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REVIEW ARTICLE **OPEN ACCESS**

Environmental Impact on Pathophysiology of Endometrial Angiogenesis in Patients with Dysfunctional Uterine Bleeding

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ABSTRACT

Dysfunctional Uterine Bleeding (DUB) is defined as excessive blood loss during menstruation which results in interfering with women's physical health, social interaction, emotional status and reducing the quality of life. It can have an unknown etiology or in combination with other systemic disease. It is also consider as an excessive bleeding of uterus without any apparent pathological reason and usually one of the diagnostic criteria is when the monthly menstrual blood loss is more than 80 ml. Numerous exogenous factor such as exposure to high concentration of environmental copper effects the pattern and integrity of newly formed blood in endometrium. The synthesis of blood vessel occurs by formation and differentiation of microvessel plexus as result of stimulation by variety of angiogenic factorsform endothelial cells. Numerous angiogenic and anti-angiogenic factors are known to contribute for blood vessels formation in endometrium. The aim of this review to elaborate the environmental and pathological causes of abnormal angiogenesis in human endometrium.

Keywords: *Angiogenesis, Dysfunctional Uterine Bleeding (DUB), vascular endothelial growth factor (VEGF), Copper.*

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INTRODUCTION

Dysfunctional uterine bleeding is known to affect 11 to 13 percent of women in their reproductive age and the severity and prevalence increases with age, as they often develop abnormal menstruation after the age 36 and 26 percent of them diagnose with DUB of unknown etiology [1, 2].

Approximately twenty-five percent of patients visiting gynaecologist or outpatient department of hospitals are due to DUB. However, this could be different statistically with respect to different populations [3]. DUB is rated as common gynaecological complication among women of reproductive age that imposes a negative impact on their quality of lives. It can have a noticeable impact on their life style, work performance, day to day activities and social interaction [4]. In addition, DUB may result in Iron Deficiency Anaemia among women due to heavy blood loss. A recent investigation among the women in the united state (USA) has shown that more than 18 million women in their young age experience Iron Deficiency Anemia due to DUB [5].

Dysfunctional uterine bleeding in normal uterus

In the absence of microscopic and/or macroscopic appearance of uterine pathology, heavy menstrual bleeding known as idiopathic DUB, and clinically called dysfunction uterine bleeding [6]. The vast majority of women with DUB have normal endometrium. Nevertheless, a small proportion of those women may have a defective clotting mechanism, such as Von Willebrand's disease [7,8] and deficiency of PAI [9]. Progesterone may have the ability to stimulate the protease inhibitors as plasminogen activator inhibitor -1 (PAI-1) [10] which can result in enhancing the thrombus formation. In normal menstruation, progesterone withdrawal, which is the key event in menstruation, may stimulate the secretion of plasminogen activator and oppose the previous action. Therefore, the reduction in the clotting function is

a feature of menstruation, and clotting deficiencies diseases are most properly co-factors or a combination of factors resulting in DUB.

Pathological cause of dysfunctional uterine bleeding

Fibroids, polyps, coagulopathy, endometrial/cervical malignancy, thyroid disease, pelvic infection especially by Chlamydia, and arteriovenous malformations are the possible causes of DUB. Iatrogenic causes include use of anticoagulants etc. Submucosal and intramural fibroids are particularly associated with DUB, although approximately 50% of DUB with fibroids has no symptoms. Uterine fibroids are the most common pelvic tumours of the female genital tract and one of the main causes of heavy bleeding. They are benign smooth muscle tumours that arise from the uterine myometrium. Although all women at reproductive age can be affected by fibroids, they largely affect women aged from 40 to 50 years old. Coagulopathy must be investigated in women who is not responding to medical management or women who has DUB at young age. Coagulopathy may be inherited or acquired and it is quite often disorder of von Willebrand's disease. Cervical and Endometrial carcinomas are significant causes of intermenstrual and post coital bleeding rather than DUB. Untreated hypothyroidism may be associated with DUB. Chronic endometrial infection may cause intermenstrual bleeding or DUB. Chlamydia trachomatis has been involved as one of the causes of DUB. Arteriovenous malformations (AVM) in the uterus may be congenital or acquired and are a rare cause of DUB. This can happen due to performing uterine curettage after pregnancy. In case of any AVM malformation is suspected, Colour Doppler image could be a useful tool for diagnosis. Uterine artery embolization must be performed in case of acute heavy bleeding after AVM. Heavy menstrual bleeding can cause as a result of treatment of patients with thromboembolic disease by anticoagulant and copper IUD. Table 1 summarises the main causes of DUB.

Table 1: Summary of main causes of DUB

Classification	Subtype
Local Uterine Pathology	**Uterine fibroids**
	Uterine polyps
	Chronic cancer
	Endometrial hyperplasia
	Chronic endometrial infection
	Arteriovenous malfunction
Local pelvic pathology and systemic disorder	**Polycystic ovaries (PCOs)**
	Hypothyroidism
	Coagulopathy e.g. Von Willebrand's disease
Iatrogenic causes	**Anticoagulation therapy**
	IUCD

Serum copper as exogenous compound and ceruloplasmin in dysfunctional uterine bleeding

The human endometrium in every month of menstrual cycle changes in response to injury and repair mechanism that is similar to lesion of endometrium, that lead to formation and degradation of blood vessels in the process and are regulated by steroid hormones such as oestrogen and progesterone [11]. The process of formation of new blood vessels is affected by many factors. There are many endogenous and exogenous stimuli known to directly or indirectly can influence endometrial angiogenesis in patients suffering from DUB. There is a great knowledge about the role of estrogen in potentiating and terminating this complex process of angiogenesis in endometrium under numerous conditions[12]. Along with hormonal influence, many factors are known to date that stimulate and regress the angiogenesis in human endometrium. Although the exact mechanism by which they control the blood vessel formation in endometrium during menstrual cycle and other physiological process are not completely elucidated. DUB that is the manifestation of abnormal menstrual cycle and estimated a 30% of the patients that consult with gynaecologist suffering from abnormal uterine bleeding. Multiple reasons could lead to DUB but imbalance in estrogen secretion consider to play an important role [13]. Copper is one of the important factor to control angiogenesis [14]. It exerts an important impact on functional capacity of numerous angiogenic factors. They can influence angiogenesis directly or indirectly in many levels of blood vessels formation [15]. Ceruloplasmin is an acute phase protein that contains copper and it is capable of oxidizing iron to transportable form to the site of erythropoiesis. The precise physiological mechanism by which this phenomenon occurs is yet to be identified [16,17]. There are many other roles attributed to ceruloplasmin such as involvement in different enzymatic reactions as a cofactor and serving as an antioxidant [18,19].Study has shown a pathological role of ceruloplasmin in many cancers when concentration is above its physiological range[20].

Copper involvement in angiogenesis

Copper concentration are critical for gene regulation, it can act in either activation or inhibition of specific gene in transcriptional level [21]. If iron supplementation is ineffective in treating anaemia, the probable reason could be investigated by supplementing copper to rule out the copper deficiency anaemia. This kind of anaemia can be explained due to decrease ceruloplasmin level since ceruloplasmin contains copper that is essential for iron movement in the body[16,21].These types of anaemia is seen when concentration of copper and ceruloplasmin decrease up to 30% of its normal physiological range. This status of copper is known as critical copper deficiency. Ceruloplasmin by binding to copper play an important role in preventing oxidative induced by copper. They act as an antioxidant by catalyzing free radical damage [22]. Acute copper poisoning can happen through drinking water that stored in copper vessels or if water contaminated with copper through fertilizer that contain copper used in agriculture. The U.S health guide line considers a higher level of copper concentration in water should not exceed beyond 1.3 mg/liter[20]. In case of copper poisoning the symptom like abdominal pain, vomiting and diarrhea are apparent which prevent excess copper absorption. The other critical and pathological copper poisoning lead to hepatocyte damage, kidney failure, coma and death. A 10 mg/day has been set as a maximum amount of daily copper intake by U.S. Food and Nutrition Board (FNB) [23]. The copper intake could be from different sources, like, water, food and copper supplementation, etc. It should be consider that people with inherited metabolic disorder, like, (Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis) could be at higher risk of copper toxicity and these individual should decrease the copper intake in considerable amount [24,25]. It is been shown that women using intra uterine device (IUD) that contains copper causes elevation of inflammation and uterine bleeding [26]. Since copper involved in the process of the angiogenesis, decrease copper concentration by chelation technique could decrease the extend of angiogenesis. There are many hypothesis and experimental evident that support the role of copper and VEGF in association with excessive and irregular menstrual bleeding [27, 28]. Involvement of angiogenesis had been investigated in many other gynaecological conditions such as pre-eclampsia, pregnancy related condition and numerous cancers, but the pattern of blood vessels formation that occur is significantly similar in DUB and this drives the fact that DUB might be a pre-cancerous condition [29,30]. Investigation have shown there is a strong correlation between anovulation and DUB in adolescents and LH, estrogen, progesterone and FSH are all in lower concentration in first year of heavy menstruation but estrodiol increased to normal concentration in year 2. In the fifth year of irregular cycle the level of all the above mentioned hormones elevated to normal physiological concentration except progesterone.

Growth factors and angiogenesis in endometrium

Following menstruation, endometrial vessels in the shedding layer need to be reconstructed. Therefore, development of endothelial cells and smooth muscle cells is promoted to form capillaries and larger vessels. This process of new vascularisation is promoted by several angiogenic factors [31]. The main angiogenic factor is vascular endothelial growth factor (VEGF), also termed vascular angiogenic factor.

It is known that ovarian steroid hormones acts as a regulatory factor for any changes in the human endometrium during the menstrual cycle, and endometrial cells are very sensitive to oestrogen. Growth factors can regulate endometrial proliferation and differentiation and may mediate the effects of oestrogen and progesterone on the endometrium in an autocrine and /or paracrine manner. Although the effects of growth factors and sex steroids on epithelial and stromal development have been investigated in several studies, little is known about factors that affect the endometrial vasculature throughout the menstrual cycle. It is thought that endothelial cells do not respond directly to oestrogen or progesterone, and growth factors may play a role as local mediators of the effects of ovarian steroids on endometrial vessels. The angiogenic basic fibroblast growth factor (bFGF) has been excluded as mediator of endometrial angiogenesis, as its levels do not change in human endometrial biopsies during the menstrual cycle and increase after menopause. On the other hand, vascular endothelial growth factor (VEGF) peptide and mRNA are present in human endometrial biopsies obtained during all phases of the menstrual cycle and VEGF is localised to both glandular epithelium and stroma. Consistent with the hypothesis that VEGF may be a paracrine regulator of the effects of sex steroids on endometrial angiogenesis, VEGF gene expression is increased by the addition of estradiol to human endometrial carcinoma cell lines [32]. Estradiol also increases VEGF expression by primary human endometrial cells in culture. These observations suggest that VEGF may play a key role in the regulation of endometrial angiogenesis throughout the human reproductive cycle. Therefore, VEGF is thought to play a crucial role as endothelial cells growth and survival promoter. It appears that VEGF expression in the whole endometrium is low during the proliferative phase, increases during the secretory phase and reaches the maximum levels during menstruation. This supports a hypothesis which suggests induction of hypoxia arising from constriction of spiral arterioles, which precedes bleeding, leads to increased production of

VEGF by endothelial cells to promote angiogenesis. However, there is no clear pattern of VEGF protein expression throughout the menstrual cycle, although expression is greater in glands than stroma.

CONCLUSION

DUB usually is a result of conditions such as fibroids and cancer of uterus, 50% of excessive menstrual bleeding occurs without any uterine pathology. Factors that are localized in endometrium controls and regulate the mechanism of menstruation such as angiogenic growth factors play a vital role in pathogenesis of DUB. There are several findings that relay copper as an enhancement of angiogenesis. Numerous investigations prove exposure to high concentration of environmental copper aggravates DUB. The complete pathological role of copper in DUB remains to be elucidated.

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