



# Monkeys, mice and menses: the bloody anomaly of the spiny mouse

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## Abstract

The common spiny mouse (*Acomys cahirinus*) is the only known rodent to demonstrate a myriad of physiological processes unseen in their murid relatives. The most recently discovered of these uncharacteristic traits: spontaneous decidual transformation of the uterus in virgin females, preceding menstruation. Menstruation occurring without experimental intervention in rodents has not been documented elsewhere to date, and natural menstruation is indeed rare in the animal kingdom outside of higher order primates. This review briefly summarises the current knowledge of spiny mouse biology and taxonomy, and explores their endocrinology which may aid in our understanding of the evolution of menstruation in this species. We propose that DHEA, synthesised by the spiny mouse (but not other rodents), humans and other menstruating primates, is integral in spontaneous decidualisation and therefore menstruation. We discuss both physiological and behavioural attributes across the menstrual cycle in the spiny mouse analogous to those observed in other menstruating species, including premenstrual syndrome. We further encourage the use of the spiny mouse as a small animal model of menstruation and female reproductive biology.

**Keywords** Menstruation · Novel model · Evolution

## Introduction

Despite the (quite literal) billions of women worldwide undergoing a menstrual cycle for approximately a third of their lifespan, menstruation is a surprisingly rare phenomenon in other animals. In fact, approximately 98% of all mammalian species do not menstruate [1]. Menses is almost exclusively restricted to higher order primates, which include humans, rhesus macaques and baboons, with the only exceptions (until very recently) being a minority of bats [2–5] and the elephant shrew [6].

Menstrual cycles differ from most mammalian reproductive cycles (“oestrous”) in that exogenous cues such as seasonal changes in temperature, rainfall, male pheromones or mechanoreceptor stimulation during coitus do not induce

ovulation (for comprehensive review of domestic animal oestrous cycles, see [7]); rather, ovulation is spontaneous and occurs cyclically throughout the year. In addition, the endometrium of menstruating species undergoes a profound and unique series of morphological and molecular changes to the functional layer, both to promote implantation and to regulate the depth of trophoblast invasion [8]; the spontaneous decidualisation of endometrial stromal cells during each menstrual cycle is specific to menstruating species. This terminal differentiation of endometrial stromal fibroblasts is maintained by high circulating progesterone, secreted by an active corpus luteum. Failure to rescue the corpus luteum through conception and successful embryo implantation results in rapid progesterone withdrawal. Without hormonal support, the highly metabolic decidua cannot be sustained, and local inflammation occurs with activation of local and leukocyte proteolytic enzymes resulting in menstrual shedding. In contrast, the uterine tissues of oestrous species do not undergo decidualisation until pregnancy is already established and proliferated endometrial tissue is resorbed at the end of an infertile cycle.

One of the leading theories of the evolution of menstruation is that it is merely a by-product of spontaneous decidualisation, and progesterone withdrawal causes disintegration of the stromal matrix architecture which degenerates the supportive structural integrity of the spiral

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arterioles [9]. Acceptance of this theory then ultimately changes our perception, and our fundamental question is no longer “Why menstruate?” but becomes: “Why spontaneously decidualise?” There are a myriad of possibilities (for a comprehensive review, see [10]), but a most widely accepted theory is that “fetal–maternal conflict” drove the evolution of human menstrual cycles. This posits that spontaneous decidualisation evolved to confer “protection” against the highly invasive early placenta and/or as a selection mechanism to prevent maternal investment in poor-quality embryos of precocial species (born in an advanced state) with haemochorial placentation [9, 11]. Indeed, this theory is supported by studies of “super-fertile” women who experience recurrent pregnancy loss; the endometrium of these women allows implantation of developmentally abnormal embryos due to altered decidualisation [12, 13]. That this unique strategy has evolved is clearly demonstrated by a recent study which elucidated that genes ancestrally expressed in other organs and tissue systems were recruited to the endometrium, with transposable elements contributing to the origin of decidualisation by conferring progesterone responsiveness to numerous genes across the genome [14]. This strategy, however, is energetically costly, with elevated metabolic demand in menstruating species prior to menstruation [15, 16], so the cost of such increased energy requirements must be offset by the benefits to the mother. Decidualisation likely evolved to balance the interests of both mother and foetus in species which have precocial young (attributable to cortisol production and advanced foetal maturation compared to altricial [born in an undeveloped state] species). In healthy females, a normally functioning decidua provides a nutritionally supportive microenvironment for embryo implantation and development, but regulating the infiltration of the trophoblast to the maternal bloody supply, protecting against detrimentally deep invasion [8, 9]. It is possible that the wild-type spiny mice, due to greater nutritional availability (as they are a mesic desert species) and preference for nesting in rocky, sheltered areas which could have seen a reduction in predation and greater safety for gestating dams and neonates, could have selected for greater placental investment in offspring during pregnancy, and thus a genetic mutation resulting in spontaneous decidualisation may have evolved.

Oestrous cycles appear to be the preferred reproductive strategy of most of the world’s species of mammals. The question of “Why do we menstruate?” has plagued us for an immeasurable number of years, and the solution is further muddled by the latest addition to this group of menstruating mammals which, phylogenetically, have little in common: the spiny mouse (*Acomys cahirinus*) [1].

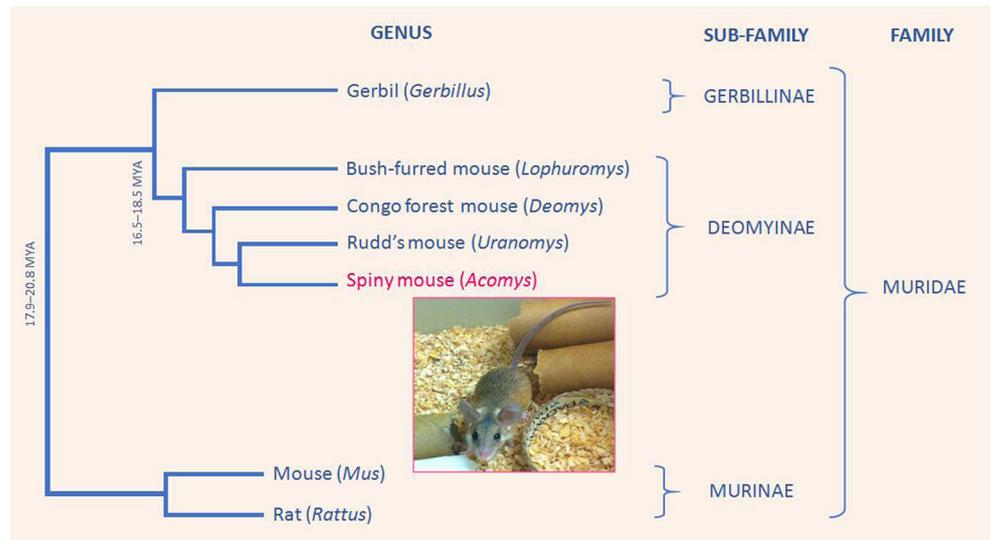
## The spiny “mouse” and menstrual evolution

Belonging to the Rodentia order, the spiny mouse is an unexpected piece of the phylogenetic puzzle given it is, to our knowledge, the only “mouse” to have a spontaneous decidual reaction and consequential menstrual cycle. Spiny mice have been used for decades in medical research, owing to their unique biological profiles. Their relatively long gestational period (~39 days) and prenatal development comparable to that of humans [17, 18] allows for highly translatable studies of neuroprotective interventions against perinatal injury [19–21], while their susceptibility to pancreatic hyperplasia makes them ideal models for investigation into diabetes mellitus [22]. Notably, the spiny mouse also has the capacity to synthesise cortisol and dehydroepiandrosterone (DHEA) unlike conventional laboratory rodents [23, 24], and is able to regenerate skin tissue and hair follicles resulting in scar-free wound healing [25], again, unusual in a rodent.

It has been difficult to contradict the long-held dogma that rodents do not naturally menstruate. However, further investigation of the uterine tissues of the spiny mouse revealed spiral arteriole formation coinciding with spontaneous decidual transformation in the absence of pregnancy, immune cell influx and nature of epithelial repair akin to that seen in other menstruating species [26] reinforcing the assertion that these are a true menstruating species.

Classification of *Acomys* situates them in the family Muridae. Based on initial dental structure analysis, spiny mice were designated to the subfamily Murinae, containing Old World rodents mouse (*Mus*) and rat (*Rattus*). Sarich (1985) was the first to propose a separate lineage, inferring that spiny mice were not related to true murines [27]. DNA–DNA hybridisation analysis conducted on the Cairo spiny mouse (the same species as our own colony) implied a closer phylogenetic relationship to the Mongolian gerbil (*Meriones unguiculatus*) than to the mouse (*Mus musculus*), suggesting that the spiny mouse should perhaps be considered a member of the Gerbillinae rather than the Murinae subfamily to which mice and rats belong [28]. It was later confirmed through genetic sequencing of two nuclear protein-coding genes Lecithin Cholesterol Acyl Transferase and von Willebrand Factor that *Acomys* (spiny mice), together with related genera *Uranomys* (Rudd’s mouse), *Lophuromys* (bush-furred mouse) and *Deomys* (Congo forest mouse), forms a sister clade to Gerbillinae [29], termed Deomyinae (originally Acomyinae [30] before later addition of *Deomys*). A summary of Michaux and colleagues’ phylogenetic assessment [29] is presented in Fig. 1. These animals have been grouped together based on shared genetic mutations, with the endocrine and reproductive profile of other species within the Deomyinae are unknown [26].

**Fig. 1** Phylogenetic tree demonstrating evolution of spiny mouse (red) in relation to other murids. Controversy of classification of this species has since been resolved using LCAT and vWF genetic sequencing and confirms *Acomys* belongs to the Deomyinae subfamily, a sister clade of Gerbillinae, as opposed to the Murinae (Old World mice and rats). Image adapted from Evolutionary History of the Most Speciose Mammals: Molecular Phylogeny of Muroid Rodents [29]



### The only menstruating rodent?

A discovery of this nature which flies in the face of accepted knowledge within the field unsurprisingly attracts scepticism and requires careful scrutiny of how this phenomenon could be possible. Indeed, it raises the question of whether other users of captive colonies of this species have also observed such menstrual-like anomalies in vaginal smears and disregarded the observation due to the accepted dogma that rodents do not menstruate. Perhaps the answer as to why menstruation had never been reported in a previously utilised laboratory species of rodent is quite simple: nobody looked for something that (supposedly) did not exist. Menstruation in a rodent is unheard of, and therefore any sightings of unexplained minute volumes of blood in female cages would likely be considered to have arisen from obscure wounds acquired through dominance establishment and fighting within cages; a commonly observed behaviour in these animals.

Frank menses in the spiny mouse was confirmed through daily vaginal lavage among sexually mature females in our in-house research colony [1]. Vaginal lavage is a common method of female rodent reproductive cycle assessment and in fact has been previously conducted on captive *Acomys cahirinus* in the 1980s [31]. This investigator did report an active luteal phase with a decidual reaction maintained 24 h after uterine trauma via endometrial scratching (a common method of inducing decidualisation in rodents) applied during diestrus. Interestingly, it was stated: “Decidual tissue examined on the 7th day of diestrus showed some pycnotic cells and there was bleeding into the lumen of the uterus...Red blood cells were seen in vaginal smears at the end of diestrus in 3 of the 5 animals with uterine trauma.” So, it is indeed very possible that the researcher was in fact observing a natural decidual reaction and early stages of sloughing of necrotic endometrium in some of her animals, but rather than describing the

bleeding as a menstrual response, she instead attributed it to the endometrial scratching.

The current lack of spiny mouse research colonies has also restricted our understanding of the incidence of this occurrence, and it is unclear whether frank menses in our females is a by-product of random selection of few individuals during breeding colony establishment (founder effect), and whether wild types may also exhibit this reproductive trait to some degree. Our colony in Australia is currently the only research colony in the Southern hemisphere. Established from 5 breeding pairs in 2002, imported from a colony at the University of Amsterdam (originally established in 1981 from 4 breeder pairs from the University of Geneva), it has clearly gone through at least two bottlenecks and detailed genetic studies are likely to show that the colony has a high inbreeding coefficient, like many of the standard laboratory mouse strains. To our knowledge and based on collaborative responses from colleagues in the United States (US), menstruation is unique to our spiny mice.

Other than geographical location of the laboratories, there are notable differences between these two colonies. Females from the US colony are greater in body mass than ours (typically 30–50 g, compared to ours of 28–39 g), and excess weight, acting via influences on the hypothalamic–pituitary–gonadal axis as in humans, may be a contributing factor to amenorrhea. Some of these animals are also kept on a natural, rather than artificially timed, light cycle [32], allowing the colony to experience the effects of seasonal changes in light and temperature, albeit a different seasonal light influence to their native desert, unlike our colony which is under controlled temperature year-round and a 12/12 light/dark cycle [33]. Clearly, whether menstruation is unique to the spiny mouse colony in Australia or common to other captive colonies and wild spiny mice is a critical issue to address before this naturally menstruating species can be more widely used. As

highlighted, environmental influences may impinge on this physiological process in other captive colonies and, unfortunately, little is currently known about the reproductive characteristics from these colonies to draw definitive conclusions regarding isolated menstruation. Careful study of the different colonies under matched conditions and genetic analysis is clearly warranted to understand more clearly the phenomenon of menstruation in these animals.

## But why this rodent?

Despite taxonomic review, certain aspects of the common spiny mouse (*Acomys cahirinus*) compels one to argue that these rodents are, in fact, rather un-rodent like. The list of aforementioned anomalies in the biology of the spiny mouse compared to other murids is impressive. Most peculiar, the primary circulating glucocorticoid in the spiny mouse is cortisol, in contrast to corticosterone utilised by mice and rat relatives [23]. It was later confirmed that spiny mice expressed enzymes required for de novo DHEA synthesis, cytochrome P450 17 $\alpha$ -hydroxylase (CYP17), and for the conversion of DHEA to androstenedione (3 $\beta$ -hydroxysteroid dehydrogenase) [24]. Conventional laboratory rodents lack CYP17; therefore, adrenal production of cortisol is absent, hence corticosterone is the major circulating glucocorticoid [34]. In conjunction with explant culture experiments, Quinn et al. (2013) also demonstrated that in spiny mice, circulating DHEA in foetal adrenal tissue was capable of C19 steroid biosynthesis from exogenous pregnenolone, and as evidenced by secretion of foetal-origin DHEA from 30-day gestational age (0.76), reaching circulating levels analogous to those during infancy in humans [24].

DHEA, one of the most abundant circulating steroids in adult humans, has protective qualities against neuronal death arising from glucocorticoid toxicity [35, 36] and interestingly, has the capacity to become a substrate for oestrogen biosynthesis, both in the placenta [37] and the ovary in post-menopausal women [38]. This may be of particular importance regarding menstruating species, who may spend up to 50% of their life post-reproductive senescence [39], as oestrogen is required to maintain a variety of daily functions (including sexual function, cognition and bone health). Once oestrogen is depleted from gonadal origins, it can be synthesised using DHEA through intracrinology, local production of sex steroids in peripheral tissues [38]. Furthermore, recent data demonstrates that stimulation of human endometrial fibroblasts obtained from women of advanced maternal age with DHEA significantly improves cellular response to in vitro decidualisation and enhances expression of receptivity biomarkers, including prolactin and insulin-like growth factor-binding protein 1 [40]. Here likely stems a fundamental

role of DHEA in endometrial maintenance across the menstrual cycle.

Both proliferation and healing/repair are paramount recurring processes in the menstrual cycle. DHEA is an oestrogen receptor (ER) agonist and has been shown to directly stimulate proliferation of human breast cancer cell lines via ER $\alpha$  [41]. Oestrogen-driven proliferation of endometrial fibroblasts occurs during the proliferative phase of the menstrual cycle, while the succeeding progesterone dominant secretory phase comprises of decidual transformation and proliferation. Oestrogen receptor expression peaks during the late proliferative phase; however, a secondary peak occurs during the secretory phase when the endometrium is receptive to implantation [42]. Although progesterone is the primary sex steroid during this window of receptivity, regulation of the progesterone receptor (PR) expression via the influence of oestrogen in the hypothalamus has been documented [43], as has upregulation of endometrial PR through oestrogenic signalling mechanisms (both ER $\alpha$  and ER $\beta$ ) [44].

Moreover, through use of a murine model of impaired wound healing, DHEA is capable of mitigating the extensive inflammatory response in ulcerated tissue, through aromatase conversion to oestriol, followed by conversion to oestradiol [45]. Interestingly, DHEA (again through oestrogenic conversion) also suppresses pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) [45], which is important to matrix degradation during shedding [46], peaking during the inflammatory menstrual breakdown and subsiding thereafter [47]. We have confirmed the presence of MIF in the menstrual debris of spiny mice [26]. Though the process of repair and cyclical regeneration of the endometrium and epithelium is markedly similar to that of wound healing [48], the correlation between the spiny mouse's ability of scar-free wound healing and skin regeneration [25] and their ability to menstruate [1] remains unexplored. These observations may merely be coincidence, given other menstruating species do not heal their skin in a scar-free manner.

Finally, DHEA production as a key common aspect of menstrual species requires further investigation into discrepancies of adrenal morphology between menstruating Old World (e.g. humans, rhesus monkeys) and non-menstruating New World (e.g. marmosets) monkeys. The foetal adrenal of the rhesus monkey, like the human, retains an identifiable foetal zone active in androgen production before birth, which later regresses prior to the development of the zona reticularis (ZR), while only post-term adrenals in the marmoset have been examined [34]. The timing of adrenarche and pubertal onset in non-human primates may provide insight into the role of androgen production in relation to menstruation. Only chimpanzees (Old World) have been identified as having a similar prepubertal adrenarche to humans [49] while rhesus monkeys even though demonstrating a distinct ZR in adulthood have been argued not to undergo adrenarche [34, 50],

but the data in this field is lacking, as it is surrounding adrenarche in New World primates. However, findings from Pattison and colleagues suggest that the marmoset have a  $\Delta 4$ -lyase enzyme deficiency which reduces their ability to synthesise DHEA, resulting in lower levels compared to those of rhesus monkeys [34, 51]. Previous work in the spiny mouse shows the ZR is absent during gestation but identifiable postpartum [24]. This area requires further study in adrenal maturation and corresponding timing of menarche in this species, but will likely provide extremely valuable insight.

## The spiny mouse and premenstrual syndrome

The spiny mouse menstrual cycle has remarkable similarity to that of higher order primates in physiological likeness, including the presence of spiral arteriole remodelling, timing and degree of menstrual shedding and repair [26]. Therefore, it is somewhat unsurprising to learn that these eccentricities in the spiny mouse extend to behavioural and mood alterations corresponding to stages of their menstrual cycle [52]. We have recently shown that increased food consumption, reduced exploratory behaviour and elevated preference for isolation occur in the premenstrual phases (late luteal/early menstrual) in the spiny mouse, and suggest a novel and natural model of premenstrual syndrome (PMS).

The selective advantages of PMS symptoms, including alterations in mood, are still not understood, though it is thought to be remnant of oestrous cycles, particularly in increased activity and energy uptake during ovulation [53]. Severe premenstrual symptoms as currently experienced by modern society is hypothesised to have arisen as result of conflicting cultural versus biological evolution, whereby women have more frequent menstrual cycles (as opposed to lactational amenorrhea) but still retain the genetic blueprint of our hunter–gatherer ancestors [54]. It may also be that some psychological and somatic symptoms experienced in premenstrual syndrome are necessary to ward off males and minimise the risk of mating during times of subfertility, which after generations has been exacerbated by lifestyle factors such as diet and stress. Gillings (2014) speculates that PMS may evolved as a means of dissolving pair bonds among infertile partners (i.e. relationships without resulting in pregnancy). This hypothesis is based on the (in part) hereditary nature of PMS, preferential direction of animosity towards partners and increases in risky and competitive behaviours during the late luteal phase to aid in seeking a new fertile mate (Gillings 2014).

Correlations between heavy menstrual bleeding and both behavioural and physiological symptoms have yet to be examined, nor has the genetic influence on menstrual bleeding been explored in the spiny mouse. Here lies potential for selective breeding of varying degrees of menstruation or PMS

symptoms, enabling further understanding of how menstruation can impact quality of life and allow thorough examination of the changes to underlying pathology. Understanding the underlying biological cues for PMS and the characterisation of a suitable model to study and manipulate the manifestations of this syndrome are important in the development of therapeutics.

## Conclusion

The spiny mouse is a potentially overlooked asset to the field of women's reproductive health, given they not only retain the ability to shed differentiated endometrium, but also exhibits corresponding mood and appetite fluctuations across the menstrual cycle and a gradual decline in fecundity spanning several years. None of these observations have previously been made in a rodent species.

The importance of this cannot be overstated. We are now fortunate enough to have a non-primate, convenient and economic small animal model which, if implemented as a species of laboratory rodent on a global scale, would provide pivotal clues to unlocking the long-held secrets of impaired uterine function, abnormal bleeding and pregnancy-associated disorders. Armed with this new evidence, the spiny mouse has the capacity to reduce the invasiveness of experimental procedures and drug trials for women, vastly improving the speed of pharmaceutical developments, and lead the field of menstruation into a new era. However, as acknowledged, there are limitations in the widespread use of the spiny mouse as a model in which to investigate physiological menstruation and associated disorders. Menstruation has not previously been reported in the other research colonies around the world, and it therefore needs to be determined whether this specific colony has “evolved” decidualisation and therefore menstruation or if, indeed, other colonies undergo these cyclic changes which may be masked by environmental influences. It also remains to be determined whether these animals menstruate in the wild, which would be a truly remarkable observation, and if other spiny mice (other than *Acomys cahirinus*) also menstruate. However, given their known aversion to handling, regular capture and examination of wild spiny mice may alter a potential menstrual cycle due to stress. Further delineation of the origin of menstruation in these fascinating mammals should be a major research direction in the future.

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