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Review

All sex steroids are made intracellularly in peripheral tissues by the mechanisms of intracrinology after menopause

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ABSTRACT

Following the arrest of estradiol secretion by the ovaries at menopause, all estrogens and all androgens in postmenopausal women are made locally in peripheral target tissues according to the physiological mechanisms of intracrinology. The locally made sex steroids exert their action and are inactivated intracellularly without biologically significant release of the active sex steroids in the circulation. The level of expression of the steroid-forming and steroid-inactivating enzymes is specific to each cell type in each tissue, thus permitting to each cell/tissue to synthesize a small amount of androgens and/or estrogens in order to meet the local physiological needs without affecting the other tissues of the organism.

Achieved after 500 million years of evolution, combination of the arrest of ovarian estrogen secretion, the availability of high circulating levels of DHEA and the expression of the peripheral sex steroid-forming enzymes have permitted the appearance of menopause with a continuing access to intratissular sex steroids for the individual cells/tissues without systemic exposure to circulating estradiol. In fact, one essential condition of menopause is to maintain serum estradiol at biologically inactive (substhreshold) concentrations, thus avoiding stimulation of the endometrium and risk of endometrial cancer. Measurement of the low levels of serum estrogens and androgens in postmenopausal women absolutely requires the use of MS/MS-based technology in order to obtain reliable accurate, specific and precise assays. While the activity of the series of steroidogenic enzymes can vary, the serum levels of DHEA show large individual variations going from barely detectable to practically normal "premenopausal" values, thus explaining the absence of menopausal symptoms in about 25% of women. It should be added that the intracrine system has no feedback elements to adjust the serum levels of DHEA, thus meaning that women with low DHEA activity will not be improved without external supplementation. Exogenous DHEA, however, follows the same intracrine rules as described for endogenous DHEA, thus maintaining serum estrogen levels at substhreshold or biologically inactive concentrations. Such blood concentrations are not different from those observed in normal postmenopausal women having high serum DHEA concentrations. Androgens, on the other hand, are practically all made intracellularly from DHEA by the mechanisms of intracrinology and are always maintained at very low levels in the blood in both pre- and postmenopausal women.

Proof of the importance of intracrinology is also provided, among others, by the well-recognized benefits of aromatase inhibitors and antiestrogens used successfully for the treatment of breast cancer in postmenopausal women where all estrogens are made locally. Each medical indication for the use of DHEA, however, requires clinical trials performed according to the FDA guidelines and the best rules of clinical medicine.

also must consider the effect of Pb release from bones

Contents

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1. Introduction

The negative impact of hormone deficiency after menopause is well known. These problems pertain to hot flushes, night sweats, vulvovaginal atrophy (vaginal dryness, pain at sexual activity, irritation/itching), bone loss and fractures, sexual dysfunction, muscle loss, loss of memory, loss of cognition and possibly Alzheimer's disease [1–7]. With the longer life span and the increased world population, more than 1.1 billion postmenopausal women are expected by 2025 with the majority of them expected to suffer from menopausal signs and symptoms [8]. The problems mentioned above also have an economic impact, the costs of menopausal symptoms being illustrated by the 10–15% lower work productivity, 23% more sick days and 40% higher health-related costs [9].

1.1. What is the exact cause of hormone deficiency after menopause?

Menopause corresponds to the cessation of reproductive life secondary to the depletion of primordial follicles accompanied by an arrest of estrogen and progesterone secretion by the ovaries. Based on the knowledge that ovarian estrogen secretion ceases at menopause in all women, systemic and local estrogens have so far been the traditional and practically exclusive treatment of vulvovaginal atrophy and hot flushes, these two most frequent symptoms of menopause affecting approximately 75% of post-menopausal women.

Since ovarian estrogen secretion stops in all women at menopause, and not all women suffer from the menopausal symptoms and signs mentioned above, there must be another factor or another variable source of sex steroids which could explain why some women are clinically free from menopausal symptoms while others (about 75%) suffer from menopausal symptoms and signs at various degrees [10–12].

2. Data review and discussion

2.1. After cessation of estrogen secretion by the ovaries at menopause, sex steroids continue to be required and are provided exclusively by intracrine local formation

Without the action of the estrogens and androgens made specifically by the mechanisms of intracrinology in each cell type of each tissue from circulating DHEA of adrenal (~80%) and ovarian (~20%) origins [13] (Fig. 1), the problems presently affecting women at menopause, especially osteoporosis and fractures, hot flushes, muscle loss, type II diabetes, vulvovaginal atrophy, sexual dysfunction, memory loss, cognition loss and possibly Alzheimer's disease, would be much more serious than presently observed with a likely greater reduction in lifespan. In other words, while serum estradiol must remain at subthreshold or inactive concentrations in the blood stream after menopause (Fig. 2), the normal functioning of peripheral tissues (except the endometrium)

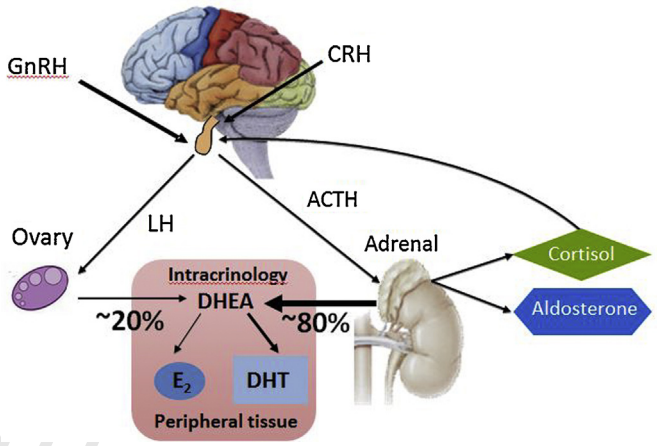

Fig. 1. Schematic representation of dehydroepiandrosterone (DHEA) as the unique source of sex steroids after menopause. Approximately 80% of circulating DHEA is of adrenal origin while about 20% is released from the ovary [13]. Accordingly, after menopause, all estrogens and all androgens are made locally from DHEA in peripheral target tissues by the mechanisms of intracrinology. The amount of sex steroids made depends upon the level of the steroid-forming enzymes specifically expressed in each cell in each tissue (Fig. 3). GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; CRH corticotropin releasing hormone; ACTH, adrenocorticotropic hormone.

requires intracellular physiological concentrations of estrogens and/or androgens (Figs. 3 and 4).

Medical research, however, has concentrated almost exclusively on the arrest of estradiol and progesterone secretion by the ovaries and how to replace ovarian estrogens. One never envisaged that

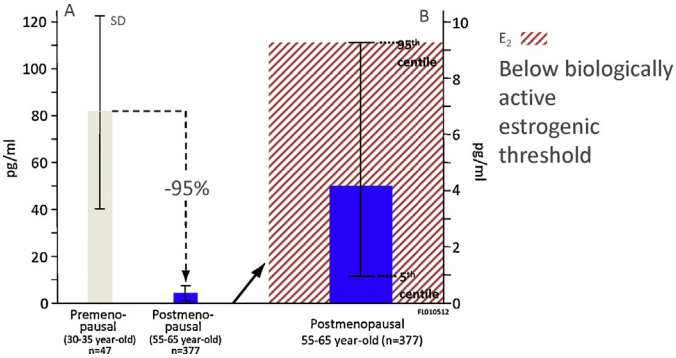

Fig. 2. Maintenance of serum estradiol at biologically inactive levels in postmenopausal women. (a) Illustration of the ≥95% fall in circulating estradiol between 30–35 year-old premenopausal women ($n = 47$) and 55–65-year-old postmenopausal women ($n = 377$) [13]. Data are presented as means ± SD. (b) Illustration of the range of biologically non significant or subthreshold serum estradiol concentrations in normal postmenopausal women. Such low levels of circulating estradiol are below the threshold of estrogenic activity (hatched area) and have no biological relevance, thus avoiding stimulation of cell proliferation in the uterus and other inappropriate tissues.

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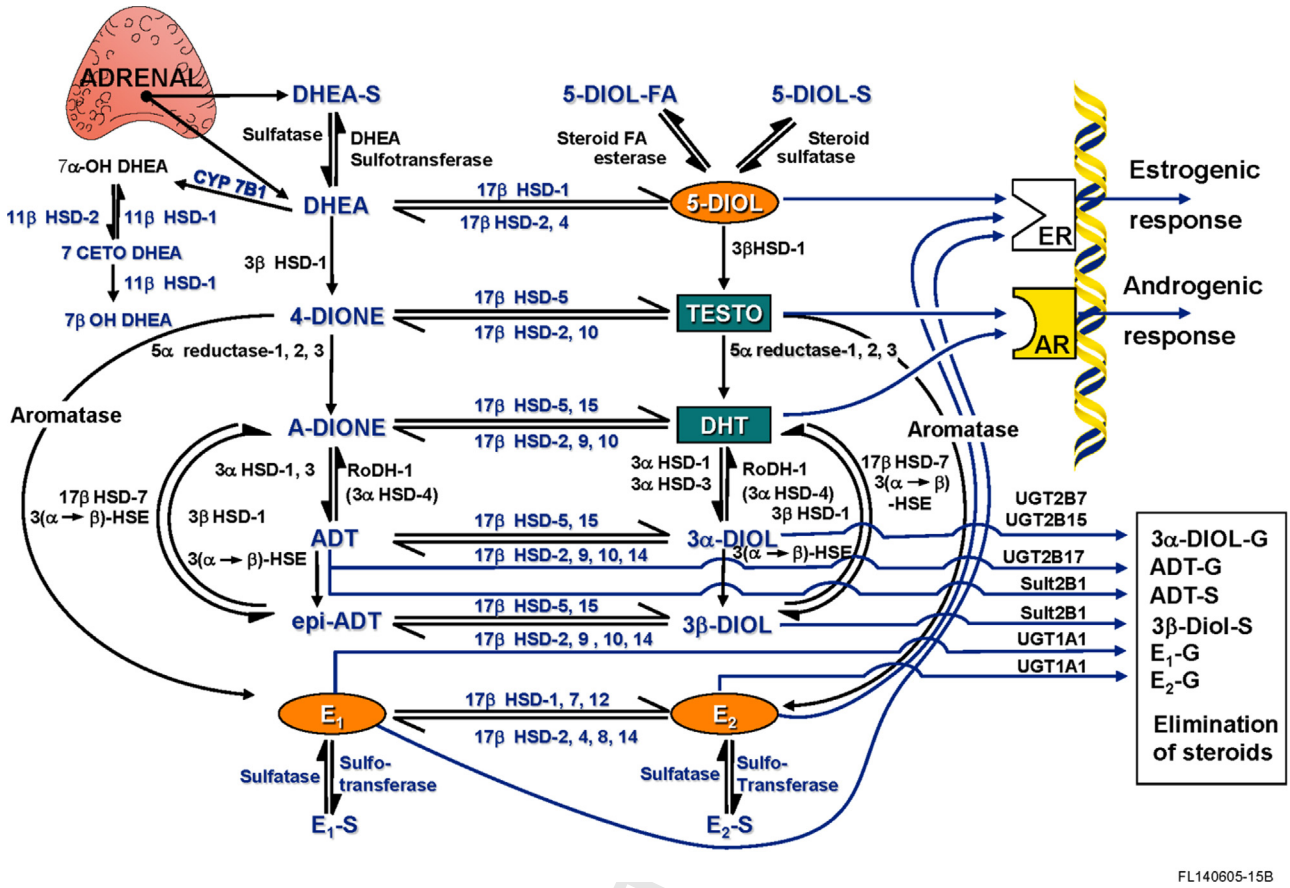

Fig. 3. Human steroidogenic and steroid-inactivating enzymes in peripheral intracrine tissues. 4-dione, androstenedione; A-dione, 5α-androstane-3,17-dione; ADT, androsterone; epi-ADT, epiandrosterone; E_1, estrone; E_1-S, estrone sulfate; E_2, 17β-estradiol; E_2-S, estradiol sulfate; 5-diol, androst-5-ene-3α, 17β-diol; 5-diol-FA, 5-diol fatty acid; 5-diol-S, 5-diol sulfate; HSD, hydroxysteroid dehydrogenase; testo, testosterone; RoDH-1, Ro dehydrogenase 1; ER, estrogen receptor; AR, androgen receptor; UGT2B28, uridine glucuronosyl transferase 2B28; Sult2B1, sulfotransferase 2B1; UGT1A1, uridine glucuronosyl transferase 1A1.

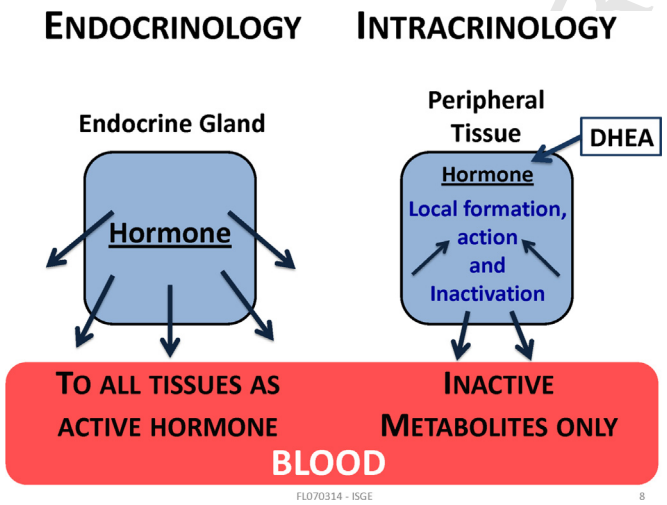

Fig. 4. Schematic comparison of the mechanisms of endocrinology where estradiol made from cholesterol in the ovary is distributed in relatively large amounts to all tissues of the body through the circulation. Intracrinology, on the other hand, uses the inactive DHEA as a precursor to make testosterone and/or estradiol according to the specific needs of each cell/tissue without biologically significant release of the active sex steroids in the circulation, thus avoiding systemic effects. Estimate of the intracellular steroids can be made by measurement of the inactive metabolites of estradiol and testosterone which must be present in the blood before their elimination by the liver and/or kidneys [50].

the arrest of secretion of estradiol by the ovaries into the circulation at menopause is a positive factor resulting from elimination of the risk of endometrial hyperplasia and carcinoma, instead of being a negative phenomenon automatically requiring estrogen replacement

2.2. Mechanisms of intracrinology

All tissues, except the endometrium, possess the intracrine enzymes able to transform DHEA into androgens and/or estrogens (Fig. 3). Humans, along with other primates, are unique among animal species in having adrenals that secrete large amounts of the inactive precursor steroid dehydroepiandrosterone (DHEA) (Fig. 1), which is converted at various levels into active androgens and/or estrogens in specific peripheral tissues according to the mechanisms of intracrinology [14–20]. The appearance during evolution of the battery of cell-specific steroidogenic enzymes (Fig. 3) combined to a high secretion rate of DHEA (Fig. 1) permits to make androgens and/or estrogens intracellularly according to the local needs without biologically significant release of active sex steroids in the circulation (Figs. 2 and 4).

Major and essential progress in this area has been made by elucidation of the structure of practically all the tissue-specific genes that encode the human steroidogenic enzymes responsible for the transformation of DHEA into androgens and/or estrogens [19,21–26] (Fig. 3).

As an exception, in order to avoid estrogenic stimulation of the endometrium, such a transformation of DHEA does not occur in the

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endometrium that does not possess the enzymes, especially aromatase, required to transform DHEA into estrogens [27–29].

It is very important to mention that an essential aspect of intracrinology is that the active sex steroids are not only made locally but that they are also inactivated locally at exactly the same site where synthesis takes place (Figs. 3 and 4). In fact, the sex steroids made from DHEA in peripheral tissues are essentially released outside the cells as inactive compounds. DHEA of adrenal, ovarian or exogenous (for example tablet or capsule) origin is distributed by the general circulation to all tissues indiscriminately. The transformation of DHEA into estrogens/androgens, however, is tissue-specific, ranging from none in the endometrium to various cell-specific levels in the other tissues of the human body. Most importantly, approximately 95% of the active estrogens and androgens made are inactivated locally before being released in the blood as inactive metabolites, thus avoiding inappropriate exposure of the other tissues [16].

Using the pharmaceutical terminology, DHEA is a prodrug, a term well known in the field [30]. In particular, see page 114 defining prodrug as follows: "a prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule" (Figs. 3 and 4).

The lower serum levels of DHEA in ovariectomized (OVX) compared to intact postmenopausal women can best be explained by the secretion of a corresponding amount of DHEA by the postmenopausal ovary into the circulation (Fig. 1) [13]. This DHEA of ovarian origin is then submitted to the same intracrine transformation mechanisms as the DHEA of adrenal origin (Fig. 3). Such an observation is supported by the finding that the postmenopausal ovary has persistent, although much reduced compared to the corpus luteum of the premenopausal ovary, transcript levels of the cholesterol transport protein steroidogenic acute regulatory, cholesterol side chain cleavage enzyme (CYP11A) and 17α-hydroxylase-17,20 lyase enzyme (CYP17), with extremely low levels of type 2 3β-hydroxysteroid dehydrogenase and aromatase (CYP19) [31]. This mechanism is further supported by the presence of 17α-hydroxylase (CYP17) protein in the stroma of the postmenopausal ovary, whereas the type 2hydroxysteroid dehydrogenase protein is absent, thus favoring the formation of DHEA [31].

It is remarkable that although the steroidogenic enzymes appeared approximately 500 million years ago with the vertebrates, it is only about 50 million years ago that the adrenals of primates gained the property to secrete large amounts of DHEA [32]. Even more recently, DHEA of adrenal origin became the main source of sex steroids, thus making possible the appearance of menopause in women [33]. Thus, it took more than 500 million years of evolution to separate the role of gonadal and DHEA-derived sex steroids, thus permitting women to be free during all the postmenopausal years from the negative systemic effects of estrogens best documented in the uterus with the risk of endometrial hyperplasia and cancer. With menopause, the women can benefit from a strictly tissue-specific formation, action and inactivation of sex steroids made in agreement with the specific age-related needs of each cell type in each tissue by the process of intracrinology [15,33].

2.3. Too low intracellular (intracrine) formation of sex steroids is responsible for menopausal symptoms and signs

While DHEA becomes the exclusive source of sex steroids after menopause, one problem is that serum DHEA levels start to decline by the age of 30 years and have already decreased by an average of 60% at time of menopause [34]. Since as mentioned above, ovarian estrogen secretion stops in all women at menopause, the only possible hormonal difference between postmenopausal women with hormone deficiency symptoms and signs and those showing no symptoms is the lower DHEA availability in the former group.

In addition to being at low levels in practically all women at menopause, serum DHEA shows large interindividual variability. With a mean ± SD concentration of 2.03 ± 1.33 ng/mL, serum DHEA in intact postmenopausal women is particularly variable with 5th and 95th centiles at 0.55 and 4.34 ng/mL, respectively, for a 7.9-fold difference [13]. A comparable variability is observed for the eleven metabolites of DHEA measured by MS/MS-based assays in that study. In addition to being decreased, on average, by approximately 60% on average at time of menopause compared with the maximal values found at the age of 30 years, the 5th and 95th centiles of serum DHEA and its metabolites vary by 8- to 12-fold in 42- to 74-year-old postmenopausal women. The large difference between low and high serum DHEA levels provides an explanation for the lack of signs of hormone deficiency in some women having relatively high serum DHEA levels while the majority of women have low serum DHEA levels and suffer from symptoms or signs of menopause.

Because there is no regulatory mechanism to stimulate the secretion of DHEA when serum DHEA is low, it is logical to believe that the only means of correcting the deficiency in DHEA is to supply exogenous DHEA to compensate for the low secretion observed in the majority of postmenopausal women. The approximately 20% but parallel lower serum levels of DHEA and all its metabolites found in OVX women, including E_2 and testosterone, suggest that the postmenopausal ovary secretes approximately 20% of total DHEA in the 42- to 74-year-old age group of intact postmenopausal women with no significant amounts of E_2 or testosterone secreted directly by the ovary.

2.4. Strict rule of no biologically active estrogens in the blood after menopause

It is logical to believe that continuation of estrogen secretion or systemic exposure to estrogens after menopause, in the absence of progesterone, would have stimulated the endometrium with the high risk of endometrial carcinoma in all women [35–37].

The consequence of the arrest of estradiol secretion by the ovary at menopause is that the concentration of serum estradiol decreases from values of at least 80 pg/mL in premenopausal women (Fig. 2A) to an average of 4.2 pg/mL after menopause with 95% of women having serum estradiol concentrations below 9.2 pg/mL (Fig. 2B) [13]. This extremely important aspect of menopause, namely the avoidance of more or less rapid appearance of endometrial cancer in all women, has certainly provided a decisive factor for the evolutional forces to choose the lineage of women having menopause and non-estrogen-secreting ovaries after the reproductive years. For serum testosterone, on the other hand, no significant change [38,39] or a small 15% decline [40] has been reported between pre- and postmenopause.

2.5. Protection of the endometrium by menopause and intracrinology

Protection of the endometrium is the most obvious reason why evolution over 500 million years has succeeded in building a hormonal system unique to the human species and able to protect women from systemic exposure to estrogens after menopause.

2.6. Clinical example of efficacy of DHEA replacement: Vulvovaginal atrophy (VVA)

When administered intravaginally, the inactive sex steroid precursor DHEA penetrates vaginal cells and is converted

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intracellularly into both estrogens and/or androgens depending upon the cell type, thus exerting rapid beneficial effects on VVA [41] as well as on sexual dysfunction [42].

Concerning sexual dysfunction, there is convincing supportive preclinical evidence of a stimulatory effect of the androgenic component of DHEA on nerve density and size by both testosterone and DHEA but not by estrogens [43,44]. Most importantly, outside the vaginal cells, there is no meaningful increase in serum estrogen (E_2) or androgen (testosterone) concentrations [45–48].

2.7. *All androgens, in women, are made intracellularly from DHEA by the mechanisms of intracrinology*

The approximately 20% higher serum DHEA in intact compared to ovariectomized women is accompanied by parallel differences for all the other steroids, thus indicating that all sex steroids originate from circulating DHEA in postmenopausal women with no direct secretion of active estrogens or androgens by the postmenopausal ovary.

It is also important to remember that women secrete approximately 50% as much androgens as men, these androgens being all made in peripheral tissues from circulating DHEA [34].

2.8. Major difference between the intracrine and classical endocrine mechanisms

The classical endocrine organs, like the ovary, synthesize E_2 from cholesterol and distribute the estrogenic E_2 to all tissues of the body through the general circulation (Fig. 4). Intracrinology, on the other hand, permits each cell/tissue to synthesize estrogens and/or androgens locally where they are acting without biologically significant release into the circulation (Fig. 4). In addition to eliminating potential risks of adverse systemic effects, the highly sophisticated mechanism of intracrinology markedly decreases the amount of active sex steroids needed to meet the specific needs of each cell in each tissue, since the locally-made sex steroids are not diluted in the general circulation before reaching their site of action.

3. Conclusion

In order to minimize the severity of the symptoms/signs/medical problems which follow the cessation of estrogen secretion by the ovary at menopause, evolution, starting 500 million years ago, has succeeded in developing the progressive presence of the tissue-specific enzymes able to make estrogens and androgens locally in the peripheral tissues independently from the ovary. This highly sophisticated enzymatic system has been joined about 20 million years ago through the secretion by the adrenals of the primates of relatively high amounts of DHEA, a compound inactive by itself but which serves as precursor of all estrogens and androgens through the action of the steroid-forming enzymes expressed specifically at different levels in each cell. Each peripheral tissue thus makes its own estrogens and androgens for its own use according to its specific needs.

In addition, it is important to indicate (Fig. 3) that the peripheral tissues inactivate locally these active sex steroids intracellularly before releasing them as inactive metabolites in the general circulation for excretion by the liver and/or kidneys (Fig. 4). The challenge for a safe treatment of menopause is to keep systemic concentrations of E_2 and testosterone within the postmenopausal range or up to the 95th centile of 9.3 pg/mL and 260 pg/mL for these two sex steroids, respectively (Fig. 2) [47]. Intracrinology thus permits the local formation of sex steroids in peripheral tissues independently from the ovary without releasing significant amounts of the active sex steroids in the blood, thus avoiding inappropriate stimulation of the other tissues, especially the uterus and permitting a long post-reproductive life of good quality, chosen by evolution as beneficial for the human species.

It is reasonable to believe that there should be no difference between the group of women who receive physiological amounts of exogenous DHEA to correct a clinically significant deficiency in DHEA versus the other group of women who happen to have sufficiently high endogenous DHEA levels [16]. As suggested by Eugster-Hausmann et al., "in the absence of sufficient evidence, specifically on the long-term overall safety of local estrogens, the amount of systemic absorption may be considered a surrogate endpoint, i.e., the less the increase in estrogen levels, the less potentially clinically relevant side-effects would be expected" [49].

It is of major importance to indicate that exogenous DHEA, like endogenous DHEA, obeys the physiological laws of menopause and intracrinology, thus providing sex steroids only to the tissues possessing the appropriate sex steroid-forming enzymes. It should be added that despite the recognized very high level of safety of DHEA, appropriate prospective, randomized and placebo-controlled clinical trials similar to those being performed for vulvovaginal atrophy [41,42,45] are needed before therapeutic use of DHEA for any indication related to sex steroid deficiency can be recommended [16].

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