DHEA and intracrinology at menopause, a positive choice for evolution of the human species

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ABSTRACT
Menopause has been chosen by evolution as the convergence of three factors, namely cessation of ovarian function (reproduction and estrogen secretion), high circulating dehydroepiandrosterone (DHEA), and intracrine enzymes able to convert DHEA into active sex steroids in peripheral tissues. The arrest of estrogen secretion by the ovaries at menopause causes a decrease of circulating estradiol below the threshold of biological activity, thus eliminating stimulation of the endometrium and risk of endometrial cancer. As much as the arrest of secretion of estradiol by the ovaries is essential to protect the uterus, it is of major importance that sex steroids continue to be made available in most other tissues which need estrogens and/or androgens for their normal functioning. Evolution, through 500 million years, has progressively provided the peripheral tissues with the enzymes able to make androgens and estrogens while high levels of DHEA, the precursor of all sex steroids, have appeared much later with the primates approximately 20 million years ago. All elements were thus in place for the functioning of intracrinology or the cell-specific formation of estrogens and androgens in peripheral tissues from the inactive precursor DHEA, with no significant release of active sex steroids in the circulation, thus eliminating the risks of adverse effects in the other tissues, especially the uterus. The presence of subthreshold levels of circulating estradiol combined with the formation of sex steroids from DHEA in specific peripheral tissues (intracrinology) makes menopause a positive characteristic supporting many years of good-quality postmenopausal life, useful for taking care of children and grandchildren. DHEA, however, decreases with age and is present at very different concentrations between different women, with the consequence that approximately 75% of postmenopausal women have too low circulating DHEA levels and suffer from symptoms/signs of hormone deficiency.

BACKGROUND
The long series of symptoms/signs/medical problems that affect postmenopausal women has a negative impact on quality of life and, sometimes, shortens life. These problems pertain to hot flushes, night sweats, vulvovaginal atrophy, bone loss and fractures, sexual dysfunction, muscle loss, loss of memory, loss of cognition and possibly Alzheimer’s disease1-7. The severity of the symptomatology related to hormone deficiency varies between races and from person to person8-10. With the longer life span and the increased world population, more than 1 billion postmenopausal women are expected by 202511. With the above-mentioned negative symptomatology, it is not obvious to imagine how menopause could have driven evolution as a decisive positive characteristic. It should also be considered that the human genome was selected in environments different from the present time12.

When analyzing the elements available for the selection by evolution of menopause as a positive characteristic of the human species, three different aspects have to be considered: cessation of ovarian function (end of reproductive life and arrest of estrogen secretion by the ovary), high circulating dehydroepiandrosterone (DHEA) levels, and availability of the enzymatic machinery permitting tissue-specific formation
of sex steroids in peripheral tissues by the mechanisms of intracrinology (Figure 1).

**MENOPAUSE: CESSION OF REPRODUCTIVE LIFE**

Menopause corresponds to the cessation of reproductive life secondary to the depletion of primordial follicles, accompanied by an arrest of estrogen and progesterone secretion. The total number of ovarian follicles decreases progressively from the age of puberty to the age of about 37 years, after which the rate of decrease becomes exponential. The period of fertile life lasting 30–35 years permits a woman to have and raise children.

**MANIFESTATION OF AGING OR AN ADAPTIVE MECHANISM FOR LATER LIFE?**

Menopause or cessation of reproductive life could be a non-adaptive manifestation of generalized physiological deterioration or an adaptive mechanism permitting a later life advantageous for the human species.

The real question for evolutionary biologists is why the egg pool in the ovary is exhausted, with loss of reproductive potential, relatively long before the end of life. In this context, one could believe that an individual who can reproduce throughout her whole life would have more offspring and then have more genes able to be expressed in the following generations compared to an individual who stops reproducing earlier. Accordingly, when looking only at the arrest of ovarian function, menopause is for many an enigma from the evolutionary point of view.

On the other hand, menopause could well be an adaptive selection in face of negative extrinsic environmental influences or a selection based upon the advantages of a sufficiently long post-reproductive life.

**NEGATIVE ASPECTS OF LATE REPRODUCTIVE LIFE**

Which elements could have led to the cessation of ovarian activity at an age when women are still in good health? An attractive argument is that the birth of children in older women would impose too strong a burden, with high risks for both the mother and children. The long period of time required for the human before independence is reached is a particularly strong argument. Moreover, one could add the negative aspect of pregnancy at a late age, especially an elevated risk of miscarriage. The fetuses of older mothers have a higher risk of being born small, being born with a defect or being born dead.

**POSITIVE ASPECTS OF A LONG POST-REPRODUCTIVE LIFE**

With menopause, on the other hand, the energy of reproduction can be redirected to permit mothers of post-reproductive age to better look after their own children or provide direct care to their grandchildren. It thus seems well founded to believe that the involvement of grandmothers permits their offspring to breed earlier, more frequently and with more success.

In fact, it has repeatedly been reported that the presence of a grandmother improves the feeding conditions of their

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**Figure 1** Schematic representation of the positive evolutive forces provided by the combination of menopause and intracrinology, including dehydroepiandrosterone (DHEA) and steroidogenic enzymes in peripheral tissues, to the human species. While menopause is accompanied by an arrest of estradiol secretion by the ovaries, the mechanisms of intracrinology provide each cell in each tissue the estrogens and androgens required for their normal functioning, without causing biologically significant increases in the concentration of these hormones in the circulation, thus avoiding unwanted systemic effects, especially stimulation of the uterus and breast.
grandchildren, thus increasing their survival chances\textsuperscript{18}. For example, in the historical populations of Germany\textsuperscript{19} and Japan\textsuperscript{25}, the survival of grandchildren has been shown to be improved by grandmothers. The grandmother hypothesis is also supported by data obtained in the Finnish and Canadian populations\textsuperscript{34} where grandmothers have been observed to be beneficial for their own children and grandchildren.

**TIMING OF MENOPAUSE IS A MAJOR FACTOR**

In a follow-up of 30 years, women who had menopause before age 47 years had 83\%, 68\% and 59\% increased risks of osteoporosis, fragility fractures and mortality, respectively\textsuperscript{26}. Similarly, oophorectomy before the age of 45 years has been associated with increased mortality related to cardiovascular disease\textsuperscript{27–32}. As a complementary observation, ovarian conservation improved survival in women younger than 65 years\textsuperscript{33}. It thus appears that the age at menopause has been selected by evolution to optimize duration and quality of life.

One significant aspect of oophorectomy performed before menopause is that it not only removes estrogens but also DHEA of ovarian origin. In fact, even after menopause, it has been estimated that approximately 20\% of DHEA, on average, is of ovarian origin\textsuperscript{34} (Figure 2). Due to the wide distribution of serum DHEA concentrations in postmenopausal women with an eight-fold difference between the 5th and 95th centiles of circulating DHEA levels, the contribution of ovarian DHEA could be much higher than 20\% in many women, resulting in greater negative consequences of oophorectomy on tissues requiring sex steroids for their normal functioning.

**LONG LIFE IS NOT A NEW BUT IS A RARE PHENOMENON**

Contrary to popular thinking, long life is not a new phenomenon starting with the human species. In historical societies when living conditions were more similar to those when human traits evolved, 30\% or more of women were beyond the age of 45 years, once the difficult periods of birth and childhood were passed successfully\textsuperscript{35}.

Looking at the few existing analogies with the human, macaques share many endocrine and reproductive characteristics with humans, including a 28-day menstrual cycle\textsuperscript{36–38}, the presence of peripheral intracrine enzymes which transform DHEA into both estrogens and androgens\textsuperscript{37–39}, and natural menopause\textsuperscript{40,41} with a decline in primordial follicles\textsuperscript{42}. However, although similarities in the hormonal changes at perimenopause and postmenopause can be seen between female macaques and women\textsuperscript{43,44}, menopause occurs at a relatively late age in macaques with few postmenopausal years\textsuperscript{45}. In another situation, suckling by offspring may last 15 years in the short-finned pilot whale, where it has been found that 24\% of females were post-reproductive for an average of 14 years after cessation of reproduction at 40 years\textsuperscript{46,47}.

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**Figure 2** Schematic representation of dehydroepiandrosterone (DHEA) as being the unique source of sex steroids in women after menopause. Approximately 80\% of circulating DHEA is of adrenal origin while about 20\% is released from the ovary\textsuperscript{34}. Accordingly, after menopause, all estrogens and all androgens are made locally from DHEA in peripheral target tissues. The amount of sex steroids made depends upon the level of the steroid-forming enzymes specifically expressed in each cell type in each tissue. GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; CRH, corticotropin releasing hormone; ACTH, adrenocorticotropic hormone. Reproduced from *Menopause* 2011;18:30–43.
It is of interest to mention that, in the earliest available census in the United States, namely in the state of Massachusetts, the life expectancy at birth in 1850 was 40 years for women, this being obviously biased by the high rate of infant mortality and infectious diseases. However, if a woman reached the age of 40 years, her life expectancy was 68 years. From studies in chimpanzees, the life expectancy of women should not go beyond the eight decade. Such a life expectancy of 80 years has apparently been sufficient for evolution to choose the lineage of women having menopause as preferable over continuous reproductive life for the benefits of the human species.

**IMPORTANCE OF ARREST OF SIGNIFICANT ESTROGEN SECRETION**

While cessation of reproduction at midlife could be seen by evolution as a positive characteristic, it was, however, essential to stop estrogen secretion in the bloodstream at the same time. 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. At the time of menopause, the ovary becomes completely depleted of estrogen-producing follicles and the secretion of estradiol by the ovary stops. The consequence is that the concentration of serum estradiol decreases from values of at least 80 pg/ml in premenopausal women (Figure 3a) to an average of 4.2 pg/ml after menopause, with 95% of women having serum estradiol concentrations below 9.2 pg/ml (Figure 3b). This extremely positive aspect of menopause, namely the avoidance of a more or less rapid appearance of endometrial cancer in all women, has certainly provided a decisive factor for evolutional forces to choose the lineage of women having menopause and non-estrogen-secreting ovaries after the reproductive years (Figure 1). For serum testosterone, on the other hand, no significant change or a small 15% decline has been reported between pre- and postmenopause.

**NEED FOR DHEA TO PROVIDE A SOURCE OF SEX STEROIDS**

While the cessation of reproduction and the arrest of ovarian estrogen secretion long before the end of life are essential characteristics of menopause, it is equally important to recognize that, in the complete absence of sex steroids, the life of women after menopause would be of poor quality and likely to be seriously shortened, since practically all body functions are modulated, to various degrees, by estrogens and/or androgens. In fact, in the absence of the estrogens and androgens made specifically in each cell type of each tissue from circulating DHEA of adrenal (~80%) and ovarian (~20%) origins (Figure 2), 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 significant reduction in lifespan. In other words, while serum estradiol must remain at subthreshold or biologically inactive concentrations in the bloodstream after menopause, the normal functioning of peripheral tissues (except the endometrium) requires intracellular physiological concentrations of estrogens and/or androgens.

Medical research, however, has concentrated almost exclusively on the arrest of estradiol and progesterone secretion by the ovary and how to replace estrogens. One never envisaged that the arrest of secretion of estradiol by the ovary into the circulation at menopause could be a positive factor resulting from elimination of the risk of endometrial hyperplasia and carcinoma, instead of being a negative phenomenon requiring estrogen replacement (Figure 1).

**INTRACRINOLGY, THE TISSUE-SPECIFIC SOURCE OF SEX STEROIDS**

A particularly remarkable and highly sophisticated achievement of evolution is intracrinology, the mechanism that permits specific and local production of sex steroids for a strictly local action, without significant release of active sex steroids into the circulation. This mechanism was named intracrinology in 1988 following observations made in the early 1980s in men castrated for prostate cancer and showing that an important proportion of the androgens present in the human prostate is made from DHEA in the prostate itself. In fact, as mentioned above, through an estimated 500 million years, evolution has progressively provided the peripheral tissues with the enzymes able to locally make and inactivate sex steroids (Figure 4). It is only about 50 million years ago that the adrenals of primates gained the ability to secrete large amounts of the precursor substrate DHEA which has recently been demonstrated to be transformed into estrogens and/or androgens by the mechanisms of intracrinology (Figures 3 and 4).

**DHEA BECOMES THE SOURCE OF SEX STEROIDS AFTER MENOPAUSE**

As mentioned above, in the presence of the steroid-forming and steroid-inactivating enzymes specifically expressed in each cell type of each human peripheral tissue (Figure 4), coupled with the availability of the precursor DHEA (Figure 2), all the enzymes able to transform DHEA into estradiol or androgens are present in the peripheral tissues (Figure 4).
elements were in place for delivery of the required amounts of sex steroids to each cell in each tissue and to minimize the negative impact of the arrest of estradiol secretion by the ovary at menopause. 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 (Figure 4).

The secretion of DHEA, however, markedly decreases with age, with a loss of 60% already observed, on average, at the time of menopause. This marked reduction in the secretion of DHEA during aging results in a parallel fall in the formation of androgens and estrogens in peripheral target tissues, a situation believed to be associated with the series of medical problems of menopause mentioned above.

CIRCULATING ESTRADIOL AND TESTOSTERONE AFTER MENOPAUSE

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 the same site where synthesis takes place. In fact, the sex steroids made from DHEA in peripheral tissues are essentially released outside the cells as inactive compounds. As illustrated in Figure 5, DHEA of adrenal, ovarian or exogenous (for example, tablet or cream) 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 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 (Figure 5).

NO FEEDBACK MECHANISM EXISTS TO CORRECT LOW DHEA LEVELS

In addition to decreasing with age, endogenous DHEA shows marked differences between different women, with serum...
concentrations being barely detectable in some women, while about 25% of women have sufficiently high concentrations of circulating DHEA, thus avoiding the symptoms of menopause becoming clinically significant\(^4,5\). Since there is no feedback mechanism to increase the secretion of DHEA when the serum concentration of this steroid is low, women with a low secretion rate of DHEA will remain deficient in sex steroids and will continue to show the symptoms/signs/problems of menopause mentioned above in the absence of replacement therapy with exogenous DHEA (Figure 5).

**NO EFFECT OF DHEA ON THE HUMAN ENDOMETRIUM**

The physiological role of the endometrium is essentially limited to pregnancy, an activity which ceases at menopause. As mentioned above, evolution over millions of years has removed, at the time of menopause, in the human species and few other primates\(^7\), the only stimulatory agent of endometrial proliferation, namely the estrogens of ovarian origin. An essential characteristic of DHEA is that it exerts no stimulatory effect on the human endometrium\(^4\). The most direct and undisputable proof of the absence of a stimulatory effect of DHEA on endometrial proliferation is the observation that endometrial atrophy is a typical and normal characteristic in all postmenopausal women despite the fact that all menopausal women have relatively high, albeit reduced compared to premenopause, serum DHEA levels. As mentioned above, the absence of an effect of DHEA on the endometrium is explained by the lack of enzymes, especially aromatase, able to transform DHEA into estrogens in the normal human endometrium\(^5,6\). This enzyme is expressed in a large number of extragonadal tissues where local estrogen biosynthesis takes place\(^6\) and is controlled by multiple factors. In order to avoid stimulation of the endometrium and risk of carcinoma, evolution did not provide the endometrium with the enzymes able to transform DHEA into estrogens.

**CONCLUSION**

Women are practically unique among species in spending about one-third of their lifetime after the reproductive years. This has been driven by evolution which chose menopause, accompanied by an arrest of estrogen secretion, as a positive characteristic in order to avoid stimulation of the uterus and endometrial cancer. However, in order to minimize the severity of the symptoms/signs/medical problems which follow the cessation of estrogen secretion by the ovary, evolution, starting 500 million years ago, has permitted the progressive appearance of the enzymes able to make estrogens and androgens in the peripheral tissues independently from the ovary. This sophisticated enzymatic apparatus has been joined, about 20 million years ago, by the secretion by the adrenals of primates of high amounts of DHEA, a compound inactive by itself but which serves as precursor of all estrogens and androgens, following the action of the steroid-forming enzymes expressed specifically at different levels in each peripheral tissue by the mechanisms of intracrinology. Each peripheral tissue thus makes its own estrogens and androgens for its own use. In addition, the peripheral tissues inactivate these active sex steroids locally before releasing them as inactive metabolites in the general circulation for excretion by the liver and kidneys. 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.

**Conflict of interest** Professor Labrie is President of EndoCeutics Inc., working on the endocrine mechanisms at menopause and postmenopause and investigating replacement therapy using prasterone (dehydroepiandrosterone) for the treatment of menopausal symptoms, especially vulvovaginal atrophy and sexual dysfunction, with clinical studies performed in collaboration with Bayer Healthcare Inc.

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**References**


