

Evolutionary Medicine

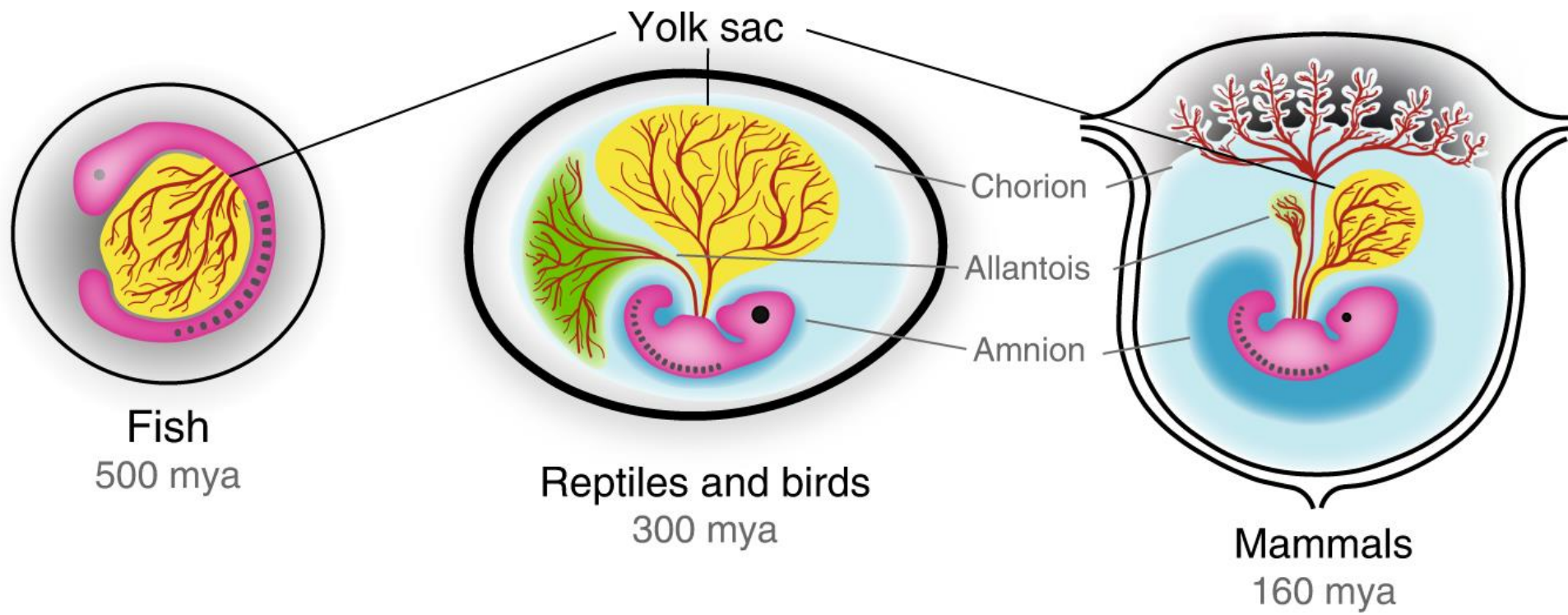
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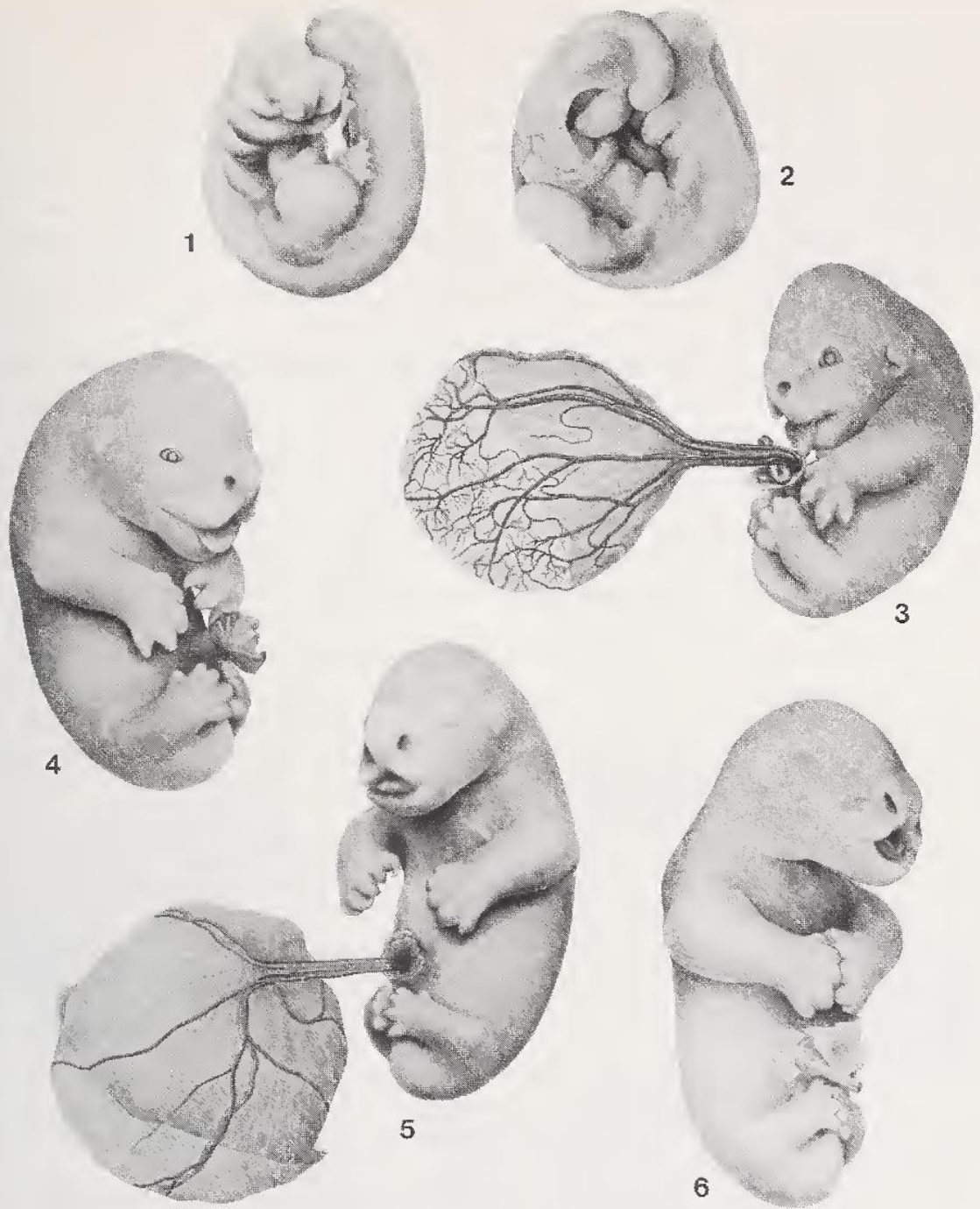
The Evolution of Mammalian Reproduction





Monotremates-oviparous

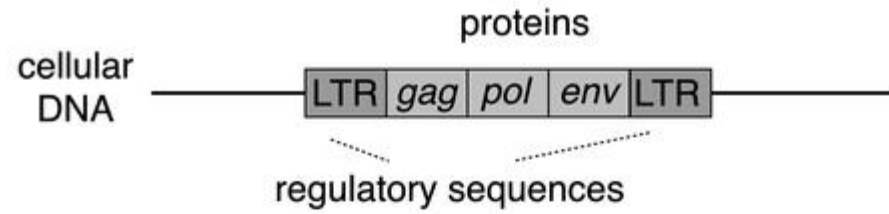




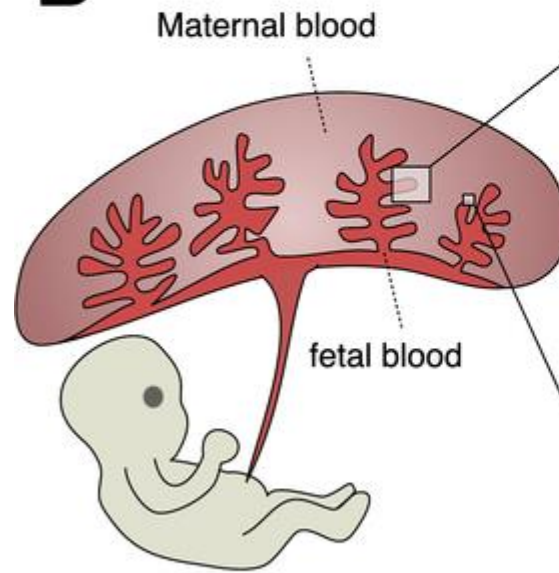
Marsupials

Placental mammals

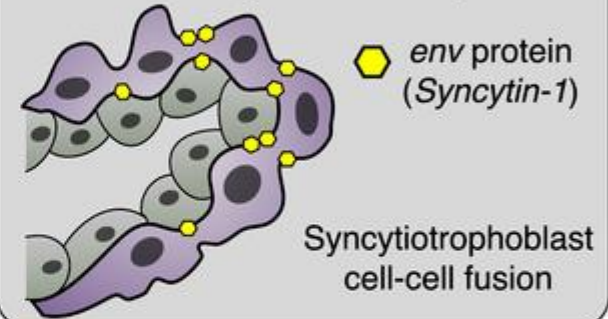
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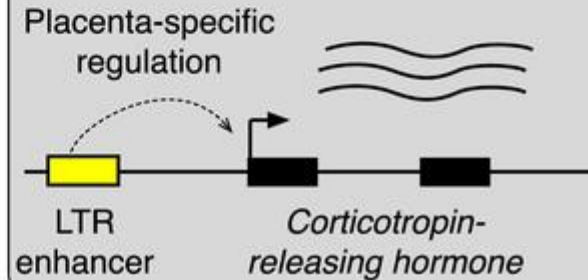
B



Retroviral protein co-option



Retroviral LTR co-option



The evolution of the female reproductive system

Developmental control over the placental female reproductive system involved the redeployment of a previously evolved toolkit to structure a new set of tissues and organs. A comparison of the basic features of female reproductive tracts in amphibians, birds and reptiles, monotremes, marsupials and placentals makes clear just what had to be accomplished, and roughly when it happened in evolutionary history. In the ancestor of the monotremes (170 mya), eggs evolved reduced yolk, and there were some uterine secretion. In the ancestor of marsupials (1520 mya), the cloaca was divided, the oviducts differentiated, an eggshell was not longer formed, the placenta originated, and the uterus began to nourish the embryo. In the ancestor of the placentals (105 mya), the uterus and placenta were elaborated, embryonic stem cells evolved the ability to invade the endometrium and take control of some placental function, and the period of internal development-the gestation period-was greatly extended.

Developmental control of these new structures is achieved with the Hoxa genes that earlier in development laid down the body axis. Hoxa 9 specified the fallopian tubes, Hoxa 10 specifies the upper uterus, Hoxa 11 specifies lower uterus, and Hoxa 13 specifies vagina. Hoxa 10 and Hoxa 11 also aid in endometrial maturation and down regulate the immune system in the endometrium to help the embryo implant. Hoxa 13 also helps control the development of the umbilical arteries.

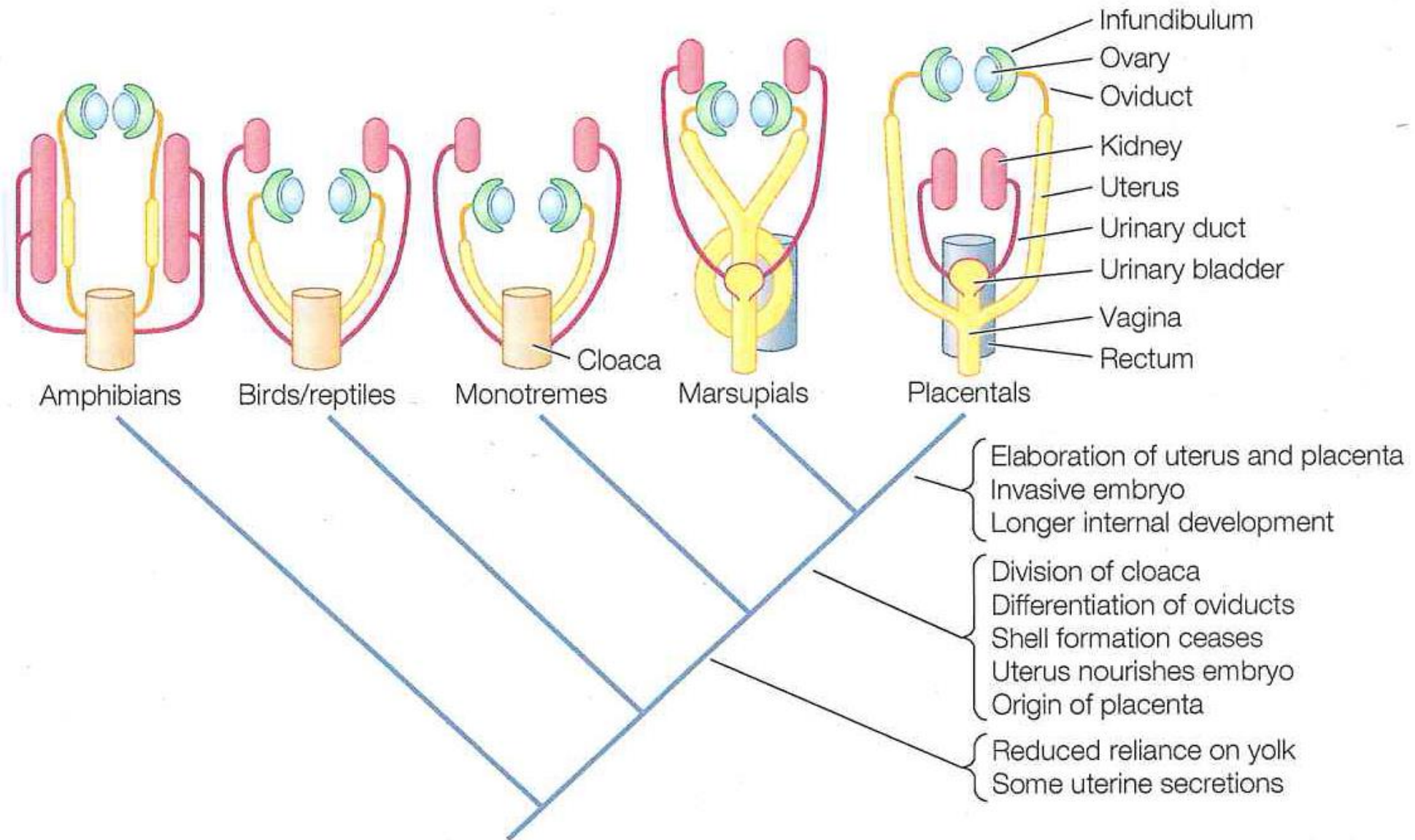


Figure 7.5 The female reproductive system of monotremes and other amniotes is radically different from that of placentals. (After Wagner and Lynch 2005.)

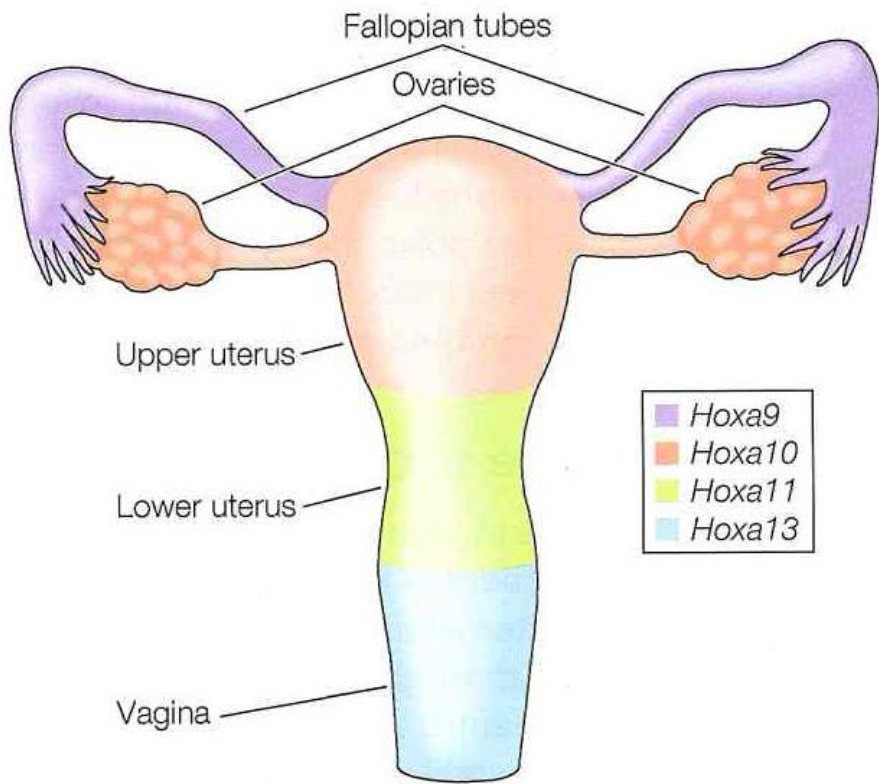


Figure 7.6 The placental female reproductive tract is controlled by the same genes that lay down the body axis earlier in development. (After Lynch and Wagner 2005.)

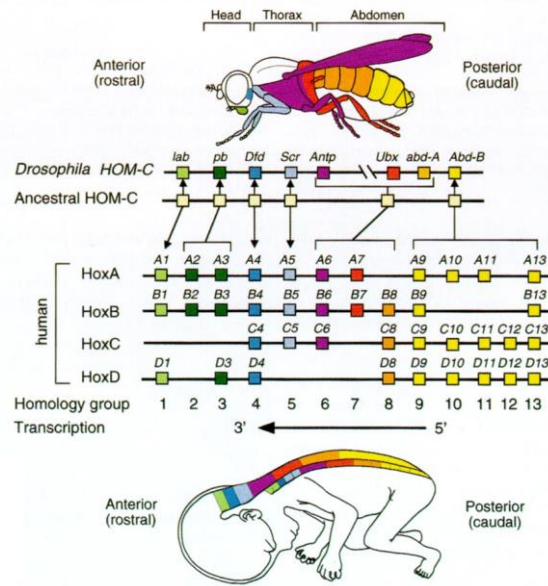
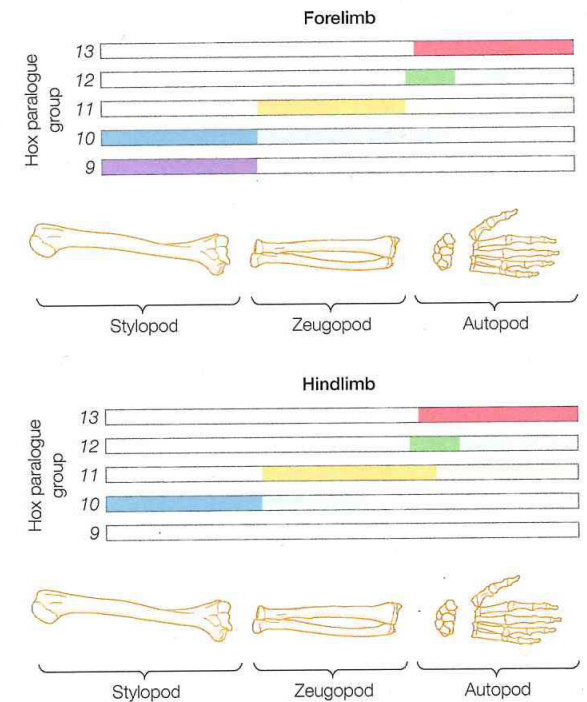


Figure 7.4 The evolutionary redeployment of a previously evolved toolkit: colinearity of Hox genes controlling vertebrate limb development. Hox paralogue group, some of the a, b, c, d copies of the Hox gene with a given number. (After Gilbert 2013.)



Reproduction



The reproductive biology of our closest evolutionary relatives has only recently begun to be unveiled. Only a handful of studies have provided the most rudimentary information on members of the genera *Pan* (chimpanzees), *Pongo* (orangutans), and *Gorilla* (gorillas). Information on the reproductive biology of lesser apes, the *Hylobates* (gibbons and siamangs), is limited to a single study of a single female (see Aramaki et al. 2010). A comparative study of captive great apes (chimpanzees, gorillas, orangutans, and bonobos) revealed reproductive hormone patterns that are similar to other mammals while exhibiting subtle differences in gonadotropins (see Shimizu et al. 2003). Reproductive senescence in chimpanzees appears to be similar to humans, with menopause occurring around the age of 50, although information on key diagnostic hormones such as FSH, LH, and AMH is lacking. Demographic evidence from wild female chimpanzees suggests that this pattern is quite conserved, with declines in oestrogen occurring in a manner that is similar to humans (see Emery Thompson et al. 2007).

Histological assessments of ovaries derived from deceased captive female chimpanzees show that the rates of follicle depletion mirror those in human females (Jones et al. 2007). Age of menopause appears to coincide with lifespan in wild chimpanzees (Hill et al. 2001), although new evidence suggests that chimpanzee lifespan can increase in response to favourable conditions in the wild (Wood et al. 2017). Female reproductive biology of orangutans, which is known from only a handful of studies, mostly from captivity, indicates physiological functions and hormonal controls that are similar to humans (Lasley et al. 1980; Nadler et al. 1984). In the wild, orangutans respond to extreme environmental stochasticity in the form of wide swings in food availability. The forests of Borneo exhibit masting in which trees fruit in concert, resulting in an abundance of food for various animals including orangutans. During this period of high caloric availability, female orangutans exhibit an increase in urinary oestrogens which is indicative of greater fertility (Knott 1999). Emerging field methods such as near infrared spectroscopy may prove to be useful in providing greater clarity on the reproductive biology of wild great apes (Kinoshita et al. 2016). Female reproductive ecology in gorillas has only recently been addressed (Habumuremyi et al. 2014, 2016). Hormonal mechanisms that are common in other mammals and primates play similar roles in gorillas.

Menopause

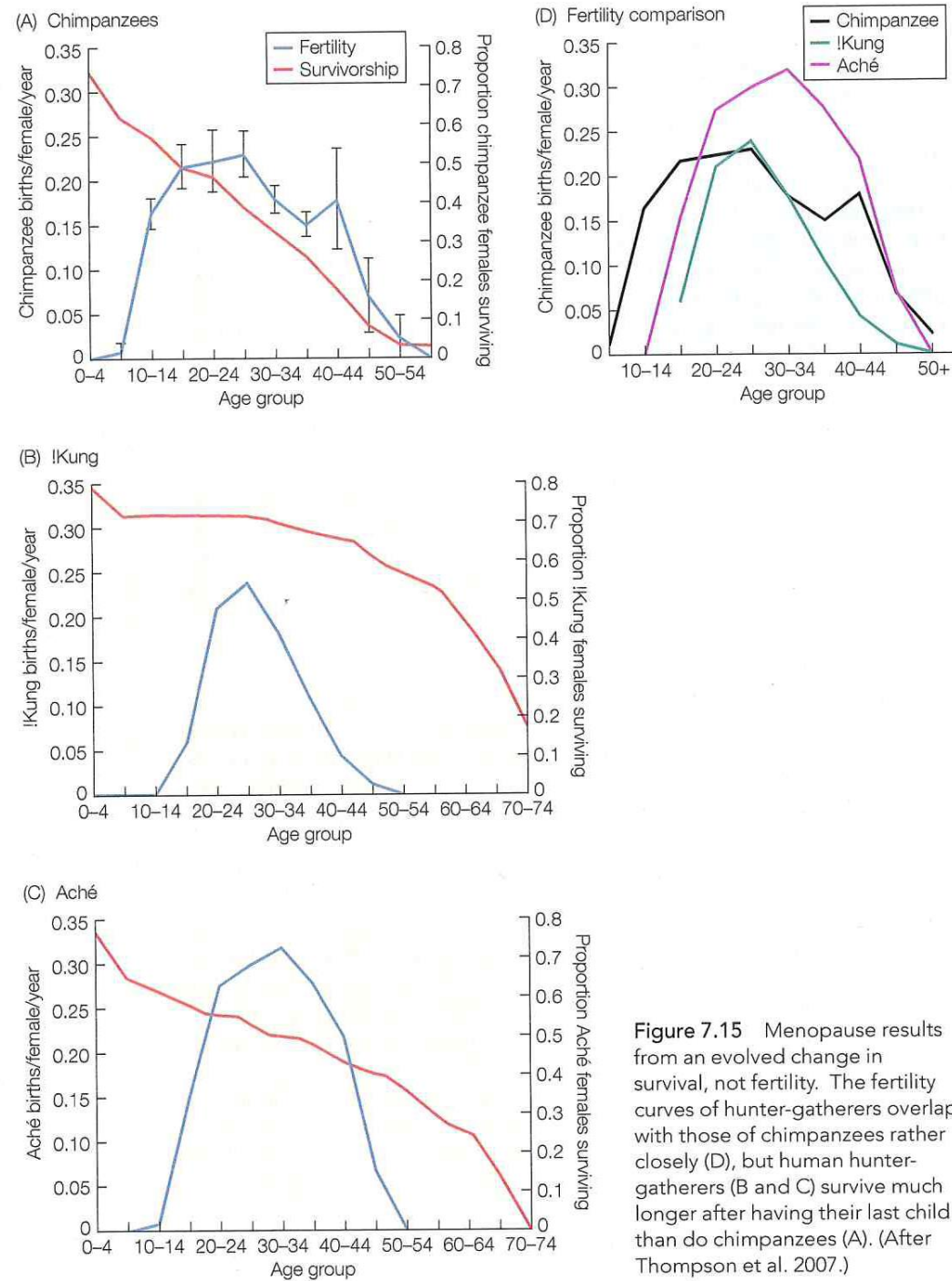


Figure 7.15 Menopause results from an evolved change in survival, not fertility. The fertility curves of hunter-gatherers overlap with those of chimpanzees rather closely (D), but human hunter-gatherers (B and C) survive much longer after having their last child than do chimpanzees (A). (After Thompson et al. 2007.)

Sexuality



Sexuality in Non-Human Primates

For the group of animals phylogenetically most closely related to us, Dixon (1998) has presented a very useful comparative overview of primate sexuality, showing that among eight non-human primate species, females of two have the capacity to experience clitoral orgasm when stimulated artificially, and also vaginal–cervical–uterine orgasm. Primates exhibit a wide variability of female orgasmic responses—a topic that is discussed below, especially in relation to a new hypothesis concerning the phylogeny of induced very spontaneous ovulation (see Pavlicev and Wagner 2016).

	Body characteristics		Reproductive behaviour
	male	female	
Gibbon			Monogamy
Orangutan			Polygyny
Gorilla			Polygyny
Chimpanzee			Promiscuity
Human			Monogamy Polygyny Polyandry

Gibbons (family *Hylobatidae*) are also named lesser or smaller apes, to indicate their phylogenetic–zoological position between the great apes and monkeys; today, they live in South-East Asia. They have a low degree of sexual dimorphism—that is, females and males are almost equal in size. The penis, the breasts, and the pubic area are small, while the testes, compared to body size, are quite large. The two species of orangutans (*Pongo pygmaeus* from Borneo and *Pongo abelii* from Sumatera) show a very marked sexual dimorphism, with males almost twice the size of females. Adult, dominant males grow impressive cheek flanges and throat pouches, enabling long-distance mating calls. Their appearance is strikingly different from that of females; their penis is a little bigger than that of gibbons, but the testes are very small. A similar constellation is present in the two species of gorillas (*Gorilla gorilla* and *Gorilla beringei*); males, especially dominant ‘silver backs’, have an impressive body, twice as big as that of females, the penis size is even smaller than that of the orangutan, and their testes are also smaller. Chimpanzees (*Pan troglodytes*) present a very different picture: sexual dimorphism is present but much lower than in orangutan and gorilla; the wider female pubic area (in this case mainly the sexual swellings and reddening on the buttocks) is very large, as are the testes, and the penis is larger (similarly long as that of humans) than in the gorilla and orangutan. Some biologists hypothesis that this last feature is necessary because the penis has to reach the cervix of a female in oestrus through the external swelling. Humans have a similarly small sexual dimorphism (men are about 10–15% taller and heavier than women; in ancestral times the difference may have been 20% as in chimpanzees), the pubic area is comparatively small, the breasts are very big, and the size of the penis is big as well, especially its circumference, while the size of the testes is similar to that of orangutans.



Orgasm

Orgasm in males is a complex yet basically still rather simple biological mechanism. Very few ejaculations occur without orgasm, which has evolved early in phylogeny and is probably present in all mammals. Males, most probably not only of our species, perceive considerably more enjoyment from orgasm than from sexual stimulation that does not lead to climax: all animal males, including humans, are orgasm-prone beings. In 50 years of fieldwork with free-living chimpanzees, McGrew (2017p.c.) did not see a single male masturbation that led to ejaculation. It is likely that our ancestors, like probably the majority of men today, preferred regular intercourse versus masturbation, even though it frequently occurs in non-human animals. Patterns of sexual behaviour of chimpanzees have been studied intensively by several groups of researchers (see Fujita and Inoue 2015); it is not uncommon for females of this species to prolong their sexual swelling and encourage copulations with different males, possibly in an unconscious attempt to confuse paternity. Multiple orgasms/ejaculations are possible for human males, but there is a refractory period of varying duration. In this respect, women, yet not all of them, are remarkably different: they can experience orgasms like pearls on a string. Female sexuality presents a very different spectrum. Kinsey et al. (1953) assured the world that there was female orgasm; their successors (see Masters and Johnson 1966), still rather ignorant about female sexual responses, thought that orgasm in women was physiologically the same event in all of them. For some time it was thought that females of non-human species do not have orgasm-like experiences. And, of course, it is not easy to define what exactly that would mean for an animal. Researchers, however, have operationalized definitions and used experimental and ethological approaches to study the sexual responses of female mammals, including primates. There can be no doubt that orgasm exists in females of non-human species; Troisi and Carosi (1998) found that in one out of three of 240 copulations the typical orgasm face was observed in macaque females.



There is a remarkable discrepancy between women who do not at all or very rarely experience orgasm and women who can have several in a row.

Whence this paradox: multiple orgasms versus none? All women belong to the same species; therefore should there not be a specific or at least typical sexual response mechanism like orgasm in males?

There isn't, despite the fact that modern functional magnetic resonance imaging (fMRI) techniques have shown that men and women activate very similar brain regions, actually most of this organ, during sexual arousal and that women who had a spinal cord injury, blocking the ordinary transmission of neural activity from the clitoris and vagina to the brain, could climax when being genitally stimulated accordingly; other pathways than the ones depending on the spinal cord are thought to exist as well. Women of all times and in all societies most probably were and are very similar in their anatomy. An exception are women of some populations among the Khoisan and other groups in Sub-Saharan Africa who have a marked steatopygia combined with a strong lordosis and often additionally very long labia, a trait that is also said to occur among women on the Andaman Islands. It is, however (despite some claims that the famous Venus figurines exhibit symptoms of steatopygia, yet their figures are just like those of generally well-fed women, doubtful that this specific anatomy was the one of our early female *Homo* ancestors; skeletal finds should have displayed the strong lordosis in women of this type.



FIGURE 16.2 Venus of Höhle Fels (Germany), 35,000 BP (Aurignacien).

Source: Venus Höhle Fels. Photo © Hilde Jensen/University of Tübingen.

What are the biological, evolutionary foundations of female orgasm? It has been found to exist in many primates and mammals, so there is a clear phylogenetic base for sexual climax during intercourse, manual or oral stimulation, or masturbation (statistically all more common in human females than orgasm via intercourse). For an evolutionary anthropologist it is problematic that female orgasm not only is no precondition for getting pregnant, but also does not seem to assist getting pregnant. It was thought along adaptationist lines that the strong contractions of the vagina and uterus would dip the cervix into the deposited sperm and help, in the way of a vacuum pump, to suck up sperm into the uterus so that its arduous travel upward to the tube towards the ovum would be assisted (see Gould 2002). But this does not really seem to be the case, as is clearly proven by the fact that non-orgasmic women get pregnant—whether as easily as women with orgasm is yet unclear, but possible. So, if the most vital advantage, facilitating pregnancy and producing offspring, is out of the race, why do females orgasm at all? It is not as costly as male orgasm with ejaculated semen, but involves circulatory and hormonal costs which could perhaps be avoided. Some researchers discuss circulatory congestion in the pelvic area as a biological reason for female orgasm, which would release it, but it seems doubtful whether pelvic congestion due to sexual arousal needs, in a physiological and evolutionary sense, orgasm to discharge the congested blood; this condition is mostly caused by pathologies of various kinds (see Perry 2001). So, the question arises: why is the clitoris there, and why is it sexually so very sensitive that women who cannot experience vaginal orgasms via intercourse quite often can climax after stimulation of that erectile organ? Why did it evolve, if it can often transmit its powerfully positive signals to the brain only after somewhat artificial stimulation? One hypothesis is that the female genitals and their function as pleasure-providing organs are by-products of the male system. Did ancestral men know about the orgasmic potential of their female partners and did they satisfy them by sensitive manual caressing, requiring dedication? Looking at sexual practices around the world, this does not seem necessarily the case.

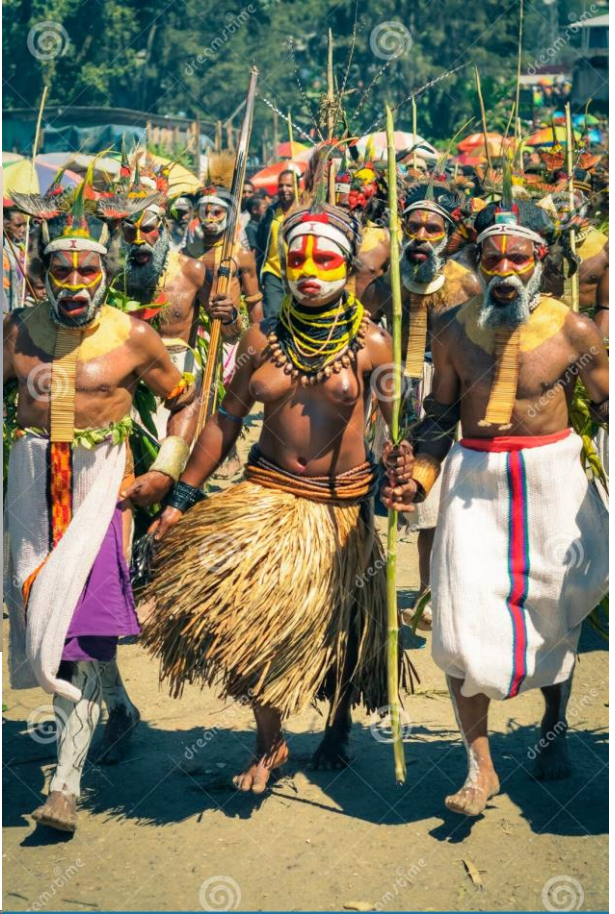


Homosexuality

Although homosexuality is no longer considered a psychiatric disorder. For evolutionary biology, human homosexuality, especially the more common male form of exclusive same-sex orientation, has always presented a challenge (the 'Darwinian paradox'): how could a behaviour, that cannot result in offspring and thereby have no obvious ultimate effects be still existent, and even prominent, in human societies? In many animal species, same-sex sexual acts are common (see Sommer and Vasey 2006) and can often be explained on a proximate or ultimate level (see Fruth and Hohmann 2006)—for example, female homosexuality in wild bonobos, which has advantages for the involved females. Smith et al. (2003) found 0.8% lesbian and 1.4% bisexual women, 1.6% gay, and 0.9% bisexual men for Australia; Gates (2011) 1.1% lesbian and 2.2% bisexual women, 2.2% gay, and 1.4% bisexual men for the United States; figures in large US cities are much higher; another Australian study found 8% homosexual persons.



The human case seems different and is in particular need of an explanation, because in the animal kingdom individuals involved in homosexual acts will, as a rule, behave heterosexually as soon as there is chance, while many homosexual men (and in smaller degree possibly also female homosexuals) have no inclination for heterosexuality at all; their sexual fantasies are, from puberty on, focused on men as attractive sexual partners (see Frankowski and Committee on Adolescence 2004). This is different in bisexual men and women. The frequency of practiced homosexuality is very different in different societies. One would expect, on the basis of the fact that humans share (except for genetic differences, which have been shown to exist for some traits) the same biologically mediated physiology and psychology, a small percentage of both male and female homosexuality in every society. There are, however, cultures where there are no reports of adults behaving homosexually, that is, having close, intimate, and/or sexual friendships with a person of the same sex. This is true for the matrilineal Austronesian Trobriand Islanders, where found no signs of male homosexuality for the times before the influx of white tourists; a few men had no female partners as wives or lovers and thus no interactive sexual lives, but they did not seem unhappy. Among the patrilineal Eipo from mountain Papua in the western (Indonesian) half of New Guinea, male homosexual play takes place between boys and adolescents, but there was no case of a male homosexual couple noted in fieldwork carried out between 1974 and the present. Eipo women were said to sometimes engage in same-sex behaviour, rubbing their genitalia on one another—‘when they are sexually unsatisfied and hot’ was given as explanation. The two cultures had thus little or no place for sexual behaviour other than between woman and man and therefore did not create chances for persons who are genetically or biologically inclined to homosexuality. The small village groups (originally up to 200) had a rather tight network of social control via gossip and other verbal behaviour, so that persons who were different with regard to sexual behaviour would find themselves talked about in a disapproving negative way.



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The origin of this sexual preference in humans is not yet fully understood and further research is underway. One evolutionary biological explanation is the reduction of intraspecific aggression, as is the case with bonobos.



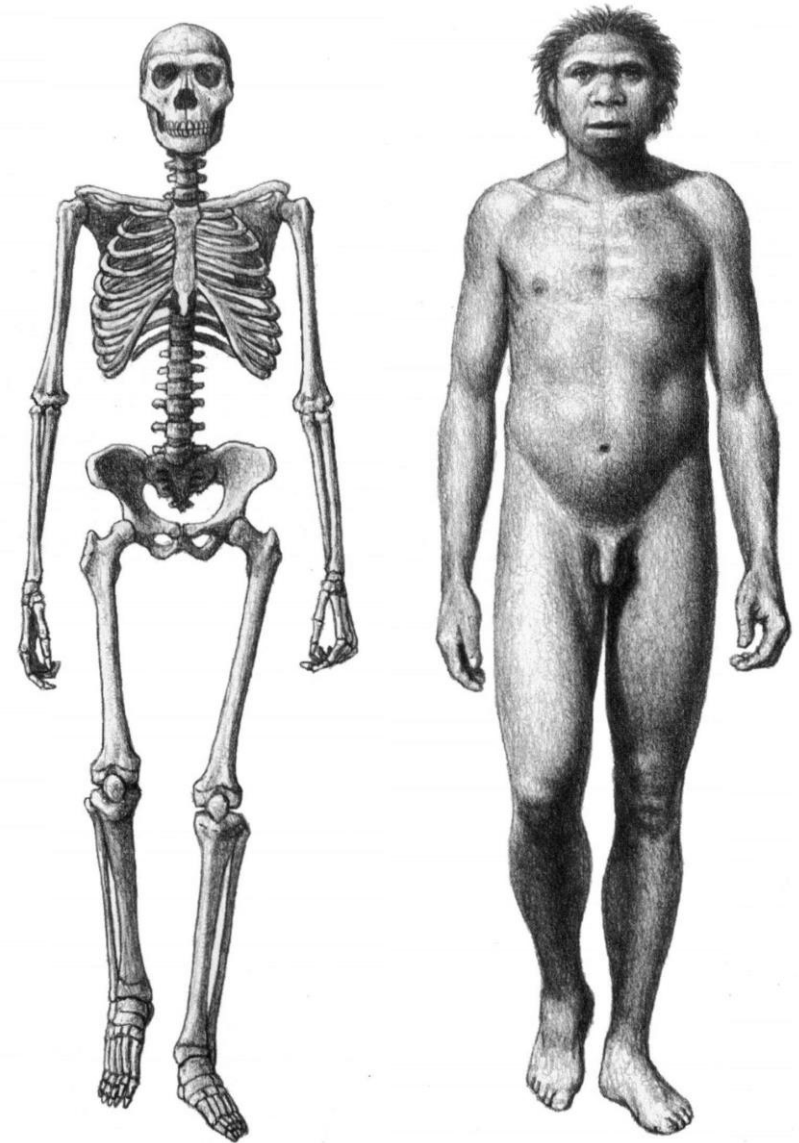
Male Reproductive Ecology

The reproductive ecology of great ape males is similar in many ways to humans. In chimpanzees, testosterone levels vary between captive and wild populations, most likely due to the different energetic and nutritional conditions, with captive populations exhibiting higher testosterone levels compared to wild communities (see Muller and Wrangham 2005). However, chimpanzees differ dramatically from human males in that reproductive strategies are more narrow. Human males exhibit a broad range of reproductive strategies ranging from high time and energy investment in mate acquisition to enhanced effort in paternal and mate care (see Bribiescas et al. 2012). Variation in testosterone levels in chimpanzee males is acutely sensitive to competitive environments with other males. Orangutan males exhibit one of the most unique suite of traits within primates with males having a binary set of phenotypes. The larger more robust males have fatty facial flanges, compete heavily with other males, and appear to be preferred by females. However, a second phenotype is smaller and less competitive, and often obtains mating opportunities by forcing themselves onto apparently unwilling females. These two strategies and phenotypes are largely controlled by testosterone. The larger phenotype exhibits higher testosterone, while the smaller phenotype does not (see Emery Thompson et al. 2012). Testosterone levels in gorillas are known from captivity and the wild. The selective importance of testosterone in male gorillas lies in the large male size, high degree of sexual dimorphism, and the high male/female ratio in reproductive groups in which a single male often monopolises mating opportunities with multiple females. Group takeovers by rival males often involve violent encounters with the resident male and infanticide if the challenging male succeeds in taking over the group. However, how testosterone plays into these reproductive strategies is unclear. Interestingly, gorilla males who affiliate with infants in their group, including those that are not their own, exhibit higher reproductive success compared to males who affiliate less. Clearly additional research is necessary to explore the full range of male reproductive strategies in great apes.



Hominid Ancestors

The reproductive biology of our hominid ancestors was likely not very different from what is seen today (see Bentley 1999). Given the similarities we have with other great apes with whom we share a common ancestor, it is all but certain that other hominids such as australopithecines and other species of our genus *Homo* were influenced by similar environmental challenges and had similar reproductive responses. Clues from the fossil record include the WT15000 which is one of the most complete fossil finds of *Homo ergaster*. This specimen showed that the appearance of many of the life history traits that we see today were already evident, including large body size, growth rates, and brain size. In addition, the Gona pelvis indicates that fetal development resulting in the birth of a relatively large-brained offspring suggested that human life history traits, including those relevant to reproduction, were already well established in early *Homo* (see Simpson et al. 2008). The evolution of pelvic morphology in our hominid ancestors has drawn significant attention due to the impact of negotiating the need to pass a large-brained fetus during birth and positive selection for upright walking, leading some to even argue that it may have contributed to the extinction of australopithecines (see Chene et al. 2013). Others suggest that the evolution of female pelvic morphology resulted in a selective negotiation between the demands of childbirth, bipedalism, and thermoregulation (see Gruss and Schmitt 2015). The energetic demands and consequences of the evolution of life history traits that define the genus *Homo*, such as large body size, large brains, and, by extension, longer lifespans and offspring altriciality, suggest that female reproductive energy demands were significant. This implies that early *Homo* evolved behavioural foraging and social strategies to meet these large energy needs (see Aiello and Key 2002).



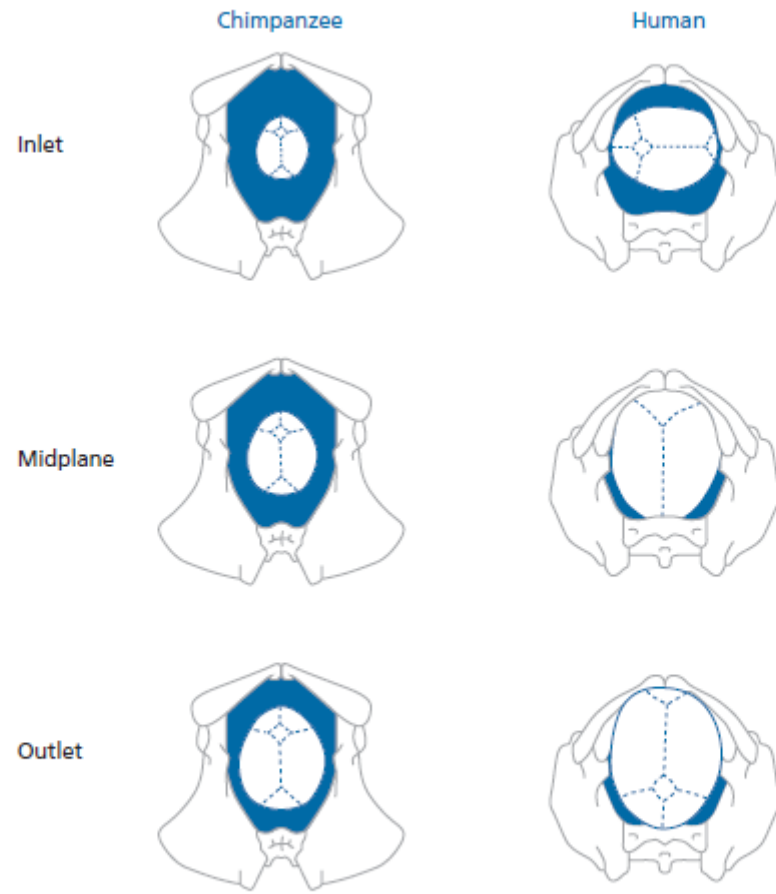
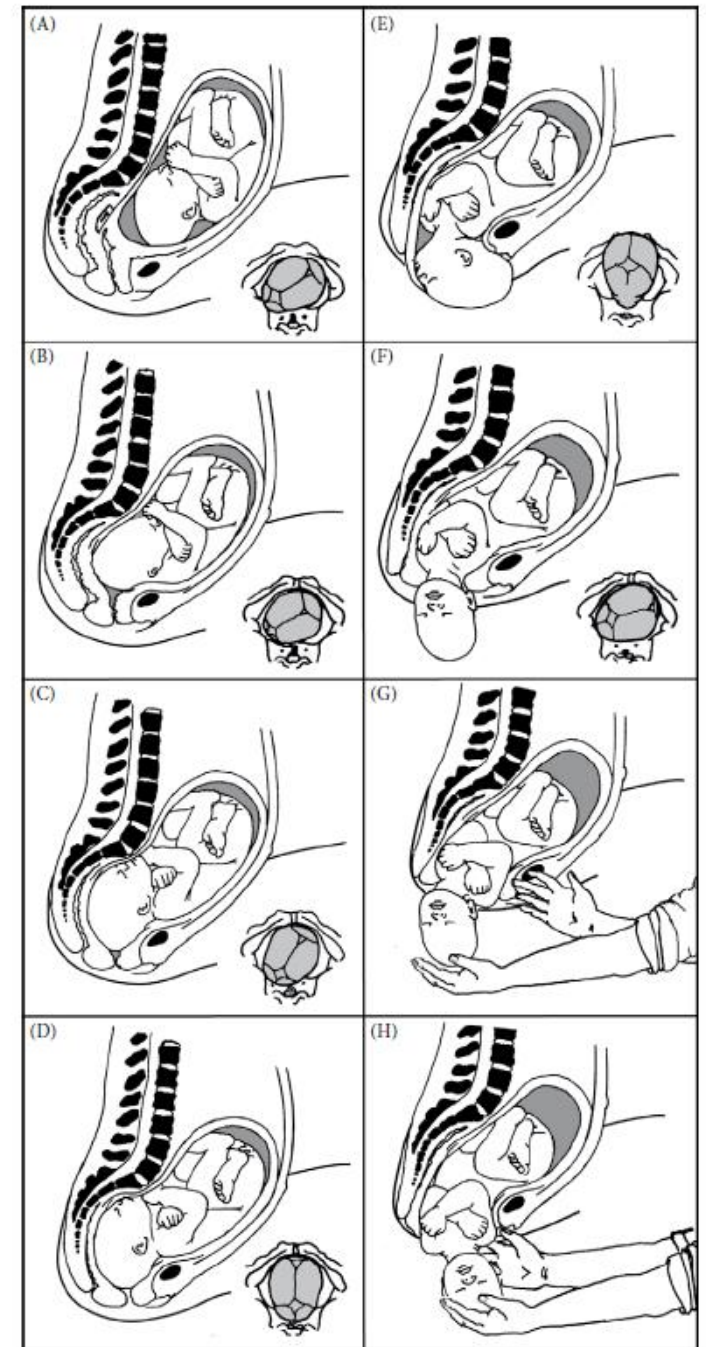


Figure 8.9 Birth is difficult in humans. The fetal head readily passes through the pelvic canal in chimpanzees, but is impeded by the comparatively narrower pelvis in humans. The figure shows a comparison of pelvic inlet, midplane, and outlet between chimpanzees and humans. From Trevathan (1999), with permission.

Birth of the human infant, from entering the birth canal facing the mother's back (A), to rotation (B–D), emergence (E–G), and manual guiding (H). Each panel is a sagittal section through the body of a mother squatting during labour. Maternal pelvic skeletal elements (pubic bone, sacrum, and vertebrae) are shown in black (other parts of the bony skeleton are not visible in this midline view). In the lower right corner of each panel is a 'midwife's-eye' view of the neonatal head as it rotates within and emerges from the birth canal. This is the most common pathway.

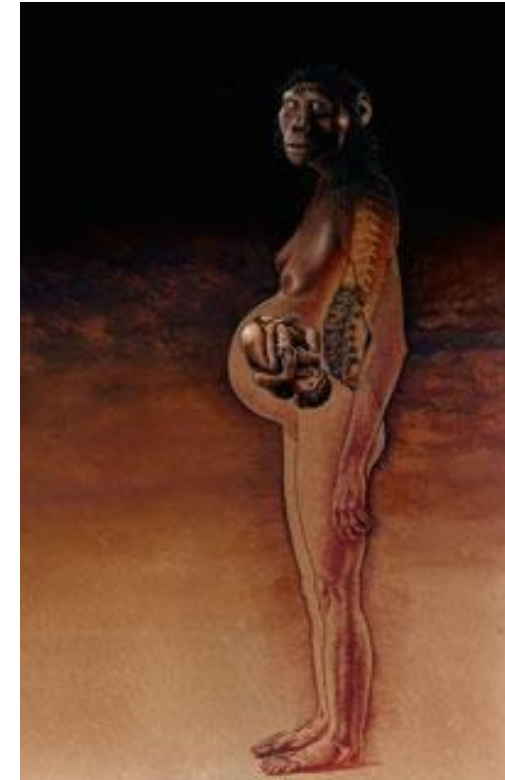


Since sexually dimorphic somatic traits are an important part of the reproductive biology of our male hominid ancestors, important information can be gleaned by examining androgen-sensitive areas of skeletal morphology and mating behaviours that are commonly attributed to sexual dimorphism signals which can be detected in the fossil record. For example, it has been suggested that decreases in testosterone compared to other great apes may have contributed to the evolution of sociality and other life history characteristics (see Cieri et al. 2014). However, testing this hypothesis is challenging. Assessing testosterone levels and androgen-sensitive landmarks on primate cranial morphology, it was found that testosterone variation between primate species was correlated with craniofacial morphology. Adding measurements from craniofacial measurements of hominid fossils provides us with an insight into the socioendocrinology of our hominid ancestors (see Doman et al. 2013).



Reproductive Strategies

Some species, including most fish, reptiles, and amphibians, produce many offspring and generally have no parental involvement in their care; few of these offspring survive to reproduce. At the other extreme are species such as whales and elephants that have few offspring and high parental investment in each, such that a high proportion of the offspring survive. There are species such as the salmon where the male mates only once and then dies, and species that have very short lives or very long lives. Each of these strategies has an evolutionary logic. Humans are towards one end of the spectrum of life-history patterns. Our lives are long, we have very few offspring, and as parents we invest greatly in their care and development. Fitness requires that a high percentage of offspring survive, and humans live successfully in wide range of environments. Relative to their lifespan, humans have a very late puberty—that is, the age at which reproduction becomes possible. This is a trade-off for having a large brain and a strong reliance on cognitive and other neural capacities. Because of the compromise needed to achieve a large brain while allowing birth through a birth canal in a narrow pelvis restructured by the demands of bipedalism, humans have evolved as a secondarily altricial species.



That is, compared with other primates humans are born at a relatively immature neurological stage and depend totally on parental support for mobility, protection, and feeding for a considerable time while brain development proceeds. In turn this requires a high level of maternal involvement, adequate spacing between pregnancies, and a clan-like family structure to assist the mother, thus driving the evolution of social structures and the allocation of roles between the sexes. These evolutionary compromises have made human childbirth a precarious event: it is thought that in the Paleolithic the chance of maternal death in pregnancy or childbirth was about 15%. The inter-birth interval is thought to have been about 3–4 years based on what is known from the few remaining forager societies. Thus if menarche occurred at about 12–14 years and the first birth about 5 years later (see Allal et al. 2004), then the average woman might be expected to have given birth to about five or six children, of whom about half might have survived. Thus, selection pressure will have given advantage to those traits that enhanced the capacity to nurture these few offspring.



Why Menstruate?

There are various competing theories about why humans and some primates such as apes, as well as the elephant shrew and some species of bats, have evolved menstruation; none of these is entirely satisfactory, although some are more plausible than others. Menstruation is the shedding of the endometrium—which undergoes progesterone-induced decidualization (differentiation) after ovulation—and the associated bleeding when progesterone levels fall at the end of the reproductive cycle. In non-menstruating species, the differentiation of the endometrium only takes place if the embryo implants, while the fall in progesterone is not followed by the breakdown of the tissue. But why is it that some mammals menstruate and others don't? Is there an adaptive value to menstruation? One hypothesis relates to the non-seasonal nature of ovulation in humans. Having evolved in tropical regions where there was no marked seasonality in day length, humans can conceive all year round. In comparison, many mammals, particularly those which evolved at higher latitudes, have a seasonal pattern of reproduction which allows offspring to be born in the spring and grow in climatic conditions which are likely to be favorable. Thus human females have evolved to ovulate throughout the year, although there is an echo of seasonality in the annual pattern of prolactin secretion which is influenced by day length. Humans therefore maintain the endometrium in a receptive state, that is differentiated repeatedly throughout the year, in contrast to seasonal breeders. The energetic cost of maintaining the endometrium in a receptive state for implantation might be reduced by having a cyclical pattern (see Strassmann 1996). However, this hypothesis does not consider the absence of menstruation in many other species in tropical regions.

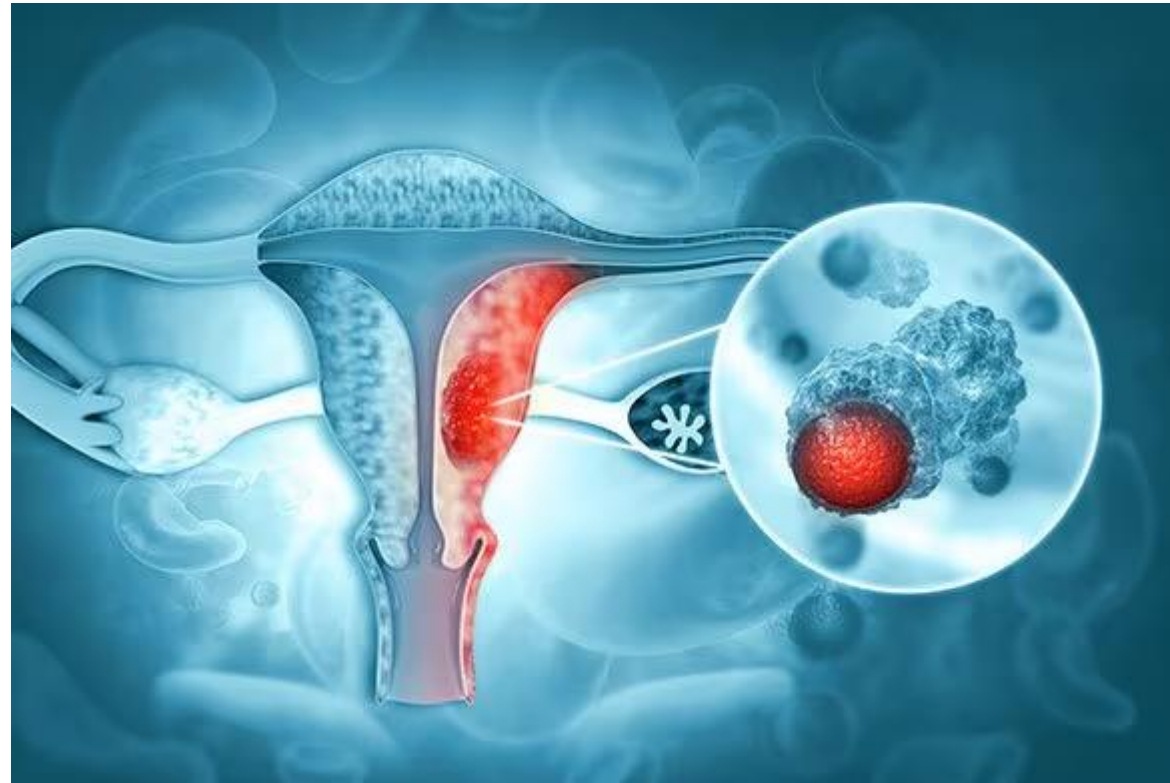


Several hypotheses focus on the decidualization of the endometrium in the post-ovulatory phase of the menstrual cycle—that is the processes involved in endometrial remodeling in preparation for pregnancy, which includes secretory transformation of the uterine glands, influx of specialized immune cells, and vascular remodeling. One hypothesis has argued that spontaneous decidualization is an outcome of maternal–fetal conflict as it evolved for advance protection against the invasive fetal tissue of the human placenta (see Emera et al. 2012). Menstruation is then just the necessary consequence of decidualization. A related suggestion posits that spontaneous decidualization may have evolved as a system for sensing the quality of an embryo, as it was found that endometrial stromal cells have a stronger response to an impaired than to a healthy embryo (see Teklenburg et al. 2010). Genome-wide screening of embryos obtained through in vitro fertilization have found that more than 70% of high-quality early embryos contain cells with large-scale chromosomal abnormalities, many of which have never been recorded in clinical miscarriage samples. Cyclical decidualization (and menstruation) could then be explained as an adaptive response to the high incidence of chromosomally abnormal embryos. Another theory links menstruation to the type of placenta that humans (and to some extent apes) have, suggesting that endometrial shedding and associated bleeding have a role in “pre-conditioning” the uterus in order to protect its tissues from the profound hyperinflammation and oxidative stress caused by deep placentation (see Brosens et al. 2009).

A well popularized but less convincing theory arising from a different perspective posits that menstruation may help to the uterus shed harmful pathogens, perhaps introduced with sperm (see Profet 1993). Shedding the entire lining rather than developing very active cell-mediated (macrophage) antibody responses, as in other parts of the body such as the gut and respiratory tract, again seems unnecessarily costly. A refinement of this hypothesis is that menstruation ensures that any residual sperm are removed. Yet menstruation occurs in some cases weeks after copulation. If this is so important, however, why is menstruation not a more frequent mammalian phenomenon?



The patterns of menstruation and, more broadly, hormonal cycling, may have clinical significance. Most Western women now experience 450–500 menses across their reproductive lives. Yet in cultures in which no contraception is used, and where family size is generally of the order of four to eight, women might only experience 100–150 menses (see Eaton et al. 1994; Strassmann 1999). Thus the patterns of exposure to estrogen and progesterone throughout the life course have changed dramatically, and this shift is thought to explain partially the greater incidence of cancers of the reproductive tract in women in developed societies.



Thank you for your attention!

