential harmful stimuli, thus allowing the body tissues to protect themselves from damage. Nociceptors are differentiated into several types according to their structural and functional characteristics. For example, myelinated A fibers rapidly conduct nociceptive signals, leading to instant recognition of intense pain, while unmyelinated C fibers transmit nociceptive information more slowly, leading to gradual awareness of shallow or burning pain. Detection of nociceptive stimulus intensity and threshold is achieved by means of specialized receptors on the nerve endings. One such receptor is the P2X3 purinoreceptor. The P2X3 receptor of the Aβ nerve encodes gradations of mechanical stimuli [30]. Previous research has shown that P2X3 expression is inhibited by estrogen receptor (ER) alpha (ER-α) binding at C-fiber nociceptors, strongly suggesting that estrogen-P2X3 interactions modulate nociceptive signaling. Reduced mechanical pain thresholds may reflect inadequate ER-α regulation of P2X3, and thus P2X3 overexpression [31,32]. The effects of progesterone on peripheral nerves are due, mostly, to its metabolism to 5 hydroprogesterone and allopregnanolone, since

the peripheral nervous system also synthesizes and metabolizes neuroactive steroids and is a target for these molecules. As reported in different experimental models, T-type calcium channels, GABA-A channels, P2X3 receptors, voltage-gated sodium channels and bradykinin signaling, which exert a role in neuropathic pain, are also affected by different kinds of neuroactive steroids. Specifically, dihydroprogesterone and allopregnanolone suppress neuropathic symptoms (allodynia/hyperalgesia) evoked by antineoplastic drugs [33,34].

Second, sex steroids are also implicated in nociception at spinal and supraspinal level [35]. The primary afferent nerve fibers from peripheral nociceptive neurons are connected with the neurons of the dorsal horn of the spinal cord. These neurons transmit the nociceptive signal to the central nervous system. Next, descending pathways from the brain modulate nociceptive signaling in the spinal cord. Neuroactive steroids derived from progesterone and testosterone and produced in the lumbosacral dorsal root ganglia and the brain can act as potent analgesics in the central nervous system. Their analgesic effects have been explained by different pain models using various receptor systems and ion channels such as the GABA-A receptors and calcium channels [36-38]. The underlying mechanism mediating this pain control is complex and remains under investigation. For example, paradoxical effects have been described, with estrogen shown to generate both antinociceptive and pronociceptive actions [39]. In addition, DHEA has been shown to decrease both thermal and mechanical thresholds, while testosterone exerts analgesic actions [40].

Changes in sex hormone levels may influence pain regulation. For example, the steroid sex milieu changes across the menstrual cycle without there being a significant change in the amount of vestibular estrogen receptors between the follicular and luteal phase [41]. During the pre-ovulatory phase of the menstrual cycle, estrogen, circulating in high levels, binds to ER-α, inhibiting P2X3 expression and increasing mechanical pain thresholds. The increase in the mechanical vestibular pain threshold, together with an enhanced structural integrity of the vulvovaginal tissue, decreases the risk of dyspareunia around the ovulatory period. By contrast, tissue depletion of estrogen and progesterone (e.g., in menopause or during lactation) is associated with a decreased mechanical pain threshold and pain hypersensitivity [42].

As previously discussed, chronic use of hormonal contraception can result in depletion of sex steroid hormones. This decrease in sex hormone levels leads to abnormal steroid modulation of the P2X3 receptors on the C-fibers, resulting in P2X3 overexpression [31,32] and in lower pain thresholds. In addition, vulvar vestibule expression of ER-β, the receptor subtype associated with increased nociceptive action, is upregulated in pain-free women taking oral hormonal contraceptives compared with pain-free non-users [41]. These findings are supported by the results of a study by Bohm-Starke and colleagues: when comparing mechanical pain thresholds in hormonal contraception users versus non-users, hormonal contraception was found to increase the sensitivity of the vestibular mucosa [43].

Finally, sex steroids are considered to be neuro-protective under inflammatory conditions by reducing neurogenic inflammation, a common effect after trauma that exacerbates the initial damage and pain [44]. This interaction is supported by clinical evidence that a drop in steroid hormones, as occurs in menopause, is associated with an increased inflammatory response to infections and a higher rate of autoimmune diseases [45]. Nevertheless, the exact mechanism is still not completely clear.

Sex hormones and vulvodynia

Several population-based studies have supported the proposed association between hormonal contraception intake and vulvodynia. Studies have shown that hormonal contraception use significantly increases (from 4 to 11 fold) the risk of developing vulvodynia [17,46-48], with studies suggesting an increased risk in general [46], or an increased risk related to: age at first use [46,47,49], the duration of hormonal contraception use [50,51], or the strength of the hormonal composition [46]. Indeed, Bouchard *et al*. showed that the relative risk of developing vulvodynia was higher when the pill used was of high progestogen, high androgen and low estrogen content [46]. Finally, one report described improvements in dyspareunia after discontinuation of hormonal contraceptives combined with topical application of estrogen and testosterone [47]. Alternatively, other studies have found no association between combined hormonal contraceptive use and vulvodynia [48-51].

In addition to the previously described effect of hormonal changes on vulvovaginal mucosal morphology, sexual function and pain perception, long-term low estrogen and progesterone levels may evoke pain hypersensitivity by promoting de novo nerve sprouting and hyperinnervation [52]. Several studies in women with vulvodynia have shown an increased density of nerve endings, in particular nociceptors, when comparing vestibular endoderm of women with vulvodynia with that of pain-free controls [53-59]. Increased innervation leads to increased sensitivity, a phenomenon well observed by several research groups that compared sensitivity to various pain stimuli applied to the vestibule between women with vulvodynia and healthy control women [60-64].

Data from vestibular punch biopsies in premenopausal women showed that, in comparison to pain-free women, women with vulvodynia had significantly lower levels of ER-α expression [65]. All the biopsy tissue from the pain-free group exhibited some degree of ER-α expression. In the group with vulvodynia, 50% of the samples did not exhibit any expression of ER-α. Equally, in the tissue from women with vulvodynia that did show ER-α expression, this expression was less distinct than in the control group. As discussed previously, lower ER-α expression may decrease the mechanical pain thresholds. However, these results are in contrast with the findings of a small study showing significantly higher total expression of ER-α in vestibular biopsy specimens from women with vulvodynia compared with ones taken from pain-free controls, all without hormonal contraception. There was no difference in the expression of ER-β, PR and AR between the two groups [66]. The difference between the two studies in terms of their findings on ER-α expression can be explained by their use of different methodologies to quantify the number of ERs.

A recent study has shown that oral contraceptive use alone

may not be sufficient to increase the risk of developing vulvodynia. Goldstein and colleagues showed that polymorphisms in AR may play a role [67]. Androgen-induced gene transcription is higher in shorter CAG trinucleotide repeat sequences [68]. Therefore, in polymorphisms with longer CAG trinucleotide repeat sequences, androgen receptor activity is lower. Goldstein *et al*. showed that women who developed vulvodynia while taking a combined hormonal contraceptive were more likely to have a long sequence of CAG repeats on their androgen receptor gene than pain-free women taking the same hormonal contraception. The authors concluded that a combination of factors, i.e., genetically lowered androgen receptor activity and decreased free testosterone secondary to hormonal contraception intake, increased the risk of vulvodynia.

Finally, hormonal contraception may negatively impact sexual desire and arousal in some women. Less lubrication during sexual activity may induce vulvovaginal dryness and dyspareunia. The experience of painful penetration may provoke fear of pain, decrease sexual desire, and elicit contraction of the pelvic floor muscles, making vaginal penetration more painful or even impossible. This vicious circle with exacerbation of vulvovaginal symptoms may also eventually lead to vulvodynia.

Conclusions

The current review shows that sex steroid hormones may influence sexual response and pain regulation. In particular, the association between changes in hormone levels, secondary to the intake of hormonal contraception, and the development of vulvodynia has been discussed.

Research has shown that hormonal contraception may change vulvovaginal morphology by causing vulvovaginal atrophy, reduced elasticity and hypolubrication. Also, sexual desire, motivation and behavior may be altered as an effect of lowered levels of neuroactive steroids in the brain. Further, sex steroids are implicated in nociception at peripheral, spinal and supra-spinal level. Therefore, hormonal contraception and the associated decrease in neuroactive steroids may interfere with nociceptive pain regulation. Nevertheless, the exact underlying mechanisms through which hormonal contraception can evoke vulvodynia are still not completely understood. Moreover, it is not clear why some women develop vulvodynia while taking hormonal contraception and other women do not. A genetic predisposition, as previously discussed, could be the explanation. Furthermore, vulvodynia is likely multifactorial in nature, with multiple physiological, sexual, psychological and interpersonal factors leading to the appearance and persistence of the vulvar pain. In clinical practice, most vulvodynia patients report several factors that are associated with the chronic pain problem. Therefore, identifying hormonal contraception as the only specific etiological factor is difficult or even incorrect.

Research into the role of hormonal contraception in the development of vulvodynia is challenging for several reasons. First, vulvodynia is an exclusion diagnosis based on symptoms and not a physiological pathology. Experts in the field suggest that the group of women with vulvodynia is probably a group of women reporting the same symptom, but with different etiological pathways. To date, studies on vulvodynia have assessed women with different etiologies together, as one single group. Trying to identify subgroups of vulvodynia patients, based on patients' medical and pain history and clinical examination, could help to overcome this bias. Second, hormonal contraceptives are a heterogeneous group of drugs. Different hormone types and doses may have different impacts on pain [69]. This point is illustrated by Greenstein and colleagues, who found that women taking hormonal contraceptives containing only 20 µg EE were more likely to develop vulvodynia than women taking hormonal contraceptives with higher doses of EE [69]. Therefore, future studies should control for the type of hormonal contraception in order to identify associations between groups of hormonal contraceptives and vulvodynia. In addition, there is a need for longitudinal studies to better evaluate the role of hormonal changes during a woman's life and in relation to the development of vulvodynia. Finally, greater dialogue between different health disciplines will help to advance research into this complex multifactorial disorder.

The findings of this review should urge clinicians to optimize their counseling on hormonal contraception. Clinicians should not limit this discussion to the thromboembolic and cardiovascular risks associated with the intake of hormonal contraception. A careful evaluation of the psychosexual well-being of the patient together with an extensive discussion of the possible physical, psychological and sexual side effects of hormonal contraception is also warranted. This will allow patients to make an informed and carefully thought-out decision, based on their personal situation. For women with vulvodynia on hormonal contraception, cessation of hormonal contraception should be discussed. Even though the range of non-hormonal contraceptive methods remains limited, a discussion on the advantages and disadvantages of hormonal contraception is warranted. In addition, vestibular application of a compounded cream containing estradiol and testosterone can be considered, given its beneficial effect on vulvar pain described by Burrows and colleagues [70].

In conclusion, more research into the impact of hormonal contraception on vulvodynia is needed. The findings will help women make informed decisions regarding their contraception and will help optimize the care of women with vulvodynia.

References

1. Skovlund CW, Mørch LS, Kessing LV, Lange T, Lidegaard Ø. Association of hormonal contraception with suicide attempts and suicides. Am J Psychiatry. 2018;175:336-42.
2. Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of hormonal contraception with depression. JAMA Psychiatry. 2016;73:1154-62.
3. Both S, Lew-Starowicz M, Luria M, et al. Hormonal contraception and female sexuality: position statements from the European Society of Sexual Medicine (ESSM). J Sex Med. 2019;16:1681-95.
4. Bornstein J, Goldstein AT, Stockdale CK, et al; consensus vulvar pain terminology committee of the International Society for the Study of Vulvovaginal Disease (ISSVD); International Society for the Study of Women's Sexual Health (ISSWSH); International Pelvic Pain Society (IPPS). 2015 ISSVD, ISSWSH, and IPPS Consensus terminol-

ogy and classification of persistent vulvar pain and vulvodynia. J Sex Med. 2016;13:607-12.
5. Harlow BL, Kunitz CG, Nguyen RH, Rydell SA, Turner RM, MacLehose RF. Prevalence of symptoms consistent with the diagnosis of vulvodynia: population-based estimates from 2 geographic regions. Am J Obstet Gynecol. 2014;210:40.e1-8.
6. Pukall CF, Goldstein AT, Bergeron S, et al. Vulvodynia: definition, prevalence, impact, and pathophysiological factors. J Sex Med. 2016;13:291-304.
7. Portman DJ, Goldstein SR, Kagan R. Treatment of moderate to severe dyspareunia with intravaginal prasterone therapy: a review. Climacteric. 2019;21:65-72.
8. Willhite LA, O'Connell MB. Urogenital atrophy: prevention and treatment. Pharmacotherapy. 2001;21:464-80.
9. Giraldi A, Marson L, Nappi R, et al. Physiology of female sexual function: animal models. J Sex Med. 2004;1:237-53.
10. Stuckey BG. Female sexual function and dysfunction in the reproductive years: the influence of endogenous and exogenous sex hormones. J Sex Med. 2004;5:2282-90.
11. Dawson SJ, Suschinsky KD, Lalumière ML. Sexual fantasies and viewing times across the menstrual cycle: a diary study. Arch Sex Behav. 2012;41:173-83.
12. Prasad A, Mumford SL, Buck Louis GM, et al. Sexual activity, endogenous reproductive hormones and ovulation in premenopausal women. Horm Behav. 2014;66:330-8.
13. Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril. 2002;77:660-5.
14. Davison SL, Davis SR. Androgenic hormones and aging--the link with female sexual function. Horm Behav. 2011;59:745-53.
15. Zimmerman Y, Eijkemans MJ, Coelingh Bennink HJ, Blankenstein MA, Fauser BC. The effect of combined oral contraception on testosterone levels in healthy women: a systematic review and meta-analysis. Hum Reprod Update. 2014;20:76-105.
16. Africander D, Verhoog N, Hapgood JP. Molecular mechanisms of steroids receptor-mediated actions by synthetic progestins used in HRT and contraception. Steroids. 2001;76:636-52.
17. Battaglia C, Battaglia B, Mancini F, et al. Sexual behavior and oral contraception: a pilot study. J Sex Med. 2012;9:550-7.
18. Johannesson U, Blomgren B, Hilliges M, Rylander E, Bohm-Starke N. The vulval vestibular mucosa-morphological effects of oral contraceptives and menstrual cycle. Br J Dermatol. 2007;157:487-93.
19. Porcu P, Serra M, Concas A. The brain as a target of hormonal contraceptives: evidence from animal studies. Front Neuroendocrinol. 2019;55:100799.
20. Bäckström T, Bixo M, Johansson M, et al. Allopregnanolone and mood disorders. Prog Neurobiol. 2014;113:88-94.
21. Guida M, Di Spiezio Sardo A, Bramante S, et al. Effects of two types of hormonal contraception--oral versus intravaginal--on the sexual life of women and their partners. Hum Reprod. 2005;20:1100-6.
22. Strufaldi R, Pompei LM, Steiner MI, et al. Effects of two combined hormonal contraceptives with the same composition and different doses on female sexual function and plasma androgen levels. Contraception. 2010;82:147-54.
23. Burrows LJ, Basha M, Goldstein AT. The effects of hormonal contraceptives on female sexuality: a review. J Sex Med. 2012;9:2213-23.
24. Caruso S, Agnello C, Intelisano G, Farina M, Di Mari L, Cianci A. Sexual behavior of women taking low-dose oral contraceptive containing 15 microg ethinylestradiol / 60 microg gestodene. Contraception. 2004;69:237-40.
25. Graham CA, Bancroft J, Doll HA, Greco T, Tanner A. Does oral contraceptive-induced reduction in free testosterone adversely affect the sexuality or mood of women? Psychoneuroendocrinology. 2007;32:246-55.
26. Graham CA, Ramos R, Bancroft J, Maglaya C, Farley TM. The effects of steroidal contraceptives on the well-being and sexuality of women: a double-blind, placebo-controlled, two-centre study of combined and progestogen-only methods. Contraception. 1995;52:363-9.
27. Wallwiener M, Wallwiener LM, Seeger H, et al. Effects of sex hormones in oral contraceptives on the female sexual function score: a study in German female medical students. Contraception. 2010;82:155-9.
28. Santoru F, Berretti R, Locci A, Porcu P, Concas A. Decreased allopregnanolone induced by hormonal contraceptives is associated with a reduction in social behavior and sexual motivation in female rats. Psychopharmacology (Berl). 2014;231:3351-64.
29. Pluchino N, Ninni F, Casarosa E, et al. Sexually dimorphic effects of testosterone administration on brain allopregnanolone in gonadectomized rats. J Sex Med. 2008;5:2780-92.
30. Chaban V. Estrogen and visceral nociception at the level of primary sensory neurons. Pain Res Treat. 2012;2012:960780.
31. Bodin P, Burnstock G. Purinergic signalling: ATP release. Neurochem Res. 2001;26:959-69.
32. Ford AP. P2X3 antagonists: novel therapeutics for afferent sensitization and chronic pain. Pain Manag. 2012;2:267-77.
33. Giatti S, Romano S, Pesaresi M, et al. Neuroactive steroids and the peripheral nervous system: an update. Steroids. 2015;103:23-30.
34. Pluchino N, Cubeddu A, Giannini A, et al. Progestogens and brain: an update. Maturitas. 2009;62:349-55.
35. Joksimovic SL, Covey DF, Jevtovic-Todorovic V, Todorovic SM. Neurosteroids in pain management: a new perspective on an old player. Front Pharmacol. 2018;9:1127.
36. Chakrabarti S, Liu NJ, Gintzler AR. Formation of mu/kappa-opioid receptor heterodimer is sex-dependent and mediates female-specific opioid analgesia. Proc Natl Acad Sci USA. 2010;107:20115-9.
37. Dawson-Basoa M, Gintzler AR. Involvement of spinal cord delta opiate receptors in the antinociception of gestation and its hormonal simulation. Brain Res. 1998;757:37-42.
38. Dawson-Basoa M, Gintzler AR. Gestational and ovarian sex steroid antinociception: synergy between spinal kappa and delta opioid systems. Brain Res. 1998;794:61-7.
39. Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppe RA, Zubieta JK. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. J Neurosci. 2006;26:5777-85.
40. Kibaly C, Meyer L, Patte-Mensah C, Mensah-Nyagan AG. Biochemical and functional evidence for the control of pain mechanisms by dehydroepiandrosterone endogenously synthesized in the spinal cord. FASEB J. 2008;22:93-104.
41. Johannesson U, Sahlin L, Masironi B, Rylander E, Bohm-Starke N. Steroid receptor expression in the vulvar vestibular mucosa--effects of oral contraceptives and menstrual cycle. Contraception. 2007;76:319-25.
42. Simon JA, Davis SR, Althof SE, et al. Sexual well-being after menopause: an International Menopause Society White Paper. Climacteric. 2018;21:415-27.
43. Bohm-Starke N, Johannesson U, Hilliges M, Rylander E, Torebjörk E. Decreased mechanical pain threshold in the vestibular mucosa of women using oral contraceptives: a contributing factor in vulvar vestibulitis? J Reprod Med. 2004;49:888-92.
44. Larson TA. Sex steroids, adult neurogenesis, and inflammation in CNS homeostatis, degeneration, and repair. Front Endocrinol (Lausanne). 2018;9:205.
45. Pozzi S, Benedusi V, Maggi A, Vegeto E. Estrogen action in neuroprotection and brain inflammation. Ann N Y Acad Sci. 2006;1089:302-23.
46. Bouchard C, Brisson J, Fortier M, Morin C, Blanchette C. Use of oral contraceptive pills and vulvar vestibulitis: a case-control study. Am J Epidemiol. 2002;156:254-61.
47. Goldstein A, Burrows L, Goldstein I. Can oral contraceptives cause vestibulodynia? J Sex Med. 2010;7:1585-7.
48. Edgardh K, Abdelnoor M. Vulvar vestibulitis and risk factors: a population-based case-control study in Oslo. Acta Derm Venereol. 2007;87:350-4.
49. Reed BD, Advincula AP, Fonde KR, Gorenflo DW, Haefner HK. Sexual activities and attitudes of women with vulvar dysesthesia. Obstet Gynecol. 2003;102:325-31.
50. Caruso S, Agnello C, Intelisano G, et al. Prospective study on sexual

behavior of women using 30 microg ethinylestradiol and 3 mg drospirenone oral contraceptive. Contraception. 2005;72:19-23.
51. Caruso S, Iraci Sareri M, Agnello C, et al. Conventional vs. extended-cycle oral contraceptives on the quality of sexual life: comparison between two regimens containing 3 mg drospirenone and 20 μg ethinyl estradiol. J Sex Med. 2011;8:1478-85.
52. Bjorling DE, Beckman M, Clayton MK, Wang ZY. Modulation of nerve growth factor in peripheral organs by estrogen and progesterone. Neuroscience. 2002;110:155-67.
53. Weström LV, Willén R. Vestibular nerve fiber proliferation in vulvar vestibulitis syndrome. Obstet Gynecol. 1998;91:572-6.
54. Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Increased intraepithelial innervation in women with vulvar vestibulitis syndrome. Gynecol Obstet Invest. 1998;46:256-60.
55. Bohm-Starke N, Hilliges M, Falconer C, Rylander E. Neurochemical characterization of the vestibular nerves in women with vulvar vestibulitis syndrome. Gynecol Obstet Invest. 1999;48:270-5.
56. Tympanidis P, Terenghi G, Dowd P. Increased innervation of the vulval vestibule in patients with vulvodynia. Br J Dermatol. 2003;148:1021-7.
57. Halperin R, Zehavi S, Vaknin Z, Ben-Ami I, Pansky M, Schneider D. The major histopathologic characteristics in the vulvar vestibulitis syndrome. Gynecol Obstet Invest. 2005;59:75-9.
58. Leclair CM, Goetsch MF, Korcheva VB, Anderson R, Peters D, Morgan TK. Differences in primary compared with secondary vestibulodynia by immunohistochemistry. Obstet Gynecol. 2011;17:1307-13.
59. Goetsch MF, Morgan TK, Korcheva VB, Li H, Peters D, Leclair CM. Histologic and receptor analysis of primary and secondary vestibulodynia and controls: a prospective study. Am J Obstet Gynecol. 2010;202:614.e1-8.
60. Pukall CF, Binik YM, Khalifé S, Amsel R, Abbott FV. Vestibular tactile and pain thresholds in women with vulvar vestibulitis syndrome. Pain. 2002;96:163-75.
61. Bohm-Starke N, Hilliges M, Brodda-Jansen G, Rylander E, Torebjörk E. Psychophysical evidence of nociceptor sensitization in vulvar vestibulitis syndrome. Pain. 2001;94:177-83.
62. Giesecke J, Reed BD, Haefner HK, Giesecke T, Claux DJ, Gracely RH. Quantitative sensory testing in vulvodynia patients and increased peripheral pressure pain sensitivity. Obstet Gynecol. 2004;104:126-33.
63. Sutton KS, Pukall CF, Chamberlain S. Pain ratings, sensory thresholds, and psychosocial functioning in women with provoked vestibulodynia. J Sex Marital Ther. 2009;35:262-81.
64. Heddini U, Bohm-Starke N, Nilsson KW, Johannesson U. Provoked vestibulodynia--medical factors and comorbidity associated with treatment outcome. J Sex Med. 2012;9:1400-6.
65. Eva LJ, MacLean AB, Reid WM, Rolfe KJ, Perrett CW. Estrogen receptor expression in vulvar vestibulitis syndrome. Am J Obstet Gynecol. 2003;189:458-61.
66. Johannesson U, Sahlin L, Masironi B, et al. Steroid receptor expression and morphology in provoked vestibulodynia. Am J Obstet Gynecol. 2008;198:311.e1-6.
67. Goldstein AT, Belkin ZR, Krapf JM, et al. Polymorphisms of the androgen receptor gene and hormonal contraceptive induced provoked vestibulodynia. J Sex Med. 2014;11:2764-71.
68. Chamberlain NL, Driver ED, Miesfeld RL. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transactivation function. Nucleic Acids Res. 1994;22:3181-6.
69. Greenstein A, Ben-Aroya Z, Fass O, et al. Vulvar vestibulitis syndrome and estrogen dose of oral contraceptive pills. J Sex Med. 2007;4:1679-83.
70. Burrows LJ, Goldstein AT. The treatment of vestibulodynia with topical estradiol and testosterone. Sex Med. 2013;1:30-3.

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