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PERSONAL PERSPECTIVE

The evolutionary origin and significance of menopause

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Abstract

Contemporary women have long life expectancy (81 y, United States), especially relative to the age at menopause (51 y, United States). Menopause is a consequence of reproductive aging and follicular depletion (ovarian failure), yielding very low circulating estrogen serum concentrations and biologically disadvantageous metabolic alterations. Stated in terms of antagonistic pleiotropy, the ongoing hypoestrogenic endocrine environment, beneficial during lactation, results in acceleration of several age-related illnesses after menopause (ie, late postmenopausal osteoporosis, cardiovascular disease, and cognitive decline). Specifically, the similar hypoestrogenic hormonal milieu present during postpartum lactation provides biologic advantages (fitness) to both mother and newborn. These precepts of evolutionary medicine encourage a reassessment of hormone therapy, and on the basis of data presented the authors propose additional opportunities for disease prevention and morbidity reduction in postmenopausal women.*

Key Words: Evolution – Menopause – Aging – Lactation – Hypoestrogenism – Osteoporosis – Heart disease.

Efforts to understand the evolutionary origin and significance of human menopause have engaged anthropologists and evolutionary biologists for decades. The adaptive hypothesis views programmed ovarian failure among humans as offering fitness by favoring females who become infertile years before death.[1] An alternate explanation, the epiphenomena hypothesis, considers menopause as a product of antagonistic pleiotropy, favoring early fertility at the expense of late fertility or as the by-product of an increase in life span or life expectancy.[3] The emergence of significant postreproductive life expectancy in humans occurred during an evolutionary time when overall life expectancy was short, with death from acute, not chronic, conditions. Paleodemographic data from Australopithecines, Neanderthals, hunter-gatherers, and proto-agricultural populations underscore the likelihood of menopause evolving with minimal life expectancy thereafter.[4] Although evolutionary medicine generally seeks to unify emerging health issues and their genetic antecedents, here, we focus on diseases appearing during the postreproductive period that are no longer subjected to the fitness-selecting forces of evolutionary biology.[5,6]

The long postreproductive life span of women seems to be an evolutionary trait of long standing, although experts interpreting the available paleodemographic data disagree.[4-7] Debate centers on when, during the course of human evolution, menopause occurred, but it is likely to have evolved

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since the time of the last common ancestor.[2] From a Darwinian perspective, the long life spans of women after menopause are not easily explained by the energetic costs of reproduction alone, revealing a capacity for somatic aging to be uncoupled from reproductive aging to some degree.[8,9] Natural selection would favor females who become infertile many years before death if the offspring require exceptional duration and intensity of parental care, as is the case with humans.[1,2] This adaptation allows the extension of maternal nurturing energies well beyond the direct energy costs of pregnancy and lactation. This adaptation is also necessary to enhance the survival of human offspring with a prolonged period of dependency (as compared with all other primates).[1,6,9]

The trend toward ever-increasing percentages of individuals reaching life spans beyond 80 or 90 years is a recent phenomenon.[10-12] Current data from more developed nations reveal no survival advantage conferred to younger populations with increasing numbers of octogenarians. Since 1900, achieving very old age is no longer an indicator of greater reproductive fitness, as it was in earlier centuries. Long life spans result from public health measures, socioeconomic factors, and cultural customs, with medical and scientific interventions accounting for a small percentage.[13] In the 21st century, the largest population expansion in US women is in those older than 65 years,[12] with survival not coupled to prior reproductive or ongoing biologic fitness.

LACTATION, ENDOCRINE MILIEU, AND PHYSIOLOGY

Nearly all states of endocrine reproductive fitness are estrogen replete, with lactation the only low-estrogen condition associated with successful reproductive effort. Mammalian lactation fulfills the precepts of evolutionary biologic selective pressure, providing mobile, adequate nutrition to enable survival of suckling offspring.[14] Lactation physiology is of particular interest because it is the only low-estrogen state that has resulted from selective genetic evolutionary pressure.[15] Menopausal women are by definition post reproductive and therefore have no access to fitness through natural selection.[1] Lactational physiology exists as an adaptive response to low estrogen, a milieu that in menopause can result in maladaptive outcomes. This antagonistic pleiotropy characterizes many of the negative physiologic outcomes of a normal occurrence, early and late menopause, in post reproductive women.[16] Although the mechanism of lactational hypoestrogenism is different (lactation vs menopause), many pathological changes are similar.

During pregnancy, estrogen, progesterone, and prolactin concentrations prepare breast tissue for lactation. Immediately after delivery of the infant, expulsion of the placenta results in a sudden drop in both estrogen and progesterone. Abrupt withdrawal of progesterone in the presence of high prolactin levels initiates lactation. With suckling, prolactin levels continue to be increased. These high prolactin levels, through their inhibitory impact on gonadotropin secretion, inhibit ovarian function to greater or lesser degrees throughout lactation. Ovarian suppression results in sustained low estrogen levels until the frequency of suckling diminishes and maternal energy supplies become adequate for further reproduction.[16]

Many maternal symptoms and physiologic alterations result from these lactational hormone shifts that are biologically advantageous for nursing infants at a maternal cost. The low estrogen concentrations during lactation induce many metabolic alterations. We will focus on the metabolism of serum lipoproteins, calcium balance, and the resorption of bone, as well as on some alterations of the central nervous system (CNS). Although we are concentrating on these specific metabolic alterations, our hypothesis is more complete, encompassing other metabolic alterations, menopausal symptoms (eg, genital atrophy), and immune function. These are included in Table 1 for completeness but are not discussed further in this article.

Hormonal effects on serum lipoproteins during lactation

Circulating low estrogen levels during lactation are associated with an increase in lipoprotein lipase enzyme activity,[17] resulting in an increase in serum lipoproteins. During lactation, such changes probably serve to increase the fat content of maternal milk, with energetic enrichment being an advantage to suckling infants.

Hormonal effects on calcium balance and resorption of bone during lactation

Approximately 200 mg/day of elemental calcium is lost from the maternal skeleton because of milk production in lactating women.[18] Ample calcium concentrations in human breast milk enhance bone mineralization of offspring at the cost of maternal calcium stores when calcium intake is insufficient.[19] This transfer of calcium results in a 3% to 9% loss of bone mineral density (BMD) at the lumbar spine during a 6-month period.[20] Loss of BMD during lactation is greater than the average loss of 1% to 2% per year observed during late postmenopause but approximates the rapid early loss in late perimenopause and early postmenopause.[20] BMD losses seem greatest during the first 5 months of lactation, with recovery to normal BMD levels after weaning.[20]

Bone density does not always return to prepregnancy levels, even after resumption of menstruation.[21] Women in whom lower bone mass is likely to persist after lactation are those nursing multiple babies, adolescent mothers, women with inadequate nutrition, and women in the later childbearing years who may not be able to regain lost skeletal mass before menopause onset.[22]

Lactation may be a contributing factor for postmenopausal osteoporosis in women whose bone density does not completely recover to prepregnancy levels upon weaning, although studies on this topic are inconclusive.[18] Some recent

*To avoid unnecessary complexity that would obscure the main thrust of our argument, we used the terms *estrogen* and *estrogenic* throughout, rather than specifying the different compounds involved. For the interested reader, estrogenic refers to the net action of the following estrogens at any time: classic estrogens (estradiol, estrone, and estriol), conjugates (eg, lipoidal estrogens), nonestrogens active at the estrogen receptor level (eg, progesterone, testosterone, and 27 OH-cholesterol), and xenoestrogens (eg, isoflavonoids, selective estrogen receptor modified compounds, and some pesticides such as DDT). Serum estradiol is the primary estrogen measured in human menopause research. Terms for the stages of menopause are those defined by the 2001 Stages of Reproductive Aging Workshop.[24]

TABLE 1. *Responses to falling sex steroids*

Adaptive during reproductive era	Affected cell systems	Maladaptive in menopause
Maintenance of capillary blood flow to critical organs	Arterial tone increased	Cardiovascular disease, hypertension
High blood fat for milk	Lipoprotein lipase	Cardiovascular disease, atherogenesis
Mobilization of calcium for milk	Remodeling cycle favors bone loss	Osteoporosis, fracture
Deterioration of genital skin, loss of bulk and elasticity	Organ turgor (genital and sexual skin)	Scarring and genital atrophy
Radiant warming of suckling newborn (vasomotor symptoms)	Vasomotor control, changes in thermoneutral zone set-point	Vasomotor symptoms, night sweats
Increased vigilance	Sleep pattern alterations	Sleep disorders
Affective and cognitive changes, decreased immune brain barrier	CNS alterations	Memory deficiency, impaired cognition, dystrophies
Decreased cellular immunity during pregnancy	Immune response to insult and foreign antigens	Failure of immune privilege, CNS vulnerability, and increased rates of cancer

CNS, central nervous system.

epidemiologic research suggests a higher bone density in women who breast-fed their infants compared with women who did not. This is observed in the presence of adequate nutrition, provided that there is a sufficient length of time with resumption of menses before the onset of menopause.[23]

If lactational bone loss is compared with that occurring during menopause, several variables must be considered. Many researchers fail to define the stage of menopause being studied. For example, late perimenopause and early postmenopause, as defined in the Stages of Reproductive Aging Workshop staging system,[25] are associated with more rapid bone loss than late postmenopause. Whereas the normal premenopausal bone remodeling cycle (resorption, reversal, formation, and quiescence) occurs over a period of 4 to 8 months, the remodeling cycle during lactation occurs at twice that frequency: every 3 to 4 months.[22] During lactation, high prolactin levels prevent gonadotropin-induced ovulation and maintain low estrogen levels, which promote bone resorption. At 6 months postpartum, exclusively breast-feeding women have prolactin levels that remain increased,[26] supporting continued transfer of calcium from bone to breast milk.

Once menses return and estrogen levels increase, bone loss abates.[27,28] Data from nutritionally healthy women corroborate this phenomenon of BMD restoration, showing that multiparity, as compared with low parity or nulliparity, is *not* associated with postmenopausal low bone mass.[29] Unlike lactation-associated bone loss, postmenopausal bone loss is not followed by restorative phase. Overall, menopause results in lower bone mass. Lowered bone mass, along with other changes associated with aging, results in measurable increases in fracture risk.[30]

Vasomotor symptoms during lactation

The low-estrogen state is frequently accompanied by vasomotor symptoms (VMS; hot flashes and night sweats) in women during the puerperium and postpartum lactation. In this setting, VMS may be integral to positively adaptive endocrinology (as opposed to the negative implications of VMS in postreproductive women). Hot flashes occurring postpartum or during menopause result from alterations in the temperature-regulatory centers of the hypothalamus. The so-called thermoneutral zone narrows in a low-serum-estrogen environment, making both hot flashes (an exothermic warming phenomenon) and sweating (ultimately a host surface-temperature evaporative cooling phenomenon) more probable.[31] During the hypoestrogenic milieu of lactation, VMS could serve a biologic purpose by increasing maternal skin surface temperature.[32] Such temperature increases provide radiant heat for infant warming.[33] Lowering caloric demands for self-warming conserves infant energy for weight gain and reduces metabolic stress on the newborn.[34,35] Therefore, VMS would probably contribute a survival advantage in terms of warming of offspring and convey some evolutionary biologic advantage.[6]

Insomnia during lactation

Lactation-associated sleep disorders probably confer biologic advantages. Easy wakefulness and heightened alertness during awakenings result in protection against predators enhanced nighttime attention to the newborn, increase the frequency of feedings, and promote greater early infant weight gain, especially in the high-mortality neonatal interval. Additional maternal endocrine changes and blunted stress responses serve to enhance lactation adequacy and prevent maladaptive sensitization of infant CNS programming.[34,36] This stabilization of both basal and stress-induced hypothalamic-pituitary-adrenal activity may be important for maintaining a constant endocrine environment, thereby preventing negative programming effects on the developing offspring. Other aspects of the lactational endocrine milieu probably serve to enhance nurturing behaviors and maternal calm during the low-estrogen state.[36]

LONGEVITY, DEMOGRAPHY, AND CHANGING PATTERNS OF DISEASE

Whether a product of natural selection advantage, chance, or constraint as the cause of design complexity, menopause confers some advantages toward survival.[38] In view of suggestions by others, one should consider any claim of adaptation against constraint and pathology as alternatives.[39] The mechanism by which the naturally occurring state of menopause (constraint or pathology) accelerates somatic aging and advances disease risks over time will be explored.

Survival beyond age 65 years of a large percentage of the female population is a very recent phenomenon in terms of evolutionary time. The earliest census data for the United States are from Massachusetts, where life expectancy at birth in 1850 (free-living white women) was 40 years, biased by

high rates of infant mortality. If a woman reached the age of 40 years, the data predicted 28 additional years of life expectancy, indicating that if one survived infancy and the high mortality of childbearing, then surviving until age 68 years was common.[40] This estimate is similar to the maximum 70- to 74-year life expectancy observed in the most fertile women, as reported by Emery Thompson et al.[41] Demographic data do not support life spans beyond the eighth decade as a frequent, naturally occurring event.

We can expect the population of US women older than 80 years to increase by more than 15 million over the next three decades.[42] Considering the large number of nursing home–dwelling women at present, these statistics stimulate thoughts regarding possible measures to slow the pace of somatic aging in postmenopausal women.[43] In less developed nations, women who lived to be very old were a relatively small percentage of those, who were biologically fittest.[44] Hunter-gatherer octogenarians were subjected to tests of reproductive fitness and were the most vigorous with respect to later-life somatic fitness.[45] With medical and scientific advances today, surviving to a very old age no longer represents evidence of selection for reproductive or other physical fitness.[46]

COMPARATIVE ENDOCRINE MILIEU OF REPRODUCTIVE AND POSTREPRODUCTIVE WOMEN: ANTAGONISTIC PLIEOMORPHISM IN ACTION

The principles of low-estrogen menopausal physiology help explain diseases that appear to increase in frequency and severity during the late postmenopause. Low serum estrogen levels in menopause, compared with low levels during lactation, result in very different metabolic and CNS effects.[2,47] It does not seem logical that VMS and sleep disorders serve any beneficial purpose later in life, although VMS in postmenopausal grandmothers caring for infants could potentially offer similar warming advantages for grand-offspring survival.

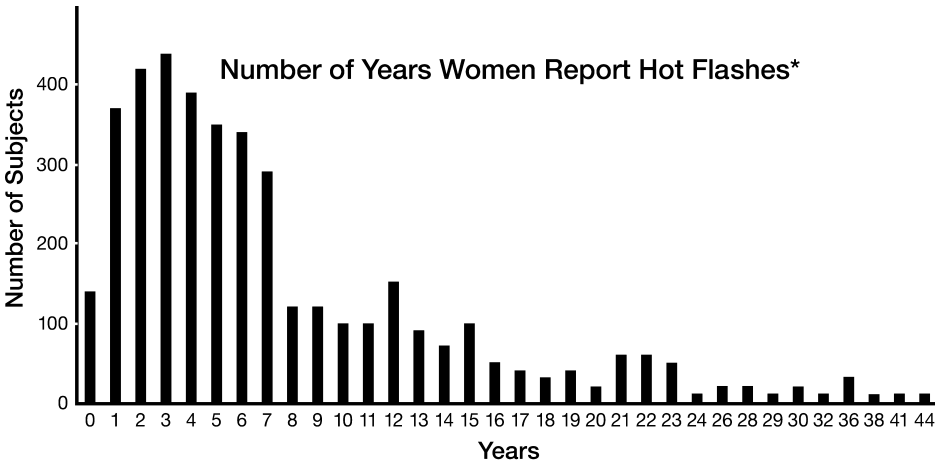
VMS affect a large majority of postindustrial postmenopausal women, with some estimates as high as 90%. Although all women are not equally affected, about one third of affected women have very severe symptoms causing multiple nighttime awakenings, severe night sweats, and disturbed cognitive function (Fig. 1).[48,49] These studies are reported from present-day sedentary populations and are not representative of hunter-gatherers.[50] Menopausal symptoms at every stage are decreased in very physically active women as compared with those who are less active.[48,50]

Because hunter-gatherers are extremely vigorous and active even through the late menopausal years, they are likely to have been among the least bothered by menopausal symptoms, as evidenced by data on sleep disorders in women from less developed nations as compared with sedentary women in postindustrial countries.[50]

Compensatory mechanisms that diminish VMS occur in 80% of postmenopausal women and seem to occur in most women 10 years after the final menstrual period.[48,50] Urogenital atrophy and vaginal dryness are highly prevalent and associated with severe disability and sexual dysfunction. Recent assessments are divided as to whether VMS may signal the presence of cardiovascular disease (CVD) in postmenopausal women. Recent data from the Women's Health Initiative suggest that persistent VMS are a marker of subclinical CVD.[51] This analysis showed that the women most likely to experience a cardiovascular event (myocardial infarction or stroke) when given either oral estrogen or oral estrogen/progestin therapy were those in late menopause *with persistent VMS*.[52] Women whose symptoms abated after the typical 4 to 5 years (Fig. 1) had much lower risk when similarly treated. CVD is the major cause of mortality for US women, equal in number to the sum of the next four causes of death; thus, refining our risk factor analyses may assist in efforts aimed at CVD risk reduction.[53]

Lipids and CVD

In contrast to the Paleolithic-era, the diet of hunter-gatherer populations, the high-glycemic-index and high-fat diets



Modified from: Kronenberg F. *Ann NY Acad Sciences*. 1990;592:52-86.

FIG. 1. Hot flashes may continue years after menopause.

characteristic of populations in more developed nations result in adverse cardiovascular risk factors and higher rates of disease.[54] In postmenopausal women, a more sedentary lifestyle and higher body-fat content result in higher circulating serum lipoprotein concentrations.[53] Plasma lipoprotein increases caused by increased lipoprotein lipase activity in the presence of low serum estrogen levels, common in postmenopausal women, further increase risk.[55-57] In menopause, low serum estradiol levels are associated with a sustained increase in total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels and a concomitant decrease in high-density lipoprotein cholesterol level—a more atherogenic lipid/lipoprotein profile.[55-57]

Although not universally demonstrated in cross-sectional studies, longitudinal data document a small but statistically significant increase in diastolic blood pressure of 0.48 mmHg across the menopausal transition in conjunction with low serum estradiol levels.[57] Another adverse effect of low serum estrogen level is an increase in cardiospecific C-reactive protein, a marker of vascular inflammation in the coronary circulation. Increased cardiospecific C-reactive protein is recognized as a marker for increased risks for CVD and thrombus formation. Low serum estrogen levels cause increases in arterial tone, with an increase in BP in both primates and humans.[47] Increases in arterial tone are associated with vascular luminal narrowing, requiring greater pressures to maintain adequate blood flow to vital organs. Increased arterial pressures over time increase vascular injury and formation of atheromata and contribute to higher rates of plaque rupture, myocardial infarcts, and peripheral vascular disease.[58,59]

Primates rendered menopausal in the laboratory exhibit adverse changes in CVD risk markers that are similar to those in female human beings with premature, surgical, or spontaneous menopause.[47,55-62] A comparison of premenopausal and postmenopausal women aged 40 to 55 years showed that, regardless of age stratum, CVD was more common in the postmenopausal group than in the premenopausal group.[60] Similarly, the degree of CVD increases the earlier the hysterectomy/oophorectomy is performed.[61,62] The cumulative effects of dyslipidemia, when compounded by abnormal serum inflammatory markers and hypertension, result in increased risks for atherosclerotic CVD, stroke, renal disease, and dementia in postmenopausal women.

Bone metabolism and chronic disease

In late postmenopause, the prolonged hypoestrogenic milieu causes a decline in BMD over time, with no rebound compensatory phase of bone formation as occurs after lactation ends in reproductively fit women. Resultant late postmenopausal skeletal fractures, particularly those of the hip, cause higher rates of disability and death. One-year mortality rates after this injury range from 15% to 20%.[61] A prospective study on the socioeconomic aspects of proximal femur fracture demonstrated that approximately 50% of women who lived independently before hip fracture were unable to regain their independent lifestyle subsequent to the fracture.[63,64] The inexorable demineralization of bone after diminished ovarian estrogen synthesis, as in late postmenopause, is biologically disadvantageous.

Low serum estrogen concentrations lead to accelerated rates of bone resorption, with reductions in bone mass; this phenomenon occurs in both lactating and postmenopausal women. Lactation-related fractures are rare. Multiple factors may account for this phenomenon, but the precise mechanisms are not known. Younger age, higher bone density, a shorter duration of accelerated bone resorption (compared with menopause), and other neuromuscular factors are probably protective, rendering the nursing mother's skeleton relatively resistant to falls and fracture.[65] Frailty, which increases risk for falls and fractures, is very rare in lactating women but quite common in older women with osteoporosis.[65,66] The human costs of osteoporosis due to prolonged low serum estrogen levels are substantial. Approximately 50% of women older than 50 years will have an osteoporosis-related fracture at some time during their remaining lifetime.

The sustained loss of muscle mass, collagen, and elastin seen in late postmenopause results in frailty, a second phase of accelerated bone loss.[66] These underlying alterations in menopausal bone, muscle, and connective tissue physiology are disadvantageous, decreasing self-sufficiency and independence as women age. Growing demands for assisted living services reflect the cumulative impact of loss of vigor in aging sedentary women.[42]

With an evolutionary medical perspective, one might organize the data regarding lactational and menopausal features and their disparate short- and long-term effects on health, as shown in Table 1. This is antagonistic plieotrophism in action.

PARADIGM REASSESSMENT

There is a paucity of evidence to demonstrate that menopause has a genetic evolutionary contribution for humans over time. Women living beyond their own reproductive fitness may improve maternal-infant care by providing additional hunter-gatherer labor and reliable food and water and by playing midwifery roles that lower infant and maternal mortality rates. However, there does not seem to be a genomic advantage to menopause per se, other than shortening the reproductive life span to allow for more rapid generation times, enhancing adaptability, and lengthening the time of protection and provisioning support of grand-offspring. Selective advantage depends on traits carried by offspring and on the "grandmother effect," not on the effect of grandmothers on menopausal fitness. [67] In these cases, the selective advantage is not related to postreproductive adaptation and does not contribute inheritable genetic alterations or novel metabolic responses to the loss of estrogen.[1,15]

Sociologic and scientific advances allow humans to experience new challenges and opportunities with respect to longevity. With current life expectancy approximating 80 years, we ask the question: is it possible for a large percentage of women to be very old and also be very healthy without specific "normalizing" physiologic interventions? The human

genome was selected in past environments far different from those of the present. Cultural evolution often proceeds too rapidly for genetic accommodation, resulting in dissociation between our genes and our lives. The mismatch between inherent biology and sedentary lifestyle fosters increasing prevalence of degenerative diseases and chronic illness.[68] We must develop an overall conceptual framework to better characterize differences between ancient and modern life histories and relationships to the emergence of disease patterns. Through such analysis, one can create a unifying approach upon which to base consistent, compelling, and effective recommendations for reduction in disease burdens for individuals and across populations of women.[2]

CONCLUSIONS

From these examples, we conclude that low serum estrogen's "natural" biologic advantage—its selective evolutionary purpose—is probably restricted to postpartum lactation. Decades of sustained estrogen deprivation, with attendant disadvantageous cardiovascular and musculoskeletal outcomes, result in greater rates of diseases and declining vigor in women. As Austad[4] stated, "Assuming the human body has been physiologically adapted to the conditions extant during the vast majority of human history, it may be well worth pursuing how the signs and symptoms of menopause are affected by dietary, exercise, and reproductive hormone regimes mimicking those of the late Paleolithic era." Adopting evolutionary premises in our approach to menopause, we view it as a state of human existence upon which evolutionary biologic pressures no longer operate. An evolutionary medicine perspective creates a radical shift in our thinking on the biodemography of this aspect of aging in women. Through the study of evolutionary medicine, we are called upon to create new approaches to menopausal health care to lower morbidity rates associated with extremes in somatic aging.

US physicians and public health officials specializing in post-reproductive health care are concerned about the expanding number of aging women whose longevity will lead to exponential growth in the population of dependent older persons. Analyzing the fundamental underlying processes that characterize the postmenopause reveals many characteristics that are biologically disadvantageous when sustained over time. Correcting the underlying cause of the pathophysiology could lessen morbidity during late postmenopause in modern Western cultures. An evolutionary medicine perspective calls for reassessing the current approach that discourages the use of estrogen support in menopause. A methodical evolutionary medical inquiry may generate options that not only lengthen disease-free life spans but also improve quality of life.[6]

FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

Careful examination of the inherent self-preserving physiologic and evolutionarily selected mechanisms for homeostasis during and after lactation may provide new insight into the prevention of disease after menopause. Furthering our understanding of energy conservation during lactation may provide opportunities for reduced caloric consumption and its attendant longevity benefits after menopause, with similar salutary effects. Perhaps, the hormonal milieu present during and immediately after lactation, an environment that restores skeletal integrity, could be harnessed later in life to prevent osteoporosis, fractures, and other infirmities so prevalent in aged women.

The profound similarities between the metabolic changes during lactation and those after menopause bring several research opportunities into focus. Lactation evokes rapid, self-regulating, compensatory mechanisms for its metabolic changes (typically within a few years), and is associated with protection against cancer. Similar metabolic changes after the final menstrual period result in well-documented adverse lifelong health consequences in late postmenopause (eg, CVD, osteoporosis, and fractures). When started in a timely manner hormone therapy has been shown to reduce risk for many of these hypoestrogenic consequences. Evolutionary principles could stimulate a research agenda and, ultimately, a shift in public policy. We need to better characterize differences between ancient and modern women's life histories, identify which of these factors affect the development of disease, and ultimately integrate epidemiologic, mechanistic, and genetic data with such principles as antagonistic pleiotropy to create a unifying concept on which to base persuasive, consistent, and effective recommendations.

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