

Preeclampsia and Periodontitis- Unearthing the Hidden Links.

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ABSTRACT-

Periodontal disease is a chronic inflammatory disease affecting the tooth supporting tissues and caused by gram negative anaerobic microorganisms. Preeclampsia is a pregnancy specific disease characterized by hypertension and proteinuria which affects 5-10% of pregnancies causing maternal & perinatal morbidity which can lead to mortality. This is due to infection and inflammatory responses. This article probes the relationship of preeclampsia with periodontitis and the various risk factors and mediators. Special lights are thrown into the pathogenic mechanism involved in preeclampsia highlighting the genetic and immunological aspects. The various protective and safer treatment modalities for preeclamptic women have also been discussed. Hence the article brings to light possible links between preeclampsia and periodontitis and evidences of the various treatment modalities being used till date.

KEY WORDS: *Periodontitis, Preeclampsia, Endothelin 1, Inflammatory Mediators, cytokines.*

INTRODUCTION

Periodontal disease is a chronic inflammatory disease affecting the tooth supporting tissues and caused by gram negative anaerobic microorganisms.[1] Though oral microorganisms initiate periodontitis, the severity of the periodontal

breakdown is orchestrated by the inflammatory response of the host.[2]

It has been proposed that endotoxins of periodontopathic bacteria in the systemic circulation may induce cytokine production.[3] This results in

the activation of inflammatory and endothelial cells resulting in endothelial dysfunction. [4]

Preeclampsia is a pregnancy specific disease by hypertension and proteinuria and affecting 5-10% of pregnancies causing maternal & perinatal morbidity which leads to mortality. [5],[6] Although the causes of preeclampsia are cloudy, maternal infection is considered as the main risk factor.[7] Translocation of periodontopathogens and its endotoxins into the utero placental unit can trigger an oxidative stress early in pregnancy which ultimately produce placental damage and cause preeclampsia. [6] It usually manifests at 20 weeks of gestation with blood pressure exceeding 140/90mm of mercury and proteinuria exceeding 30mg in a 24 hour urine sample. It is also characterised by generalised oedema and in severe cases, alterations in coagulation systems and liver function may occur.[8]

PHYSIOLOGICAL MECHANISM OF NORMAL PREGNANCY

The placenta which is totally derived from the foetus after conception invades and grows totally supported by the maternal uterine tissue. As the foetus grows, the need for the nutrition increases causing decrease in space which becomes a critical parameter for the survival of both the mother and the foetus. As pregnancy progresses amniotic fluid levels of prostaglandin E₂ (PG E₂) and inflammatory cytokines such as TNF- α and IL-1 β rise until a critical threshold level is reached to induce rupture of the amniotic sac membrane,

uterine contraction, cervical dilation and delivery.[9]

PREECLAMPSIA AND THE MEDIATORS INVOLVED

Preeclampsia, which occurs only during pregnancy primarily, affects the pregnant women. The manifestations are increased blood pressure, maternal protein urea and also associated with high levels of pro inflammatory cytokines. [10] Increased maternal serum levels of pro inflammatory cytokines such as IL-1, IL-8, IL-6 are also associated with pre-maturity or low birth weight.[11] C-reactive protein which is an acute phase reactant which is synthesized in response to pro-inflammatory cytokines by the liver is also associated with pre-eclampsia.[12] Where CRP is a short pentraxin produced in the liver, another counterpart in the pentraxin family is the long pentraxin called Pentraxin 3(PTX3). PTX3 is produced by a variety of cells including fibroblasts, mononuclear phagocytes, vascular endothelial cells and smooth muscle cells.[13] Pentraxin 3 is known to cause endothelial dysfunction and inflammation in preeclamptic women. PTX3 levels have been found to be elevated at the time of normal pregnancy. However, the levels are significantly higher in preeclamptic women when compared to normal pregnancy.[14],[15] Other factors like Endothelin 1, Sflt-1, Nitric Oxide, Tumour Necrosis Factor alpha, Thromboxane A₂ have also been suspected to play a role in Preeclampsia.[16],[17],[18],[19]

RISK FACTORS OF PREECLAMPSIA

The common risk factors for preeclampsia are diabetes mellitus, obesity, family history of preeclampsia, mother's age, history of chronic kidney disease, hypertension, anti-phospholipid antibody syndrome and multiple gestations.[20] Another important risk factor is the chronic systemic inflammatory challenge in the body.[21] Periodontitis has been implicated as a systemic exposure and is considered a potential risk factor for adverse pregnancy outcomes such as preeclampsia.[22],[23]

CLASSIFICATION OF PREECLAMPSIA

American Congress of Obstetricians and Gynaecologists (ACOG) classified preeclampsia based on the severity using parameters such as blood pressure and systemic involvement. They categorised preeclampsia as mild to moderate and a severe group. Mild to moderate preeclampsia include blood pressure of 140 to 159 mmHg systolic and/or 90 to 109 mmHg diastolic.

Severe preeclampsia is said to set in if one or more of the following criteria are present; i.e. BP is ≥ 160 mmHg systolic and/or ≥ 110 mmHg diastolic (on 2 occasions at least 6 hours apart, while the patient is on bed rest), proteinuria of ≥ 5 g/24 hours or $\geq 3+$ (on 2 random urine samples, collected at least 4 hours apart), oliguria < 500 mL/24 hours, cerebral or visual disturbances, pulmonary oedema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, fetal growth restriction.

National Institute for Health Care and Excellence (NICE, UK) classified the severity of disease based on BP measurement alone. They were broadly classified as mild (BP is 140 to 149 mmHg systolic and/or 90 to 99 mmHg diastolic), moderate (BP is 150 to 159 mmHg systolic and/or 100 to 109 mmHg diastolic) and severe (BP is ≥ 160 mmHg systolic and/or ≥ 110 mmHg diastolic).

HELLP SYNDROME

WEINSTEIN in 1982 classified the severe form of preeclampsia associated with haemolysis, elevated liver enzymes and thrombocytopenia in to a separate entity named HELLP. HELLP stands for H=haemolysis, EL=elevated liver enzymes, LP=low platelet.[24] The three features constitute the triad and presence of one or two elements results in partial HELLP. Women with increased gestational age and with multiparous pregnancy are more prone to develop HELLP than preeclampsia.[25],[26] Hypertension, proteinuria, epigastric pain, nausea and vomiting are the common symptoms noticed in most of the women with the HELLP syndrome. [27]

PATHOGENIC MECHANISMS OF PREECLAMPSIA

There are two mechanisms governing the pathophysiology of preeclampsia. One is the circulating inflammatory mediators and another is the placental ischemia.[28],[29] As pregnancy progresses, due to abnormal placentation, there is placental hypoxia and ischemia. This causes an increase in the level of soluble endothelial growth factor (VEGF) receptor sFlt which lacks the

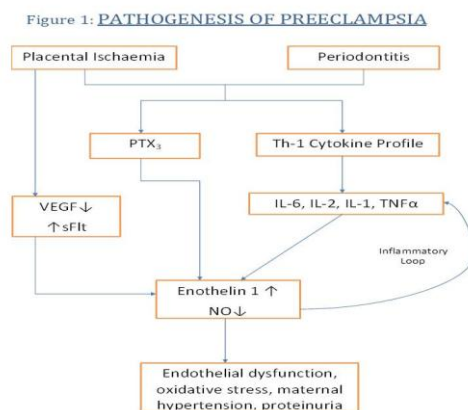
anchoring transmembrane and cytoplasmic domains, making it soluble, thereby producing a decrease in the binding VEGF making it unavailable for normal function.[29] This leads to endothelial dysfunction as VEGF plays a major role in the maintenance and propagation of endothelial cells.[30](Refer Figure. 1)

Another important mediator with increasing evidence in the pathophysiology of preeclampsia is endothelin 1. Endothelin 1 is one of the most powerful vasoconstrictor in the body. Taylor et al in 1990 concluded that endothelin 1 was found in normal pregnancy but its concentrations increased profoundly in preeclamptic women.[31] The concentration of Endothelin 1 also increased with the severity of the disease.[32] There also exists an important link between Endothelin 1 and inflammatory mediators. Endothelin 1 could stimulate neutrophils to release elastase, activate mast cells and stimulate monocytes to produce a variety of cytokines such as IL-1 β , IL-6 and TNF- α which plays an important role in the initiation and progression of periodontal disease.[33],[34],[35]

Periodontitis is a chronic inflammatory disease that results from a complex poly-microbial infection, leading to tissue destruction.[36] One of the key pathogens in the progression of periodontitis is *Porphyromonas gingivalis*.[37] During initiation and progression of periodontal disease, inflammatory cytokines are also known to play an important role. Several reports have suggested a relationship between the progression of periodontitis and the expression of IL-1, IL-6, IL-8

and TNF α in gingival tissues.[38],[39] In-vitro studies have shown that *P.gingivalis* stimulates the expression of Endothelin 1 with upregulation of proinflammatory cytokines and intercellular adhesion molecule 1 in the gingival epithelial cells in an autocrine or paracrine manner. [33],[40] IL-1 β , a proinflammatory cytokine, was found to correlate with Endothelin 1 levels in the gingival tissues which can attribute to the inflammatory loop seen in periodontitis. Additionally, the secreted IL-1 β in turn stimulates the expression of ET-1 in gingival tissues.[41]

Vascular effects of endothelin 1 are mediated by at least 2 receptor subtypes, Endothelin receptor type A (ET_AR) and Type B (ET_BR).[42] There are 3 known ET receptors, ET_A, ET_B and ET_C. ET_A receptors mediate vasoconstriction and cell proliferation whereas ET_B receptors are important for ET clearance, endothelial cell survival, release of NO and prostacyclin and the inhibition of ECE-1. ET_C receptor is scant and additional studies are required to further characterize this ET receptor subtype.[43]



GENETICS OF PREECLAMPSIA

While it has been traditionally assumed that preeclampsia is a self-limited disease that resolves once the baby and placenta are delivered, some studies have shown that this maternal endothelial dysfunction can last for years after the episode of preeclampsia .[44],[45]The children born after a pregnancy complicated by preeclampsia have also been shown to be at high risk for complications like diabetes mellitus, cardiovascular disease, and hypertension.[46],[47]Moreover, it is believed that paternal genes also play an important role in the development of preeclampsia. This is evidenced by the risk of preeclampsia in women with pregnancies of men who have previously been involved in pregnancies complicated with preeclampsia.[48],[49] A large genetic association study of preeclampsia was published by Goddard et al[50] that reported a study evaluating 775 SNPs in 190 genes in more than 350 preeclamptic mother and offspring pairs and 600 control pairs. They detected six genes with significant maternal-fetal genotype interaction related to preeclampsia in IGF₁, IL₄R, IGF₂R, GNB₃, CSF₁ and THBS₄. These findings and others suggest a multifactorial polygenic inheritance with a genetic component in the development of this disease.[51],[52]

IMMUNOLOGICAL ASPECT

In normal pregnancy, there is a shift towards a Th₂-type immune response which protects the baby from a Th₁- type (cytotoxic) response which could harm the baby with its products like interleukin-2, IL-12,

interferon γ (IFN γ), and tumor necrosis factor α (TNF α). [53] Type ₁ CD₄⁺ T cells (Th₁) produce an array of inflammatory cytokines including INF- γ . IL-2 and TNF α and are major effectors of phagocyte-mediated host defence, protective against intracellular pathogens. Type₂ CD₄⁺ cells (Th₂) produce IL-4, IL-5, IL-13, IL-10 and IL-6. Whilst IL-4 and IL-10 are considered to be anti-inflammatory cytokines, IL-6 has proinflammatory properties.[54] Th₂ cytokines are associated with strong antibody responses[55] and also promotes the growth and differentiation of eosinophils.[56] Clark et al in 1998 reinforced this hypothesis by murine studies and established that proinflammatory cytokines like IL-2, IFN and TNF α , being Th₁ in nature, induce miscarriage which can be reversed by the inhibitors of Th₁ cytokines and administration of Th₂ cytokine IL-10.[57] Thus inflammation appears to be the link between the adaptive immune response and the occurrence of preeclampsia. Systemic inflammation in preeclampsia appears to favour a preponderance of Th₁- type reaction.[53]

TREATMENT OF PREECLAMPSIA

Magnesium sulphate is the most effective agent used in the prevention of eclampsia in patients with preeclampsia. It acts by decreasing the blood pressure thereby preventing vasoconstriction. In addition, it has an anti-seizure effect. In preeclamptic women, it reduces the pulsatility index in uterine, umbilicus and fetal arteries[58],[59] and normalizes placental interleukin-6 secretion.[60] It also supports as an anti-inflammatory agent.

Aspirin has anti-inflammatory actions. Its effect of restoring balance between thromboxane and prostacyclins in the vasculature is used in the prevention of preeclampsia. However, considerations must be given to the toxicity in the gastro intestinal tract and renal function effects.[61] The initial randomized studies showed that aspirin, being an anti-platelet agent reduces the risk of hypertension and proteinuria.[62],[63],[64] Later studies of larger trials were disappointing as they failed to produce statistical evidence of the desired outcomes.[65]

Calcium supplementation: The role of calcium supplementation in preeclampsia is explained by reduction in parathyroid calcium release and intra cellular calcium concentration thereby reducing smooth muscle contractility and promoting vasodilation.[66] This indirectly increases magnesium levels preventing eclampsia.[67]

Antioxidants: Since preeclampsia is suggestive of increased oxidative stress and derangement of oxidative stress,[68] antioxidants such as vitamin E and C are employed in management of preeclampsia. However, a multi-center, randomized, double blinded trial study made by the World Health Organisation on the use of antioxidants such as Vitamin C and Vitamin E has not proved to be effective in management of preeclampsia.[69]

Endothelin antagonists: since endothelin nitrous oxide has been proved to play a role in the pathogenesis of preeclampsia, studies have been made to investigate on endothelin antagonists to

play a role on the treatment of preeclampsia. The use of endothelin antagonist in early stage of pregnancy induces birth defects according to some studies.[70] Investigations to find the therapeutic and preventive measures of maternal and fetal morbidity from preeclampsia are still under progress.[71]

Nitric oxide donors: as preeclampsia is manifested with reduced synthesis of vasodilators and increased synthesis of vasoconstrictors. Investigations have been made on the therapeutic use of nitrous oxide donors in the treatment and prevention of preeclampsia. Consistent observations have proven that nitrous oxide donor supplements have been effective on the treatment of preeclampsia.[72],[73],[74],[75]

Corticosteroid treatment has been shown to accelerate foetal lung maturation through a complex interaction of hormones and intercellular signalling that leads to differentiation of the surfactant lipid-protein pathway and thus increases lung compliance[76] *Betamethasone* has been recommended as a drug of choice for promotion of foetal lung maturation[77] and is proved to be safer and more protective.[78]

Garlic has been used in the form of dried powder for the treatment of preeclampsia as it reduces both systolic and diastolic blood pressure.[79] It also increases the production of nitric oxide and was reported as a platelet inhibitor and a vasodilator too.[80]

COCHRANE REVIEWS:

Cochrane review suggested insufficient evidence on nitric oxide precursors in the prevention of preeclampsia and its complication.[81] Another review concluded that calcium supplementation seems to approximately reduce half the risk of preeclampsia, especially in high risk women with previous low calcium intake.[82]

The Cochrane review in 2006 and 2008 concluded that there is insufficient evidence to recommend increased intake of garlic and antioxidants for the prevention of preeclampsia and its complications.[83],[84]

However, a systematic review by Duley L in 2007 showed that anti platelet drugs, especially low dose aspirin has moderate benefits when used for preeclampsia and its consequences.[86]

STUDIES

Ide M and Papapanou PN in 2013 concluded that maternal periodontitis is significantly associated with preeclampsia.[86] Matevosyan NR in 2011 concluded that maternal periodontitis is strongly associated with preeclampsia and prematurity.[87] Consensus report of the joint EFP/AAP workshop on periodontitis and systemic diseases concluded that there is a significant association between chronic periodontitis, prematurity and low birth weight.[88]

Lopez et al in 2002 conducted a randomised controlled trial in which it was concluded that periodontal treatment reduces significantly the incidence of premature birth or low birth weight in women with periodontitis.

However, Michalowicz in 2006[89] and Offenbacher in 2000[90] did a randomised control trial and found that periodontal treatment did not significantly alter the incidence of preeclampsia.

CONCLUSION

This review sheds light on the various potential pathogenic mechanisms by which periodontitis influences preeclampsia. An insight into the immunological and genetic aspects predisposing preeclampsia, has led to the development of treatment modalities aimed at inhibiting the actions of various inflammatory mediators. This has led to the understanding of the importance of prevention of periodontal disease in pregnant women. This warrants for more research and systemic reviews to be carried out in different ethnic population.

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