American Journal of Medicine and Medical Sciences 2025, 15(8): 2694-2698
DOI: 10.5923/j.ajmms.20251508.58

Morphofunctional Disturbances in the Fetoplacental Complex in Anemia Associated with Heavy Menstrual Bleeding

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Abstract Introduction. Iron deficiency anemia (IDA) is an important pathology affecting the reproductive health of women, especially during pregnancy. Increased iron requirements during pregnancy, along with heavy menstruation (HMB), are considered a leading risk factor for IDA, which, in turn, contributes to the formation of fetoplacental insufficiency and intrauterine hypoxia. Despite a large number of studies, morphological changes in the mother-placenta-fetus system with a combination of HMB and IDA have not been sufficiently studied, especially at the ultrastructural level. Materials and methods. A prospective study was conducted in medical institutions of the city of Samarkand with the participation of 400 pregnant women divided into two groups. The main group (n=300) consisted of patients with verified IDA and a history of heavy menstruation; the control group (n=100) consisted of conditionally healthy pregnant women without these risk factors. Clinical, laboratory, and instrumental diagnostic methods were used, as well as morphological examination of the placental complex, including light and scanning electron microscopy. Results. In women with IDA, pronounced morphological changes in the umbilical cord were revealed: ischemia of blood vessels, destruction of the endothelium, the development of sclerosis and atrophy, especially in grade III anemia. Electron microscopy showed a violation of the microrelief of endotheliocytes and destruction of cell contacts. Alternative changes in collagen fibers and shortening of the length of the umbilical cord were also noted. A significant relationship was established between the severity of vascular disorders and the severity of anemia. In an environmentally unfavorable environment, the identified changes were more pronounced. Morphological disorders in the umbilical cord in IDA indicate a violation of oxygen and nutrient transport to the fetus, which increases the risk of hypoxia, IUGR, and premature birth.

Keywords Anemia, Iron deficiency anemia, Pregnancy, Heavy menstruation, Abnormal uterine bleeding, FIGO, Placental insufficiency, Iron deficiency, Maternal and fetal health

1. Introduction

Anemia is one of the most significant global health problems, affecting about a quarter of the population, especially women (including 51% of pregnant women) and young children (43%) [2,4,8]. In most cases (50–75%), anemia develops against the background of iron deficiency (ID), which is recognized as the most common micronutrient disorder and is among the main factors increasing the number of years lived with disability (YLD), according to the 2016 Global Burden of Disease study [13]. The prevalence of iron deficiency anemia (IDA) among women who menstruate varies from 30 to 60% depending on the region of residence and is most common in low- and middle-income countries [4,6]. According to various studies, abnormal uterine bleeding (AUB) in 25-50% of cases causes IDA [1,4]. The FIGO Committee on Menstrual Disorders (Menstrual Disorders Committee – MDC) continues to work on standardizing the description of the characteristics of the menstrual cycle and symptoms of abnormal uterine bleeding (FIGO 1 system), including heavy menstrual bleeding (HMB), as well as the causes of these disorders, both related and unrelated to organic pathology of the endometrium and myometrium (FIGO 2 system, PALM-COEIN) [4,10]. Anemia, especially iron deficiency anemia (IDA), occupies a central place among pathological conditions that negatively affect the functioning of the mother-placenta-fetus system. According to the World Health Organization (WHO), IDA affects more than 40% of pregnant women worldwide, especially in low- and middle-income countries [3]. During pregnancy, the need for iron increases almost threefold, which makes the woman's body vulnerable to the development of deficient conditions even with initially normal hemoglobin levels. The physiological role of iron goes beyond hematopoiesis: it is necessary to ensure cellular respiration, myelination processes of the fetal nervous system, the functioning of enzyme systems, and adequate placental blood flow. In IDA,

Received: Aug. 2, 2025; Accepted: Aug. 23, 2025; Published: Aug. 25, 2025
Published online at http://journal.sapub.org/ajmms

there are violations of angiogenesis, a decrease in the activity of iron-dependent enzymes, and the development of hypoxia, which together leads to a deterioration in the structure and functions of the placenta [7,14]. Numerous studies confirm that women with anemia are more likely to develop placental insufficiency, accompanied by morphological changes in the form of reduction of the vascular network of the villi, fibrinoid deposits, placental infarctions, and a decrease in the thickness of the trophoblastic layer [11,12]. These disorders, in turn, contribute to intrauterine growth retardation, low birth weight, hypoxia, and even perinatal mortality. Of particular concern is the effect of anemia on the developing nervous system of the fetus. It has been proven that iron plays a key role in the maturation of neurons and the synthesis of neurotransmitters. Iron deficiency in the antenatal period is associated with an increased risk of developing autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), as well as a decrease in cognitive functions later on [9]. According to the results of a large cohort Swedish study, anemia detected before the 30th week of pregnancy is associated with an increased risk of neuropsychiatric developmental disorders: the risk of ASD increased by 1.44 times, ADHD - by 1.37 times, and the risk of a decrease in intellectual abilities - by 2.2 times [14]. The authors emphasize that even latent iron deficiency, in which the hemoglobin level remains within the normal range, can have a negative impact on the mother-placenta-fetus system. Thus, anemia not only reduces the oxygenation potential of the placenta, but also provokes a cascade of morphological and functional disorders in the fetoplacental system, which explains the high frequency of obstetric and perinatal complications in this group of patients. Despite the large number of clinical and epidemiological studies devoted to the diagnosis and treatment of iron deficiency anemia (IDA), the morphological aspects of its effect on the organs of the reproductive system remain insufficiently studied. Especially little attention in the scientific literature is paid to morphological changes in the mother-placenta-fetus system in women with chronic heavy menstrual bleeding (HMB) as one of the leading factors in the development of IDA. Modern research in the field of the fetoplacental complex is mainly focused on studying hypoxia, placental insufficiency, and general pathological conditions (for example, preeclampsia or fetal growth retardation) [5,14]. However, structural and ultrastructural changes in the placenta, umbilical cord, and endometrium with a combination of HMB and IDA have so far been described only in isolated publications, mainly in the form of casuistic observations. There is especially little data on the results of scanning and transmission electron microscopy, which makes it possible to identify subtle subcellular changes indicating a violation of metabolic and vascular processes in the placenta. Thus, the morphological aspect of HMB and IDA remains a "bottleneck" in the interdisciplinary scientific agenda, despite its high importance for understanding the mechanisms of reproductive losses and pregnancy complications.

2. Materials and Methods

A prospective study was conducted at the medical facilities of city polyclinics No. 2 and 7 of Samarkand and city maternity hospital No. 2 with the participation of 400 patients stratified into two groups. The main goal of this stage was to determine the effect of heavy menstrual bleeding (HMB) and iron deficiency anemia (IDA) on the mother-placenta-fetus system.

The main group (300 patients) included women with a history of heavy menstrual bleeding and laboratory-confirmed IDA (Hb <110 g/l, ferritin <30 ng/ml). The examination complex included routine methods of clinical, laboratory examination, and instrumental methods of research within the framework of existing clinical protocols in obstetrics, approved by the Ministry of Health of the Republic of Uzbekistan, as well as instrumental studies of the state of the mother-placenta-fetus system. The control group (100 patients) included conditionally healthy pregnant women without HMB and IDA.

We used the following research methods: macroscopic analysis, light optical research, scanning electron microscopy, and statistical analysis methods.

3. Results and Discussion

When studying the umbilical cord, we focused on the circulatory system. It is represented by an arterial section with two arteries and venous fragments with one vein. The arteries differed from the veins by a more developed elastic membrane and an increased content of elastic fibers. In the case of anemia in the mother, ischemia of the umbilical cord vessels was observed compared to those with uncomplicated pregnancy, especially in grade III (Fig. 1, 2). Endothelial cells of the arteries are tightly connected to each other by means of complex junctions. These cells, through thin processes that penetrate the basal membrane, were connected to the underlying leiomyocytes, forming a single endotheliomuscular system. Endothelial cells of arteries and veins had a greater range in size - from 0.3 to 0.6 μm. In groups with pathology, there was a disruption in the structure of the junctions between them, as well as necrotic fragments of the endothelium. The volume of some of the vessel walls was increased due to the development of sclerotic processes, especially in grade III (Fig. 1, 2). Partial or complete atrophy of endotheliocytes is characteristic of these areas. Disruption of the microrelief of the endothelium was clearly visible when using scanning electron microscopy (Fig. 2). There was a change in the structure of the folds, which are outgrowths of the plasmolemma. In some areas they were close to each other. In others, on the contrary, and this was observed more often, their rarefaction was revealed, up to complete absence. Alterative changes are more characteristic of these fragments. The connective tissue of the umbilical cord consists of thin myofibrils with a small admixture of colleague fibers (Fig. 1, 2). Fibroblasts with long processes are randomly located among them. Stromal canals were found between fibrous structures. Their walls were reinforced with processes of fibrocytes. There were no significant changes in Wharton's jelly. The size of erythrocytes was 5.60 ± 0.60 μm. The shape of some of them was changed in favor of microcytes, deigmacytes, spherocytes, and individual poikilocytes. Clinical data of women with anemia indicate a higher risk of fetoplacental insufficiency, premature birth, and intrauterine growth retardation, which confirms the importance of the identified morphological changes in the umbilical cord. Given that paracentral and especially peripheral attachment of the umbilical cord may be a marker of impaired placental circulation, such features deserve special attention during ultrasound monitoring of pregnancies complicated by anemia. Comparison of morphological parameters with the control group showed that in women living in ecologically unfavorable areas, the frequency of severe anemia is higher, and the identified changes in the vessels of the umbilical cord are more pronounced. This suggests that environmental factors, including micronutrient deficiencies and chronic hypoxia, exacerbate vascular disorders caused by anemia. Disruptions in the architectonics of the vascular wall, identified by electron microscopy, may be a consequence of both systemic hypoxia and iron deficiency, which are necessary to maintain normal vascular tone and cellular regeneration. Additionally, it is worth noting that shortening the length and thickness of the umbilical cord, although it may depend on the method of amputation, still correlates with the severity of anemia and impaired metabolic processes in the fetus. The lower the hemoglobin content in the mother, the higher the frequency of identified alterative and destructive changes in the endothelium of blood vessels, which reflects the severity of fetoplacental insufficiency. Thus, anemia, especially grade III, has a significant impact on the vascular system of the umbilical cord, manifested in the form of ischemia, sclerotic changes, disruption of the architectonics of the endothelium, and collagen structures. These changes represent the morphological basis of impaired oxygen and nutrient transport to the fetus, contributing to the development of hypoxia and intrauterine growth retardation.

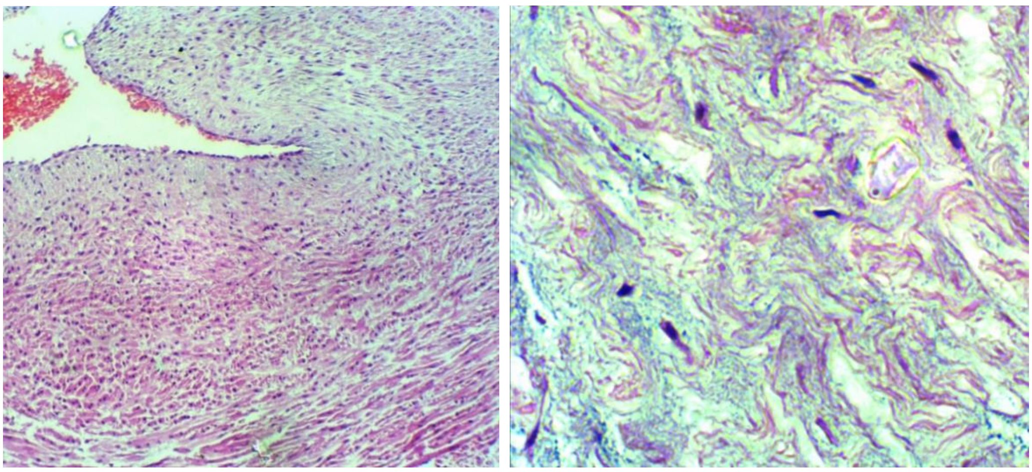

Figure 1. Fragments of the umbilical cord in grade III anemia. Vessels are ischemic with a small number of erythrocytes inside (A). Stasis of erythrocytes along the surface edge of the endothelium. Disruption of the structure of endotheliocytes with smoothing of the surface and disruption of the structure of the folds. Disruptions in the structure of collagen fibers (B). Fig. B (x400) fragment of Fig. A (x100). Light microscopy. Hematoxylin and eosin staining

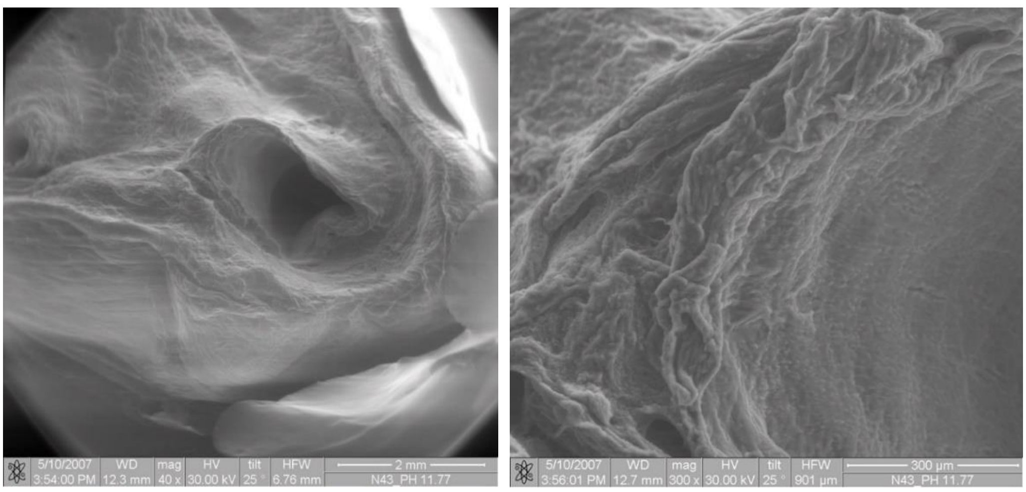

Figure 2. Fragment of the umbilical cord in grade III anemia. Vessels are ischemic. The structure of endotheliocytes is disrupted with smoothing of the surface and disruption of the structure of the folds. Alternative changes. Cells differ sharply in shape and size SEM. Fig. B (x300) fragment of Fig. A (x40)

The changes we identified in the umbilical cord indicate a pathology of the circulatory system, mainly in the form of ischemia.

The placentas of women in the control group had a rounded shape (54%) or an irregular oval shape (46%). Their dimensions were: 16.5 ±0.5 x 14.5 ±0.3 x 2.5 ±0.2 cm, and the mass: 430.50 ±30.0 g. On the smooth fetal surface of the placenta, a main type of vascular distribution was equally revealed, which passed as part of the chorionic plate. The maternal part consisted of closely spaced 12-16 cotyledons, or isolated cotyledons. Macroscopically, on linear, parallel sections through the entire thickness of the placenta, generally thicker cotyledons were found in the center, and, conversely, flattened cotyledons closer to the edge of the placenta. Approximately the same feature was found in relation to the plethora of placental tissue: the cotyledons in the center were more plethoric than at the edges.

The fetal part of the placenta is represented by a section of the chorion – the true chorion, consisting of the chorionic plate, from which branching tertiary villi extend (Fig. 3).

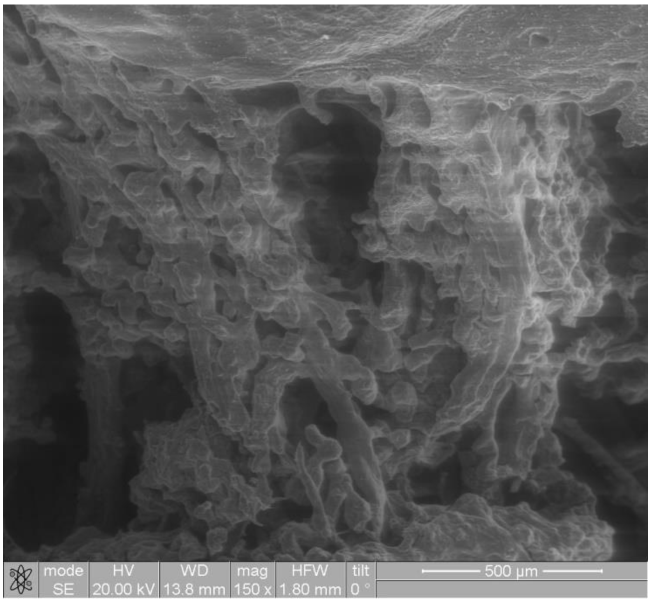

Figure 3. Placenta of a woman in the control group

The fetal part of the placenta is represented by a section of the true chorion, from which branching villi extend (SEM (x150)).

The chorionic plate is a three-layered membrane. Its base was connective tissue, in which large vessels of the umbilical cord branched. On the outer side, facing the cavity of the amniotic sac, it is covered with amnion and lined with amniotic epithelium, and on the inner side, it is lined with trophoblast, whose cells are partially absent and replaced by fibrinoid (Langhans' stria). Fibrinoid separates the chorionic plate and the intervillous space (IVS).

In the chorionic plate, the umbilical vessels penetrating from the umbilical cord branch profusely, and their branches enter the base of the stem villi. Anastomoses between fetal vessels of adjacent stem villi are absent. Its connective tissue is thinned in the terminal region.

When studying the histological characteristics of the maternal and fetal surfaces, no pathological changes were found. Moderately pronounced plethora was observed in some vessels of the maternal surface. Some placentas showed some expansion of the fibrinoid layers.

The conducted study of pathomorphological changes in the uterus-umbilical cord-placenta system in anemia allows us to draw several key conclusions about the mechanisms of development of this pathology. Changes in the structure of the umbilical cord are particularly pronounced, where the predominance of vascular ischemia is observed, especially in the later stages of anemia (grade III). There is a violation of the structure of endotheliocytes, the development of sclerosis and atrophy, which is confirmed by the results of electron microscopy. These changes affect the functionality of the umbilical cord vessels and can lead to impaired blood circulation, which poses a potential threat to the normal course of pregnancy and fetal development. In particular, studies have shown a violation of the microrelief of the endothelium, deformation of cells, and disruption of their connections. These pathologies indicate possible disturbances in metabolic processes that may affect the delivery of oxygen and nutrients to the fetus. The development of ischemia and sclerotic processes in the umbilical cord, as shown in this work, is critical for diagnosis and early intervention in complicated forms of anemia in pregnant women.

In the morphological study of placentas from women with ecological norms, we predominantly observed compensatory processes aimed at maintaining fetal viability. This includes, first of all, moderately pronounced plethora. In addition, there is an increase in the exchange surface between the maternal and fetal bloodstream (expansion of the capillary surface, the presence of pinocytotic vesicles, the formation of invaginations and outgrowths on the surface of endotheliocytes), as well as changes aimed at improving exchange in the placenta in the form of heterophagy and activation of endotheliocytes.

However, pathological changes were formed in parallel with adaptive variants, which primarily manifests in sclerosis, as well as in fibrinoid necrosis. It should be noted that the destructive processes are still insignificant and, apparently, cannot fully affect the condition of the fetus.

The study of the morphological features of the placentas of women with ecological norms showed that in most cases (54%) the placentas have a rounded shape, while 46% of the observed placentas have an irregular oval shape. The average size of the placentas is 16.5 ±0.5 cm by 14.5 ±0.3 cm with a thickness of 2.5 ± 0.2 cm, and the mass of the placenta averages 430.50 ±30.0 g.

The maternal surface of the placenta is characterized by a uniform distribution of vessels, and the fetal part is represented by the chorion with branching villi, forming tertiary villi that actively participate in metabolic processes. An important observation is the presence of moderately pronounced plethora in the vascular network, as well as changes in the structure of the fibrinoid layer, which may be the result of adaptive reactions of the body to environmental conditions.

4. Conclusions

The made based on pathomorphological changes, emphasize the importance of early diagnosis and correction of the condition of mothers with anemia, in order to minimize health risks for both the mother and the child.

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