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RESEARCH ARTICLE

ROLE OF CYTOKINES IN PRE-ECLAMPSIA: A REVIEW

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Abstract

Preeclampsia is a serious and life-threatening pregnancy complication. Reduced uteroplacental perfusion and oxygen tension; impaired trophoblastic differentiation and invasion; altered placental production of immunomodulators and growth factors are all considered important aspects of the aetiology of the condition. The placenta expresses a variety of pro and anti-inflammatory cytokines, adipokines and cytokine-like angiogenic growth factors, production of which is altered in preeclampsia, driven (at least in part) by hypoxia. Altered levels of cytokines have been measured in the circulation of women with preeclampsia. While the placenta undoubtedly makes an important contribution to plasma cytokine levels, production by maternal peripheral blood mononuclear cells (PBMCs) and other tissues is also likely to be significant, although to what extent remains undetermined. Increased placental expression of soluble receptors occurs with preeclampsia, resulting in elevated circulating concentrations which confer impaired angiogenesis, deficient placental vascularisation, increased placental apoptosis and endothelial dysfunction. The extent to which these changes reflect a response to the disorder, as opposed to being a causative factor in the development of maternal disease is a matter of some debate. Nevertheless, convincing evidence is now accruing that autocrine/paracrine interactions between placental cytokines/growth factors and the maternal endothelium plays a central role in the pathogenesis of preeclampsia.

Introduction:-

The term "cytokine" term is commonly used to define a class of small to medium sized (8-20 kDa range) extracellular signalling proteins typically involved in the regulation of recruitment, activation, proliferation and cell-

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to-cell communication of the immune system . Many cytokines, have more widespread actions, and interact with homeostatic systems such as the endocrine and nervous system. In addition, a number of other protein factors are known which, although not specifically involved in immune activation or resolution, exhibit cytokine-like characteristics. Examples of these discussed in this review include adipocyte derived cytokines (adipokines) and angiogenic-growth factors (angiokines) and various members of the transforming growth factor (TGF)-beta superfamily. Immune mediators, including cytokines, are intimately involved in many aspects of pregnancy – from implantation and placentation, to cervical ripening and uterine activation [1]. Indeed, pregnancy-specific immunomodulation is a prerequisite for successful initiation, maintenance and completion of pregnancy [2]. An over exuberant immune reactions on the other hand associated with the major pregnancy pathologies including recurrent miscarriage, pre-eclampsia, gestational diabetes and preterm labour [3]. The placenta express a wide variety of molecules and hormones [4] typically associated withimmunomodulation and inflammatory activation [3]. Cytokine-related growth/angiogenic factors and theirreceptors are also important regulatory factors of significance in both placental andendothelial pathophysiology [5].

Pre-eclampsia is a relatively common syndrome in pregnancy manifesting in maternal hypertension, proteinuria, and endothelial dysfunction [4] various coagulopathies and an increased systemic inflammatory response [6]. Although the causes of preeclampsia are complex and only partially understood, there is consensus that factors released by the placenta, possibly as a consequence of faulty placentation, may trigger the onset of maternal disease [7]. In this review we will summarise what is known of placental cytokine expression in the context of the causes of preeclampsia and its manifestation, and discuss potential mechanistic links between placenta, cytokines and the disorder.

- **Placental Cytokine Expression In Normal Pregnancy**

Cellular sources and gestational age dependence:

A wide variety of cytokines are produced by placental tissues [4] (including theextraplacental membranes, the amnion, chorion and decidua); these are listed in Table 1. [which is submitted separately]

Placental cytokine expression varies with gestational age. Cytokines are produced by the resident cells of normal healthy placental tissues, as well as by infiltrating leucocytes. Cytokinereceptors are also expressedin placental tissues, indicating that they are bothsources and targets of these important biological mediators.

In the first trimester of pregnancy, tumour necrosis factor (TNF)-alpha, interleukin(IL)-1 alpha, IL-1beta, IL-6, and macrophage inhibitory factor (MIF) expressionhave been documented in placenta/trophoblast and decidua. Placentaltrophoblasts are major producers of the inflammatory cytokines, althoughthese are also secreted by fetal macrophages (Hofbauer cells) andstromal cells in the placenta [8]. In first-trimester deciduas, mRNA and proteinsfor IL-1 beta, IL-1alpha, IL-6, and TNF alpha have been localizedto cells of immune origin [9], but are also produced by other decidual celltypes [8]. Immunodetectable MIF has also been identified in first-trimesterdeciduas [10]. At term, mRNAs for the pro-inflammatory cytokines TNF-alpha,IL-1alpha, IL-1 beta, and IL-6 have been identified in placenta/trophoblast anddecidua and these cytokines are produced and secreted by both tissue types.In the fetal membranes, it has been reported that the chorion containsmRNA for TNF-alpha, IL-1 beta, IL-6, but expresses protein for only IL-1 beta andIL-6 [11], while amnion expresses all three proteins[11]. IL-1 beta is produced byboth trophoblasts and placental macrophages, and trophoblast also release IL-1alpha [12]. IL-1 alpha and IL-1 beta production has been detectedduring the first trimester and at term, declining over the course of gestation [13].

IL-6 is the only villous placental cytokines whose production has been shown to be regulated with the onset of labour [14]. Placental tissues also express and secrete anti-inflammatory cytokines [15].Reports of IL-10 production in the fetal membranes have been inconsistent. Immunohistochemicalresults indicate that abundance of IL-4 and IL-10 in the placenta decreases withincreasing gestational age, while decidua production of these cytokines increases[16]. In contrast, others [17] have been found that secretion of IL-10 by trophoblastin culture was stable over gestation. IL-10, IL-4 [18] and IL-1 receptorantagonist (IL-1ra) [19] have been detected in amniotic fluid collected at term.Increases in amniotic fluid concentrations of both IL-10 [20]and IL-1ra [21]havebeen observed between the second trimester and term.

Amniotic fluid IL-1ra may be derived from the amnion and/or chorion, which arereported to produce this cytokine at term [22]. IL-13 mRNA has been identified in placental trophoblasts from all stages of gestation, but IL-13

immuneoreactivity has only been identified in firsttrimester placenta [23]. A member of the CXC chemokine family, IL-8 is produced constitutively by all the tissues of gestation in the later stages of pregnancyalthough expression of mRNAfor this chemokine does not appear to change[24]. Amniotic fluid containsdetectable levels of IL-8 [25] and another CXC chemokine, GRO-alpha [26]throughout gestation and concentrations of both these chemokine's increase withadvancing gestational age [26]. Similarly, the CXC chemokine ENA-78, which, like IL-8, is aneutrophil attractant, has also been detected in amniotic fluid and is produced bygestational membranes in vitro [27]. Amniotic fluid concentrations of the chemokine IL-16decline from mild-gestation to term [28]. The CC beta chemokine family contains anumber of well characterized chemokine's including the monocyte chemo attractantproteins (MCPs), RANTES (Regulated on activation and normal T-cells expressedand secreted),and the macrophage inflammatory proteins (MIPs). Thesechemokine's primarily activate monocytes, lymphocytes, basophils, and eosinophils.MCP-1 mRNA is present in mid-trimester and term deciduas [29] and the placentathroughout gestation with increased expression in the third trimester, coincidingwith an increase in production of MCP-1 protein [30]. Secretion of MCP-1 fromthird-trimester deciduas, chorion and amnion has also been reported and thiscytokine is also present in amniotic fluid [31]. Of the other CC chemokines, mRNAfor MCP-2 has been detected in placenta [32] and RANTES is secreted from thechorion, deciduas and placenta at term [33]. RANTES is also detectable in amnioticfluid in the second and third trimesters and concentrations of this chemokinesdecrease with advancing gestational age [33]. MIP-1 alpha has also been detected inamniotic fluid at mid gestation at term [34] although it is present in only aproportion of women in absence of labour [35]. Constitutive secretion of MIP-1alpha from gestational tissues has also been reportedalthough cultured humanchorionic [36] and decidual [37] cells from term pregnancies produce thischemokine when stimulated with inflammatory cytokines or bacterial products.

- **Placental Cytokines: Maternal And Placental Aspects**

Within the placenta, cytokines are involved in modulating four fundamental processes [38]:

1) Maternal-Placental Immune Dialogue
2) Trophoblast Invasion and Differentiation
3) Placental Growth, Proliferation and Apoptosis
4) Placental Metabolic and Endocrine Homeostasis
5) Placental Angiogenesis

Establishment of placental immune privilege around the time of implantationinvolves coordinated actions of cytokines such as IL-1, IL-11, leukaemiainhibitory factor (LIF), colony stimulating factor (CSF)-1 and interferon (IFN)-gamma at the feto-maternal interface [39]. The pro-inflammatory cytokines IL-1, LIF promote trophoblast differentiation towards aninvasive phenotype, whereas TGF-beta exerts generally inhibitory functions inthe placenta, most notably on trophoblast proliferation, invasion anddifferentiation [40]. Another immunosuppressive cytokine, IL-10, alsoinhibits invasion through decreased placental MMP release [41]. Angiogeniccytokines vascular endothelial growth factor (VEGF) and placental growthfactor (PIGF) are expressed in the placenta and modulate extra villoustrophoblast proliferation but not invasion or migration [42].TNF-alpha, INF-gamma and placental-TGF-beta are also inducers of trophoblast apoptosis [43], whereas VEGF and PIGF have anti-apoptotic properties [44]. Finally placental angiogenesis has been shown to be regulated by factors such as VEGF/PIGF [44] and leptin [45].

In addition to their intra-placental actions cytokines produced by the placenta enter the maternal circulation and interact with maternal endothelial and hematopoietic cells, although it must not be forgotten that cells within the vasculature are also sources of cytokines [46]. TNF-alpha, which is produced by fetoplacental macrophages and trophoblasts, exerts potent effects on endothelial and platelet functions promoting enhanced coagulation micro vascular leakage, vasoconstriction, endothelial activation, tissue factor, and inflammatory cytokine production [47]. It is likely that the placental cytokines play a major role in the second half of pregnancy which is a defining characteristic of preeclampsia. However placental angiogenic growth factors also have a profound influence on the pathogenesis of preeclampsia via their effects on maternal vascular endothelium [48]. Numerous studies have also documented abnormal cytokine production in thepre-eclamptic placenta. Expression array studies conducted by Pang andcolleagues [49] indicated widespread regulation of expression of cytokines andtheir receptors in the placentas of pre-eclamptic pregnancies, findings that aresupported by more focused studies.

Anti-Inflammatory Cytokines

While preeclampsia appears to be associated with a general increase in placentalcytokine production, decreased expression of IL-15 and IL-10, togetherwith reduced serum IL-10 concentrations have been described.

Additionally,links between a distinct IL-10 genotype and risk of preeclampsia have also beenidentified [50], and an intriguing relationship between HLA-Ggenotype and PBMC IL-10 expression has recently been described [51].

It is interesting to note, however, that negative correlations between blood pressureand circulating IL-10 levels have been observed [52], a relationship that has beendocumented experimentally in non-human primates. These observations mightpredict therefore, that preeclampsia would be associated with reduced systemicIL-10 bioactivity, a possibility that is certainly supported by several reports.

Angiogenic Cytokines

A number of growth factors/cytokines with angiogenic properties have been activelystudied in the context of preeclampsia (Figure 1). The VEGF family, has been of great interest, due to its known association with hypertension andnephropathy, and its role as a biomarker of endothelial dysfunction, inflammation,platelet activation and tissue hypoxia [53]. VEGF is produced by endothelial cellsin response to hypoxia, mechanical stretch, and vasoconstrictors such asangiotensin-II and endothelin [53]. The placenta also expresses VEGF and in addition expresses and secrets placental growth factor (PIGF)[54], which shares marked homology with VEGF and acts via its receptors[55]. Activity of VEGF and PIGF are modulated in part by binding to solublereceptors and other binding proteins [52]. A soluble form of VEGF receptor 1, solublefms-like tyrosine kinase-1 (sFlt-1/sVEGFR 1), is produced by the placentaand is readily detectable in maternal plasma [56]. Animalstudies [56] and human pharmacological findings [57] collectively suggestthat antagonism of VEGF activity results in hypertension and proteinuria.Evidence from immunehistochemical [54]and mRNA expression studies [58]Indicates that placental VEGF expression is decreased with preeclampsia, althoughincreased [59] or unaltered [60] expression has also been reported.Bates et al [61] recently presented evidence of dysregulation of VEGF mRNAsplicing with preeclampsia, resulting in changes in ratios of active and inactiveisoforms. PBMCs also contribute to circulating sFLT-1 levels. Somewhat surprisingly PBMCs fromwomen with potent driver of placental VEGF expression [62], whereasPIGF expression, in contrast is down-regulated by hypoxia and villous capillariesis observed. There is substantial evidence of alterations in circulating VEGF, PIGF, and sFIT-1levels with preeclampsia. Earlier studies reported increased VEGF levels inmaternal circulation with preeclampsia [63]. However there is now some consensus thatin women with established disease, levels of VEGF and PIGF are significantlyreduced [64], while sFlt-1 levels are increased compared to controls[65], preceding the onset of clinical disease by several (up to 10) weeks[66]. Enhanced urinary VEGF clearance rates in preeclampsia probablycontribute to this phenomenon, in addition to altered VEGF expression andproduction [67]. Assay that measure free VEGF and PIGF report the mostdramatic decreases in maternal plasma VEGF/PIGF concentration withpreeclampsia [68]. Lower plasma VEGF/PIGF concentrations [64] andhigher sflt-1: PIGF ratios [65] are also present with severe or earlier onsetdisease. Soluble sFlt-1 in preeclampsia serum has been shown experimentally toinhibit VEGF-mediated angiogenesis [69], therefore increased sFlt-1 inpreeclampsia production and increased sFlt-1 production and decreased VEGFactivity could be an explanation for the angiogenic abnormalities seen in severepre-eclamptic pregnancies, possibly reflecting a response to hyperoxic conditionslater in pregnancy [70]. The fact that these changes can occur prior to developmentof preeclampsia, and that sFlt-1 abrogates the angiogeniceffects of VEGF in the placenta [71], suggests that the angiogenic imbalancecharacterized by decreased VEGF/PIGF activity and increased sFlt-1 levels mayhave a causative role in pre-eclamsia through impaired placental vascularisation.

Adipocytokines

Leptin mRNA expression in placentas from pre-eclamptic pregnancies is markedly higher thannormotensive controls [72]. The cellular source is probably thesyncytiotrophoblast and villous vascular endothelial cells [73], althoughinterestingly villous mesenchymal cells were identified immunohistochemically asthe source of increased leptin production in pre-eclamptic placentas in one study. Placental leptin is exported to both the maternal and fetal compartments [74], so in theory the greater production by the placenta in preeclampsia could contribute to elevated circulating levels in bothmother and baby. These findings are corroborated by reports of elevated maternalplasma leptin concentrations with preeclampsia [75], although thisrelationship has been reported to be markedly influenced by maternal body massindex and has not been found in all studies [76]. Some researchers havefound that the increase in leptin is evident only in the third trimester [77], whileothers found that they precede onset of clinical disease and are evident in midpregnancy [78]. Cytokines such as IL-1beta and TNF-alpha stimulate placentalleptin expression, and a correlation between maternal serum leptin and TNFalpha has been described [79]. The effects of elevated leptin in preeclampsia havebeen speculated to include enhanced fetal growth and protection againstinflammatory cytokine-induced apoptosis, [80] reflecting a compensatory or protective role. Leptin may play a direct role in pathophysiology of preeclampsia by TH1 stimulation and sympathetic activity [80] (Figure 1). Like

leptin, maternal circulating adiponectin levels are altered in preeclampsia, at least in the third trimester. However, there are conflicting reports of the nature of the alteration, with some finding evidence of increased levels [81] and others reporting decreased levels [82]. These apparent conflicts may relate to differential responses according to BMI [83]. The presence of different forms of adiponectin in the circulation might also contribute to the discrepancies observed. Adiponectin is expressed in the placenta and is a product of the placental syncytiumand regulated by cytokines such as TNF-alpha and IL-6 [84]. Corbetta and co-workers described adiponectin expression in fetal tissues [85], although surprisingly were unable to confirm its expression in the placenta. Adiponectin is usually attributed anti-inflammatory actions [86], and hence may counter the pro-inflammatory effects of other adipokines.

A molecule only recently identified as an adipokine is visfatin, also known aspre-B-cell colony – enhancing factor (PBEF). Visfatin, an insulin mimetic shown tobe responsive to plasma glucose [87] and free fatty acid concentrations, is alsoexpressed in the placenta and gestational membranes as well as immune cellsVisfatin expression is responsive to regulation by inflammatory signals [88]. Its association with inflammatory NFkappa B signalling may implicate placental visfatin, as no study describing visfatin in pregnancy with or without pre-eclampsia is known. [89].

Cytokines and Placental Prostanoids

During normal pregnancy the placenta produces roughly equivalent amounts of thromboxane and prostacyclin, two potent vasoconstrictor and vasodilator. However, in pre-eclampticpregnancies the production of thromboxane greatly exceeds that of prostacyclin[90]. This disruption of placental prostaglandin synthesis is not observed inIUGR (Intra-uterine growth retardation) without hypertension. A decrease in placental IL-8 production associated with the decrease in prostacyclinhas been reported for villous tissuesfrom pre-eclamptic pregnancies. Treatment of these tissues with IL-8 improvesplacental prostacyclin production suggesting a role for this cytokine inmaintaining prostaglandin balance during pregnancy. Pro-inflammatory cytokinessuch as TNF-alpha and IL-1 beta are stimulators of placental PG production viaenhanced expression of the COX-2 enzyme [91]. Activation is also able tostimulate placental COX-2 expression and PG production at physiologicaloncentrations (Keelan& Mitchell, unpublished observations). Hence, disturbancein placental prostanoid level might be secondary to changes in local cytokinesproduction and action.

Placental Hypoxia and Hypoxia Inducible Factor

Hypoxia inducible factor (HIF) is a heterodimeric transcription factor that isregulated by hypoxia. HIF-1 is expressed in the placenta in a gestational-age dependent fashion [92], with levels being higher in the first trimester declining as oxygen levels increase later inpregnancy [92]. The work of Dahl and colleagues suggests that HIF activation is closely involved in regulating placental morphogenesis, angiogenesis and trophoblast differentiation [93], while Caniggia and Winter proposed thatpre-eclampsia can result from a failure of the placenta to respond appropriately tochanging oxygen tension during placental development by reducing HIF expression. Under hypoxic conditions, HIF-1 is stabilized and transactivates oxygen regulated genes such as VEGF and iNOS. Mice lacking the HIF-1 beta sub-unit, with subsequent loss of responsiveness to hypoxia exhibit abnormalities in trophoblast population in their placentas, combined with aberrantplacental vascularisation [94]. A recent report by Schaffer and colleagues demonstrated however, that in murine pregnancy mechanisms exist to protect theplacenta from acute hypoxia and subsequent HIF-1 activation [95]. Nevertheless, studies of placental structure in human high altitude pregnancies suggest that the placenta is able to adapt to protect itself fromthe effects of hypoxia. The extent to which such protective mechanism mightbe significant in the establishment of the pre-eclamptic placenta is uncertain.

Placental Cytokine Expression in Response to Hypoxia

Hypoxia regulates the expression of a number of genes that have importantimplications to our understanding of the pathogenesis of preeclampsia. VEGF, an archetypal hypoxia-driven geneis expressed in the placenta under the influence of HIF activation as is Flt-1 [96] and leptin [72]. A newly-identified form of VEGF called endocrine gland derived VEGF (EG-VEGF) is also hypoxia-responsive and a product of trophoblast cells [97].

These data regarding hypoxia-induced increased VEGF expression are somewhat in conflictwith findings of decreased placental VEGF expression and maternal plasmaconcentrations with preeclampsia [56], although reports to the contrary have also been published. Increased circulating sFlt-1 a concentration with preeclampsia has been consistently described [6]. In contrast hypoxia down-regulates placental PIGF expression [62]. Collectively, these changes are postulated to result in reduced angiogenic activity and hence impaired placental perfusion. Expression

of TGF-beta3 in the placenta is increased by hypoxia/HIF-1 [98], and alterations in expression of this cytokines have been put forward as a causal factor in the failure of trophoblastic invasion and maturation associated with pre-eclampsia. A marked decrease in transcription of TGF-beta3 after 9 weeks of gestation in normal pregnancy has been documented correlating with an increase in trophoblast differentiation and invasion [98] and increased perfusion.

However, TGF-beta3 is over-expressed in placentas from pre-eclamptic pregnancies, inhibition of TGF-beta3 expression or activity restores the invasive capability of explants of pre-eclamptic placentas to normal levels [98]. Importantly, elevated levels of HIF-1 have been documented in placentas from pre-eclamptic pregnancies, while placental HIF-1 expression is in turn up-regulated by TGF-beta [99]. Hypoxia also induces the expression of several pro-inflammatory cytokines in the placenta including IL-1 alpha, IL-1 beta and TNF-alpha, presumably acting through the HIF-1 alpha transcription factor. Placental IL-6 expression however, does not appear to be hypoxia-regulated [100]. IL-1 beta also increases expression of HIF-1 alpha and VEGF in the placenta [101].

With respect to anti-inflammatory cytokines, IL-10 production in pre-eclampsia derived trophoblasts has been reported to be reduced with hypoxia, although incontrast trophoblast IL-6/8 production was increased in cells from both normaland pre-eclamptic placentas. Whether this observation is related to increase HIF-1expression with preeclampsia remains to be determined. Science IL-10 is a potent suppressor of pro-inflammatory cytokines production (TNF-alpha in particular), finding may indicate that the pre-eclamptic placenta responds abnormally to hypoxia with inadequate IL-10 production, resulting in increased production ofinflammatory cytokines, thereby contributing to the maternal intravascular disease.Reduced IL-10 bioactivity within the placenta might also influenceinvasion/differentiation through diminished suppression of placental proteaserelease, although increased expression of placental IL-10 receptors documented withpre-eclampsia might compensate for the low levels of ligand. The recent finding thatIL-10 may have compensatory vasodilators effects in maternal vasculature early in pregnancy adds further interest to this observation [102]. Hypoxia has been explored as the cause of elevated expression and production of activin A and inhibin A [103]. However, contrary to expectation, two groups found that hypoxia lowers activation within the placenta disproving what was otherwise an attractive hypothesis [103].

Cytokine Polymorphisms and Preeclampsia

Preeclampsia has an inheritable component, and as such has been the subject ofmany genetic studies. Among theseseveral studies of maternal genotype (not fetal/placental)have been published to explore associations between preeclampsia and polymorphisms in cytokine genes.In a study of siblings from 150 Dutch families, nine polymorphisms in the TNF/LTApromoter region were studied but none showed any significant linkage withpreeclampsia [104]. Interestingly in the study the presence of the TNF-1 haplotypewas significantly associated with preeclampsia or HELLP syndrome, but not foundin similarly affected sisters. Livingstone et al. [105] also failed to find evidence ofaltered genotypic frequencies of TNF-alpha mutant alleles in women with severepreeclampsia. Similar negative findings have been reported by others [106]. Incontrast, several other studies have found interesting associations between TNFpromoter polymorphisms and preeclampsia. In a recent study involving 133finishwomen with preeclampsia investigators found two polymorphism in the TNF-alpha promoter (-308A and -580T) to be associated with susceptibility topreeclampsia (the variant A allele being overrepresented in the preeclampsiagroup). In contrast, Heiskanen at al [107] found significant genotype distribution ofthe C-805T polymorphism in women with preeclampsia (reduced incidence of thevariant T allele) suggesting a protective effect of the variant allele. In a much largerGerman study of 1480 women in significant association was found between the TNFalpha -308A allele and increased urinary protein secretion but not hypertension,although when combined with an IL-6 promoter polymorphism carriers of bothalleles did have significantly elevated blood pressure [108]. Circulating TNF-alphaconcentrations were measured in these studies, unfortunately, so the functionimpact of the polymorphism on expression and secretion of TNF-alpha is unknown.Hefler et al. [109] studied three polymorphisms in the IL-1 beta andIL-RA genes and their association with preeclampsia in a Hispanic population, but foundno evidence of a causative association. A mutation in theinhibin-alpha gene was investigated in 50 women with preeclampsia, but this was notsignificantly associated with the condition.Maternal VEGF polymorphisms and preeclampsia have been studied. Papazoglou et al[110] found no significant associations between any of three VEGF polymorphisms (-2578C/A, -634G/C, 936C/T) and preeclampsia. However, increased frequency of the936C/T polymorphism in association with severe preeclampsia suggests that this allelemay affect disease severity. In the most recent study of this topic to bepublished Banyaszet al [111] explored the association between two VEGF polymorphisms and risk of preeclampsia in 84 women with severe preeclampsia and 96 normotensive controls. Carriers of the +405G allele had decreasedsusceptibility to preeclampsia. Again, VEGF protein/ bioactivity

were not measured, andthe mechanistic significance of this association awaits explanation. No data on placentalVEGF polymorphisms and preeclampsia have been described.

In summary, studies of cytokines polymorphisms and preeclampsia have beeninconclusive due to small sample size, variations in study populations, and lack ofphenotypic data on cytokines production, plasma concentrations or bioactivity.

Conclusion:-

Studies performed over the past two decades have helped to shed considerable lighton the role of placental cytokines and cytokine-like factors in the pathophysiology ofpreeclampsia. Despite the surprisingly large amount of contradictory data that hasbeen published.The collective weight of evidence now strongly supports the view thatinteractions between increased placental cytokine expression and decreasedangiogenic activity (due mainly to elevated circulating soluble receptors levels)constitute an important link between the etiology of the disorder and thepathogenesis of maternal disease. There remain several outstandingquestions requiring clarification.

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The authors confirm that the data supporting the findings of this study are share upon request/ available within the article as supplementary materials/ openly available and [URL/ DOI] are given in references [1-110] at the end of the paper.

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