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Evolution of Estrus, Brain Function and Menopausal Symptoms

Lasley Bill L[1]* and Mc Connell Daniel S[2]

[1]*Center for Health and the Environment, University of California Davis, Davis, California*

[2]*CLASS Laboratory, Department of Epidemiology, The University of Michigan, USA*

***Corresponding Author:** Lasley Bill L, Center for Health and the Environment, University of California Davis, Davis, California.

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Abstract

The evolution of the human brain was critical in the expression of basic reproductive strategies and permitted the transition of reflexive estrous cycles to our present social-sexual menstrual cycle. An inventory of the reproductive strategies of our progenitor female mammals provides clues to help explain the causal pathway of menopausal symptoms of today. Such an inventory of progressive adaptations reveals the conservation of key endocrine mechanisms that were modified and seldom abandoned. Evolving to fill emerging environmental niches, ancient mammals adapted hormones they inherited from fish and reptiles to construct increasingly complex breeding systems which led to reproductive isolation resulting in new species. Each new species retained similar basic endocrine foundation but profoundly different controls for breeding. The neural peptide, gonadotropin hormone releasing hormone (GnRH), is the most fundamental hormone in the control of reproduction and changed little in control, composition and structure from fish to mammals. This neural signal acts directly on the limbic system to invoke autonomic reflexes through episodic pulses of secretion. Progesterone is also a consistent and critical control factor across mammalian evolution and acts through feedback loops to modulating GnRH. The evolution of a larger more complex brain aided by the development of placental hormones and more complex adrenals, gradually converted a reflexive estrous mating strategy to a strategy with social-sexual contexts. Environmental cues were incorporated into the neural control of breeding seasons and more complex social systems limited fecundity. Primates replaced most of the reflexive physiology and behavior using progesterone to modulate the neural control centers. Cyclic, prolong hiatuses in progesterone production in higher primates led to the acquisition of mate choice in females and a social-sexual reproductive strategy. Progesterone domination can act to dampen the pulse frequency/amplitude of GnRH secretion and suppresses the reflexes of early reproductive strategies. Lower progesterone may lead to conflicts between higher control and relic reflexes leading to unnecessary and unwanted autonomic responses.

Keywords: *Evolution; Reproductive Strategies; Gonadotropin Hormone Releasing Hormone; Progesterone; Estrus*

Introduction

The reproductive strategy of higher primate species is the evolutionary culmination of a line of mammalian species that have evolved to meet the challenges of a changing environment. Speciation depends largely on diverging reproductive strategies. The appearance of a new species is the result of adaptations that support sustained reproductive success within a given group while limiting cross breeding with individuals outside that group. Geographic separation along with anatomic and physical adaptations are important in this respect, and so are neurologic, behavioral and physiologic adaptations. Increased brain development is a key feature in the evolution of primate

species, particularly the higher primates, and the shift towards a social-sexual reproductive strategy stands out as one of the hallmarks of human evolution. Modest modifications in basic reproductive physiology/behavior preserve critical elements in a complex mechanism to culminate in new species that continue that continue that process. Critical elements are the indelible traits that survive the processes of evolution and provide a rear-view mirror for tracing the thread of evolution that characterizes extant species. Some non-critical elements are also retained, not because they are needed for survival but often because the was no requirement to abandon them. Identifying these vestigial, non-critical elements may provide a roadmap to understanding how some non-useful, and possibly, unwanted traits are transmitted. One such group of traits is the constellation of autonomic responses often associated with the menopausal transition.

Reproduction is a basic and essential trait to every species and its elements are attributed directly to extinct species that passed them forward to modern, extant species. Producing offspring requires a reproductive strategy that is unique to each species and it is that quality that most permits speciation. It is the inability to hybridize that keep species pure and a large part of that reproductive separation is a direct result of the uniqueness of species-specific reproductive traits. While geographic separation can provide a sufficient barrier to hybridization, it is the differences in morphology, physiology, olfaction, karyotype, behavior, and endocrinology that, in concert, are far more important. Almost all extant mammalian species have closely related species such as wild horses and zebras, cape buffalo and gaur, lions and tigers, etc., yet, unless forced by captivity or artificial assistance these species will not hybridize in natural conditions. That absolute barrier is a result of evolution making changes in its reproductive strategy to formulate new reproductive qualities to permit a species to adaption, in order to sustain its lineage in a new environment. Despite this evolutionary radiating of fish to birds/reptiles and finally into thousands of unique mammalian species, the basic fundaments of reproduction have remained relatively stable. It is the persistence of a few key elements that both permit the creation of a variety of sustainable reproductive strategies and maintain durable new lifestyle systems. It is also the persistence of archaic traits that lead to unnecessary and sometimes unwanted qualities (such as menopausal symptoms). By characterizing a variety of present day species it is possible to trace the evolutionary path of component traits that inadvertently provide the causal pathway for menopausal symptoms. Once a species has reached a stable plateau of reliable procreation, then the dual priorities for sustainability of that species is for the individual to 1) stay alive until successful reproductive age has been achieved, and 2) successfully reproduce in an available/appropriate environmental niche. Once these goals have been reached then evolutionary influences are of little consequence. Adapted attributes that arise in an individual after reproductive success has been achieved, play no role in future lineages. It is only in the next generation that evolution acts by limiting or augmenting its genetic composition. If environments change then the challenges to live long enough to reproduce may limit which individuals successfully reproduce. Individuals that lack the qualities to successfully reproduce do not pass their genetics to the progeny. In that way the individual aspect of reproductive physiology is determined by environmental selection on specific reproductive, physiologic, or behavioral traits that will be passed on. If a sufficient number of individuals with selected traits are allowed to reproduce with individuals with the same selected traits, then a new species has the opportunity to evolve. In most cases such events are accompanied by behavioral, anatomical or even chromosomal adaptations that prevent crossbreeding and the emerging species takes on unique reproductive characteristics. This is what happened over eons to mammals that became primates that led to humans. Classified by their reflexive reproductive strategies these early species were largely referred to as estrus (as in struck by impulse in the Latin etymology of estrus) or more appropriately classified by their most prominent reproductive features, such as menstruation. Menstrual cycles are evolutionary products of modified estrous cycles that evolved over hundreds of millions of years, as much from behavioral changes as any physiologic process. This scenario is equally true for males and females, but the effects are much more prominent for females than males. Males also have evolved species-specific traits but these are more subtle, have different physiologic consequences but do not lead to prominent adverse expressions in mid-aged human.

Once created, evolved, established and incorporated, a species-specific endocrine mechanism is seldom, if ever, removed from potential use in future lineages. In the case of reproductive physiology, existing hormones can be adapted directly into a new reproductive strategy and

often used for a different function. Unused or vestigial hormones can lie dormant, then reappear as a useful element of a new reproductive strategy. They can also reappear for no apparent useful purpose. This indelible nature of reproductive strategies explains why over eons the basic hormones involved in fish, reptiles and mammals sexual function remain relatively immutable. In the case of the proteinaceous brain hormone molecules, they are often modified in both structure and function. The steroid sex hormones (estrogens, progestins and androgens) are particularly resistant to structural change even as evolutionary processes modifies their use in reproductive strategies. Progestins are usually associated with pregnancy maintenance events, androgens are nearly always associated with masculinization whereas the role of estrogens are not as well understood and their roles are still being investigated. The function of brain and pituitary hormones can be profoundly modulated by changes in estrogen production through changes in pituitary sensitivity and reserve [1]. Progesterone at low circulating levels can exert an amplifying effect but suppressive at higher concentrations [2]. Sex steroids are made in only two peripheral organs, the gonads and the adrenals and have a major role in developing and directing brain activities and functions. In contrast, the sex hormones made in the brains are structurally species-specific and often serve different reproductive functions in different species. Reproductive hormones from the brain support and regulate the steroid-producing organs of the reproductive tract. In the reproductive strategies of the small rodents, which are our archival models [3], some brain sex hormones support the development and function of the steroid producing organs, which, in turn, modulate the production and influence of brain hormones to modulate sexual behavior. In aged rodents, a decline in the positive estrogen feedback is associated with a general hypothalamic circadian disruption [4], and an attenuation of the midcycle Luteinizing Hormone (LH) surge has been attributed to reduced estradiol responsiveness of kisspeptin neurons [5].

Even in the relatively simple rodent model, this double feedback system has all of the necessary components to provide ample building blocks for the evolution of more complex reproductive strategies. Large components of the hormone patterns of extinct rodent species are still recognized in the reproductive strategies of extant mammalian species. This feedback resonance between brain signals and the reproductive tract remains as the basic foundational regulatory element in all mammalian species and provides the plasticity for evolving the multitude of species-specific reproductive systems we find today.

Historically, the behavioral manifestations of reproductive strategies have been most useful in describing and characterizing most species. The advent of sensitive hormone assays over the recent five decades have led to the quantification and profiles of reproductive hormones that now define all but the behavioral aspects of reproduction. The unique pattern of progesterone and estrogen production accurately reflects ovarian activity and permits discussions of species difference in detail. Estrogen production profiles have most often been used to illustrate the maturation processes of females, waves of ova production, and the onset and support of mating behaviors. Recent investigations now question the accuracy of estrogen production measurements, and this unease has led to more reliance on the quantification of progesterone production as the more reliable indicator of female reproductive endocrinology. This growing concern is particularly true for the more recent understanding women's reproductive health and a paradigm shift is now occurring. For more than seventy years estrogen replacement has been most often used to attenuate menopausal symptoms. However, there is little empirical evidence that indicates low estrogen is in the causal pathway for menopausal symptoms. This, then is the estrogen paradox*: How can estrogen replacement be beneficial if estrogens are not low?* This is a current point of contention, and one reason estrogen profiles are not used in the following discussion. The second reason is that progesterone, not estrogen production rate has been associated with vasomotor symptoms which can be an early and long-last menopausal symptom [6]. By tracking the role of progesterone in a wide variety of reproductive strategies though millions of years of evolution it is now clear that it has always played a major role. In addition recent reports have indicated that central neural events downstream of the control of LH by kisspeptin are directly involved in VMS in both animal [7] and human [8] models.

One brain hormone, a very small peptide (GnRH), is unique in its history and over-powering influence on reproduction. In very modest structurally different versions, it is ubiquitous in its central role is all fish, reptiles and mammals is the basic element in explaining both

the path of reproductive strategies and the evolution of menopausal symptoms. This hormone is synthesized deep in the oldest part of the brain and transmits it secretion to many other parts of the brain including the hypothalamus. The identification and synthesis of GnRH was the basic of the Nobel Prize shared by Roger Guillimen and Andrew Schally in 1972 [9]. It was key to understanding basic reproductive endocrinology over the past fifty years and now to explain the causal pathway for menopausal symptoms. The potential importance of this peptide and similar analogs was not immediately recognized in its fundamental role in basic reproductive endocrinology. Once synthesized and experimentally applied, it was clear that this single small neural peptide could ignite, drive or absolutely stop all reproductive functions. This was demonstrated in the green iguana by transforming a non-reproductive female to full sexual receptivity with only one treatment [10].

GnRH is at the origin of all aspects of reproductive endocrinology, even before mammals appeared. A complex of brain cells that synthesize and secreted that neuropeptide, still serves as the master control of the entire system. This complex of neurons (KNDy) produces GnRH, the smallest of all reproductive hormone and acts by eliciting pulsatile signals of this neuropeptide to key sites in the larger brain including the limbic system and the pituitary originally thought to be the master endocrine organ. In fact, The pituitary then controls all sex steroid production as a direct result of the modulation of pulses of the GnRH neuropeptide that is delivered to it in response to environmental, nutritional and external cues. The group of neurons that produce and release this neurotransmitter in discrete pulses (KNDy) is the genesis of all reproductive function in the widest range of vertebrate species. This peptide is the pivot point between the environment and successful reproductive strategies. Cues from both the soma and the environment provide direct information for regulating this peptide and its response to those cues determine the activity of all other aspects of reproduction. Administration of analogs of this molecule can exogenously start, stop or alter reproductive processes in fish, reptiles and mammals.

GnRH turned out to be not just controller of pituitary luteinizing hormone (it was known as luteinizing hormone releasing factor, or LRF for years) it turned out to be the primary or principal initiator or ignition switch for most of all reproductive endocrinology [11]. From the central control center in the primitive brain, this neurotransmitter sends it pulsatile message to various portions of the brain, including the limbic system and hypothalamus. At the level of the limbic system ion the primitive brain, control of autonomic reflexes could be elicited and act at the level of the hypothalamus to control the gonads via the gonadotropic hormones. Today, analogs of this molecule use in clinical use to control puberty in humans and a major component of menopausal symptoms.

The conservation of mechanisms from fish, birds and mammals is demonstrated by the one experiment in which an analog of the small GnRH peptide which is still the propagator of all basic reproductive processes in humans was able to initiate seasonal reproductive activities in a reptile that was not in season [10]. This illustrates the profound conservatism and resilience of the basic reproductive elements in vertebrate species and although structure-function of these elements may be modified they essentially remain an integral part of the reproductive strategy in evolving species. In the case of menopausal symptoms, they likely represent obsolete mechanism that have ceased to functional and may be unwanted. It is not possible to describe the original mammalian reproductive system or how it operated. However, we can inventory extant species and their natural history and assume the most basic reproductive systems represent those that have evolved the least and therefore closest to the original mammalian strategy. We assume this because evolution of biological system usually adds additional complexity to already complex biological systems and seldom simplifies them. The earliest mammals were probably small furry fossorial creatures [12] that had little or no social structure. They were largely prey species for larger animals that had evolved in a different direction. The main survival pressure for the small, prey niche was to produce offspring early and often. Since internal fertilization was already inherent in all mammals, the survival of early prey species required efficient and timely mating with the shortest possible time spent in gestation, maturation and conception. Maturation to adulthood, development of mature germ cells, and mating must be tightly controlled with an emphasis on the production of the largest number of viable offspring in the shortest possible time as these species like had relatively short lifespans. The model we can use today for this type of reproductive strategy is the laboratory rat and its close relatives. Figure one illustrates the key features of this strategy using the principal hormone progesterone to indicate major events.

The KNDy nuclei in the primitive brain provided the constant positive factor, through GnRH, to initiate, promote and sustain reproduction. The green iguana study [10] demonstrated that GnRH alone could start and maintain basic reproductive activities with the primitive brain. However, at the same time, progesterone became the primary modulator of the downstream directives of GnRH/LH/FSH in mammals which were responsible for gamete maturation and key sex steroid production to support the reproductive tract. The most basic function of progesterone enhances gonadotropin action at low levels of production by inducing ovulation [2] and then suppressing gonadotropin support of gametogenesis during pregnancy to halt additional ova production until the pregnancy had ended (Figure 1). KNDy modulated GnRH directed reproductive function by altering the pulse frequency and amplitude of GnRH transmission while progesterone fine-tuned the production rate and actions of pituitary gonadotropins which supported somatic and behavioral changes. All of these mechanisms were reflexive in mammals which lacked a higher brain systems and females were completely and continuously responding to the GnRH pulse generator. Females automatically, through reflex actions, altered their behavior, odor, food preference, physical activity, sexual receptivity and body control to coincide with the time of potential fertility. This fundamental endocrine foundation of mammalian early female reproductive strategies remains today in most extant species and some of the motor reflexes also remain. As new environmental niches become available and as the higher brain develops to override the primitive brain, the evolutionary process allowed some of the unnecessary autonomic reflexes to be attenuated with volition replacing them. As each new species evolved to fill developing niches, an unlimited number of variations in reproductive strategies emerged. Success of a new strategy was proven by the appearance of a new lineage with a unique reproductive strategy.

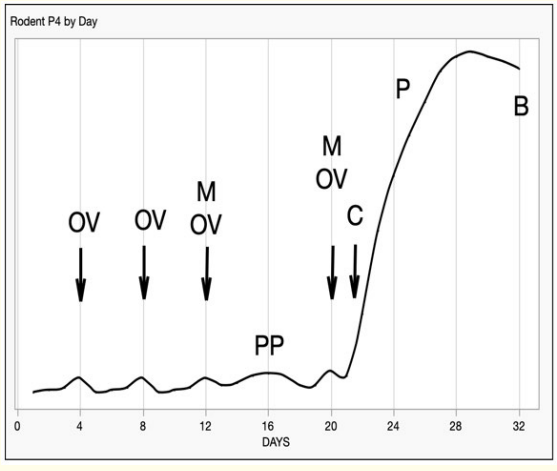

Figure 1: *Rodent. The pattern of progesterone production is depicted to illustrate the major events in a generalized prey species like the rat. In the female, puberty occurs early in life by the GnRH pulse generator KNDy, in which this neuropeptide is transmitted to various areas of the primitive brain through pulse frequency/amplitude modulation. At sexual maturation ovarian cyclicity is initiate in which mature ova are ovulated (OV) spontaneously every few days. Ovulation is facilitated by a small transient rise in progesterone occurs and the females is behaviorally receptive to mating. If no mating occurs this cycle is repeated, however if mating occurs (M) the transient pre-ovulatory rise in progesterone is extended (PP, pseudopregnancy) as a safeguard for embryos if conception (C) was the result of this mating. When mating does result in conception, the production of progesterone is extended further to maintain the pregnancy (P) until birth (B) of the litter. This reproductive strategy promotes high productivity in the shortest possible time with a minimum sexual interaction. All of the individual elements of this strategy are reflexive. In this strategy the reproductive system is always on and functioning as the GnRH pulse generator maintain an instant on condition between ovulations. Mating is limited by physical and behavioral changes determined by the frequency/amplitude of the pulse generator and mating cannot occur outside a narrow window of sexual receptivity of the female. In this early model, progesterone in the primary end-organ controller by facilitating ovulation/mating, delaying the next ovulation in pseudopregnancy and maintaining the pregnancy if conception occurs. Through evolution, progesterone is conserved as a major controller of ovarian function by its feedback to the brain.*

The term estrus is applied to the physiologic-behavioral reproductive pattern in almost all non-primate mammalian species. This term is largely based on the reflexive changes in the female body condition and behavior that alerts males to her potential and immediate potential fecundity. At this level of evolution most of the female's life is associated with either simply surviving or some component of her reproductive strategy. This over-emphasis on reproduction is at the expense of the development of social aspects of existence. The behavior and olfactory signals change are associated with the female's disposition from avoiding physical contact to soliciting copulation. Brain hormones produced at this time have physiologic and psychotropic actions that facilitate ovulation, mating, early pregnancy and later maternal behaviors. All of these events in estrous cycle mammals are autonomic and not being under any willful control [13]. These are essentially reflexes that occur in a rhythm that is orchestrated to match the tempo of the production and maturation of mature ova as a consequence of hormone feedback loops.

The rat model [14] exemplifies a relatively simple reproductive strategy evolved for maximal production yet includes all of the key elements that provided the building blocks for the reconfiguration of mechanisms to the evolved species-specific strategies we can observe eons later. Solitary prey species individuals such as rodents, generally lack complex social structures that facilitates access to other individuals for mating, despite the need for timely mating to produce offspring during a relatively short lifespan. For prey species, the key adaptation is the rapidly recurring waves of mature ova and mechanisms to attract male attention when conception was most likely. Mechanisms to both enhance the likelihood of conception if mating occurred plus a fail-safe mechanism that reinstated the female for an ensuing potential pregnancy also evolved to save time if the current mating was unsuccessful. This is not a simple system but one that provided enough plasticity and complexity to accommodate future adaptations that would be needed to fill new environmental niches. Optimal reproductive efficiency is achieved by employing behavioral, olfactory, and somatic reflexes combined at the expense of conscious control and social interactions. The physical act of mating triggered additional reflexes in response to the likelihood of conception. This simulated ovulation and the production of progesterone which acted as a brake on the next cohort of matured follicles. However, if no embryos were present then the progesterone declined and a ovarian cycling resumed.

As mammals evolved a larger body size and smaller litters, the overall reproductive strategy evolved to accommodate the specific needs of the divergent environments that were being encountered and then reproductively isolated within in them. Supporting greater nutritional needs of bigger fetuses and neonates required smaller litters and less frequent pregnancies that could be timed to coincide with food availability as depicted in Figure two. The inherent control of gonadal function by brain hormones permitted environmental cues to be transduced directly to support the development of mature ova.

Reflexive mating strategies were inherited from polyestrous rodents was dampened by the development of increasingly complex neural links that began to regulate random mating and more complex social-sexual behaviors that reduced conflict (Figure 2). A much larger change evolved in the lifestyle of females. Now with time available that was not involved in reproduction, of which prey species had precious little, the females of larger mammalian species had more time and energy to learn and move from completely reflexive to adopting a loose social structure. Recognition and bonding to herd-mates and relatives had little effect on the acts of reproduction but was a major move towards the ability to exercise will on their environment, mating partners and offspring. Higher brain function was beginning at this time to have a role in reproduction as ungulates and their herd mentality evolved.

The reproductive strategies evolved by carnivores is extremely diverse that a generalized scheme cannot adequately represent them all. From the solitary hunting leopard to the lioness in her pride to the she-wolf in a pack where older half-sisters share most rearing responsibilities including lactation, the same hormones are employed. Similar to herbivores, seasonality is common among carnivores and

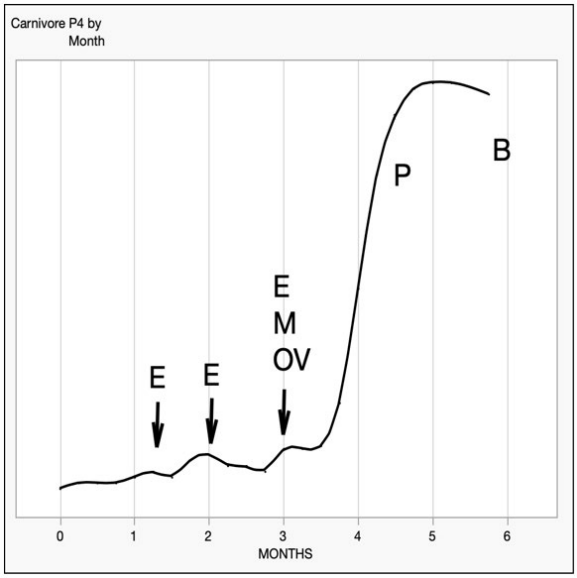

Figure 2: *Carnivore. A generalized depiction of the reproductive strategy of a solitary carnivore that is also an induced ovulator. These species are largely seasonal with GnRH inducing estrus (E) periods with the potential for ovulation and conception. However, ovulation (OV) only occurs when induced by mating (M) during estrous. This linking of mating to ovulation optimizes conception in solitary species that ordinarily have no physical, social or sexual contact. Lactational anestrus and maternal behavior usually follows birthing but exceptions to this rule permits a dominant female to conceive and birth offspring but have little postpartum responsibility in rearing them. In some canine species, the hormones that support lactation that are usually produced in postpartum females can be produced by younger females in the family and these individuals become wet nurses to the litter delivered a more dominant female. Suppression of reproduction of younger females by older more dominant females also occurs indicating that a social-sexual organization of a reproductive strategy is being developed in this group of mammals. Carnivores that live in groups or prides are not always obligatory ovulators and parenting can be more equitably distributed among family members.*

GnRH serves to recrudesce or awaken the gonads at the appropriate season though the same channels of hypothalamo-pituitary support. The same hormones are employed as all other mammals although the protein structures are highly species specific within this group. Estrus behavior in females occurs episodically within a breeding season and ovulation often requires the addition of coital stimulation [15]. Progesterone serves again in all carnivores to both safeguard the possibility of conception and prevents additional mating behavior during gestation and lactation. Complex social systems are common but varied in regard to consorting, mate choice and dominance roles. In some carnivore species, ovarian function is curtailed by either female-female suppression by dominance which permits the mother to be freed from a maternal role and allows older female siblings take on most maternal responsibility. Social conditions play as much a role in controlling hormonal actions as does environmental and nutritional conditions. The adaptation that allows female siblings to care for their half-siblings may be unique to some carnivores and requires adapting lactational hormones to support milk production outside of a post-partum condition. This role of sharing parental responsibilities should not be confused with the theoretical grandma role of menopause women as it is obligatory and a heritable trait whereas menopause is not.

As the larger, longer-lived species adapted to fill the new niches for grazers and browsers many steps were needed to meet the requirements of seasonality that would ensure that gestation and lactation coincided with food resources. We still recognize in our domestic production mammals the foot prints that evolutionary selection that took over millions of years. An early step was the increased modulation of the GnRH pulse generator (KNDy) that now would require a change its tempo and strength to match the seasons of the year. Increased GnRH was required to stimulate gamete production at the time that forage was available, and, like the prey species, estrus behavior permitted mating at only this time. But unlike the small prey species that exhibited continuous fertile ovarian cycles, this shift in GnRH pulses was an awakening of the whole reproductive system allowing females to recover from the metabolic stress of a previous gestation of a large fetus. Behavior estrus was still a basic reflex and was associated with minimal social aspects. For most ungulates [16], mate potential was usually ever-present in herds or flocks so that courtship/mate selection was not needed. A non-fertile mating did not result in a pseudopregnancy but instead, a return to estrus and fertility if it occurred within the breeding season. Control of progesterone production became shared by the brain, pituitary and the contents of the uterus early post-mating. This permitted the development of a more complex and robust reproductive strategy with strong failsafe mechanisms. Environmental cues such as daylength and forage became as important as internal cues such as maturity and nutrition in the control of GnRH pulsatility. The core elements of the basic mechanisms illustrated in Figure one for a model small prey species can be recognized in the basic reproductive strategy of the much larger herbivores as shown in Figure three. The main differences are the increasing control of the environment over mating and fecundity as well as the ability to shut down the GnRH pulse generator in the off-season in the larger ungulates. Social structures were developing at the same time as harems and family groups was adopted by many species.

While both the sex steroids and brain proteinaceous hormones were adapting to more specialized reproductive strategies with limited random mating, increased pair bonding and shared parental responsibilities were also developing. Within these seasonal breeders, a wide degree of variation occurs in terms of time and frequency of conceptions but the basic estrous cycle in females remained. The same small neural peptide, GnRH, inherited from fish and reptiles, was regulating all reproduction through amplitude and frequency modulation of its pulsatile release. The major adaptations relative to the rodent system involved the fidelity in the use of individual reproductive hormones. For example, progesterone in rodents was a transient hormone that insured both the rapid return to fertility in the case of a failed mating and protection of the conception in a successful mating, it also became the clock for ova maturation the rhythm of the ovarian cycle in ungulates. Most ungulates have a spontaneous increase in progesterone production following estrus that safeguards the potential success of estrus-induced mating regardless of whether conception was achieved or not. This adaptation represented a major shift in reproductive endocrinology by elevating the role of progesterone from a passive operator to the key regulator in the tempo of ovarian cyclicity.

In contrast to the evolution of the generalized carnivore reproductive strategies some ungulates (Figure 3) and other larger herbivores developed a herd or harem system. Having fewer and larger offspring presents different evolutionary pressures than of litter-bearing rodents. Large volumes of a low calorie nutrition which was seasonal in abundance favored a limited birth season which in terms determined the breeding season. Figure three depicts a general herbivore female ovarian activity cycle. Living in groups for protection from carnivores, a mechanism for mate choice has a low priority. The herd provides a loose social structure in which physical dominance may be the only factor of consequence in mate choice. Males and females co-mingle with the exception of dominant males allowing or preventing access of other males to receptive females. As browsers or grazers, the food resources over-shadowed any other modulators of reproductive strategy. To this point in evolution the estrous cycle was an apt descriptor for most surviving reproductive strategies. All of the hormonal double feedback systems were in play and some reflexive body rigidity at sexual receptivity still exists in the domestic horse, cow and pig today.

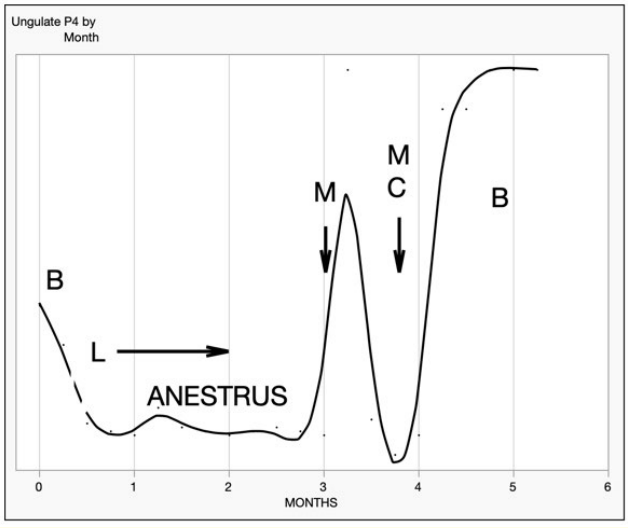

Figure 3: *Ungulates. The reproductive strategy of larger ungulate species that were progenitors of our meat-producing domestic animals is depicted by a stylized longitudinal profile of progesterone production. Compared to the relatively constancy of potential fecundity in the smaller prey species (figurer one), Seasonality is the major characteristic in these much larger grazers/browsers. Only during the breeding season, multiple estrous periods occur until a fertile mating takes place. Serial estrous periods are associated with increasing day length which controls GnRH pulse strength and intensity and coordinates mating, gestation and birthing at optimal times for optimal nutrition. After birthing a prolonged lactational period with shortening day lengths, females experience a prolonged period of anestrus or obligatory infertility associated with parenting and limited asexual social interactions. Mating occurs only at estrus with little if any courtship or pair bonding. A spontaneous rise of progesterone immediately follows each estrous period for 12-16 days and this luteal phase safeguards the possibility of conception whether or not mating has occurred. As progesterone falls at the end of a non-conceptive luteal phase, an ensuing estrus period and ovulation occurs spontaneously.*

Progesterone slowly evolved to be the second most important and widely employed hormone in the complex of reproductive hormones through evolution. The role of progesterone as a primary regulating signal was present from the most primitive of reproductive strategies. With the advent of internal fertilization, mechanisms for efficient mating were needed. The simplest and perhaps the most archaic was likely that of the polyestrous rodent. As a prey species in which quantity off off-spring is advantageous over quality off progeny, a highly efficient ovarian cycle is invented in which progesterone is employed modestly. In this adapted strategy, young females mature quickly and generate mature ova every few days unless impeded by progesterone. With little social constructs to promote opportunities for mating, this strategy employed a triple autonomic reflex that optimized propitious mating. The hormone dynamics associate with the apex of ova maturation, ovulation and a priming of the uterus for maintaining a pregnancy. Concurrent with these hormonal dynamics, changes in the female's odor, morphology of the genitalia and sexual behavior, facilitate mating and conception.

The advent of the early primate species brought four major adaptations in reproductive strategies. Most important was the rapid development of the higher brain. A larger brain led to more conscious control of lifestyle and less reliance on reflexes. As early primates (Figure 4) developed more conscious control and complex mating strategies, strong behavior traits led to consorting and mate choice [17]. A larger fetal adrenal developed and this led to additional steroid hormone support for brain development and additional components to the adult adrenal. Most significant was the appearance of a pituitary hormone in the placenta which provided support to the fetal adrenal and developing brain. Together, these emerging developments created a social-sexual lifestyle. These traits were likely necessitated by a changing environment which led to new arboreal niches that accommodated emerging frugivores and browser species. The higher brain power above the limbic system led to more volition and less reliance on reflexes. However, most prosimian species retained the classic

estrous cycle type of mating and limited actual mating to a confined estrus period. Mating outside the estrus window of receptivity was not possible and a social-sexual lifestyle was just developing. A larger brain also led to more complex lifestyles and social systems of colonies and troops with more separation of gender roles. As early primates developed more conscious control over mating as they moved down from the trees to the savanna where they were more vulnerable to predation. Complex mating strategies allied with strong social behavior traits evolved and led to consorting and mate choice. A larger fetal adrenal began to be developed prior to the dawn of primates, probably in tree shews [18] that left their young unattended for long periods of time. This larger fetal adrenal provided more steroid support to the developing brain and forced a slower maturation of the neonates. This trait was incorporated by the more successful ensuing species and led to not only additional steroid hormone support for fetal brain development, it led directly to an additional layer in the already complex adult adrenal. True primates also included pituitary hormones in the placenta which provided support to the fetal adrenal, developing brain and control in the timing of parturition. Together, these emerging traits permitted the development of a complex a social-sexual lifestyle which is primarily based on gender-specific roles. As the estrus component of mating declined and the social role of females became more defined in primates, the development of mate choice evolved in order to insure the survivability of the most fit offspring. Mating outside a window of estrus emerged as part of social-sexual consort pairing and mate selection. Loss of complete reliance on reflexive mating required delaying the optimal time of a fertile period so that conception would more likely favor the selected mate. Females could anticipate her fertile period in order to facilitate conception with as much planning of paternity as possible as a more fit male would insure the survivability of the offspring. This delay between the last domination by progesterone in the previous unsuccessful ovulation and the next ovulation lengthened the period of time that progesterone did not dominate the increase in estrogen production acting on the reproductive tract. This hiatus led to a deepening of the endometrium to the point it was a deciduous organ that required sloughing and menstruation appeared as the predominate visual identifier of this type of ovarian cycle.

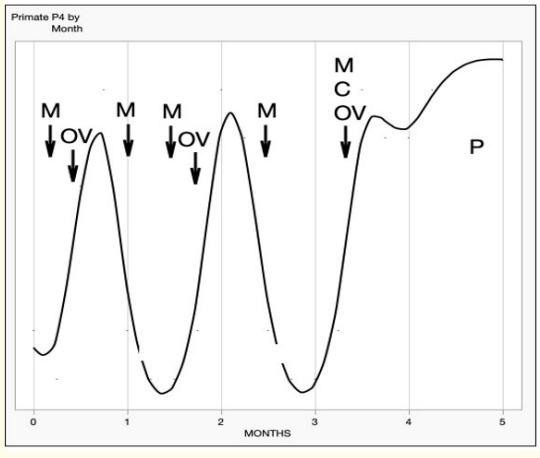

Figure 4: *Primates. A stylized reproductive strategy of a higher primate is depicted with emphasis on progesterone production and major events. The most adaptive characteristics of this type of reproductive strategy are multiple matings (M) that not necessarily associated with ovulation (OV), sloughing of the endometrium (hatched areas) and a placenta that produces most of the progesterone of pregnancy. Conception (C) can only occur when mating coincides with ovulation, but non-conceptive matings that are not associated with ovulation play a major role in the social-sexual lifestyle of these species. Sloughing of the endometrium (menstruation) is a result of the decline of progesterone production that was initiated by spontaneous ovulation 12-14 days earlier. The prolonged period of low progesterone production following menstruation is often associated with courtship and female mate selection. This social-sexual aspect of non-conceptive mating and mate selection adds a new complexity to the social network most primate species and increases the likelihood of strong paternity. Many primate species retain some aspects of estrous behavior near the of ovulation and sex skin swelling of the perineum. GnRH pulses is reflected in the pulsative nature of progesterone in many species and, in turn, these pulses are modulated by a biphasic feedback of progesterone on GnRH pulse strength and tempo. A decline in the response of progesterone production to changes in GnRH secretion modality can lead to a failure of higher brain centers to control the vestigial reflexes of the estrous cycle.*

Despite these four major changes that the primate advent presented, the basic endocrine components of female reproduction remained intact but essentially ignored. Instead, the emphasis in classification was based primarily on the observed cyclic bleeding that was simply the result of the deeply vascularized endometrium necessitated by the widening gap in progesterone domination. Thus the new nomenclature for an ovarian cycle was the menstrual cycle, which intellectually separates those species that possessed it functionally from their hereditary progenitors although there was no substantial change in the endocrine foundations [19]. The primary change that did occur was that of the loss of many reflexes and attenuation of autonomic control. Species with smaller brains and little or no higher control over the autonomic nervous system all retained the classic estrous cycle traits defined mainly by their highly reflexive behavior at mating. GnRH which controlled the onset and sustaining of reproductive function in fish, reptiles and ensuing mammals remained essentially the same in the primate/human as it functioned in fish, reptiles and all non-primate mammals. In most ways the evolution from the estrous cycle to the menstrual cycle required changes that were no greater or less great that many of the previous evolutionary steps made. The biggest event in the evolution of reproductive strategies was the renaming of many female reproductive patterns as something other than estrous. The single most important physiologic adaptation of these new menstrual species was that of progesterone in primates now primarily used to dampen limbic reflexes of the estrous cycles that had always acted to initiate and sustain all previous reproductive strategies. This change in the role of progesterone to attenuate the autonomic reflexes of estrous cycles in the evolution of menstrual cycles relied solely on the ability of the ovary to produce progesterone in a predetermined rhythm than allowed the higher neural centers to control the lower brain. This quality of the ovary is established at puberty and remains as long as sufficient oocytes are maturing in that predetermined rhythm. Since oocyte are finite but lifespan of humans keeps expanding, and expanding after reproductive life had ended, this trait was not under a direct influence of evolution. Living longer may be helpful in highly social species as aunting behavior can be a benefit to the pack or troop. Some canine species have incorporated aunting as a routing strategy. But in primates, the ability to outlive reproductive function is a relative new trait that probably has not had enough time to be incorporated into a lineage that would affect the fecundity of younger reproductive age females upon which evolution can act. Females that live beyond forty often have a reduction in ovarian progesterone production and a loss of the ability to suppress the basic estrous cycle reflexes which now bubble to the surface. The persistence of GnRH from deep in the ancient brain in fish and reptiles, can potentially send signals to the limbic system to awaken the autonomic nervous system to initiate reflexes that no longer have any reproductive function.

Gorillas, chimpanzees and orangutans most resemble humans in their physical size and form and considered to be our closest evolutionary relatives. This is reflected in the expression of their reproductive strategies although their sexual behaviors are distinctly different and reveal a wide range of social-sexual attributes. Separation and timing of conceptions are largely controlled by lactation-induced anovulation which can last for months to years. Mechanisms for mate selection ranges from prominent advertisements of sex skin swellings to relative slight tumescence of the labia. Similarly, menstruation ranges from copious to slight sloughing of the endometria. Social-sexual behavior also ranges from incidental pairs in the orangutan to extreme homosexual and female domination in the bonobo [20]. They are all considered to be non-seasonal menstrual cycle higher primates that differ greatly in terms of social structures. Gorillas live in male-dominated troops, orangutans are solitary, and chimpanzees have two very distinct socials systems defined for the two easily identified species. In terms of their reproductive physiologies, they all use the same hormonal mechanisms with only modest differences in the timing of events associated with pregnancy. The great apes are long-lived, and females often outlive their capacity to conceive and enter into a menopausal state. However, whether these older females experience any of the classic menopausal symptoms as do women is still a point of conjecture. Despite a relatively wide range of reproductive adaptations all of the great apes have more similarities in reproductive endocrinology that do they have differences [20]. Major reproductive hormones are retained for the same essential purpose as in all primates, protein hormones retain their basic physical structures as evolved by lower primates and are produced cyclically in essentially the same patterns.

Some primate species not only dampened the GnRH drive to eliminate estrous reflexes through higher brain suppression but took another step to remove the stimulus to the limbic system altogether. The placenta developed in higher primates to replace the role of the ovary in terms of pregnancy progesterone production and the role of the brain to support the ovary was also diminished. In combination with the larger, more developed fetal adrenals which produced additional steroids for peripheral conversion to active sex steroids, the feto-placental unit functioned as a separate unit. With these adaptations GnRH pulses declined and the limbic system was no longer a target for reprising old archaic reflex mechanisms. Pregnant women became a non-sexual member of a complex social-sexual system but without the antagonism between the autonomic archaic estrus reflexes and conscious control. A post-partum shift from an asexual condition to lactation require reengaging the brain and the potential for limbic system interference to conscious control by re-emerging GnRH pulsatility and recrudescence of the ovaries.

The reproductive strategy employed by humans was derived through an unplanned culmination of a series of small evolutionary changes selected by natural forces for existing species to adapt to newly environmental niches, in order to propagate, and become new species. Conversely, the shaping of the human strategy was the result of existing species incorporating stepwise alternatives to previous adaptations in reproductive mechanisms. The most obvious demonstrations of this process are the behavioral changes in mating strategies. Ranging from being completely reflexive in fish, reptiles, and most non-primate mammals, to copulation becoming largely willful and elective in humans. Once limited to the window of optima conception, coitus was originally severely restrained and had little if any social construct. For humans, ability to copulate has become as significant to social behavior as it is to procreation. Yet, despite extreme alterations in the ability to ensure a next generation, each species has retained the essential physiologic elements that were operational in fish and reptiles. That small molecules (GnRH) from deep in the ancient brain of the iguana that could singularly turn on reproduction, remains today as the ignition switch for all reproductive functions in all extant mammalian species including humans. In essence, the most fundament element of vertebrate reproduction remained relatively unchanged while the expression of reproductive strategies are species-specific.

Each evolutionary step has brought with it beneficial, deleterious and/or neutral side issues. The primary beneficial effect is largely speciation and the emergence of new lineages that are better adapted than their progenitors. The neutral side effects are vestigial mechanisms waiting in reserve in anticipation that the next environmental opportunity may require their rejuvenation. The negative side effects are those that usually adversely affect an individual after it has reached reproductive maturity. Cancer, arthritis, diabetes, etc., are defects often associated with aging and are not only unaffected by evolution but persist since their genes have already been passed along. This is also the case with menopausal symptoms. The prevalence of hyperplastic diseases in the reproductive tract of older women is an example of how opportunistic evolutionary adaptations can inadvertently increase the risk of disease in older individuals.

In fish and reptiles, the limbic system is the ceiling of the brain and controlled most physiologic functions which were largely reflexive. As this ceiling of the ancient brain was subserved by the development of higher brain control centers, some of the autonomic or reflexive systems such as core temperature, hunger and appetite, cognition, memory, and sleep cycles were subrogated by the development of cerebral cortices and came under the shared control of conscious processes. That small molecule, GnRH, passed stepwise from fish to human was still delivered to the limbic system but in species with higher brain control centers, those responses are suppressed. In higher primates that control was dependent on the presence of a normally functioning of the newly adopted menstrual cycle in which progesterone served as the suppressor of ova development between recurring fertile periods. With age and declining ovarian function, the suppressive effect of the higher brain centers decline and the archival reflexes begin to re-emerge. Reflexes long-since buried become apparent just as old cobble stones reappear when overlying asphalt is worn way in our refurbished streets. The increased bumpiness in volition appears as reflexes attempt to control of core body temperature, quality of sleep, etc.

McConnell [6] provides proof of concept to this evolutionary explanation by showing that a reduction in progesterone production during the menopausal transition is the first step in the causal pathway for vasomotor symptoms. The role of progesterone changed as new reproductive strategies evolved. Originally, progesterone was a facilitating factor to safeguard early embryos and support gestation. Later progesterone also became a regulatory factor that acted as a brake by attenuating the signaling by ignition switch in the female ovarian cycle. As the ability of the ovary to produce progesterone, the attenuating power declined and the signals from the KNDy/GnRH ignition switch to the limbic system to stir the archaic reflexes which have little beneficial function and can be perceived as symptoms.

An apt analogy for menopausal symptoms may be considering them as the ghosts of former estrous reflexes still rattling around in the attic of the primitive brain of humans. A current contentious issue is whether any other species of animal experiences anything similar to the classic menopausal symptoms of women. If our premise that every species has a unique reproductive strategy is correct and that is what makes them a species, then the answer is probably no. However, age-related reproductive senescence is quite common in many species including many primates particularly when captivity has protected them into very old age. Many female chimpanzees have been documented as exhibiting age-related infertility and these reports indicate that all of the physiological mechanisms for menopausal symptoms appear to be present. The caveats are that these animals are unable to report their symptoms, if any, and that largely most of the documented case records have been collected from captive animals that were unlikely to have reached old age in the wild. Over one hundred years ago a conscious choice was made to invest our research efforts into investigating the reproductive biology of the macaque monkey specie in the hope it would be a model for the human female. It isn't. Most macaques are seasonal breeders, and their reproductive senescence coalesces with the seasonal non-breeding infertility and the two phenomena are difficult to separate. If any non-human animal most replicates the human female reproductive strategy in physiologic terms it is the orangutan but too few exist in environments in which good scientific data can be collected. It is possible that the grandma helper could influence an future evolutionary trend by protecting children that have the additional care of an aged female in the core family. These grandmas would enhance the ability of these protected children to pass their genes onto the next generation and influence the gene pool to favor the likelihood of long-lived females to be born in the next generation. This scenario is the most likely pathway that a state of age-related reproductive senescence with, or without, adverse physical symptoms, could be retained in multiple species. More likely, menopausal symptoms in women is a results of an extended life-span that occurs because of, but outside of evolution.

The human reproductive strategy represents slight modifications of many higher primates. The most important adaptations were a much greater integration of social and sexual behaviors and the elimination of the restriction of mating to the window of greatest potential fecundity. The role of the key hormones remained as with all other mammalian species but their ability of hormones to elicit reflex actions was sharply curtailed. Most prosimians (lemurs) limited coitus to the period of estrus as social aspects such as courtship and mate choice was emerging and lost in altogether in humans. Parallel to this decrease in sexual reflexes, increases in social-sexual interactions increased and social-sexually behaviors became intertwined. Sexual dimorphism, division of labor and the complete loss of estrous behavior ensued in true primates. The lack of overt signals to coordinate mating with a fertile period led to coitus often not occurring with ovulation and a decline in mating efficiency. Progesterone production spontaneously increases following spontaneous ovulation whether or not mating occurred. Non-conceptive ovulations resulted in a pre-timed rise in progesterone which results in menstruation. This resulted in the adaptation of a mechanism to immediately repeat the processes for next fertile period. Progesterone declines to initiate the development of ova for the next fertile period and this repeats until conception occurs. In all mammals, progesterone and LH are produced in discrete surges in response to the GnRH pulses and this accelerates pituitary hormone synthesis and release [1]. These pulses or waves of hormone release limits the use of circulating concentrations to characterize hormone profiles. The exact nature of these pulses are still being investigated.

In reproductive age women the post-ovulation spontaneous rise in progesterone is 12 to 14 days in duration which is approximately the length for all larger mammals. This domination of the KNDy nuclei is sufficient to suppress the increase of GnRH pulses and permit a

gradual return to a fertile status. However, if the strength-duration of the progesterone rise is inadequate, then the GnRH pulses increase and the vestigial estrus reflex attempt to reappear. This then stimulates the limbi-autonomic nervous system and the release of LH to occur as GnRH pulses reach sensitive organs. Unconscious regulation of basic control centers of core body temperature, sleep, activity and cognition can occur and does as the ability to produce adequate progesterone in older age.

Conclusion

The preservation of vestigial autonomic pathways involved in physiologic and behavioral reflexes of estrus in lower mammals, are normally suppressed in women by cyclic changes in progesterone production. This suppression is mediated in lower brain centers that control GnRH secretion. Menopausal symptoms, therefore, may be the result of the re-appearance of these transient autonomic reflexes as progesterone production declines. Relief from such symptoms by hormone replacement therapy suggest a hormonal deficit being responsible as estrogen replacement is often effective in reducing discomfort and is thought to address the causal pathway of decreased ovarian steroid production. However, a decline in estrogen production has not been documented to be associated with the occurrence of menopausal symptoms, thus the benefit of estrogen supplementation remains a paradox. A review of the evolution of brain-mediated reproductive strategies in female mammals reveals a continuous central role of progesterone in regulating GnRH pulse frequency/amplitude stimulation of the limbic system. In the evolution of species-specific reproductive strategies, GnRH-induced autonomic reflexes in fish, reptiles and early mammals are now recognized as the basic driving force of all reproductive activities. Early species utilized cyclic changes in progesterone production to modulate GnRH pulse amplitude/frequency and control fecundity. Later evolving mammals employed progesterone to modulate the nature of GnRH pulses in response to environmental cues. Solitary mammals adapted GnRH-progesterone interactions to coordinate fertility with mating as a counter to chance encounters. Primate species developed strategies in which ovarian progesterone modulated GnRH to permit female mate choice while placental progesterone completely suppressed GnRH pulses subsuming female sexual activities during pregnancy. The development of higher brain capacities in higher primate species increasingly suppressed the limbic-derived reflexes and permitted the development of a social-sexual reproductive strategy. In humans many of the autonomic reflexes of progenitors species are suppressed until the feedback system fails because of aging. Failure to suppress autonomic reflexes through an aged-related decline in progesterone results in transient unnecessary and unwanted changes in basic physiology.

Data Availability

There are no new data associated with this article.

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