Molecular blockade of angiogenic factors: A new therapeutic tool for the treatment of abnormal uterine bleeding

Dear Editor,

Abnormal uterine bleeding (AUB) has been one of the most common gynecological symptoms among adolescent and peri-menopausal age group.[1] Combined oral contraceptive pills (OCP), progestin, non-steroidal anti-inflammatory drugs (NSAIDs), anti-fibrinolytic agents, danazol, and gonadotropin releasing hormone (GnRH) agonists are presently advised as pharmacotherapeutic agents.[2] Combined OCPs are targeting the bungled co-ordination of unopposed estrogen stimulation and hampered progestational induction of tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) in anovulatory dysfunctional uterine bleeding (DUB). It counteracts the proliferative and angiogenic effect of estrogen on endometrium.[3] GnRH agonists like leuprolide and androgenic synthetic steroid like danazol induce chemical menopause by reducing follicle stimulating hormone and luteinizing hormone. However, their use is associated with various adverse effects. NSAIDs like naproxen and mefenamic acid are used to reduce the vasodilating prostaglandin imbalance in case of ovulatory DUB.[2] Although, the basic pathophysiological mechanism of AUB lies around the impaired hemostasis with vascular derangement and disturbed neo-angiogenesis, the current medical strategies are not directed to attack the step of disturbed angiogenesis. This correspondence is an attempt to propose a hypothetical view on the use of molecular angiogenic factor inhibitors in the treatment of AUB.

Physiological angiogenesis is the key mechanism for degeneration and regeneration of endometrium of female reproductive cycle. The maintenance of endometrium and its shedding is a well co-ordinated mechanism that swings between hemostasis and neo-angiogenesis. In normal menstrual cycle, estradiol increases the Fetal liver kinase-1/Kinase insert Domain Receptor (Flk-1/KDR) i.e., Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) expression in endometrial endothelial cell during proliferative and mid-secretory phase also to a lesser extent. It also induces human endometrial stromal cells (HESC) to express vascular endothelial growth factor (VEGF) and endometrial endothelial cells to express angiopoietin-2 (Ang-2). This ultimately stimulates angiogenesis necessary for proliferation of endometrium.[4] Expression of VEGF receptor is also stimulated by hypoxia and VEGF itself. Progesterone induces an angiostatic and vessel stabilizer factor, named angioprotein-1 (Ang-1) to counteract this process.[3] In the secretory phase, progesterone not only induces TF mRNA and PAI-1 but also inhibits the expression of HESC matrix metalloproteinase-1, 3, and 9.[2] Besides being an initiator of coagulation cascade TF is also involved in angiogenesis via protease activated receptor-2.[5] Specifically in the cases of anovulatory DUB, myoma and use of long term progestin only contraceptives (LTPOC), there is increased expression of VEGF, basic fibroblast growth factor and transforming growth factor-β and increased micro vessel density.[6] LTPOC induced dysregulation of endometrial blood flow results in hypoxia/reperfusion generating reactive oxygen species that can directly damage endometrial vessels or result in decreased expression Ang-1 and enhanced expression of Ang-2 and VEGF. Furthermore, LTPOC results in the focal induction of TF to directly activate intracellular signaling cascades leading to formation of thrombin. Conjointly these mechanisms give rise to fragile blood vessels.[3] Increased expression of VEGF/VEGFR is also found in endometrioid endometrial carcinoma in which AUB is a potential risk factor.[6] In case of carcinoma, increased endometrial cell proliferation is mediated via the up regulation of same.

Thus, it is evident that angiogenic molecules like VEGF, TF are novel targets for therapeutic intervention. However, these angiogenic molecules like VEGF are also necessary for normal maintenance of endometrium. VEGF inhibition can be mediated by direct neutralization of VEGF and inactivating functional VEGF receptors. So, intervention should be done in a local short acting and reversible way preferably by blocking VEGF receptors. However, VEGF inhibitors like bevacizumab, aflibercept are already in market[7] and ramucirumab, a monoclonal antibody is also designed against VEGFR-2. Among these, bevacizumab is proved to be well tolerated in a phase II clinical trial.[8] Recently, there is a drug named, Icon, an immunoconjugate molecule that hinder neo-angiogenesis and also target pre-existing vascular lesion.[5] A reversible VEGF/FGF receptor tyrosine kinase inhibitor, named as PD 173074 (trade name Calbiochem) is already designed and it claims to inhibit autophosphorylation of FGF receptor and over expression of VEGFR-2 *in vitro*.[9] It also inhibits FGF and VEGF induced angiogenesis *in vivo*.[7] In 2002, Nowak, *et al*., also obtained a patent of a compound that includes type I interferons, pirfenidone, heparin, heparin-like polyaromatic anionic compounds, heparin-sulfate-based compounds, secreted or soluble FGF receptors, and/or

arginine-glycine-aspartic acid peptide. It inhibits the response of angiogenic growth factors and suitable for topical use.[10] These targeted molecular drug therapies may reduce the burden of systemic side effects of other drugs. So, clinical trials of these drugs can be carried out as a search for a new tool for treating AUB to find out its applicability in therapeutic settings. The risk-benefit ratio and cost and availability issues of these particular drugs should be explored.

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DOI: 10.4103/0976-7800.109647