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Original Research Article

AN ORIGINAL PAPER FROM THE ALIGARH MUSLIM UNIVERSITY REGARDING MICROVASCULAR DENSITY AND VASCULAR CHANGES IN ENDOMETRIAL SAMPLES IN DYSFUNCTIONAL UTERINE BLEEDING

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ABSTRACT

BACKGROUND

Menorrhagia, a common gynaecological problem, accounts for up to 20% of outpatient clinic visits by women of reproductive age. Our intent was to study the various histopathological changes in dysfunctional uterine bleeding and the changes in blood vessels viz number morphology and finally to correlate with the clinical findings.

METHODS

About 200 patients were included in the three-year study, which was carried out in the Department of Pathology in conjunction with the Department of Obstetrics and Gynaecology. The study group consisted of individuals in the reproductive age group who did not use an oral contraceptive drug or an intrauterine device and who showed signs of irregular, intermittent, protracted, or heavy menstrual bleeding coagulation problem was excluded initially. Ethics committee clearance and consent from patients were taken as per protocol.

RESULTS

In this study the varying patterns observed were proliferative pattern, secretory pattern/ therapy related changes, disordered proliferative endometrium endometrial hyperplasia and hyperplasia with atypia. The patterns which showed a significant change in the number and structure of blood vessels come under the proliferative pattern of endometrium viz disordered

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proliferation, endometrial hyperplasia and hyperplastic endometrium with atypia. All other patterns did not have a significant change in vasculature.

CONCLUSION

As a result, it was determined that abnormal vascular morphology in the various endometrial patterns mentioned above might be the pathogenic cause behind dysfunctional uterine haemorrhage abnormal endometrial angiogenesis and poor vascular maturation are linked to AUB. Our study and literature review validates the body of research showing that low levels of antiangiogenic factors and high levels of proangiogenic factors impede the maturation of vasculature, making them more brittle and permeable. This is consistent with our theory, and these pathways seem to be crucial to the pathophysiology of AUB. Examining the changes in angiogenesis in these individuals may reveal targets for AUB treatment.

KEY WORDS

Endometrial Hyperplasia, Disordered Proliferation, Vascular Changes, Microvascular Density, Congestion and Dilation of Vessels.

INTRODUCTION

Menstrual bleeding disturbances are a social and medical issue. Since abnormal uterine bleeding (AUB) significantly lowers quality of life, it has a major socioeconomic impact. Up to 20% of outpatient clinic visits among women of reproductive age are related to menorrhagia, a frequent gynaecological issue.[1] In addition to causing iron deficiency anaemia and necessitating a hysterectomy, the condition involves causes significant social discomfort and lowers life quality. About 50% of individuals with menorrhagia arrive without apparent uterine disease, despite the condition being frequently linked to fibroid and polyps. In cases when fibroids, adenomyosis, or polyps are not identified as the underlying cause of the AUB, is typically brought on by a main endometrial problem. cellular process and regulatory mechanism of menstruation may be the reason for abnormal bleeding.[1,2] When there is no other obvious extragenital cause for bleeding in a patient, and the pelvic examination is normal, the diagnosis of dysfunctional uterine bleeding (DUB) should be made.[2,3] AUB may both be the consequence of aberrant vascularization in the endometrium as a result of changes in the angiogenesis and vascular maturation processes, taking into account vascular modulation and function.[4] In the age of antibodies and molecular testing, the goal of the current study was to examine the different histopathologic patterns of endometrium and the density of endometrial blood vessels in DUB patients using routine laboratory stains.

The World Health Organisation criteria, which is frequently used, or the more standardised endometrial intraepithelial neoplasia (EIN) criteria are the two classification schemas that characterise EH, a histologic diagnosis.[4] The degree of the lesion determines the likelihood of cancer progression. Atypia-related lesions are most likely to proceed to cancer and to be diagnosed with endometrial cancer at the same time. The majority of women with EH are perimenopausal or postmenopausal. Obesity, tamoxifen use, polycystic ovarian syndrome, estrogen-only hormone replacement, and persistent anovulation are important risk

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factors for endometriosis (EH). Atypical endometrial glands on Pap smears, postmenopausal bleeding, and abnormal uterine bleeding are examples of clinical symptoms.

A range of morphological endometrial changes are represented by the uterine pathology known as endometrial hyperplasia (EH). Compared to a normal proliferative endometrium, it is primarily characterised by an increase in the endometrial gland-to-stroma ratio. The possibility of endometrioid endometrial cancer (EC) progression is what makes EH clinically significant, and "atypical" forms of EH are thought to be premalignant lesions.[4,5]

As a result of a variety of potential circumstances, it is assumed that the majority of EHs arise from a background of persistent oestrogen stimulation of the endometrium without progestin resistance.[5] According to prior estimates, EHs account for 15% of all occurrences of postmenopausal haemorrhage. The majority of women with EH will present clinically with abnormal uterine bleeding (AUB).[5] The primary risk factors for developing EH are comparable to those for developing EC. Two patient groups that are particularly at risk include (i) obese perimenopausal and postmenopausal women, who may have irregular anovulatory cycles due to peripheral aromatization of androgens to oestrogens in adipose tissue, and (ii) premenopausal patients with polycystic ovarian syndrome (PCOS).

The aetiology of the condition is not the focus of therapeutic alternatives, which are often dependent on trial and error. The development of novel therapeutic options for this condition requires an understanding of its pathophysiology.

Decidualized human endometrial stromal cells (HESC) express more tissue factor (TF), the main initiator of coagulation, during the progesterone-dominated luteal phase. Additionally, progesterone increases plasminogen activator inhibitor-1 (PAI-1), a second hemostatic component of HESCs. Conversely, progestins stabilise endometrial stromal and vascular extracellular matrix by inhibiting the production of HESC matrix metalloproteinase (MMP)-1, 3, and 9. Withdrawing progesterone during infertile cycles causes a reduction in HESC TF and PAI expression as well as an increase in MMP activity and the release of inflammatory cytokines, which in turn promotes regulated menstrual haemorrhaging and associated tissue sloughing. The endometrium is highly vascular, non-hemostatic, and proteolytic due to unrestrained angiogenesis. This is contrasted with the well-ordered biochemical processes involved in endometrial bleeding linked to anovulation.

The cause of abnormal bleeding linked to long-term use of progestin-only contraceptives is unregulated angiogenesis that leads to big, fragile endometrial vessels rather than defective hemostasis. This aberrant angiogenesis is a result of progestational endometrial blood flow inhibition, which promotes local hypoxia and the creation of reactive oxygen species, both of which boost the angiogenic factor production.[6,7] This leads to vascular fragility, which encourages bleeding. Irregular bleeding linked to endometrial polyps and myomas is also caused by aberrant angiogenesis.

Continuous exposure to oestrogen without any opposition from progesterone, polycystic ovarian syndrome, tamoxifen, or hormone replacement therapy results in disordered proliferation and endometrial hyperplasia. The reversion of hyperplasia to normal endometrium constitutes the major conservative treatment for preventing the development of adenocarcinoma. EH is clinically significant because it can progress or frequently occurs simultaneously with endometrial carcinoma. Currently, the main treatments for EH without atypia are hysterectomy or cyclic progestin, respectively.[8,9] For the management of EH,

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however, definite standard treatments and clinical trials of hormonal therapy are still pending. Furthermore, people with endometriosis (EH) who want to maintain their fertility have difficult treatment options that need nonsurgical care.

MATERIAL & METHODS

About 200 patients were included in the three-year study, which was carried out in the Department of Pathology in conjunction with the Department of Obstetrics and Gynaecology. The study group consisted of individuals in the reproductive age group who did not use an oral contraceptive drug or an intrauterine device and who showed signs of irregular, intermittent, protracted, or heavy menstrual bleeding. Coagulation problem was excluded initially. The control group consisted of twenty patients who had prolapsed uterus and/or uterine/cervical fibroid which were the causes for abnormal bleeding. Specimens from hysterectomy or dilatation and curettage (D&C) procedures were evaluated, and if necessary, special stains like reticulin were utilized. On the basis of architecture and atypia endometrium was divided into disordered proliferation, endometrial hyperplasia without atypia and endometrial hyperplasia with atypia. Progesterone changes and proliferaive phase and secretory phase endometrium were not taken for analysis.

By calculating the average number of blood vessels in ten high power fields (HPF) and comparing the results with a control, the overall vascularity of the endometrium was assessed. In ten high-power fields (HPF), the quantity of blood vessels exhibiting vascular dilatation and congestion was also counted. Arterioles, and thin-walled capillaries were counted. Vascular sinuses that showed dilation were not included. The statistical test used was student's unpaired t-test. P values more than 0.05 was considered non-significant (NS) and the values < 0.05 and < 0.001 was considered significant (S) and highly significant (HS)

Our goal is to look at the basic functions of angiogenesis and vascular maturation in AUB patients. We also think that, albeit through different pathways, aberrant endometrial angiogenesis plays a significant part in the aetiology of AUB.[10,11]

OBSERVATIONS

180 DUB cases in all were examined. The highest percentage of patients with dysfunctional uterine bleeding, 107 instances (59.4%), were identified in 40-50yrs age group, with 49 cases (27.2%) occurring in 30-40yrs age group. The age group of 21 to 30 years old had the fewest patients observed. Menorrhagia (38.9%) was the most common presentation type among the DUB, followed by polyhypermenorrhea (21.20%). The lowest percentage of cases (1.10%) had an amenorrhea.

Endometrial pattern	Number of Cases	Percentage
Nonsecretory pattern	75 .00	41.60%
1) Proliferative pattern	17.00	9.40%
2) Disordered proliferative endometrium	37.00	20.50%
3) Endometrial hyperplasia	21.00	11.70%
Secretory pattern	105 .00	58.40%
1) Secretory pattern	34 .00	18.90%
2) Hormonal changes	71.00	39.00%

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Table 1. Different endometrial histology patterns in the research group

Endometrial Patterns	No of cases	Mean number of blood vessels/10HPF	Mean number of dilated vessels/10HPF	Mean number of congested blood vessels/10HPF
1.Proliferative pattern	17	3.4±0.4	0.7± 0.2	0.9±0.07
2.Disordered proliferative endometrium	37	3.9±0.8	0.9±0.1	1.2±0.1
3.Endometrial hyperplasia	16	5±0.4	2.7±0.2	1.0±0.1
4.Endometrial hyperplasia with atypia	5	6.9±0.6	3.4±0.4	1.4±0.1
SECRETORY pattern		±	±	±
1)Secretory pattern	34	4.7±0.1	1.1±0.1	0.8±0.4
2) Hormonal changes	71	12.56±1.06	6.93±0.46	3.9±0.86
Total	180			

Table 2: Results of Examination of the study group's microvascular density, dilatation, and congestion

Table 1 displays the different endometrial histopathology patterns observed in instances of DUB. Hormonal therapy may have contributed to the secretory pattern's dominance over the proliferative pattern among the 180 case studies. Just 75 patients had non-secretory endometrial patterns, compared to 105 cases with secretory patterns. The majority of instances in the non-secretory endometrial pattern were disordered proliferative (20.50%) (Figure 1, 2). The highest percentage of instances in the other group was caused by hormonal alterations on the endometrium (39.00%). (Fig 3)

When it came to patients with nonsecretory endometrial pattern, the most common cause of DUB was disordered proliferative endometrium (20.50%) (Figure 2), which was followed by hyperplasia (Figure V), which claimed 21.00% of cases.

Twenty patients made up the control group. These patients had other medical conditions such as non-hormone producing ovarian tumours, serosal and intramural leiomyomas, and cervical lesions with regular cycles and no abnormal bleeding. Their histopathological diagnoses indicated that the endometrium was either in the proliferative or secretory phase.

The study group and control groups' microvascular density, congested blood vessels, and dilated blood vessels were measured. The results are displayed in Tables II and III. The data were compared, and a significant calculation was made, as indicated in Table IV.

In disorganised proliferative endometrium and endomerial hyperplasia without atypia (Fig. 4, 5), number of blood vessels/10HPF (mean vascular density) was not significantly elevated, but it was in endometrial hyperplasia with atypia. It didn't matter in the conrol group ($p>0.05$). When compared to the control group, there was a significantly significant ($p<0.001$) increase in the number of blood vessels in the endometrium due to hormonal changes. In the current investigation, the mean vascular density significantly increased in

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42.50% of the instances (hyperplastic endometrium, 21.00%; secretory and hormonal change endometrial, 39.00%); in contrast, the mean vascular density did not significantly rise in 57.20% of the cases.

In this investigation, vascular dilatation was observed in 71.70% of the patients, along with hyperplastic endometrium and disorganised proliferation. In relation to vascular congestion, the majority of cases (70.70%) in the same group demonstrated a statistically significant increase in the quantity of vascular congestion.

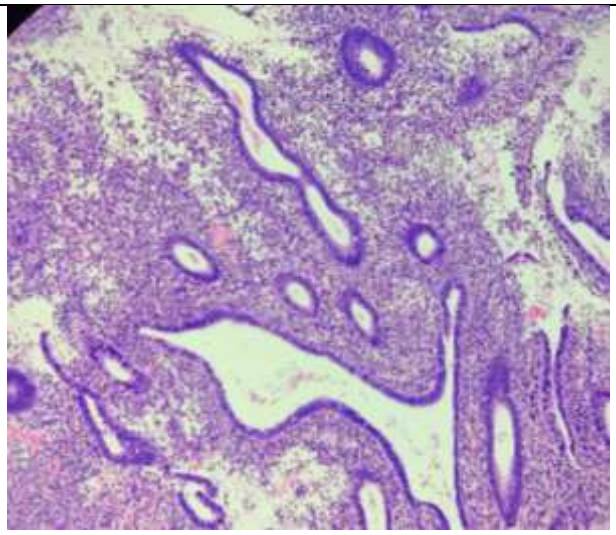

Figure 1. Disordered proliferative endometrium. 10x

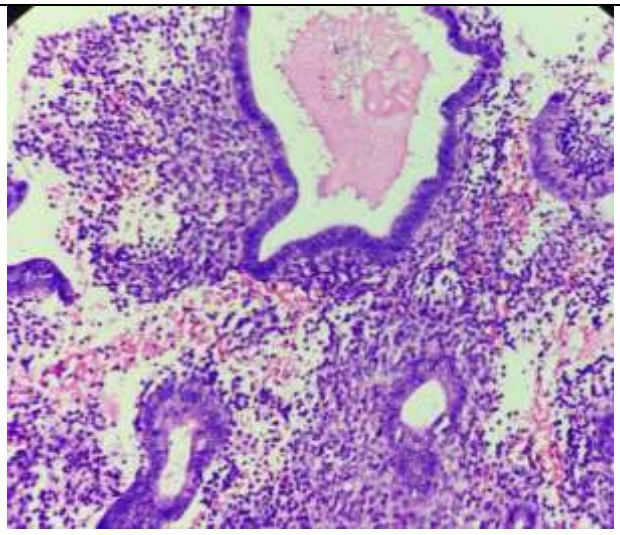

Figure 2. DISORDERED proliferative endometrium. 20x

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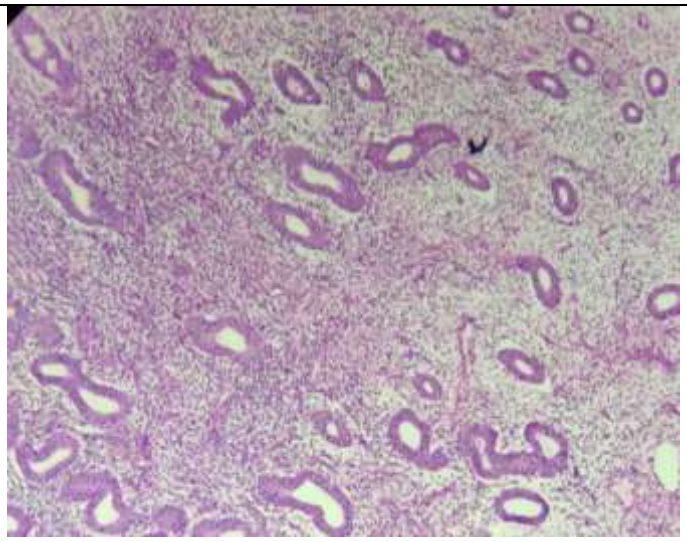

Figure 3. Hormonal change endometrim- showing pseudodecidualization of endometrial stroma. 20x

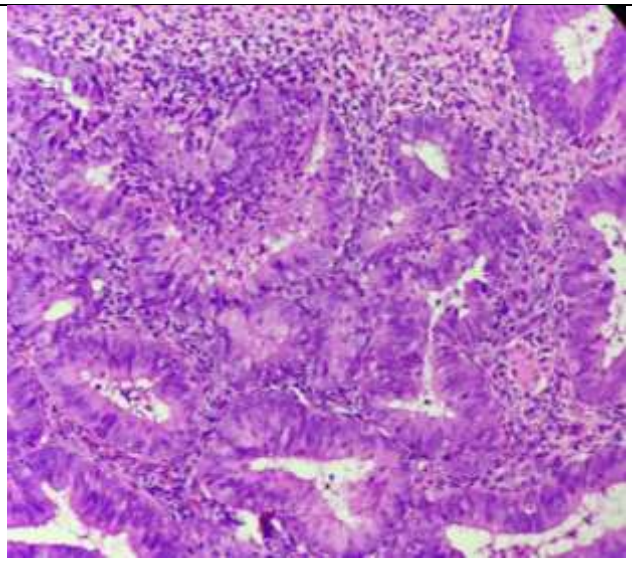

Figure 4. Endometrial hyperplasia with back to back glands. 20x

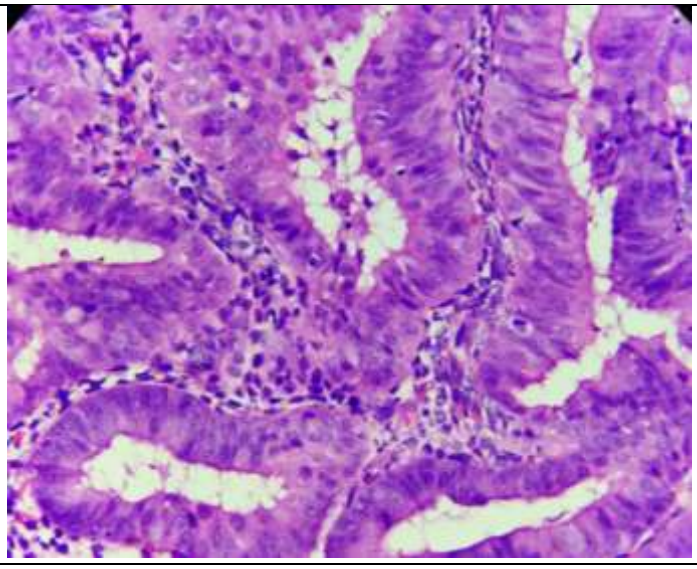

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Figure 5. Crowded endometrial glands with very little stroma in between glands. Glands are lined by columnar cells. no nuclear atypia in the cells. 40x

DISCUSSION

Considering vascular modulation and function, AUB may originate from both abnormal vascularization in the endometrium and modifications in the angiogenesis and vascular maturation processes.the uterine condition known as endometrial hyperplasia (EH) represents a spectrum of morphological endometrial alterations. It is principally marked by an increase in the endometrial gland-to-stroma ratio relative to a normal proliferative endometrium. In this study the varying patterns observed were proliferative pattern, secretory pattern/ therapy related changes, disordered proliferative endometrium, endometrial hyperplasia and hyperplasia with atypia.[12,13,14,15] The patterns which showed a significnat change in the number and structure of blood vessels come under the proliferative pattern of endometrium viz disordered proliferation, endometrial hyperplasia and hyperplastic endometrium with atypia. 42.50% of the patients in this study (21 percent of cases with hyperplastic endometrium and 39 percent with secretory and hormonal change endometrial) had a significantly higher mean vascular density. In this investigation, vascular dilatation was observed in 71.70% of the patients, which encompassed hyperplastic endometrium and disorganised proliferation.

All other patterns did not have a significant change in vasculature. Large vessels which are thin walled and tortuous without a properly developed wall, present in the superficial endometrium lead to menorrhagia in hyperplastic endometrium and malignancy. In these situations, menorrhagia may be brought on by an additional local molecular process, such as prostaglandins (PGF2α and PGE2), prostacyclins (PGI2), nitric oxide, decreased endothelin-1 levels, and increased expression of VEGF-A and its receptors, such as VEGFR-1 and VEGFR-2. All the above finding call for more molecular research.

Given that angiogenesis has been suggested to be relevant, Goteri et al. set out to investigate whether there were differences in the expression of VEGF, HIF-1alpha, and microvessel density (MVD) in women with and without adenomyosis. Their conclusion was that VEGF-mediated angiogenesis may be connected to the development of adenomyosis. The anomalous placement of the ectopic foci may be involved in the upregulation of VEGF production, the enhancement of HIF-1a expression, and the development of more vessels. However, there does not seem to be a relationship between the increased expression of VEGF and HIF-1alpha or between the enhanced MVD in the adenomyotic foci. Whereas the same factor can affect the vascular proliferation in endometrium in hyperplasia and disordered proliferation and carcinoma.[16]

The secretory phase of the endometrium exhibits significant dilatation and congestion, as noted by Makhija et al.[17] Previously, ovulatory dysfunctional uterine bleeding was primarily linked to reduced endometrial vasoconstriction and impaired vascular plug formation, which resulted in excessive bleeding.[18,19] This observation may account for the abnormal bleeding observed in patients with hormonal change endometrium. Also it a common practise to give hormonal therapy as the first line of management for abnormal uterine bleeding.

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The unopposed estrogen stimulation leads to endometrial hyperplasia and malignancy. Living stone and Fraser suggested that the large vessels which are thin walled and tortuous without a properly developed wall, present in the superficial endometrium lead to menorrhagia in hyperplastic endometrium and malignancy.

On the other hand, menorrhagia can also result from low amounts of endothelin-1 released from vascular endothelium, low levels of PGF2α and Nitric oxide (both secreted from vascular endothelium), and local prostaglandin (PGE2 and PGI2) effects. Another significant element leading to menorrhagia is elevated tissue plasminogen activator, which in turn leads to enhanced fibrinolytic activity, as indicated by studies by Livingstone and Fraser[20] and Shaw.[21]

The overexpression of VEGF-A and its receptors in capillaries, such as VEGFR-1 and VEGFR-2, has been shown in Mints et al.'s study[22] to improve vascular permeability, induce fenestration in capillaries and venules, and stimulate the growth of vascular endothelial cells. These angiogenic facors cause the menorrhagia in these individuals. Therefore, in addition to the vascular morphological alterations in the various endometrial patterns that were previously mentioned, a number of biochemical and molecular variables also play a significant role in menorrhagia.

In the study by Erdem et al, cd 34, endoglein and VRGF were used to assess the microvascular proliferation and density. In the majority of vascular regions, endoglin and anti-CD 34 were used to measure microvessel density (MVD). There was no difference in VEGF expression between EC and EH, however it was much higher in EC and EH. There were no variations in MVD across the groups based on CD 34 staining. On the other hand, EC had considerably higher mean MVD counts than EH, as determined by endoglin. Despite being substantially greater in EC, VEGF expression did not connect with other angiogenesis-related metrics. Compared to CD 34, it was concluded that MVD utilizing endoglin appeared to better represent neoplastic angiogenesis.[23]

Zhang etal did a marvellous work on endometrial biopsies for vascularity assessment through immunohistochemical staining of MMP-2 and -9, VEGF, and endometrial MVD using an antibody to CD34.To corroborate the finding in our study, the work by Zhang etal showed that Women with anovulatory DUB who had endometrial hyperplasia had far greater frequencies of MMP-2 and -9 expression in endometrial stroma and VEGF expression in endometrial glands than in the control group. Furthermore, compared to the control group, women with anovulatory DUB who had endometrial hyperplasia had a significantly higher mean score of endometrial MVD. MMP-2 and -9 expressions in endometrial stroma and endometrial MVD were statistically linked with VEGF expression in endometrial glands in women with anovulatory DUB.[23]

Vascular endothelial growth factor A and its receptors (1 and 2), Tie-1, and the ratio of angiopoietin-1 to angiopoietin-2 were all significantly elevated in AUB patients. Numerous investigations revealed that patients with AUB expressed distinct pro- and antiangiogenic factors, indicating abnormal vascular development and compromised vessel integrity. In patients with AUB endometrial microvessel density (MVD) was similar overall. Patients with AUB had increased MVD and higher expression of proangiogenic markers, especially following brief hormone treatment.[24] Longer-term exposures gradually eliminated this effect, but both short- and long-term exposures changed the way vessels matured.

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CONCLUSION

As a result, it was determined that abnormal vascular morphology in the various endometrial patterns mentioned above might be the pathogenic cause behind dysfunctional uterine haemorrhage. Abnormal endometrial angiogenesis and poor vascular maturation are linked to AUB. Our study and lieraure review validates the body of research showing that low levels of antiangiogenic factors and high levels of proangiogenic factors impede the maturation of vasculature, making them more brittle and permeable. The change in the vascular morphology concerning mean vascular density, dilatation, and congestion in the proliferative and secretory patterns was suggested by the different studies. In these situations, menorrhagia may be brought on by a local molecular process, such as prostaglandins (PGF2α and PGE2), prostacyclins (PGI2), nitric oxide, decreased endothelin-1 levels, and increased expression of VEGF-A and its receptors, such as VEGFR-1 and VEGFR-2. All the above finding call for more molecular research. This is consistent with our theory, and these pathways seem to be crucial to the pathophysiology of AUB. Examining the changes in angiogenesis in these individuals may reveal targets for AUB treatment.

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