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ROLE OF ANGIOGENIC FACTORS IN THE MANAGEMENT OF PRE-ECLAMPSIA.

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Abstract:
Preeclampsia is a pregnancy disorder causing different maternal and fetal morbidity and mortality. Currently the diagnosis is based upon the new onset of hypertension and proteinuria. There is strong clinical need for increased screening to avoid unnecessary resource use and for better outcomes. The angiogenic factors placental growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin, all originating at least in part from the syncytiotrophoblast, are biomarkers with predictive potential for preeclampsia and related adverse outcomes. Recent work with the soluble fms-like tyrosine kinase 1/placental growth factor ratio has identified key measurement cutoffs, with one having a high negative predictive value for preeclampsia. The two-stage theory and angiogenic imbalance are two notable postulates of the disease. Together, they propose that there is a lack of cytotrophoblastic invasion of the uterine spiral arteries in pre-eclampsia. The lumen of these arteries remains narrow instead of converting to the wide channels seen in normal pregnancy, and result in poor placental perfusion. Coupled with maternal susceptibility, this process leads to the release of mediators, including an excess of anti-angiogenic factors that result in the clinical manifestations of the disease.
Current review explains the role of angiogenic factors in the pathogenesis and management of pre-eclampsia
Keywords: Angiogenic factors, management of pre-eclampsia, pregnancy, placental growth factors.

Introduction:

Preeclampsia, a systemic syndrome of pregnancy clinically characterized by new onset of proteinuria and hypertension, is associated with significant morbidity and mortality to both mothers and fetus. Pre-eclampsia is distinctive placenta-mediated disease with poorly understood pathogenesis. Because it's exact required etiology is unknown. Treatment requires controlled experiment and involves delivery of the fetus and placenta. It is, therefore, not surprising that pre-eclampsia is a major cause of direct maternal death and significant perinatal mortality owing to iatrogenic preterm delivery, stillbirth, and intrauterine fetal growth restriction (IUGR). In 2015, hypertensive disorders of pregnancy, and especially pre-eclampsia, accounted for 14% of the overall global maternal mortality ratio of 216 per 100 000 live births, with the highest proportion of deaths in low and middle-income countries (LMIC) [1].

Finding out the true cause of pre-eclampsia will lead to decrease e in maternal and perinatal morbidity and mortality. Numbers of attempted experiments have resulted in a myriad of postulates [2]. Currently, the most important pathogeneses are those related to defective placentation, genetic predisposition, immune maladaptation, poor tolerance to inflammatory changes, angiogenic imbalance, and lack of a healthy nutritional state. To improve understanding of what is known about the pathogenesis of pre-eclampsia, many of the important ideas have been integrated into the two-stage theory, initially described by Chris Redman and co-workers, and extended by Roberts and colleagues. [3][4][5].

The aim of the present review was to summarize current knowledge on the pathogenesis of pre-eclampsia, including details of the two-stage theory and, in particular, the role of angiogenic factors. Pregnancy concentrations of angiogenic factors by gestational age, and their role in the prediction, diagnosis, and overall clinical management of pre-eclampsia are also reviewed. Pre-eclampsia is associated with clinical risk factors such as maternal age of 40 years or older, nulliparity, and body mass index of 35 or higher, among others. Maternal age younger than 20 years is also a risk factor for pre-eclampsia [6] [7]

Some investigators have not identified young maternal age as a risk factor for pre-eclampsia irrespective of the maternal age cutoff used.10 It seems that the occasional finding of maternal age 19 years or younger as a risk factor for eclampsia, but not for pre-eclampsia, may be due to under-diagnosis of pre-eclampsia[8][9]. Irrespective, in 2014, chronic hypertension, obesity, and severe anemia were reported as the factors that impose the highest predisposing risk to pre-eclampsia. Two stage pathophysiology has described well.

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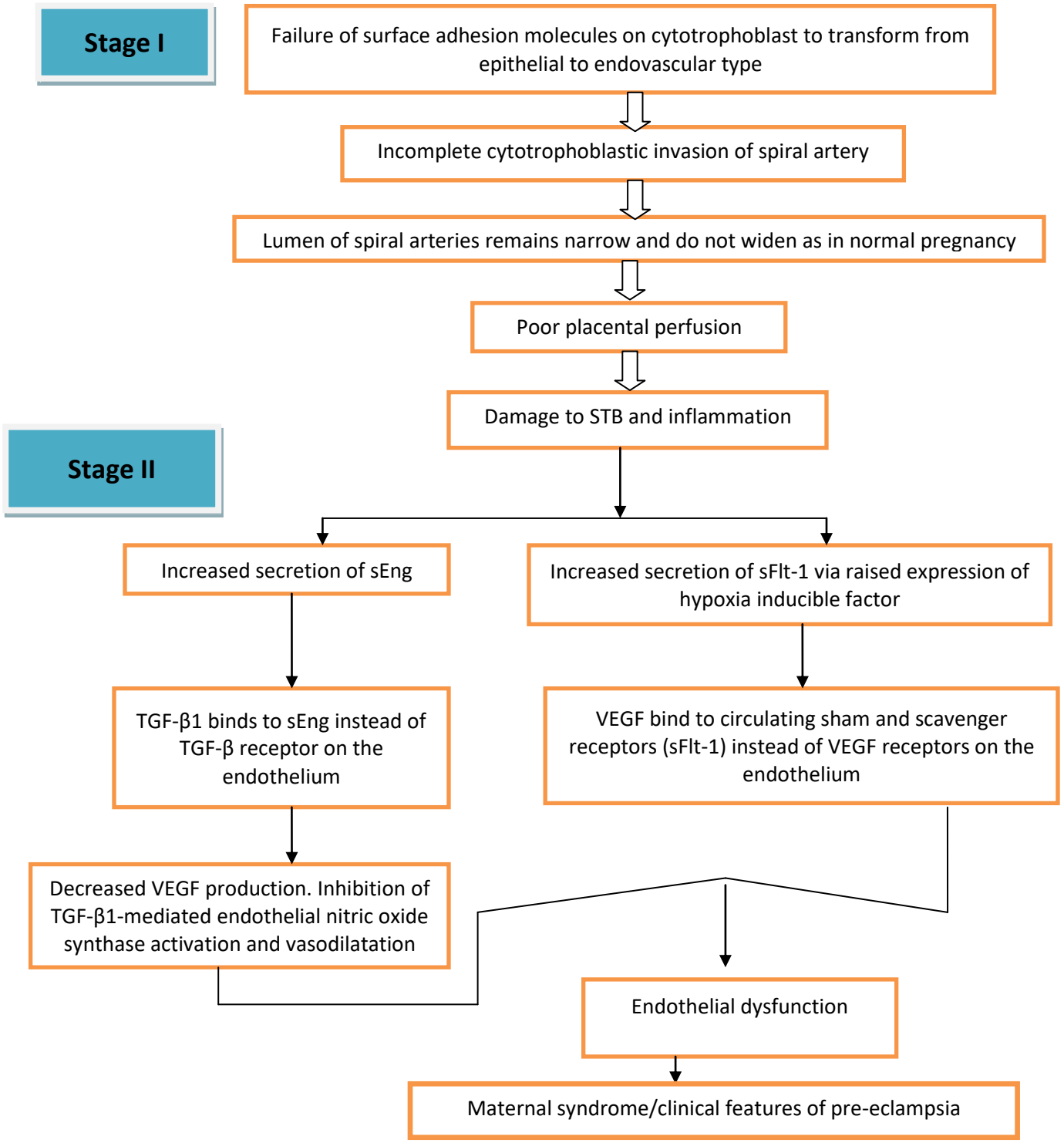

CLINICAL MANIFESTATIONS OF PRE-ECLAMPSIA

The unifying mechanisms that explain the clinical manifestations of preeclampsia are vascular endothelial damage and micro-angiopathy[10]. In its commonest variety, pre-eclampsia manifests principally as newonset hypertension and proteinuria after 20 gestational weeks [11]. Hypertension develops when poor placental perfusion in a susceptible pregnancy leads to the release of proinflammatory cytokines and increased levels of sFlt-1. These substances activate the maternal vasculature and cause endothelial damage. The resultant effects are decreased production of vasodilators such as nitric oxide, and increased formation of superoxide and endothelin-1. There is also an increased vessel responsiveness to angiotensin II. Together, these changes result in increased total peripheral resistance, decreased renal blood flow and/or excretory function, and ultimately the development of hypertension. In some cases, severe hypertension and other forms of severe pre-eclampsia develop. It is important to emphasize that the vasoconstrictor ability of endothelin-1 might be second to none[12][13]14].

Glomerular endotheliosis and proteinuria are key features of pre-eclampsia in the renal system. Importantly, the initial discovery of albumin in the urine of women with pre-eclampsia (after postpartum convulsion) is probably attributable to the work of John Lever in 1843.[15] In pre-eclampsia, the glomerular barrier loses its charge selectivity ability, and this leads to proteinuria[16]. Proteinuria tends to follow or manifest at the same time as hypertension, but rarely precedes it. By contrast, podocyturia tends to precede proteinuria and might be used to predict pre-eclampsia[17].

ROLE OF ANGIOGENIC FACTORS IN THE MANAGEMENT OF PRE-ECLAMPSIA

The assessment of circulating level of angiogenic factors such as PIGF or sFlt-1 as standalone biomarkers and/or in combination with other variables has demonstrated their clinical utility in pre-eclampsia. Some of the clinical roles are gaining acceptance, as discussed below, and have been included in organizational guidelines.[18][19]

Circulating levels of angiogenic factors are useful for the prediction of pre-eclampsia and other placenta-mediated diseases [20]. Changes in the levels of these biomarkers are observed long before the clinical manifestation of pre-eclampsia, and their systemic concentrations act as markers of disease severity [21]. For instance, sFlt-1 is elevated approximately 5 weeks, and PIGF approximately 2 weeks, before the symptomatology of pre-eclampsia is manifest [22]. Again, the predictive ability of either sFlt-1 or PGIF is lower than that of the sFlt-1/PIGF ratio. Therefore, the sFlt-1/PIGF ratio is a good predictor of pre-eclampsia. A combination of PIGF, maternal factors, mean arterial pressure, and uterine artery pulsatility index measured between 11 and 14 gestational weeks has a 100% detection rate for pre-eclampsia occurring before 32 gestational weeks at a false-positive rate of 10%[23]. Generally, the application of predictive models to the population at risk tends to improve the detection rate.

Novel Therapies

Therapeutic manipulation of the circulating levels of angiogenic factors has been proposed to manage pre-eclampsia. This type of novel therapy has been used to increase the concentrations of proangiogenic factors such as VEGF and PIGF, and/or to decrease the levels of anti-angiogenic factors (such as sFlt-1 and sEng) that have been implicated in the pathogenesis of pre-eclampsia. At the time of writing, these novel therapies are undergoing preclinical or clinical evaluation as indicated in the following examples. The therapies that are currently undergoing clinical trials include selective removal of sFlt-1 through apheresis and administration of relaxin to increase the secretion of VGEF.44 In addition, the inhibitory action of esomeprazole on sFlt-1 and sEng, as well as its antioxidant effect on pre-eclampsia, is undergoing clinical trial in South Africa [24][25]. The therapies that are currently being assessed preclinically include the administration of recombinant human PIGF to reverse angiogenic imbalance, neutralization of excess sFlt-1 with high levels of VEGF expressed by adenovirus, and administration of drugs that block hypoxia-inducible factor-1alpha (HIF1a) to prevent the secretion of sFlt-1 and sEng.44 The drugs that block HIF1a are ouabain, YC-1, and metformin. Apart from metformin, however, the safety of these drugs (i.e., ouabain and YC-1) in pregnancy is a concern.

Prognostication

Reduced gestational circulating level of sFlt-1 has been associated with hypothyroidism during and

after pregnancy[26]. It is possible that some other long-term health issues after a pregnancy complicated by pre-eclampsia may be dependent on the circulating levels of angiogenic factors. Future studies are required to make this clarification.

Other clinical conditions such as isolated IUGR may affect the levels of angiogenic factors and influence test results. This is particularly important when sEng is the biomarker; therefore, patients must be informed of the limitations of measurements. Use of the sFlt-1/PIGF ratio in pre-eclampsia has not been approved in some guidelines. The extent to which these biomarkers satisfy the criteria for an ideal screening test may be debatable. For instance, the American College of Obstetricians and Gynecologists has raised concerns about the low positive predictive value and lack of evidence showing that aspirin and other strategies will reduce the incidence of pre-eclampsia among women categorized as high risk by first-trimester predictive tests[27]. The recently published ASPRE (Aspirin for Evidence-based Preeclampsia Prevention) trial48 has hopefully assisted in providing much-needed clarity about the prophylactic efficacy of aspirin. In the trial, women at high risk of preterm pre-eclampsia (based on multiple risk factors including PIGF) were randomized at 11–13 gestational weeks into two groups receiving either 150 mg of aspirin or placebo from 11–14 to 36 gestational weeks. The incidence of preterm pre-eclampsia was lower in the aspirin than in the placebo group: 1.6% versus 4.3% [28]. The Italian Advisory Board has requested additional local multicenter data before approval of the sFlt-1/PIGF ratio [29]. Such local data are also required in LMIC such as South Africa; in the interim, the use of the test is strongly recommended given the enormous burden of the disease in this setting. Other important considerations are test availability and laboratory turnaround time. Encouragingly, it has been indicated that the results of sFlt-1/PIGF ratio using Elecsys Preeclampsia Immunoassays (Roche Diagnostics) can be available within 18 minutes.36 However, the costs mightlimitthe affordabilityofthe testin LMIC. Unfortunately,these are the settings where the burden of pre-eclampsia is highest. Hopefully, future technologic advancement will result in cost reduction [30].

CONCLUSION

Among the different postulates explaining the pathogenesis of preeclampsia, the two-stage theory and angiogenic imbalance are the most reasonable cause. Assessment of circulating levels of angiogenic factors has vatious clinical roles that might prevent adverse outcomes of pre-eclampsia.

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