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Perspective

Menopausal Symptoms Resulting from Evolutionary Errors

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Abstract

Mammalian evolution can be described as a series of adaptations of each species developing their own reproductive mating strategy. Humans evolved from mammalian species that reproduced with simple mating strategies that relied largely on autonomic control of behavior that was synchronous with their reproductive physiology. Through evolution, these rudimentary neuronal mechanisms were gradually overlaid with new adaptations that provided additional benefit for survival and potentially speciation. However, not all ancient traits were erased by new traits but were simply overwritten by the new, more beneficial, traits. In combination, however, some evolved traits led to mixed results with unintended and often with unwanted results. For example, through evolution, estrus, or the psychic manifestations of "heat", (the desire to mate) was suppressed. This trait, which was common to many female mammals, was dampened in higher primate species and ultimately was replaced by a social-sexual reproductive mating system that permitted "mate choice". While this and other adaptation were largely beneficial to extant primate lineages, the advent of a prolong life span in humans has led to the re-emergence of ancestral neural links, which we now refer to as menopausal symptoms. Therapies, including diet, hormones and lifestyle changes can provide symptomatic relief, they cannot reverse the culminations of the evolutionary process.

Keywords: *Menopause; Evolution; Mating Strategy; Primate; Aging*

Evolutionary errors and menopausal symptoms

When reviewing issues in the management of menopausal symptoms, we need to also consider the contributions of missteps in evolution in the context of the genesis of menopausal symptoms. In examining the evolution of mammalian reproductive strategies, we find that higher primates, and humans, evolved a social-sexual reproductive strategy that included three adaptations that led to some unexpected outcomes [1]. Three evolutionary mal-adaptations that affected women were first, an elective delay of mating, second, the development of a more complex fetal adrenal cortex and, and third, the ability to live longer. While these adaptations resulted in successful higher primate lineages, some offered the human female mixed results. In this group of "mixed" results are a group of physiological changes associated with women's aging processes. We now identify them loosely as menopausal symptoms. Modern women, with these relatively recent evolutionary adaptations, may be still evolving, with final "trait choices" not yet made. However, late-age inherited traits cannot be reversed or resolved by evolution alone. Despite demonstrated survival advantage to the human species, these three critical evolutionary adaptations, when joined together in women, lead directly to the unintended and unwanted health issues that we are now struggling to understand.

To appreciate how evolution can be both beneficial and adverse at the same time, visualize a tree with expanding branches. Each new limb develops with different basic inherent traits based on the environmental factors it encounters. Each branch then sprouts leaves and seeds that have individual characteristics that determine their ultimate survival. These seeds can be compared to potential individual species each having their own individual survival potential. Humans are on a limb that is furthest away from the trunk. Generations produced here possess the most recent adaptations that evolution has had to offer. Some of these new traits will have long-lasting benefit while other traits…will offer less, or even bring damage, to some species [1]. Humans, on a relatively new branch, are still in the process of selecting which of these relatively recent adaptations are best suited for continued survival. However, it is unlikely that nature itself can repair the missteps of evolution as humans mostly now live in controlled environments in which environmental pressures and evolution are no longer major driving forces. In addition, even if some negative aspects of menopausal symptoms were life- or quality of life-threatening, the fact they occur well after the reproductive capacity has ended, means that evolution will no longer have an impact on the next generation. In terms of post-reproductive age adaptations, good neutral or bad, they are indelible etched as a permanent, functional traits and must be accepted as incorporated unless they somehow adversely affect future fecundity or offspring survival. This is not to dismiss the benefit of some lifestyle/diet changes, but they will not address the basic issue.

Evolution exerts it effect only at the inception of each new generation. After reproductive success of the individual has been achieved and surpassed, the selection pressures brought about by the environment no longer have adaptive influences. Adaptations that are expressed later life, or after reproductive success, are no longer traits that can be preferentially selected or necessarily be less likely to survive through evolution. This is why susceptibility to diseases such as late-age cancer, dementia and debilitating menopausal symptoms are not inherited traits that can be negatively selected for elimination in future generations. As Jerrilyn Pryor explains in Estrogen Errors [2], therapies play a role in some of the current misunderstandings in women's healthy aging and now, we understand, nature does as well.

Breast cancer is not typically listed as a menopausal symptom but will likely be added soon. Specifically, the increase incidence of breast cancer during early perimenopause is temporally related to a shift in adrenal steroid production ten years earlier in the late reproductive stage of the menopausal transition (MT). This timing coincides with a generalized reduction in fertility and the first indication that the MT beginning. The risk of breast cancer is inversely proportional to the age at first pregnancy. The acquired trait of concealed ovulation, which permitted mate choice and enhanced troop cohesiveness in higher primates, also allowed for social constraints on fertility. Modern constraints on marriage in many human societies often limits first conceptions to several years post puberty. Thus, an evolutionary benefit of the social-sexual mating strategy in primates, which greatly benefited them and now defines the human reproductive mating strategy, can delay first conceptions and by doing so, increase the unintended, unwanted consequence of increased risk for breast cancer in later life.

The evolutionary development of a more complex fetal adrenal cortex originally allowed some higher primate species to gestate longer to produce larger and more developed fetuses. The complexing of a side chain to a pre-existing luteinizing hormone (LH) molecule in the higher primates' placenta led to a new hormone, chorionic gonadotropin (CG or hCG in humans) and the direct stimulation of this new fetal zone (FZ) to respond to the growth of the placenta through the luteinizing hormone receptor (LHR). This resulted in the synthesis and secretion of weak androgens. These weak androgens from the FZ, when converted to estrogens, promoted uterine/breast development during pregnancy. A transformation of the FZ to a definitive zone (DZ) occurs in the early postpartum period. The adult form of the early DZ is the zona reticularis (ZR) which may be unique to higher primates and retains the functional receptors for luteinizing hormone (LH) a trait evolved in the primate FZ [3]. As a consequence, women, not men, produce increasing amounts of adrenal androgens by the ZR as the perimenopause progresses. The ZR is stimulated by increasing circulating pituitary LH to produce both strong and weak androgen during the MT [3-5]. Following the last menstrual period (LMP), increased LH production provides sole support for the ZR and is the primary source of *de novo* progesterone and T production in mid-aged women [6]. This presents a health issue in the post menopause when spikes of adrenal androgens, and their estrogen byproducts, are unchecked by high circulating levels of cyclic progesterone from the ovary.

The prolongation of human lifespan, well after the reproductive potential exists, is a largely result of societal gains rather than evolution. This extension of life is beyond evolutionary control and is not accommodated by it. Depletion of gametes at mid-age results in a decrease in ovarian production of estrogen and progesterone, decreased negative feedback control of gonadotropin secretion and increased stimulation of the ZR. This gender-specific rise in LH results in a gender-specific rise in adrenal weak and strong androgen production which and provide the only source of estradiol through the peripheral conversion of T post LMP. This, however, is not a steady-state relationship and the resulting variable low baseline levels of progesterone has the ability to modulate pituitary sensitivity to LH [7], resulting in waves of T and ultimately increases in circulating estrogen levels through peripheral conversion of adrenal androgens. Episodes of increased T production in the post menopause can provide the mechanism for "cyclic" levels of sex steroids in women well after reproductive capacity has passed. The ancient traits of human progenitors that evolved cyclic sex steroids to create the psychic manifestations of "heat" now emerge and exert autonomic control signals that no longer have useful physiologic functions. Alterations in basal body temperature, appetite, quality of sleep, brain fog, physical activity and emotions are some of the unexpected and unwanted results of evolutionary missteps from adaptations in the reproductive strategy of the human species. Collectively, these unintended events generated by archaic signals from the autonomic nervous system are the ghosts of previous reproductive strategies [1], still rattling around in the attic of human brains.

Menopausal symptoms are the consequence of environmental pressure that "promoted" the adaptation of specific physiologic traits that led to diverse primate lineages [1]. These adaptations focused mainly on deriving differences in reproductive strategies. As a group, extant primate species present an array of reproductive strategies, and species, that range from least like the human such as prosimians, to most like humans such as in the great apes. Within each of these large groups are subgroups that have unique traits that identify that subgroup as individual species or subspecies. Each species or subspecies, in turn, retains the individual reproductive traits that determine their ability to survive, reproduce and potentially speciate. Humans (homo sapiens) are currently the only monolithic primate group in terms of this type of absolute speciation. Although historically, this was not true as hominoid subspecies have previously existed. While the closest non-human primate relatives of humans share many inherited traits that contribute to the array of menopausal symptoms in humans, none of these other species have the same combination of contributing adaptive traits and therefore none of them share the same expression of symptoms as humans. There is no "animal model" or non-human species that permits experimental testing on the human condition called menopausal symptoms [8]. This lack of an essential research resource limits experimentation that could reveal physiological mechanisms underlying one of the most important issues in women's healthy aging. Progress is therefore necessarily slow and therein lies the problem in developing novel therapies as well as the physician's dilemma.

Can modern medicine correct nature's evolutionary mistakes? Yes, in many cases inborn errors of metabolism, functional deficiencies, over-abundance, mal-adsorption, etcetera can be remedied by therapy. Successful therapies usually treat the symptoms and do not generally address the cause. This has been true with menopausal symptoms where estrogen therapy has been evading scientific progress for decades. Therapy, in the absence of a basic understanding of the mechanism, can be dangerous and misleading. In fact, dampening the symptoms with misguided therapy can inadvertently camouflage the causal pathway. The example of estrogen's ability to resolve many menopausal symptoms without revealing the cause is the theme of Jerilynn Pryor's book "Estrogen Errors".

Recent epidemiological studies now show that decreased estrogen production by the aging ovary is not the primary cause for menopausal symptoms to emerge. While the prevailing dogma supports the concept that deceased ovarian function in association with declining estrogen production during the menopausal transition (MT) is mechanistically related to many menopausal symptoms. However, there are no reports in the literature reporting a quantitative decline in circulating estrogen during the time interval. A decline in progesterone production in mid-age is the more likely cause [9] and the key to understanding the neurologic mechanism that initiates a cascade of events that lead to the list of maladies that we now refer to as menopausal symptoms. Interestingly, that list is still growing because social standards continue to change and in the context of a social-sexual reproductive strategy, the two are fundamentally

linked. This then raises important questions regarding the biology of menopause today, predicting its impact tomorrow and developing basic tools that can intervene to resolve the unwanted consequences of past evolutionary errors in the future. For the first time, large epidemiological studies are providing a broader understanding of the physiological foundations of the MT and begin to link the seemingly unrelated pattern of expressed symptoms within a unifying causal concept. With this giant step forward, there is hope that with a deeper understanding, improved diagnoses, and therapies will be developed. Both women and their physicians are now much better equipped to deal with these issues than ever before, but not quite there yet.

Disclosure

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