Intracrinology: The Open Door To The Future

March 7, 2018

Fernand Labrie, Celine Bouchard and Rosella E. Nappi kicked off ISGE 2018 with this opening symposium on Intracrinology in menopause.

Intracrinology and DHEA – the exclusive source of sex hormones post-menopause

Introducing the concept of intracrinology, Dr Labrie explained how the study of intracrinology began in the 1980s with the discovery of a novel combination therapy for prostate cancer and the observation of the role of androgens, made locally in the human prostate. The inactive precursor dehydroepiandrosterone (DHEA, also known as prasterone), produced by the adrenal glands, is transformed by enzymes into estrogen and androgens in peripheral tissue, with no biologically significant release of active hormones in to the circulation; only acting on the cells they are formed within before being deactivated. In the absence of ovarian oestrogen and androgen production, and the resulting loss of estradiol in blood and activity in all tissues, DHEA transformation within the cells becomes the only source of sex steroids within the post-menopausal woman.

DHEA reduces with age

The problem is that serum DHEA, the only source of intracellular estrogens and androgens after menopause, continues to reduce from 30 years of age and in addition, is highly variable between women. With increases in life expectancy, the reducing DHEA levels continue to reduce with the impact on quality of life more likely to be felt. Signs and symptoms of sex steroid deficiency are hot flushes, night sweats, insomnia, nervousness, lack of concentration, depression, vulvovaginal atrophy, sexual dysfunction, muscle loss, bone loss - fractures, loss of memory, loss of cognition, and possibly Alzheimer's disease.

DHEA and the vagina

Dr Celine Bouchard discussed the correlation of vulvovaginal atrophy (VVA) with the decrease in DHEA and how the administration of vaginal DHEA pessaries can be used to treat menopausal symptoms of VVA and GSM (genitourinary syndrome of menopause). DHEA exerts both estrogenic and androgenic activity on the vagina.

What is a healthy vagina?

A healthy vagina consists of 3 layers:

1. **The epithelium** protects against infection (vaginal microbiome, immune response), provides lubrication and comfort in sexual activity depending on its length, width and strength.
2. **The lamina propria** demonstrates elasticity and vaginal engorgement during sexual activity
3. **The muscularis** are 2 muscular layers - circular and longitudinal, providing contraction

Importantly, the nerves present in the lamina propria and muscularis are vital in the sexual response.

The role of estrogen in a healthy vagina

- **Increase in vaginal thickness** - associated with a decrease of basal cells and increase in superficial cells, lowering of pH and Increase in vaginal secretions

Both animal and human studies have found that when vaginal estrogen is reduced, collagen fibres also reduce, with increased activity of proteinease causing collagen

degradation. Stress urinary incontinence has also been reported by the Women's Health Initiative (WHI). However, no effect of estrogen has been shown on nerve endings.

DHEA has an androgenic action on all 3 layers of the vagina

Studies have shown that androgens produced by DHEA exhibit the following effects:

1. Increase epithelium thickness
2. Increase density of collagen fibres and thickness in the lamina propria
3. Stimulate nerve endings in the muscularis
4. Increase density of androgen receptors in all layers
5. Increase in vaginal weight - an effect 50% due to estrogens, 50% due to androgens

DHEA clinical trials

Serum DHEA reduces by at least 60% post-menopause, causing VVA symptoms in roughly half of post-menopausal women, increasing with age if untreated.

Clinical trials of DHEA suppositories for symptoms of VVA, including Labrie's 2016 published study, met FDA guidelines and had 4 primary endpoints:

- Reduction in parabasal cells
- Increase in superficial cells
- Reduction in vaginal pH
- Improvement of dyspareunia (pain in sexual activity and one of the most problematic VVA symptoms)

Sexual dysfunction: An unmet need

Dr Bouchard explained that sexual dysfunction is a second indication of prasterone and an unmet medical need. Labrie's 2015 study, a sexual function questionnaire, showed an improvement in all domains including arousal, lubrication, pain, orgasm, and satisfaction when 0.5% prasterone was administered intravaginally. Given that DHEA-formed estrogens and androgens are not released in significant levels in the blood, some other mechanism has to explain the beneficial effects. The androgenic action of DHEA on the nerve endings in the vagina could explain Labrie's findings, a parasympathetic response would result in these positive effects that intravaginal DHEA seems to have on sexual dysfunction.

The impact of VVA and GSM on quality of life

Dr Rosella Nappi began her presentation by explaining how much of a medical challenge VVA is due to it being underreported by women, under-recognised by HCPs and, as a result, under-treated. Recent surveys suggest that HCPs should be proactive and encourage open and sensible conversation on intimacy to help patients disclose their symptoms, as well as carry out diagnostic examinations.

Nappi's 2012 study surveyed 3520 postmenopausal women between 55-65 years of age to assess knowledge of vaginal atrophy. It found that almost half of those surveyed reported vagina symptoms, with only 4% attributing those symptoms to vaginal atrophy and 63% unaware that vaginal atrophy is a chronic condition. Of the half reporting symptoms, the most common symptom was vaginal dryness followed by dyspareunia.

Use it or lose it

Leiblum and Bachmann's 1983 study found that women who remained sexually active had significantly higher levels of androgens. Leiblum concluded from this, and other studies that had found women who had regular intercourse had little or no discomfort and greater responsiveness, that some support for the adage 'use it or lose it' was obtained in the research. However, Dr Nappi, suggested that reduced blood flow and perhaps a lack of elasticity, for instance, from significantly reduced DHEA could account for feelings of discomfort, but of course DHEA levels were not measured at that time. There is a strong association between VVA and Female Sexual Dysfuntion (FSD), with Levine's 2008 study finding that women with FSD were nearly 4 times more likely to have VVA than women without FSD.

Terminology & Symptoms

In 2012, the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of Trustees of The North American Menopause Society (NAMS) agreed that GMS is a more medically-accurate, all-encompassing and publicly acceptable term than VVA. They also defined that GMS symptoms may include but are not limited to:

- Genital symptoms of dryness, burning and irritation
- Sexual symptoms of lack of lubrication, discomfort or pain, and impaired function
- Urinary symptoms of urgency, dysuria and recurrent urinary tract infections

In addition, other conditions, such as pelvic floor abnormalities or vulvodynia, should not better account for these symptoms.

The distress of sexual problems

Rosen et al, 2009 found that women in a relationship are nearly 5 times more likely to be distressed from sexual dysfunction. Reed et al, 2009, found that depressive symptoms amplified the menopausal experience or alternatively, severe vasomotor symptoms worsened depressive symptoms. Infact, Reed's 2017 study showed that vaginal dryness during intercourse was positively and independently associated with having moderate-to-severe depressive symtoms.

Summary:

- The action of both androgens and ostrogens on the 3 layers, make for a healthy vagina
- A locally-administered therapy with both effects is needed
- Nerve response from androgenic action is needed for sexual response
- A proactive approach by HCPs, inc examinations, is needed to encourage women to disclose symptoms

Women should not only live longer but also maintain a good quality of life.

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