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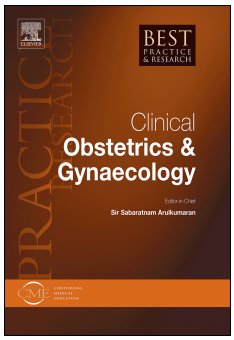

The Significance and Evolution of Menstruation

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The Significance and Evolution of Menstruation

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Abstract

Historically, the evolutionary origins of menstruation have been based two theories: the ability to eliminate infectious agents carried to the uterus with spermatozoa and the comparative conservation of energy with menstruation compared to its absence. In the menstruating species, more recent theories have identified spontaneous decidualization as the key adaptive mechanism. Spontaneous decidualization is seen as a mechanism to provide the mother with protection from the invasive characteristics of the embryo. Physiologically menstruation involves complex interactions of inflammation and vascular mechanisms to stabilize the endometrium and allow a regulated loss of endometrial tissues and blood. A variety of human illnesses can be better understood as vulnerabilities associated with these evolutionary developments including recurrent pregnancy loss, placenta accreta, ectopic pregnancy, endometriosis, adenomyosis, dysmenorrhea and chronic pelvic pain. While the evolutionary aspects of these diseases indicate why such illnesses can occur, in some instances they also provide a basis for treatment, prevention and future research direction.

Key words

Evolution, spontaneous decidualization, phenotypic plasticity, genetic assimilation, stem cells, menstrual suppression

A Introduction

Menstrual function has been a topic of a plethora of interests from the writings of the ancients though early cultural practices, common taboos, to present day interests in gender studies(1). Of late, the evolutionary basis of human disease, particularly the emergence of chronic illness has provided a basis for detailed studies of the processes and significance of menstruation. Menstruation can be defined as the shedding of the superficial lining of the uterine endometrium that occurs in the presence of a sterile menstrual cycle and is associated with a reduction in progesterone. This paper is directed to the exploration of the evolutionary emergence, its physiology and its significance in relation to the development of clinical disease states. In reviewing this topic reference is made to several excellent review sources (1-4).

B. Evolution of Menstruation

C. Historical Considerations

The process of evolution permits advancing fitness to survive and reproduce through adaptive processes. Any explanation for the emergence of menstruation should allow selection to benefit an individual's survival to reproduce. What is then is the adaptive benefit of menstruation? Aristotle suggested that menstrual fluid provided inanimate matter that acted on semen to effect the development of embryos(5). Galen thought menstruation was a way of eliminating excess blood (6). Menstruation was likened to the proestrus bleeding seen in dogs but this was shown not to be associated with the correct timing of the cycle (7). More recent approaches have included menstruation as associated with sexual response (8) and a method of eliminating un-implanted embryos (9). There have been two prominent theories to explain why some animals menstruate while others do not. One theory has suggested that menstruation was a process that

permitted the uterus to eliminate bacteria contaminating sperm that had entered the uterus during copulation (10). This proposed theory has been shown to unlikely by Finn (11). A second theory indicated the adaptive development of menstruation came about as a consequence of energy conservation through menstruation(12). There is greater energy saved through menstruation than would occur as a consequence of regenerating the endometrial lining. This theory was also refuted on the basis of the complex function of the uterus that is required to function in different orderly ways to secure a successful pregnancy(2). These theories unfortunately do not assist in supporting the evolution by natural selection.

To be consistent with evolution of menstruation beyond the non-menstruating mammals requires appreciation that menstruation occurs at the end of a complex series of changes that prepare the uterine lining well in advance of the menstrual action(2). While the theories of Profet and Strassmann discounted the possibility of uterine pre-decidualization as a function of the menstruating primates, in fact it is evidence this takes place (13-15). Finn proposed that decidualization through advanced differentiation of the endometrial stroma is the essential feature of the menstruating mammals (2).

C. Current Theories

Decidualization is present among both the menstruations and non-menstruating species. The non-menstruating species undergo decidualization in vitro by trauma to the endometrial lining or in vivo following fertilization and contact with the conceptus. The menstruating species decidualize through the presence of progesterone from the ovary following ovulation and before conception. In the menstruating species, decidualization can occur during sterile cycles and is

not dependent on contact with a conceptus. The emergence of spontaneous decidualization in the menstruating species is thought to have evolved to accommodate those species that have particularly invasive placentation

The species that do menstruate include humans, apes, the elephant shrew and certain bats(16). The bleeding that occurs from the dog at proestrus is not from the uterus but from the vaginal wall. These species experience spontaneous decidualization as preparation for the potential invasion of the embryo(16). This differentiation is characterized by angiogenesis and the influx of natural killer cells as an approach to limit the invasion of the embryonic cells into the uterine lining(17;18). The process of decidualization occurs as a consequence of the release of progesterone from the corpus luteum days before the entry of a fertilized ovum. The decidualization acts to deal with the correct intake of the foreign embryonic material, limit the invasion. The mother and embryo do not possess the same genes and therefore their interests are not identical. The embryo seeks to extract all the energy possible form the mother while the mother wishes to secure the success of this and future pregnancies. Notable actions that protect the mother are the presence of NK cells that cause apoptosis in the advancing trophoblastic cells and limit invasion(17;19). A similar function is the continuous block of large decidual cells with tight junctions to prevent invasion(20). The menstruating species have been shown to have greater invasiveness in the placenta (17;18).

The process of spontaneous decidualization is therefore identified as the evolutionary dive to permit menstruation. It exists to provide fitness to the mother by preventing excessive invasion, allowing success of the pregnancy and preserves the uterus for future pregnancies. There are two current theories as to why the spontaneous development of decidualization occurred. The first is the early protection of the mother from excessive invasion of fetal tissues. It has been suggested

spontaneous decidualization has emerged in the species associated with the greater placental invasiveness(16). An alternative explanation is that this process has evolved to permit embryo selection by the mother(21). Endometrial stromal cells generate a response to impaired embryos but only after being decidualized(21). The apparent mechanism of the evolution involves the processes of implantation and the common denominator appears to be cAMP that is activated during spontaneous and fetal initiated decidualization(22).

C. Phenotypic Plasticity and Genetic Assimilation

Phenotypic plasticity is a term that is used to denote an individual organism can modify its appearance or phenotype based on variations in environmental exposure(23). Both temperature and light are known to affect the phenotype of plants and some animals through biochemical responses, while pressure can change plant development and exposure to other organisms alter behavior (23). Phenotypic plasticity is considered to be a defining feature of living organisms(24). Such plasticity occurs when an organism is exposed to environmental variation and there is no fixed trait that is suited to the exposure, indicating that conditions are favorable to genetic selection(25). The process of plasticity can both be gained and lost depending on the continued environmental exposures. The process of plasticity can eventually lead to genetic accommodation whereby the new phenotype emerging from the environmental exposure becomes an adaptation through genetic mechanisms. When this process is complete, the process is termed genetic assimilation such that a new trait is constitutively expressed (26;27)

The internalization of the environmental stimulus may have played a role in the development of spontaneous decidualization in menstruating species. Examples of this have been noted in the

generation of the thorax of Drosophila after exposure to ether (28). A similar environmental action is present in association with the determination of sex of the offspring in the turtle(29).

Genetic assimilation can may develop from either an environmental stimulus or a mutation. The former is considered to be a much more common method due to the fact that environmental exposure will affect many more individuals and that mutation is normally independent of the environment (30). At present the biochemical mechanism appears to be a progesterone dependent activation of the cAMP signalling pathway. Progesterone does not act immediately to decidualize suggesting other intermediary approaches are required. As cAMP is a more potent activator of endometrial stromal cell differentiation than progesterone and blocking the effects of cAMP inhibits differentiation, cAMP is thought to be the signalling pathway inducing decidualization (16).

Species that were able to assimilate the spontaneous decidualization process would have had greater fitness or survival capability than those dependent on the embryo to generate decidualization due to the ability to provide improved protection from excessive invasion of the conceptus. The benefits of spontaneous decidualization appear to be greater that the energy requirements associated with the physiological experience of menstruation and associated blood loss. In general, the evolutionary advantages from the processes resulting in spontaneous decidualization and subsequent menstruation appear to favor the mother, particularly in protection from placental invasion as well as protecting the mother possibly from limited embryos as well as protecting the uterus for future pregnancies. There are exceptions to this as menstruation can be seen as a pleiotrophic effect of the beneficial trait of spontaneous decidualization and the benefit can be lost in the presence of excessive embryonic invasion.

B. Physiology of Menstruation

The actual process of menstruation can be studied through the many component parts including societal, feminist and gender perspectives as well as the more physiological processes of endocrine control, inflammation, hemorrhage and vascular regulation(1). Although this chapter is directed to the more biological aspects and the relationship to human disease it is important to note the complex nature of this condition contained in the female sex. It has been the source of much misunderstanding, prejudice and harm essentially forever and readers are referred to excellent texts to appreciate the profundity of these concepts(1).

C. Inflammation

Menstruation occurs as a consequence of failed implantation of an embryo, the resulting decline in progesterone from the corpus luteum and the disruption of the outer third of the endometrial tissues with subsequent uterine bleeding(31). In addition to the reduction in progesterone there are changes that are fundamentally associated with inflammatory in nature (32). The components of such inflammatory action are the emergence of inflammatory mediators (33). One theory indicates a two-step process(1). The decidua is responsive to reductions in steroid hormones and responds by the release of cytokines, chemokines, chemokine ligands and adhesion molecules(34). The second phase is associated with entry of leukocytes that release matrix metalloproteinase into the tissues that result in tissue disruption (35;35). The matrix metalloproteinases are able to disrupt the extracellular structures of the endometrium in the glandular layer as a consequence of progesterone withdrawal. There is no such disruption in the basal layers of the endometrium as there remains significant progesterone receptor presence(36). Another component of the inflammatory response is the influx of endometrial neutrophils that

contain high levels of matrix metalloproteinase that result in tissue breakdown and reduced clearance of disrupted tissue (37;38). Inhibitory studies of COX-2 and NF-kappa B at the time of progesterone withdrawal decreases the amount of bleeding from the uterus and supports the role of cyclo-oxygenase and NK-kappa B in the prostaglandin regulation of leukocyte influx and tissue breakdown (39).

The decidualized stroma is therefore instrumental in not only the processes of implantation but failing a successful pregnancy, initiates the processes of cellular inflammation and destruction of the outer tissues, preparing for the onset of the next menstrual cycle through initiation of repair mechanisms. Alteration in this process has been associated with the development of dysfunctional bleeding (40;41).

C. Vascular Control

The vascular anatomy of the endometrium begins with the uterine or ovarian artery branching into the arcuate artery which surrounds the uterus, further dividing into the radial arteries that penetrate the muscles and supply blood to all layers. The radial arteries branch into the basal and spiral arteries that supply the endometrium. The basal arteries are not responsive to hormonal influence but the spiral arteries that supply the functionalis layer are highly sensitive to hormonal influence (42;43). There is evidence that vasoconstriction of the spiral arteries of the uterus occurs with the onset of menstruation. There is conflicting evidence if this involves actual tissue hypoxia however(1). The control of blood flow is thought to be in part the balance of prostaglandins. PGF2a and endothelin -1 are known to be vasoconstrictors while PGE2 is a vasorelaxant. The decrease in PGF2a to PGE2 may result in increased blood flow(44). Additional factors associated with changes to the spiral arterioles include the maturation and

proliferation of the smooth muscle cells that may regulate the diameter of the vessels and permit increased blood flow (43;45;46).

The process of blood loss is also controlled by the hemostatic system. The steps to coagulation and blood loss control include the formation of a platelet plug and subsequent formation of fibrin from collagen, tissue factor, platelets and Von Willibrand factor. Subsequent control comes from both the intrinsic and extrinsic pathways to result in the conversion of prothrombin to thrombin and ultimately the conversion of fibrinogen to fibrin and a stable clot. The process of fibrinolysis plays an important part in the excessive bleeding disorders and is managed successfully in many cases with the inhibition with tranexamic acid(47). Von Willibrand's Disease, in which there is an altered VW factor, accounts for a significant proportion of women having heavy bleeding.(48;49)

B. Implications for understanding diseases and disease processes

The information from the study of evolution and menstrual physiology provides insight into a number of significant disease states. Of interest, it has been suggested that the process of labor and delivery in women is a form of menstruation as there is a continued dependence on the spontaneous decidualization and the abnormalities and physiological defects that lead to complications during pregnancy and parturition are detectable already during spontaneous decidualization in the non-pregnant state and at the onset of menstruation. It is suggested that these limitations and might be determined before the onset of pregnancy(50).

C. Recurrent pregnancy loss is associated with alterations in the function of stem cells in the endometrial cavity. Stem cell deficiency, accelerated stromal senescence and deficient

decidualization have been shown to limit the differentiating capacity of the endometrium and predispose for pregnancy failure(51).

C. Both endometriosis and adenomyosis have been noted to express aggressive endometrial stem cells that display greater invasiveness (53). Endometriosis is thought to be associated with the implantation of endometrial cells in the peritoneum following retrograde menstruation although this phenomenon is widespread among women without the disease. Endometrial cells are not all the same and some are stem cells with the power of regeneration (52). It has been suggested that the proportion of endometrial cells that are stem cells involved in retrograde menstruation may effect the development of endometriosis (1). This observation is consistent with the variation in response of the endometrial implant tissues to pharmacological treatment as some case of endometriosis are resistant to the effects of therapy with progestational agents (53). .

C. Placenta accreta is a condition in which there is excessive invasion of the placenta into or through the uterine wall. In extreme cases it can result in complete invasion beyond the confines of the uterus and enter other pelvic organs such as the bladder. It is a not infrequent complication of prior Caesarian section and carries with it risks of severe morbidity and mortality(54-57). One possible explanation for this extreme event appears to be a defect in the balance of the properties supporting the fetus and the mother. For the fetus, the invasiveness is essential for survival. Decidualization is the defence that protects the mother from excessive invasion. Decidualization of uterine tissue provides maternal protection by limiting invasive fetal proteins and the presence of uterine NK cells induces apoptosis in trophoblastic cells. There is deficient decidualization in the uterine tissues associated with placenta accreta permitting excessive placental invasion and reduced placental separation following expulsion of the baby with subsequent hemorrhage. An associated condition with substantial morbidity that is

due in part to deficient or absent decidua is that of tubal ectopic pregnancy where there is a risk of rupture of the tube and severe hemorrhage.

C. Chronic pelvic pain is a condition that is caused in large measure from repeated pain from one or more pelvic organs. When recurrent peripheral pain sensation becomes sufficient, alterations in the spinal cord occur permitting the development of pain sensitization. Under these circumstances the pain becomes continuous and can develop into a chronic pain state. This state is clinically recognizable by the finding of cutaneous allodynia on the abdominal wall and perineum (58;59). Women who experience chronic pelvic pain and have cutaneous allodynia have a greater rate of prior dysmenorrhea and prior years of severe dysmenorrhea(60). One of the most significant secular changes in human physiology over the years has been the lifetime exposure to menstruation. Owing to earlier menarche, later life expectancy, pregnancy and lactational amenorrhea, women with two pregnancies and lactational periods who live to the age of 52 will have experienced more than 400 menstrual cycles (Figure 1)(61). The physiological ability to accommodate this repetitive pain may be deficient among some women generating a maladaptive state. Some women with our current pain physiology appear to be unable to cope with the changing demands of repetitive severe pain. This process is termed hyperalgesic priming and has been characterized biochemically in animal studies. The markers for the development of chronicity include identification of protein kinase epsilon among other markers in animal studies (62;63). These processes may well be present in women with severe dysmenorrhea who progress to the chronic pain state (60). The therapeutic implications are the need to recognize the presence of severe dysmenorrhea and manage it effectively with anti-inflammatory agents and menstrual suppression (64-66).

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B. Summary

While most medical literature describes the “what”, “when” and the “how” of illness, evolution has merit in describing the “why” of illness, particularly increasing our understanding of the chronic illness. Awareness of the significance and evolution of menstruation provides an opportunity to explore the treatment and future research opportunities of a wide variety of experiences of the human condition. As awareness of the importance of decidua in the health and stability of pregnancy and the new developments in stem cell research, there are excellent opportunities to make significant improvements in a number of reproductive health problems.

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Conflict of Interest

The author declares there is no conflict of interest

Practice points

- Specific questioning about the impact of menstruation is often necessary to realize the menstruation is not normal but severely painful.
- Inhibition of prostaglandin production and menstrual suppression are important approaches to the treatment of dysmenorrhea.
- Menstrual suppression may act to prevent the development of chronic pelvic pain. It can reverse pelvic pain sensitization as defined by the initial presence and later disappearance of allodynia but takes time.

B. Research Agenda

Certain approaches to care and a research strategy can be considered as a result of the evolutionary aspects of the development of disease:

C. Endometriosis, adenomyosis and recurrent pregnancy loss may be associated with alterations in the endometrial stem cell function and may benefit from further investigations of stem cell heterogenicity and treatment. A more in-depth comprehension of distinguishing stem cell characteristics and altered regulation in this prevalent disease is needed (67;68).

C. Appropriate concern regarding the significant risk of placental abnormalities including accreta, placenta praevia and possibly even amniotic fluid embolism may be avoided by generous application of primary and secondary Caesarian section. Patient education may play a role in appropriately informing women of the risk associated with these procedures(69).

C. Among women with dysmenorrhea, menstrual suppression with various modalities may play a part in the prevention of chronic pelvic pain through the prevention of hyperalgesic priming of the pain system. As 30% of women with chronic pain state their painful menstruation began in adolescence, greater attention should be directed to the diagnosis and prevention of this condition. (70;71).

C. The principles of regenerative medicine in relation to the uterus may provide a basis for improving the decidualization necessary for embryonic implantation and therapy for recurrent pregnancy loss(62)(72).

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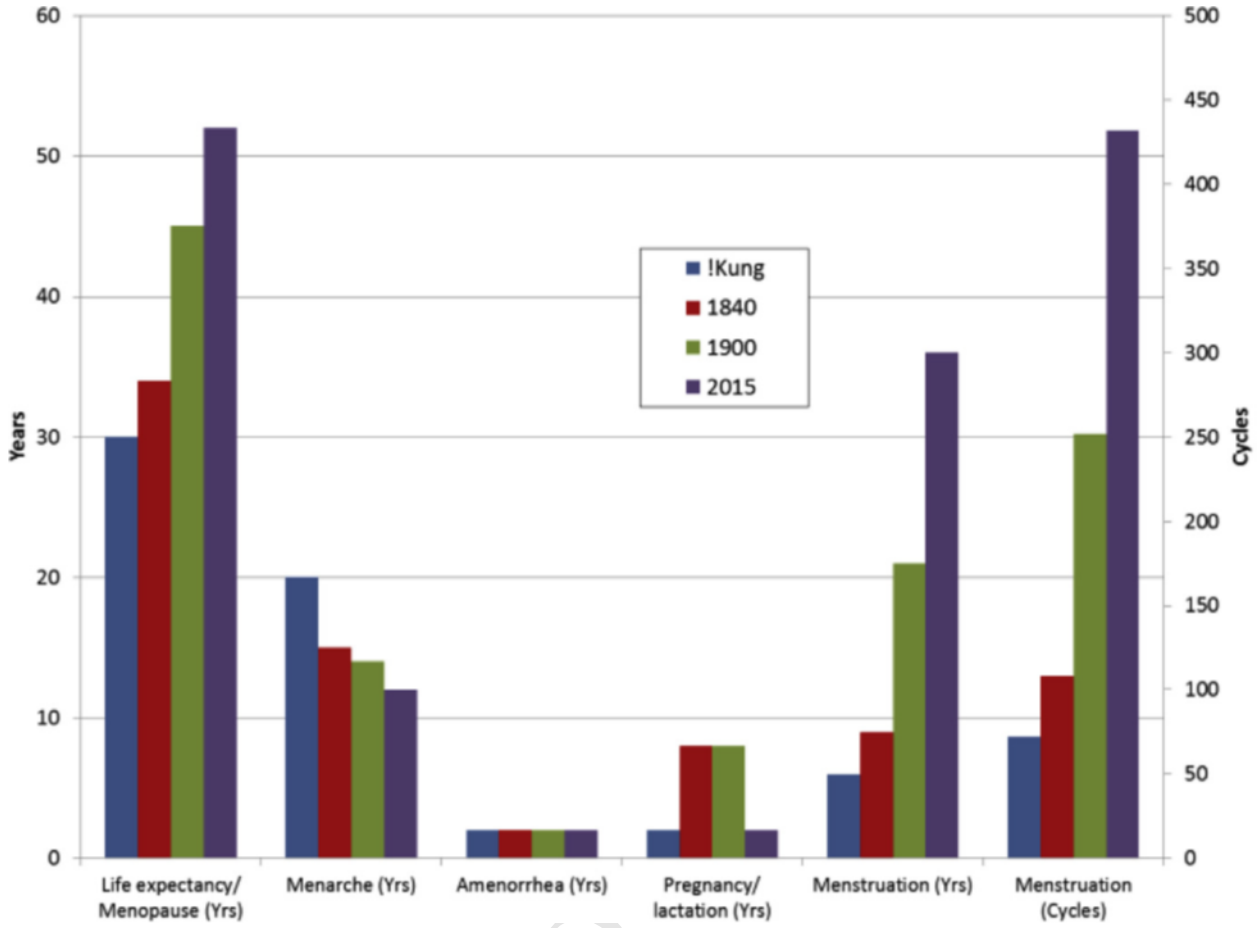
Figure. Estimates of lifetime menstrual frequency.Jarrell & Arendt-Nielsen. Evolutionary Considerations of Chronic Pelvic Pain. Am J Obstet Gynecol 2016.


60
50
40
30
20
10
0
Years
500
450
400
350
300
250
200
150
100
50
0
Cycles
!Kung
1840
1900
2015
Life expectancy/ Menopause (Yrs)
Menarche (Yrs)
Amenorrhea (Yrs)
Pregnancy/ lactation (Yrs)
Menstruation (Yrs)
Menstruation (Cycles)

Highlights

- Evolution is being recognized as an important vehicle to understand menstruation
- The Evolutionary development of spontaneous decidualization appears to provide the basis for our current understanding of menstruation and may be the key to management of a variety of reproductive disorders