International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Review Article

Menstrual Cycle and Hemostatic Modifications: A Review

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Received: 15/05/2016 *Revised: 27/05/2016* *Accepted: 31/05/2016*

ABSTRACT

Physiologically, menstrual cycle is a complex process involving cell replication and growth under the influence of hormones, growth factors, neurotransmitters, regulatory molecules and hemostatic mechanisms. During this process, there is platelet aggregate formation, coagulation cascade activation, synthesis and activation of various procoagulant molecules and fibrin clot formation, aiming to control bleeding. Subsequently, activation of the fibrinolytic system is observed for remodeling the tissue.

This review considers articles that evaluated hemostatic and hematological alterations during menstrual cycle in order to better understand this physiological process.

There is evidence that menstrual cycle is associated with procoagulant (platelet aggregation, coagulation factors and fibrinolysis inhibitors) and anticoagulant (fibrinolysis system activators) changes. However, data are still conflicting for each phase. Current literature confirms that the most important modifications in hemostasis occur due to the fundamental role of progesterone, although follicular and bleeding phases also take place with a balance between the pro and anticoagulant factors. Additional randomized and well controlled clinical studies are required to clarify the hemostatic changes and its consequences in women health.

Keywords: Menstrual cycle; hemostatic modifications; menstruation physiology.

INTRODUCTION

Menstrual cycle is a complex physiological process involving cell replication and growth under the influence of hormones, growth factors, neurotransmitters, regulatory molecules, immunological and hemostatic mechanisms. [1] Menstrual cycle depends on the balance between the hypothalamic-pituitary-ovarian axis and requires the secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus in a critical range of amplitude and frequency. [2]

During menstruation, there is platelet aggregate formation, activation of the coagulation cascade, several procoagulant molecules and fibrin clot, aiming to control bleeding. [1] Subsequently, the activation of the fibrinolytic system is observed due to elevated levels of endometrium-derived plasmin and plasminogen activators for tissue remodeling. [3,4]

In the luteal phase, progesterone induces an increase of angiopoietin-1 expression, which is able to stabilize newly formed blood vessels. It also stimulates the synthesis of tissue factor and other coagulant activator molecules, giving to this phase procoagulant properties, which would

reduce the chance of bleeding in case of implantation of the blastocyst. [5,6] In the follicular phase, the procoagulant components would be less activated. [7,8]

Hemostatic changes during menstrual cycle have been subject to studies on thrombosis development. Literature describes, for example, the evaluated biochemical, hemostatic and fibrinolytic parameters throughout the menstrual cycle, such as coronary heart disease risk factors in women who are premenopausal. There is variability in the levels of progesterone and estradiol during the cycle, as well as intra and inter-individual differences in PAI-1 and D-Di in the follicular, luteal phases [9] and menstruation. [10,11] However, hemostatic changes and their consequences in women health are still conflicting.

This review considers articles that evaluated hematological and hemostatic alterations during menstrual cycle in order to better understand this physiological process.

Hematological and hemostatic alterations during the menstrual cycle

Menstruation

During menstruation, from30 to 40mL of blood are eliminated along four to six days, although it is difficult to precisely quantify it. [2,12] In the endometrium, stimulated and developed by the secretion of ovarian steroids, there are blood stasis, vasodilation and diapedesis of leukocytes throughout the tissue. The diapedesis of red blood cells forms microthrombi in the stroma and endometrial glands atrophy. [2]

Intracellularly, progesterone level reduces, destabilizing the lysosomal membrane of stromal cells and inducing release of prostaglandins and fibrinolytic enzymes. These enzymes determine the breakdown of mesh reticular fibers that hold the endometrial stroma cells. With increasing circulatory difficulty, there may occur tissue ischemia and anoxia of the cells, release of metabolic mediators, necrosis, breakdown and consequent shedding of the endometrium, resulting in bleeding. [3,13]

At the tissue level, the reduction in endometrial thickness determines the folding and collapsing of spiral arterioles and satellite venues. Arterioles which were compressed and lengthened, due to the fall of steroids levels become shorter and get closer to the endometrial surface. [12] The contraction of smooth muscle cells of the media tunica and the degeneration of spiral arterioles aggravate vasoconstriction. Endometrium is dehydrated, allowing glands and arterioles to get closer to each other, leading to slower local blood flow. [13]

Menstruation comes from premenstrual bruises and diapedesis of red blood cells. [14] The process does not occur in the entire endometrial surface region, being intermittent and predominant in places where the accumulation of stromal cells is increased, and the dissolution of crosslinked fibers is more intense. [13] Blood stasis, ischemia, and leukocyte infiltration probably damage the circulation, leading to an accumulation of endometrial cells degraded products. These products would be responsible for the onset of the menstrual process, which would not take place if the lymphatic system was more effective. [13]

There are evidences that the endothelium of endometrial blood vessels produces a wide variety of vasoactive substances with paracrine and angiogenic action. These substances are essential to maintain the balance between inhibition and stimulation of angiogenesis, vasoconstriction and vasodilatation, besides antithrombotic mechanisms. [3]

Menstrual blood clots itself in the uterine cavity are dissolved by the action of endometrial fibrinolysis. These materials contain fibrin, fibrin degradation products (FDP), α2-antiplasmin inactive, plasminogen activators and active plasmin. [12,13] There are also lysed stromal cells, inflammatory exudate, blood cells, reticular fibers, blood vessels, glands and proteolytic enzymes. [3,13]

In the end of menstrual period, hemostasis is ultimately guaranteed by the constriction of spiral arterioles in the basal

layer and especially by the radial arterioles in the myometrium surface. [15] Bleeding interruption is accomplished by local hemostatic mechanisms, including platelet aggregation, fibrin deposition and thrombus formation. The tissue factor and thrombin play a key role in controlling the menstruation through the activation of pro-coagulation molecules (coagulation factors, plasminogen activator inhibitors -PAI and fibrinolysis inhibitors activated by thrombin). On the other hand, this mechanism is regulated by plasminogen activators and by plasmin on fibrinolysis, which limits clot formation within the uterine cavity. [1] The tissue is regenerated, the new capillaries grow in order to ensure the normal circulation and promote tissue metabolism. [16]

Hemostatic alterations during the menstrual cycle

Role of platelets in the menstrual cycle

Menstruation is described as a physiological hemostatic process that leads to formation of a platelet aggregate and subsequently fibrin clot. Activation of the fibrinolytic system occurs afterwards due to elevated levels of endometrium-derived plasmin and plasminogen activators. [4] Furthermore, it has been speculated that endometrial stromal cells synthesize the platelet derived growth factor, which acts in an autocrine and paracrine manner, complementing the action of epidermal growth factor. [12]

Platelet function is regulated itself through arachidonic acid (AA) metabolites (mainly thromboxane-TXA2) release, inducing platelet aggregation. Vascular endothelium, in turn, converts AA into prostacyclin (PGI2), a vasodilator which inhibits and reverses platelets aggregation. [14] Blood loss is further controlled by thrombin that determines fibrin clot formation. [17]

Literature reported fluctuations in the platelets count during the menstrual cycle, with an increase in this count in the ovulatory phase [18] and a reduction in menstruation [19,20] compared to both proliferative and secretory phases. [20]

Platelet function was evaluated in other moments of the menstrual cycle by Feuring et al [7] and Roell et al, [21] who found an increase in platelet function during the luteal phase. These researchers also observed the increase of procoagulant von Willebrand factor (vWF) levels, in response to an increase in progesterone during this phase.

These data differ from a previous study developed by Yamazaki et al, [22] who observed exacerbated platelet aggregation induced by adenosine diphosphate (ADP) and adrenaline during the follicular phase. Similarly, Melamed et al [23] found a reduction in platelet aggregation, regardless to the agonist used for luteal phase. Bolis et al, [24] on the other hand, reported that the levels of this biomarker were reduced during the peri-ovulatory period. Contradictorily, Repina et al, [25] in a longitudinal study, did not observe variation in platelet aggregation parameters during the follicular and luteal phases.

To test the hypothesis that platelet-leukocyte aggregates (PLA) play a significant role in blood coagulation and inflammatory processes during the menstrual cycle, contributing to increased susceptibility of inflammatory diseases and thromboembolic events in a specific cycle phase, Rosin et al [26] evaluated PLA formation by flow cytometry in 20 healthy women during their menstrual cycle. The numbers of platelet sand PLA were higher in ovulation when compared to the other phases of the menstrual cycle. Similarly, P-selectin expression reached the peak on 14th day of the cycle, suggesting strong estrogen effects on platelet-leukocyte interactions and a variation in platelet function during specific phases of the normal menstrual cycle.

Robb et al [27] investigated the influence of the menstrual cycle in platelet activation by evaluating the concentration of soluble P-selectin, cluster differentiation (CD) 40 ligand and the formation of

platelet-monocyte aggregates (PMA). However, there was no change on these markers or significant correlation between them and the estrogen or progesterone concentrations.

Toth et al [6] studied the platelet activation variability throughout menstrual cycle by determining the platelet count and endothelial cells microparticles (MP) in peripheral blood by flow cytometry in healthy women. They observed that during the luteal phase, women had a higher number of platelet MP, and expression of annexin V, CD61 and CD63, as well as E-selectin expression in endothelial MP. Researchers concluded that these parameters may be additional risk factors, contributing to a procoagulant state in young women.

Influence of other coagulation components in the menstrual cycle

The influence of hormones in the menstrual cycle, coagulation and fibrinolysis is unquestionable. During the follicular phase, estrogen, besides inducing endometrial proliferation, stimulates angiogenesis through the activation of human endometrial stromal cells (HESC), which express the vascular endothelial growth factor (VEGF) and endometrium endothelial cells, which express angiopoietin-2 (Ang-2). [5]

In the luteal phase, progesterone induces decidualization around blood vessels and increases the expression of angiopoietin-1 (Ang-1) in HESC, which is able to stabilize newly formed blood vessels. Progesterone also stimulates the synthesis of tissue factor (TF) and PAI-1, giving the luteal phase significant pro-coagulant properties, which reduce the chance of bleeding in case of blastocyst implantation. If this does not occur, reduction in progesterone levels creates a pro-hemorrhagic environment around the blood vessels that promotes menstruation. [5]

Chairet et al [28] reached similar conclusions regarding the role of progesterone during the luteal phase of the menstrual cycle. When they evaluated the potential of thrombin generation and other hemostatic parameters in 102 women during the follicular and luteal phases of the menstrual cycle, they found that the thrombin levels in the luteal phase are higher than in the follicular phase.

However, the developments and hemostatic changes are still conflicting. There are reports that the factor VIII (FVIII), fibrinogen and antithrombin (AT) levels may remain unchanged, [29] be reduced [18] or be increased during the luteal phase. [7] The same occurs with the Vwf, [30-32] urokinase type plasminogen activator (u-PA) and PAI-1 [33] levels. A Ara et al observed that prothrombin time and the clotting time values during menstrual phase were significantly lower when compared to both proliferative and secretory phases. [20] Studies regarding fibrinogen levels are also inconclusive. Some researchers have obtained reduced levels of this protein in the follicular phase, [7,8] and others during the luteal phase. [34,35] There are even studies that did not verify changes throughout the menstrual cycle. [21,25]

A longitudinal study including 39 women showed a decrease in the concentration of fibrinogen and vWF during the first three days of menstruation period, with a peak in the luteal phase. [30] In contrast, Onundarson et al [31] in a cross-sectional study found no differences in these parameters. This study did not find any association between levels of estradiol, progesterone or testosterone neither with vWF nor FVIII. However, the results obtained by Miller et al [32] observed reduced vWF levels during the first four days of the menstrual cycle, and the highest levels were observed in the 9th and 10thdays of the cycle.

Cederblad et al [18] investigated the variation of the number and aggregation of platelets, coagulation factors and fibrinolysis during the menstrual cycle in 30 healthy women. Results indicated that fibrinogen levels were lower during menstruation compared to the luteal phase. A reduction in thrombin, factor VII, factor X levels and platelet aggregation was

observed during the menstrual period. The fibrinolysis was more active in the luteal phase and menstruation compared to the follicular phase. Similar results were obtained by Larsen et al, [36] although they observed no changes in the fibrinolysis parameters.

Differently from Cederblad et al, [18] Dapper & Didia [37] obtained the highest fibrinogen levels during menstruation, followed by the ovulatory, luteal phases and reaching a minimum during follicular phase. In contrast, Siegbahn et al [29] observed no changes in fibrinogen and AT levels, platelets count or activation during none of the studied periods. Fibrinolytic parameters presented a lower concentration in the luteal phase compared to the others. [29]

Fernandez-Shaw et al [38] demonstrated that during ovulation and peri-ovulatory stage, there is an activation of the plasminogen-plasmin system. During menstruation, such system appears to play a disintegration of the endometrium, conferring in coagulability to the menstrual blood. They suggested that during the ovulatory phase, the same system is likely to contribute to the removal of fibrin fragments of the walls of the uterine cavity, facilitating spermatozoids migration. This process would be coordinated by sexual steroids and antiplasminic local inhibitors.

The action of the plasminogen activators in the uterine luminal fluid and in the endometrium is intensified during the proliferative phase, reaching a peak in the middle day of the cycle and decreasing during the luteal phase, increasing again in the beginning of the next phase. [13] The plasminogen activators, which convert plasminogen in plasmin, are also found in the late luteal phase and menstruation, being released by the vascular endothelium of the degenerate endometrium. [3] PAI-1 and PAI-2 inhibitors are also present in the endometrium and can act in the tissue remodeling during the follicular phase and menstruation. [13]

It is known that macrophages and leukocytes are usually able to synthesize plasminogen activators. Besides, there is a physiological leukocytosis during the premenstrual phase. [39] Bulmer et al [40] reported that endometrial lymphocytes are numerically increased in late luteal phase and, in consequence, tissue type plasminogen activator (t-PA) and PAI-1 levels would also be higher in this period.

A study performed by Astedt & Casslen [41] indicated that estrogen can increase t-PA levels in the endometrium and in the luminal fluid. Schatz et al [42] obtained similar results when evaluating the endometrium during menstruation. However, it was demonstrated that progesterone stimulates the synthesis of PAI-1 and PAI-2 in vitro. [42-44]

Koh et al [8] investigated coagulation and fibrinolysis biomarkers, including platelet function in 30 women throughout the menstrual cycle and they found no difference in these markers during the menstrual cycle. However, there was an associated reduced fibrinolytic stat at mid-cycle.

Maki et al [45] and Basu [46] reported that menstruation is accompanied by increased FDP levels. However, Cole & Clarkson [47] when evaluating serum levels of FDP in 331 women after menstruation, found no significant correlation between blood loss and FDP levels.

In relation to D-dimer (D-Di) levels, there can also be a variation during the menstrual cycle, with reduced values in the follicular [8] and luteal phases, [9] being even lower in the mid-cycle. [8] For theα2-antiplasmin, reduced levels were observed during the follicular phase. [48]

Menstrual cycle and myocardial acute infarction

Hemostatic changes during the menstrual cycle have been the subject of studies on the development of thrombosis. Giardina et al, [9] in a prospective study, evaluated biochemical, hemostatic and fibrinolytic parameters throughout the menstrual cycle as risk factors for coronary heart diseases in premenopausal women. They found variability in progesterone and

estradiol levels during the cycle, as well as intra and inter-individual differences in PAI-1 and D-Di in the follicular and luteal phases. Preliminary studies by Hamelin et al [10] and Mayer [11] demonstrated that most myocardial acute infarction (MAI) took place during menstruation.

Subsequently, a cohort study conducted with 669 women hospitalized due to MAI, whose gynecological history was also considered, showed a correlation between heart attack and menstruation. [49] These researchers suggested that, for young women, in the absence of other risk factors, the early follicular phase (menstruation) may be the most susceptible moment for the occurrence of a cardiovascular event.

It is known that PAI-1, the most important physiological regulator of the plasmin generation, inhibits t-PA and u-PA. [50] A reduced fibrinolytic activity, evidenced by the increase in PAI-1 and t-PA, is an important parameter for the severity of thrombosis and atherosclerosis. [51] Giardina et al [9] found reduced levels of PAI-1, t-PA and fibrinogen in women who are premenopausal and suggested that this group is less susceptible to coronary heart diseases. Furthermore, they reported a correlation between total cholesterol, low density lipoprotein cholesterol (LDL) and PAI-1, as well as between total cholesterol and fibrinogen. They concluded that these characterizing parameters contribute to a better understanding of the hormone-homeostasis physiological balance and can be an early marker for coronary events in young women. This study raised the following question: is the cyclical variation in hemostatic parameters such as reduced levels of PAI-1 the cause of heart protection observed in these women? In contrast, Chung et al [52] found reduced levels of PAI-1 during the follicular phase. Dorr et al, [33] Ricci et al [35] and Chung et al [52] observed low t-PA levels for post-ovulatory, ovulatory and luteal phases.

Other alterations during the menstrual cycle

Since the menstrual cycle induces several changes, both in the reproductive organs and systemic, it has been speculated that menstrual blood loss can modify blood cells count. [18,30,53] Makinoda et al [53] evaluated complete blood count (CBC), erythropoietin, stimulating factor granulocytic colony (G-CSF), cytokines and sexual hormones levels during the menstrual cycle in healthy women. They did not observe any changes in CBC, overall leukocytes, granulocytes, platelets, levels of erythropoietin and interleukins. However, G-CSF levels increased during ovulation when compared to other phases of the cycle. They concluded that the menstrual blood loss does not change CBC and G-CSF may play an important role in the mechanisms of ovulation.

It is assumed that women have higher neutrophil counts than men, due to the action of estrogen and progesterone on leukocytes. Accordingly, there are studies that suggest that ovulation has some resemblance to inflammatory processes, since the total leukocyte count may change during this step. [54,55]

Bain & England [56] revealed a variation in total leukocyte count (especially neutrophils) over the cycle, associated with the change of estrogen and progesterone levels. They reported a peak in neutrophils count in the premenstrual phase, followed by neutropenia during menstruation and another peak after this moment. No changes were observed in lymphocytes count; and eosinophil count showed a cyclic variation inversely proportional to the number of neutrophils and monocytes. Platelets count showed slight modifications, being observed a greater number during and after menstruation.

CONCLUSION

Current evidence indicates that menstrual cycle takes place with important hemostatic modifications, starting by hormonal changes and participation of growth factors, neurotransmitters and regulatory molecules. It suggests that in the

luteal phase of the menstrual cycle there is a greater participation of procoagulant components (platelet aggregation, coagulation factors and fibrinolysis inhibitors) than in other phases of menstrual cycle. However, there are reports in the literature that confirm the importance of follicular and menstrual phases in the hemostasis changes. Definitive conclusions in this regard and its consequences in women health are still conflicting, confirming the need of further investigation.

ACKNOWLEDGMENT

The authors thank FAPEMIG, CAPES and CNPq/Brazil. LMSD is grateful for CNPq Research Fellowship (PQ).

Conflict of interest

The authors declare that they have no conflicts of interest regarding this article.

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How to cite this article: Freitas LG, Gomi de Loures CDM, FerreiraSilva MV et al. Menstrual cycle and hemostatic modifications: a review. Int J Health Sci Res. 2016; 6(6):320-328.

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