Is Female Health Cyclical? Evolutionary Perspectives on Menstruation

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Summary

In recent health policy papers, the social sciences insist that given the increased risks of heart diseases, diabetes, and other chronic conditions women face worldwide, biomedical research should step away from reducing female health to female reproductive health. Arguably the global women’s health agenda goes much beyond reproductive concerns, but we contend that it is mistaken to conceptualize women’s health as separate from women’s evolved reproductive system. This paper elaborates on the evolutionary question “why do women menstruate?” to review the support for the hypothesis that cyclical immunity is central to the modulation of health and diseases in female bodies. We conclude by outlining the possible implications of conceptualizing female health as cyclical for future research and women’s lives.

Key words: evolutionary medicine and public health; menstrual cycle; cycling life-history; inflammation; ecology; digital health;

Highlights:

Symptoms and susceptibility to infection vary across the phases of the menstrual cycle

Women with different cycling life-histories vary in their susceptibility to chronic diseases

There is a paucity of data on global patterns of menstrual cycle diversity

The ecological determinants of women’s menstrual lives are poorly understood

Word count: 3406
Women's Health

Until recently, little was known about female health. In the US, women were generally not included in clinical trials until 1993, when the National Institute of Health (NIH) Revitalization Act was passed to include women and minorities in NIH-funded research [1]. Although female health is better understood than before [2], sex and gender inequity in health care persists: women are not systematically included in trials [3,4] and research on women has focused on a limited section of Western society, leading to a limited understanding of how health varies among women of different social classes, ethnicities and countries. Further, it was only in 2009 that it was revealed that there had been a strong and widespread bias towards males in animal studies too [5]. Sex-biased research is problematic because it fails to consider that women and men differ in how they both develop diseases and respond to therapies. As Johnson [2] puts it: “When we fail to routinely consider the impact of sex and gender in research, we are leaving women’s health to chance.”

Most biomedical research on female health focuses on reproductive health, which, as pointed out by social sciences, reduces female health to women’s reproductive function [6]. Recent health policy reports thus call for a research program that moves beyond the study of reproduction to tackle the future challenges for the women’s health agenda, cardiovascular diseases (CVD), cancers, autoimmune diseases, diabetes and mental health [7]. From an evolutionary perspective, however, the regulation of the reproductive function is viewed as the very foundation of health. This is because reproductive features have a great impact on reproductive fitness, and are thus particularly malleable to evolution by natural selection. This evolutionary force is constrained by resource allocation trade-offs [8], and thus energetic investment in reproductive function imposes constraints on the potential for the body to be “healthy”, i.e. to invest in immunocompetence (see Glossary). The core insights to be taken from an evolutionary approach is that the body is best viewed as an evolved system of interconnected functions (growth, immunocompetence, reproduction), and from the perspective of natural selection, health is only a means to the end of reproduction [9]. While it is well-known that the neuro-endocrine and immune systems are intimately connected, the biomedical sciences have yet to conceptualize reproductive health as foundational for non-reproductive health.
There is now considerable variation in life history trajectories globally, with millions of women experiencing no or few childbearing events [10]. This shift in childbearing patterns correlates with a change in menstrual cyclicity: women either experience an increased number of menstrual cycles during their lifespan and/or they experience altered menstrual cycles, whereby ovulation is suppressed following the use of hormonal contraceptives [11–13]. Recent studies suggest that naturally cycling women experience a metabolic trade-off between investment in immunocompetence and investment in reproduction: which function is prioritized depends on the timing in the menstrual cycle [14–16]. Given this, what are the consequences of increased, and/or altered patterns of, cyclicity of sex hormones on women’s health and diseases? First, we review recent findings according to which menstruation has been shaped by an evolutionary conflict between the embryo and a “choosy” uterus [17,18] and the evidence for the hypothesis that immunity is cyclical in female bodies. Second, we evaluate the support for the modulation of female health and diseases with respect to the menstrual cycle phase, the cycling life-history and the use of hormonal contraceptives. Third, we examine current knowledge of menstrual cycle diversity across populations, groups and over the life-course to highlight the gaps in our understanding of the ecological determinants of women’s menstrual experience. Finally, we speculate on the implications of conceptualizing female health as cyclical for female health research.

The Evolutionary Origin of Menstruation: Inflammation and Immunity

Here we use an evolutionary approach to query why women menstruate at all and why such knowledge matters for understanding the evolution of immunity in female bodies. In doing so, we illustrate how asking evolutionary questions translates into new hypotheses and predictions about variation in physiological mechanisms [19].

It is widely acknowledged that menstruation is rare among placental mammals, though it depends on how menstruation is defined [20]. In dogs, bleeding correlates with ovulation, originates in the vagina (not the uterus) and in the absence of a pregnancy, the endometrium is reabsorbed. In humans, by contrast, menstruation results from the cyclical shedding of the inner lining of the uterus and occurs when a successful pregnancy has not been established. This human pattern, profuse uterine bleeding that occurs in the absence of pregnancy and after ovulation, is only observed in a few mammal species
including humans, chimpanzees, gibbons, barbary macaques and a few species of bats and rodents [20–22]. In addition to being rare, menstruation is potentially costly [20, but see 23], thus why it has evolved at all has puzzled evolutionary biologists for more than 20 years (Box 1).

A consensus is now emerging that menstruation is the by-product of uterine evolution in response to foetal-maternal genetic conflict over resources [24], a particularly intense phenomenon in humans due to both trophoblast invasiveness and a high rate of genetic abnormalities [18, 21]. In menstruating species, the uterus undergoes modifications before rather than after implantation [17, 18], and is under maternal rather than embryonic control [18]. This process of early preparation of the uterus, referred to as spontaneous decidualization, is thought to optimize the trade-off between embryo selection and implantation through a bi-phasic immune response [18, 25]: first, an acute inflammatory response to select viable embryos and second, a profound anti-inflammatory response to enable implantation (Box 1). In non-conceptive cycles, the response is triphasic as it further includes menstruation, an acute inflammatory process that is essential for the regeneration of the endometrium [25]. Understanding why menstruation evolved at all thus brings to the fore the question of how immunity and its associated inflammatory patterns are regulated throughout the menstrual cycle. Is female immunity then best conceptualized as cyclical?

In mammals including humans, the immune system differs between males and females [4, 26]. As compared to men’s, women’s bodies face additional resource allocation trade-offs with regards to immunity [27]: (1) a trade-off between embryo selection and embryo implantation during the menstrual cycle and (2) a trade-off between host immunocompetence and fetus growth tolerance during pregnancy [28]. The regulation of those trade-offs is partly achieved through the actions of progesterone and estrogen, two sex hormones produced by the ovaries and for which there are receptors on many immune cells [29]. It is generally admitted that estrogen has both inflammatory and anti-inflammatory properties, depending on the dose [30], and that progesterone is mainly anti-inflammatory [31]. For instance, a drop in progesterone levels acts as a trigger for the inflammatory events of menstruation and the onset of labour [32, 33]. During pregnancy, increasing evidence suggests that rising levels of estrogen and progesterone modulate the immune response in a way that enables fetus survival and growth [28, 34]. However, although it is known that the endocrine and immune systems are tightly connected, less than
10% of immunology articles include sex as a confounding variable [4]. There is a paucity of data on how sex influences immunity at various stages of the life course [4].

A few studies have investigated the hypothesis that the second phase of the menstrual cycle is characterized by a biased investment in reproduction at the expense of immunocompetence, which, at the proximate level, translates into high levels of progesterone and an anti-inflammatory environment. The phase most clearly associated with markers of inflammation is menstruation, with both increased levels of pro-inflammatory factors as compared to the late follicular phase [35] and elevated risk of CVD (12.3% vs 7.4% in all other phases, [36]). However, whether progesterone correlates with an increase or a decrease in inflammatory biomarkers such as CRP is unclear (Table 1). Another line of research focuses on the menstrual variation of Lymphocyte T helper (Th), following Wegmann’s hypothesis [37] concerning the modulation of the adaptive immune system during pregnancy (Box 2). It is hypothesized that around the time of implantation, the system should be biased towards the production of anti-inflammatory factors (Th2 route) and away from a pro-inflammatory response (Th1 route), otherwise harmful to pregnancy [38–40]. However, support for the prediction that the Th1/Th2 route is modulated in a way that promotes an anti-inflammatory environment during the luteal phase is weak, which can be attributed to methodological issues, confounding factors such as sexual activity [40,41], and the possibility that implantation, placentation and the first trimester of pregnancy are pro- rather than anti-inflammatory phases [28]. Pinpointing the exact cell population or mediator which is being up or down-regulated in a distinct menstrual cycle phase has proven challenging. The only robust result is that menstruation is an acute inflammatory event [33].

The Cyclical Modulation of Female Health and Diseases
An evolutionary cyclical model for female health predicts that the menstrual cycle modulates disease susceptibility, development and severity in at least two ways: (1) as a function of the menstrual cycle phase and (2) as a function of the cycling life-history, which depends on reproductive history and the use of hormonal contraceptives (Box 3). Here we review how menstrual cycling modulates both the manifestation of chronic diseases and the susceptibility to infection and show that female health is indeed best conceptualized as cyclical.
Menstrual cycle phase

It has been shown that the menstrual cycle exerts a modulatory effect on chronic diseases, such as cancers, autoimmune diseases, migraine, asthma, cardiac arrhythmia, uterine fibroids, irritable bowel syndrome, diabetes, mental health and epilepsy [39,42]. During or next to the inflammatory phases of the menstrual cycle (ovulation and menstruation), symptoms are aggravated, while during the non-inflammatory phase (mid-luteal), symptoms are improved (Figure 1a). However, the results are mixed for multiple sclerosis, and unknown for female biased autoimmune diseases such as Hashimoto’s thyroiditis (Box 4). Further, the cyclical experience of chronic diseases could be due to changing perception of disease severity, epigenetic regulation and the microbiome, all inter-related [43]. Beyond the impact of the mid-luteal phase on chronic diseases, future research should investigate whether the follicular phase, characterized by high levels of estrogen and promoting cell division, is deleterious for cancer progression and treatment.

The stage of the menstrual cycle is known to influence susceptibility to bacterial [44], viral and fungal infections [31]. Infection susceptibility is more likely in the non-inflammatory phase of the cycle (mid-luteal) associated with high levels of progesterone. For instance, infection from Chlamydia is more frequent in the luteal phase, which is also characterized by less anti-chlamydial activity [26]. Similarly, Wira et Fahey [45] argue that there is a window of vulnerability for HIV infection in the 7-10 days following ovulation, a period during which estrogen and progesterone suppress components of the innate, cell-mediated and humoral immunity [46,47]. Many unknowns remain, however. For instance, while young adult females develop more adverse reactions to the yellow fever virus vaccine and influenza vaccine [43], how the menstrual cycle influences response to vaccination is not documented. Similarly, how microbiome diversity changes during the menstrual cycle has received little attention [50].

Cycling life-history

The extent to which women cycle through their lives might influence their overall inflammatory «load» (Figure 1b), also conceptualized as inflamm-aging [49]. Beyond the well documented correlation between gynecological cancers and lifetime exposure to reproductive hormones [11,12], recent research suggests that a woman’s cycling life-history influences her risk to develop non-reproductive cancers and
CVD, the top two causes of death worldwide. Yet, most research focuses on estrogen exposure, rather than overall inflammatory load.

Sex differences in CVD are pronounced, with pre-menopausal women experiencing lower risks of heart failure, atherosclerosis, ischemia, cardiac hypertrophy and myocardial infarction than aged-matched men [50]. This pattern is thought to result from the exposure of pre-menopausal bodies to estrogen, which possibly act through its anti-oxidant properties, its regulation of cholesterol, its impact on calcium metabolism and its many receptors on the heart. However, a recent meta-analysis of 1903 studies revealed that hormone replacement therapy (HRT) has no effect, compared to placebo, on coronary events, cardiac death and re-vascularization [51]. The emerging picture is that estrogen exposure in fact has limited explanatory power for understanding sex differences in CVDs [50,51]. However, increasing evidence suggests that sex differences in the severity of myocarditis can be attributed to differences in the immune response to infection [52] - indeed myocarditis can be due to a viral infection - but how endogenous estrogen contributes to sex differences in the inflammatory response to heart diseases has been little studied [39].

Studies show that the cycling life-history correlates with susceptibility to various cancers, but no overall conclusion can be drawn. Use of oral contraceptive (OC) correlates with an increased risk of pancreatic cancer [54] and a decreased risk of renal cancer [55]. Later menarche correlates with a lower risk of lung cancer [56] but with an increased risk of non-Hodgkins lymphoma [57], and is associated with both increased and decreased risk of thyroid cancer depending on the study [58,59]. Life history traits such as age at menarche, age at first birth, parity, age at menopause and breastfeeding duration have not been systematically investigated. Accounting for lifetime exposure to cycles of inflammation through menstrual cycling can shed light on why the reproductive life course may have opposing effects on cancer risk depending on cancer type. This is because, on the one hand, inflammation produces free-radicals and thus increases the risk for cancerous mutations, and on the other, anti-inflammatory events increase the susceptibility to infection, thus increasing the risk for the 20% of cancers caused by pathogens [60].
Why We Need an Ecology of Menstruation

Emerging evidence suggests that patterns of menstrual cyclicity have far-reaching implications for female “non-reproductive” health. Thus, understanding the ecological determinants of menstrual cycling diversity among populations, between individuals and over the life course is key to tackling the women’s health agenda. We first outline current knowledge on menstrual cycle variation and the methodological challenges inherent to the study of menstrual cycles. Second, we illustrate how the study of variation in women’s menstrual experience can shed new light on the social and pathogenic causes of diseases.

What are the global patterns of menstrual cycle diversity? According to a comprehensive review based on 21 studies across 11 populations, there is extensive variation between human populations in cycle length (Figure 2), period length (3.5 to 6 days), levels of steroids and probability of ovulation [61]. Such variation is partly determined by ecological determinants. For instance, progesterone levels respond to energy balance both within and between populations, and ovulation is suppressed in conditions of resource scarcity [73,74]. Between populations, studies find that ecological factors such as poverty and rurality influence variation in ovarian functioning [64], but no clear population patterns have emerged [61]. This gap in our understanding can be attributed to methodological biases such as small sample sizes, differences in definitions [61] and the underestimation of variation due to the exclusion of women with medically irregular cycles, about 30% worldwide [65]. Further, the study of the menstrual cycle is taxing on participants: to quantify variation at both the individual and cycle levels, almost daily sampling for at least 5 cycles is recommended [66]. Finally, there are multiple factors that influence metabolic investment in reproductive functioning, including age, social capital, pathogen load, nutritional status and parity [27]. In this context, the use of digital health technology might offer a promising avenue given its potential to gather daily data over several cycles in various populations.

Much phenotypic variation between or within individuals can be understood as the result of phenotypic plasticity in response to external (e.g. psychosocial stress, mortality risk, quality of the early environment) and internal stimuli (age, pathogen load, energetics) [67]. An adaptive response, that is, a response that enhances lifetime reproductive success, might often entail long-term survival costs. Thus, how can we know that a phenotypic response leading to a deviation from the “norm” is the manifestation of a pathology, as predicted by the biomedical model, or a healthy bodily response given the ecological
circumstances [68]? Life-history theory (LHT,[8,69]) predicts that when resources are limited, an organism faces resource allocation trade-offs between the fitness functions of growth, immunity and reproduction. In conditions of uncertainty about future reproductive opportunities (e.g. low life expectancy), LHT predicts that resource allocation will be biased towards investment in current rather than future reproduction, at the cost of health. In this line, socio-economic hardship and perception of increased mortality risk correlate with both an accelerated life-history (an earlier age at menarche and age at first birth) and an increased morbidity [70,71]. How ecological uncertainty influences menstrual cycle characteristics and lifetime number of menses has, to date, remained unexplored.

The study of variation in premenstrual symptoms between and within women might yield insights into current and future health conditions. It has been proposed that “premenstrual syndrome” (PMS), a condition of unknown etiology for which 50% of Western women seek medical treatment [72] can be partly understood as an inflammatory disease [16,35,72,73]. A cross-sectional study of 277 women aged 18-30 years found that women with PMS showed a 2-fold increase in markers of inflammation [35]. Most recently, a study based on a sample of 2939 midlife women established that premenstrual symptoms (PMSx), which are experienced by over 80% of women, were associated with systemic inflammation [72]. Although it is becoming clear that women with PMS or PMSx also experience a dysregulation of inflammatory patterns, why this is the case is unclear. Biological anthropologists have proposed that pronounced premenstrual symptoms such as fatigue, cramps and depression might be used as a cue to an undiagnosed infection [74]. The rationale is that persistent pathogen populations, for instance the bacteria Chlamydia that infects up 70% of women, expand in the luteal phase due to the anti-inflammatory effect of progesterone [16,74]. The resulting higher pathogen load before the menses would lead to a heightened inflammatory reaction and trigger pre-menstrual symptoms (PMSx). A pioneer study based on 500 medical records found that being infected with Chlamydia was indeed associated with increased PMSx [16]. Tracking individual variation in menstrual cycle health is thus likely to provide information on changes in ecological stressors, which, from a treatment perspective, offers the possibility to address causes rather than symptoms only.
Towards a Cyclical Model for Female Health

Accumulating evidence suggests that in humans, the female immune response is modulated by the hormones governing the menstrual cycle in a way that enables the implantation of a healthy embryo, even in the absence of fecundation. Given the modulation of inflammatory patterns imposed by the menstrual cycle on the body, female health is best conceptualized as cyclical because symptoms and susceptibility to infection are expressed differently across the phases of the cycle, and women with different cycling life-histories vary in their susceptibility to chronic diseases. From an evolutionary perspective, the regulation of the reproductive process is foundational to health, reproductive and non-reproductive health are tightly connected, and thus efforts to improve female health worldwide will greatly benefit from understanding how ecological factors (pathogens, social inequalities) shape variation in women’s menstrual lives.

A significant limitation to our approach is the difficulty of studying the menstrual cycle, as it requires fine-grained data over numerous cycles. Recent years have seen a flourishing of period tracker apps for smart phones, and millions of women are now using them. Although the pool of users is currently biased towards well-off women and self-reported data face reliability issues, mobile phone apps compensate with a unique potential to document previously unknown phenotypic diversity. Yet, available apps do not currently permit the tracking of many relevant variables, as the in-built data categories are constrained by a biomedical model that pathologizes PMS, for instance. In order to fulfill their mission to provide insights back to their users, digital health should integrate an evolutionary ecological perspective to understand the causes and consequences of variation between and within women.

Shifting towards a cyclical model of female health will contribute new questions for biomedicine. During which phase of the menstrual cycle is it best to administer chemotherapy, vaccination and other medicine? Can PMS be treated with antibiotics? Should the cycling life-history be considered when calculating chronic disease risk? For decades, biomedical research has shied away from tackling female health because of its complexity. Using the new tools available and putting the research in the hands of users, now is the time to face that complexity.
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Box 1: Evolving theories of the evolution of menstruation

Menstruation refers to the cyclical shedding of the endometrium, i.e. the inner lining of the uterus [18], and is triggered by falling progesterone levels. It is costly (loss of iron, loss of tissue, narrowing of the fertility window) and relatively rare in mammals [20,21]. Thus, a number of adaptive functional hypotheses were put forward for explaining why menstruation evolved in the first place [75], including the fertility-signal hypothesis [in 19], the energy-economy hypothesis [23] and most famously, Profet’s pathogen-hypothesis [20]. Profet argued that rather than being the manifestation of a defective, “polluted” female body, menstruation was an adaptation to cleanse the uterus from external pollution, i.e. pathogens brought about by sperm. Profet’s original hypothesis was quickly rejected, however, for both lack of evidence [77] and theoretical issues [13]. The elevated number of menses many contemporary women experience is likely to be an evolutionary novelty [11,13] as up until recent times, women worldwide would have spent most of their reproductive lives pregnant or exclusively breastfeeding. In both cases, high progesterone levels suppress ovulation and the subsequent production of a secretory endometrium (i.e. the decidua) and thus there is no menstruation because there is nothing to shed. Given that natural selection can only act on features that are expressed, the idea that menstruation per se serves an adaptive function was abandoned. Hypotheses for the origins of menstruation turned to by-product explanations [78], whereby menstruation was viewed as the outcome of uterine evolution in the face of fetal invasiveness [78] and genetic abnormalities (i.e. a choosy-uterus [18,21]). In humans and other menstruating species, the “preparation” of the endometrium for pregnancy (i.e. the decidualization process), under maternal rather than embryonic control: it occurs every cycle in the absence of embryonic cues (i.e. it is spontaneous) and involves the activation of both pro and anti-inflammatory pathways (Figure I). In the case of compromised or no implantation, the decidualization process ends with menstruation, a massive inflammatory event which, through the recruitment of stem cells, enables the regeneration of the endometrium. The evolution of spontaneous decidualization coupled with cyclic menstruation has been hypothesized to be a major evolutionary adaptation that optimizes the balance between embryo selectivity and embryo receptivity [17,18,21,79]. Menstruation is thought to be indispensable to the establishment of successful pregnancy as it “continuously rebalances the receptivity and selectivity traits of the endometrium, thus increasing the likelihood of reproductive success” [23].
Figure I: The human menstrual cycle is characterized by both pro and anti-inflammatory processes. The human menstrual cycle involves the tight regulation of inflammatory processes that enable the implantation of a healthy embryo. It is characterized by both an ovarian cycle (top graph) and a uterine cycle (bottom graph) that are regulated by hormones (middle graph).

The figure represents a 28 days cycle idealized as an average cycle, however at least 30% of women experience shorter or longer cycles at some point or during the entire reproductive history. By convention, the cycle starts with the first day of the cycle (start of the menstrual bleeding) and ends the day before the onset of menstruation. At the beginning of the ovarian cycle, the follicle stimulating hormone (FSH) is produced by the pituitary gland located at the base of the brain. It stimulates the development of follicles and oocyte maturation within the dominant follicle. The granulosa cells of the follicles start producing estrogen (E2), FSH levels decline, and gonadotropic cells in the anterior pituitary gland start producing the luteinizing hormone (LH). LH continues to rise as more E2 is being secreted; starting around day 10 of the menstrual cycle E2 sharply rises, which is followed by a massive LH surge, and a smaller spurt of FSH. The oocyte matures through completion of the first meiosis, commencement of the second meiosis and is arrested in metaphase, all of which happens within the 24 hours post LH surge. Next, the oocyte is physically expelled from the follicle, marking the ovulation (i.e. follicular rupture), and which is followed by an acute inflammatory reaction to repair the damaged tissue. After ovulation, the empty follicle (corpus luteum) starts producing progesterone to enable the endometrium to prepare for implantation. At the later stage of the cycle, the corpus luteum produces estrogen as well. The uterine cycle. During the proliferative phase of the uterine cycle, estrogen promotes the repair and thickening of the inner lining of the uterus (endometrium); during the secretory phase, rising levels of progesterone (P) levels enable the decidual cell reaction (DCR), a process by which the endometrium prepares for implantation and which involves the recruitment of immune cells and the differentiation of endometrium cells into secretory cells producing proteins and growth factors. The DCR afford the uterus the capacity to (1) discriminate between healthy and compromised eggs due to an acute inflammatory reaction (ca. [Days 18-21]) and (2) allow for the implantation of a blastocyst due to a profound anti-inflammatory reaction (ca. [Days 23-27]). Thus, the “receptive window” [Days 20-24] is governed by both pro and anti-inflammatory processes [24]. If the oocyte is not fertilised, the corpus luteum degenerates, progesterone levels are not maintained, and an acute inflammatory reaction follows. The end result is menstruation, which corresponds to the third phase of the decidual cell reaction in a non-conceptive cycle [24]. Although most current knowledge derives from animal studies, accumulating data suggest that the second phase of the cycle is a tri-phasic process involving the deployment and resolution of inflammatory processes.
Box 2: The evidence for cyclical immunity

The hypothesis according to which the luteal phase is characterized by a biased investment in reproduction promoting an anti-inflammatory environment has been investigated by studying the menstrual modulation of the adaptive immune system, focusing on patterns of production of immune cells (Lymphocyte T helper (Th)) and their mediators (signaling cells). Specifically, recent research has investigated the menstrual modulation of the so-called “Th1/Th2” route, i.e. the relative importance of the immune response to two types of threats: extra-cellular pathogens (Th1 response, cell-mediated, mainly pro-inflammatory and activated by estrogen) and intra-cellular pathogens (Th2 response, humoral/blood, mainly anti-inflammatory and activated by progesterone). Interest in the Th1/Th2 route stems from the work of Wegmann [37], who hypothesized that pregnancy was a Th2-like phenomenon and best understood as a state of immune suppression. In this line, it was found that a defective Th2 response was linked to spontaneous abortions [80].

With regards to the menstrual regulation of the Th1/Th2 route, however, results are mixed. A study based on 13 women, using blood samples and lymphocyte activation methods in the two phases of 1 cycle found that in vitro cytokine production by lymphocyte was promoting a Th2 cell response in the luteal phase as testified to by an anti-inflammatory response [38]. They found no change in the production of Th1-pro-inflammatory mediators. Conversely, Oertelt-Prigione et al. [39] found no evidence for menstrual variation of Th1 and Th2 mediators in a sample of American women and Lee et al. [81] found no patterns of variation in a sample of 22 healthy Korean women. Although there are too few studies to conclude, it is possible that the original hypothesis, focused on the adaptive immune system, was misleading.

The view that pregnancy is biased towards a Th2 response has been challenged by data showing that the first and last trimesters are rather biased towards a Th1 response [28], and that implantation and placentation are mainly pro-, rather than anti-, inflammatory [28]. Future research might focus on the menstrual modulation of the innate immune system, as recent data suggests that it has a critical role in both feto–maternal immune adjustment and successful placentation [28]. In any cases, significant advances in understanding how immunity cycles in female bodies require new methods enabling data collection over multiple days, multiples cycles and multiple individuals.
Box 3: Hormonal contraception, menstrual suppression and its impact on health and diseases

Hormonal contraception has been deemed the “innovation” of the century for its role in women’s empowerment and economic development. In addition to the benefits of controlling one’s fertility, hormonal contraceptives enable women to reduce or suppress menstruation (amenorrhea), and the debilitating symptoms and conditions associated with it (e.g. PMS, migraine and pain, endometriosis) [82]. There is no evidence that the suppression of menstrual cycling has deleterious effects on non-smoking women, rather research shows that prolonged use of hormonal contraception reduces the risk of reproductive cancers, in particular endometrial and ovarian cancers. Such beneficial outcomes are thought to result from a reduction of the number of mutations in epithelial cells following the suppression of cell division mechanisms otherwise activated for healing the ovary and the endometrium [83]. For explaining the ontogeny of ovarian cancer [42], the “incessant ovulation” hypothesis (i.e. the role of repetitive wounding of the ovaries) was initially favoured, but the “incessant menstruation” hypothesis (i.e. the role of repetitive exposure to iron-induced oxidative stress through retrograde menstruation) is gaining support. Given that menstruation is associated with biomarkers of systemic inflammation (Table 1), it is possible that “incessant menstruation” hypothesis extends its relevance to non-reproductive cancers. In addition, if the suppression of inflammatory events through the suppression of menstrual cycling has long-term benefits, it might entail short term costs. Users of hormonal contraceptives are predicted to be at an increased risk of infections. Progesterone-based contraceptives like Depo-Provera (or DMPA, a commonly used contraceptive in sub-Saharan Africa) have routinely been utilized to facilitate infection in rodents [47] and studies on mice have shown that exposure to Depo-Provera is associated with poor response to herpes virus [84]. There seems to be an emerging consensus that progestin-based contraceptives increase the susceptibility to viral infections [85], and a recent meta-analysis of cross-sectional and longitudinal studies in humans suggests that DMPA adds to the risk of male-female HIV transmission [but see 26,86]. It has also been found that users of hormonal contraception show a reduced immune response as compared to others. For instance, bacterial count are higher in users of combined oral contraceptives compared to non-contraceptive users, after controlling for differences in sexual activity [26]. Yet, there are many unknowns as to how hormonal contraceptives shape susceptibility to and response to infection, for instance, how contraceptive users and non-users differ in their response to vaccination.
Box 4: The menstrual regulation of auto-immune diseases

Autoimmune diseases (AD) are sexually dimorphic: about 80% of patients living with AD in the West are women. The dimorphism is particularly pronounced (>85%) for thyroid autoimmune disorders (e.g. Hashimoto’s thyroiditis (HT), and Grave’s disease (GD)), Sjögren’s syndrome, Addison’s disease, systemic sclerosis and systemic lupus erythematosus (SLE). There have been several hypotheses for why females are more prone to AD: female sex hormones increase an individual’s susceptibility to AD; male sex steroids exert a protective role; X-linked genes normally silenced “escape” inactivation or are mistakenly duplicated; females are more exposed to exogenous triggers due behavioural, cultural and psychological factors; and male and females differ in their microbiota [87]. The pathogenesis of autoimmune diseases remains unclear [88]. Although many factors are involved (genetic, epigenetics, infection, hormones and the microbiome [30]), sex hormones play an important role in the etiology and course of chronic inflammatory diseases: sexual dimorphism to many ADs is more pronounced after puberty (e.g. in the case of systemic lupus erythematosus (SLE); the ratio of female to male shifts from 3-4:1 to 9:1) and many autoimmune disorders show a strong link with estrogen (the link with progesterone exists, but is poorly understood to date [31]). However, estrogen is involved in both pro and anti-inflammatory pathways in a dose specific manner and whether it is a friend or a foe with regards to AD is still debated [89]. A number of studies suggest that estrogen has opposite effects on Multiple Sclerosis (MS) and Systematic Lupus (SLE) [30]: while it is found to be protective of MS through anti-inflammatory and neuroprotective effects, exposure to estrogen might actually increase flares of SLE and Hashimoto’s thyroiditis (HT). For instance, early menarche, intake of exogenous hormones and the follicular phase all increase rather than decrease the development and severity of SLE. In addition, among patients with PCOS, a condition in which estrogen is the dominant hormone throughout the reproductive life, the prevalence of HT is higher [90]. Existing studies thus suggest that the menstrual cycle and the cycling life-history modulate the course and the severity of ADs in a disease-specific way. Yet, the study of the menstrual modulation of ADs has been confined to a few conditions, and little is known about the role of menstrual cycling for the most female-predominant AD, i.e. Hashimoto’s thyroiditis, Sjögren’s syndrome and Addison’s disease.
Figure Legends

Figure 1: Toward a cyclical model for female health (a) The menstrual cycle phase. The menstrual cycle modulates disease susceptibility, development and symptoms. For instance, some symptoms are exacerbated during the inflammatory phases of the menstrual cycle (ovulation and menstruation), while susceptibility to infection is increased during the mid-luteal phase of the menstrual cycle, when high progesterone levels lead to an anti-inflammatory environment. Only two reviews have been conducted on the role of the menstrual cycle phase on various diseases [39,42], and many unknowns remain. For instance, given that estrogen both stimulates cell division and fluctuates during the menstrual cycle, does the menstrual cycle phase influence how cancer progresses? Similarly, given high progesterone levels impair the response to infection, does the menstrual cycle phase influence response to vaccination? (b) The cycling life-history. The cycling life-history, i.e., how many menstrual cycles women experience through their lives, is highly variable among women, depending on age at menarche, number of pregnancies, duration of breastfeeding, age at menopause and the use of hormonal contraceptives and hormonal replacement therapy. Given that menstruation is an acute inflammatory event [32], that progesterone is anti-inflammatory and that estrogen can be either inflammatory or anti-inflammatory depending on the dose, the cycling life-history is likely to influence the overall inflammatory load [49] of a woman and thus her risk of chronic and long-term illnesses.

Figure 2: Variation in cycle length across 11 human populations. Reproduced from [65]. Existing data on global patterns of menstrual cycle diversity show that median period length can vary from 28 to 36 days, and that period length can vary from 3.5 to 6 days (not shown on graph, [61]). However, existing studies are too few, generally based on a small number of cycles and conducted in a limited number of populations. The ecological determinants of menstrual cycle diversity are, overall, little understood. Reproductive ecologists have shown that on the one hand ovulation may be suppressed in conditions of resource scarcity, and on the other, that steroid hormones levels vary between populations without necessarily impairing the ovarian function [63]. Yet, the impact of poverty, rurality, social class and infections on menstrual cycle characteristics (cycle length, period length, pre-menstrual symptoms) has yet to be fully uncovered.
Figure 2

| Sample                        | Age    |
|-------------------------------|--------|
| 2 Canada/US                   | 15-44  |
| 3 US (MA) housewives          | 19-42  |
| 4 US, Mt Sinai Study          | 19-41  |
| 5 US (CA)                     | 21-39  |
| 6 UK                          | 15-53  |
| 7 UK                          | 18-49  |
| 9 Denmark                     | 20-35  |
| 10 Denmark                    | 25-34  |
| 11 Switzerland                | 20-40  |
| 12 Japan                      | 20-39  |
| 13 India (Bhuta)              | 24-36  |
| 14 India (Bengalee)           | Adult  |
| 15 South India (urban)        | 25-34  |
| 16 South India (rural)        | 25-34  |
| 17 Papua New Guinea           | 18-44  |
| 18 Mali                        | 15-53  |
| 19 Mexico                     | 20-35  |
| 20 Guatemala                  | 18-39  |
| 21 Bolivia (altiplano)        | 20-38  |

Legend:
- mean ± standard deviation
- median
| Country   | Sample Size | Year  | Month | Sampling (N samples/cycle) | Days of Sampling | Findings Per Menstrual Cycle Phase |
|-----------|-------------|-------|-------|---------------------------|------------------|-----------------------------------|
| Polish    | 27          | 2015  |       |                           |                  |                                   |
| American  | 8           | 2008  | mixed |                           |                  |                                   |
| Swiss     | 16          | 2005  |       |                           |                  |                                   |
| Swiss     | 102         | 2016  |       |                           |                  |                                   |
| Austrian  | 18          | 2010  |       |                           |                  |                                   |
| USA Mixed | 259         | 2012  |       |                           |                  |                                   |
| Canada    | 41          | 2016  | urban |                           |                  |                                   |
| Bolivian  | 61          | 2015  |       |                           |                  |                                   |
| Italian   | 18          | 2010  |       |                           |                  |                                   |
| Swiss     | 8           | 2006  | serum |                           |                  |                                   |
| Turkish   | 88          | 2016  | blood |                           |                  |                                   |
| Swedish   | 12          | 2016  | blood |                           |                  |                                   |
| Swiss     | 15          | 2006  | serum |                           |                  |                                   |
| American  | 8           | 2008  | blood |                           |                  |                                   |
| Austrian  | 18          | 1997  | blood |                           |                  |                                   |
| Polish    | 7           | 2013  | urine |                           |                  |                                   |

Table 1: Variation of an inflammatory biomarker (CRP) across the menstrual cycle.

N: Sample Size; NC: Nb of cycles; M: Menses; MF: Mid-Follicular; POV: Per-Ovulation; ML: Mid-Luteal; DOL: Day of Ovulation; days of sampling; range of CRP levels. Days not mentioned: No changes.

Note: To interpret the level of effect on CRP levels, + or – indicates positive or negative effect of the menstrual cycle phase on CRP levels. Day 0 is the day of ovulation; range of CRP levels: [-] from to; [:] days of sampling; [;] positive or negative effect of the menstrual cycle phase on CRP levels.
Glossary

**Adaptive immune response:** It is the second line of defenses against pathogens (microorganisms harmful to the body). The adaptive immune response is highly specific, involves immunological memory and can provide long lasting protection.

**Biomarkers of inflammation:** Measurable indicator that correlates with levels of inflammation. Common biomarkers include acute phase-proteins such as CRP and fibrinogen.

**Blastocyste:** Name given to the embryo between the 5th and 7th day after fecundation.

**CRP:** C Reactive Protein is an acute phase protein produced by the liver and adipocytes, and it is a marker of low-grade systemic inflammation and cardiovascular disease risk.

**Cycling life-history:** We call it the life time number of cycles of menstruation, which determines a lifetime inflammatory load. It is influenced by the age of menarche, the number of pregnancies, the duration of breastfeeding, the age at menopause and the duration of use of hormonal contraceptives and hormone replacement therapy.

**Cytokines:** Small proteins involved in cell signalling and acting as immunomodulating agents. Interleukins are a sub-type of cytokines.

**Decidual cell reaction:** It corresponds to the preparation of the endometrium for implantation of the embryo and is a characteristic of menstruating species. After ovulation, rising levels of progesterone trigger cellular and vascular changes in the endometrium, which involve the recruitment of immune cells and the production of growth factors and proteins by endometrial cells. In the absence of successful conception, the decidual cell reaction ends with menstruation.

**Endometrium:** Name give to the inner lining of the uterus.

**Immunocompetence:** It is the ability of the body to mount an immune response following exposure to a pathogen. It is the contrary of immunodeficiency.
**Inflammation:** It is a complex biological response to harmful stimuli and is considered a part of the innate immune response. It is correlated with, but is not a synonym of, infection.

**Innate immune response:** It is the first line of defense against pathogens and includes features such as the skin, mucosa and immune cells. The innate immune response is activated immediately after an invading pathogen has been detected and acts within hours. This non-specific response can then activate a second line of defense: the adaptive immune response.

**Life history theory:** A branch of evolutionary theory which asks: for each sex, each life-stage and each ecology, how are resources allocated between the different fitness functions of growth, survival and reproduction in a way that optimizes lifetime reproductive success? Life-history theory fundamentally uses a holistic perspective and predicts that when resource are limited, organisms will face resource allocation trade-offs between different fitness functions.

**Lymphocyte T helper:** Immune cells which are part of the adaptive immune system. They help up or down regulate the immune response.

**Oocyte:** Refers to an egg cell, i.e. an immature ovum, produced by the ovary.

**Parity:** The number of live births of a female so far.

**Phenotypic Plasticity:** The ability of a genotype to express different phenotype as a function of the environment.

**PMS:** Pre-menstrual syndrome, a chronic condition of unknown etiology experienced by women before their menses. It is characterized by a wide variety of symptoms including depression, fatigue, cramps and headaches. It is debilitating for 5-8% of women in the West, a condition referred to as premenstrual dysphoric disorder, and is usually treated using hormone therapy and/or psychological counselling.

**Trophoblast:** Tissue that forms the outer layer of the blastocyst and will later become a major part of the placenta.
Outstanding Research Questions

(1) How does the number of menstrual cycles relate to the rate of aging?

(2) Is the response to medical interventions (e.g. chemotherapy, vaccination) influenced by the phase of the menstrual cycle?

(3) Does microbiome diversity change between the phases of the menstrual cycle, between cycles and as a function of the reproductive history?

(4) What is the contribution of hormone-driven inflammatory events and cell-division processes on cancer progression?

(5) Can population differences in sex hormones levels contribute to explain variation in disease susceptibility and progression?

(6) What is the influence of the menstrual cycle phase and the cycling life-history on patterns of DNA methylation (epigenetics)?

(7) How are menstrual cycle characteristics (cycle length, period length) shaped by the ecology (social class, pathogen load)?