Indian Journal of Dental Sciences.
September 2011 Issue:3, Vol.:3
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Review Article

Indian Journal
of Dental Sciences

E ISSN NO. 2231-2293
P ISSN NO. 0976-4003

Preeclampsia - An Oral Infectious Etiology?

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Date of Submission : 17/02/2011
Date of Acceptance : 26/02/2011

Abstract
Preeclampsia is a common hypertensive disorder of pregnancy, affecting 5-10% of pregnancies and contributing significantly to natural and periodontal morbidity and mortality. It has been recently studied that women were at higher risk for preeclampsia, if they had severe periodontal disease at delivery. Periodontal disease may provide a chronic burden of endotoxin and inflammatory cytokines, which serve to initiate and exacerbate atherogenesis and thrombogenesis. It is possible that the placenta may be similarly burdened in pregnant women who develop preeclampsia. Preeclampsia and periodontitis are both mutlifactorial diseases and obtaining a good oral hygiene measures can reduce the risk for periodontal disease there by also reducing the further risk for preeclampsia in the pregnant women.

Key Words
Pigmentation, Laugier-Hunziker syndrome, Peutz-Jeghers syndrome.

Introduction:
Periodontitis is an inflammatory disease that affects the supporting tissues of the teeth, causing progressive destruction of connective tissue attachment and loss of alveolar bone. This causes formation of a periodontal pocket defined as apical migration of junctional epithelium as well as deepening of gingival sulcus, along with production of pro inflammatory cytokines. Due to its chronic inflammatory nature, periodontitis can be considered as a systemic exposure leading to a variety of systemic illnesses.[1] Periodontitis causes bleeding gingiva when brushing, spacing of teeth due to pathologic migration, mobility and areas oflocalized pain.[2] This disease characterized as a chronic low-grade systemic stressor is associated with various systemic illness such as atherosclerosis, diabetes and respiratory disorders.[1] Detection of oral pathogens in atherosclerotic plaque confirms their role in development and progression of atherosclerosis leading to coronary heart disease.[1]

Preeclampsia is a dangerous disease of human pregnancy, which affects both the mother and her fetus. It is defined as blood pressure >140/90mmHg on two separate occasions after week 20 of gestation and $\geq$ + 1 proteinuria.[3] It is a common obstetric syndrome affecting approximately 7-10% of pregnant women and remains one of the two most common causes of maternal mortality in the developed world. There are two syndromes in preeclampsia. The first is maternal, characterised by endothelial cell activation, hypertension and proteinuria. The second is foetal, manifested primarily by intrauterine growth restriction. The symptoms of this syndrome appear during the second and third trimester of pregnancy. Although this disease is of major obstetric importance throughout the world, it remains enigmatic. Despite extensive research, neither its cause nor possible mechanism has been clearly defined.[4] It is characterised by abnormal vascular response to placentation, reduced organ perfusion, vasospasm, activation of the coagulation system, inflammatory-like responses, oxidative stress and some perturbations in volume and blood pressure control, affecting the placenta, kidney, liver and brain. Recent studies suggest that periodontal inflammation plays a key role in causing preeclampsia or its manifestations. Normal pregnancy evokes a mild increase in the systemic inflammatory response that becomes considerably greater in preeclampsia.[5] Periodontal disease may also serve primarily as a vascular stressor and bring an additional infectious / inflammatory burden to the placental-foetal unit, thereby increasing the risk of preterm delivery in preeclamptic women.[6] Based on this concept, some authors have hypothesized that infection might be involved in the aetiology and pathogenesis of preeclampsia, both in terms of its initiation (by increasing the risk of acute uteroplacental atherosis) and/or its potentiation (by amplifying the maternal systemic inflammatory response).[5]

Incidence of Preeclampsia:
The incidence of preeclampsia in India is around 10% and around 2-5% in the U.S.[7] It occurs mostly in the second or third trimester i.e. around 32nd week or as early as 20 weeks, though it is rare. It is more common in women with first pregnancies, women having pre existing hypertension, diabetes, autoimmune diseases like lupus, inherited thrombophilias like Factor V Leiden, or renal disease, women having family history of preeclampsia, obese women and in women with multiple gestations.[8] The single most significant risk for developing preeclampsia is in women who suffered from the same disease in their earlier pregnancy.[9]

Degree of Severity:
Preeclampsia can be divided based on its degree of severity into mild and severe. Mild preeclampsia is characterized by diastolic blood pressure above 90 mmHg but < 110mmHg; diastolic blood pressure is 20 mmHg above the reading in early pregnancy and mean arterial pressure exceeding 105 mmHg. Severe preeclampsia has systolic pressure more than 160 mmHg, or diastolic blood pressure $\geq$110 mmHg on atleast two occasions atleast 4 hours apart; proteinuria $\geq$ 5 gm in 24 hours; oliguria $\leq$ 400ml in 24

hours, cerebral or visual disturbances and severe headache or epigastric pain.[10]

Predisposing Factors:

Some of the general predisposing factors of preeclampsia are:-

1. Preeclampsia in an earlier pregnancy, family history of mother or sister suffering from preeclampsia[8]
2. Immunological: primigravida, new partner[3]
3. Vascular disease: essential hypertension, family history of hypertension, renal disease, diabetes mellitus, connective tissue disease like systemic lupus errythmatosis[11]
4. Hyperplacentosis: multiple pregnancy, diabetes mellitus, uterine malformation, molar pregnancy and hydrops fetalis[10]
5. Inflammatory diseases: periodontitis

Major predisposing factors given to explain cause of preeclampsia could be as-[9]

1. Endothelial cell injury
2. Immune reflection of placenta
3. Compromised placental perfusion
4. Altered vascular reactivity
5. Imbalance between prostacyclin and thromboxane
6. Decreased Glomerular Filtration Rate with retention of salt and water
7. Decreased intravascular volume
8. Increased central nervous system irritability
9. Disseminated Intravascular Coagulation
10. Uterine muscle stretch (ischemia)
11. Dietary factors including vitamin deficiency
12. Genetic factors
13. Elevated serum lipid ratio
14. No prenatal care

Pathophysiology of Preeclampsia:

There are alternate segments of vasodilatation and vasoconstriction throughout the body causing vasospasm. The constricted segments contribute to the heightened peripheral resistance and hence the hypertension.[12] In the dilated segments there are endothelial cell breaks in the capillary wall and through these breaks there is exudation of plasma proteins leading to cardiovascular changes. Due to extravasation there is increased haematocrit, low platelet count and decreased fibrinogen. Haemolytic anaemia may also be present.[10]

Preeclamptic women undergo certain morphological changes of various organs of the body like in kidney there is decreased glomerular filtration rate, rise in blood urea, nitrogen, creatinine and uric acid, non-selective proteinuria comprising albumin and globulin and in severe preeclampsia acute renal failure may develop due to acute tubular necrosis which is reversible after delivery. Liver may undergo periportal haemorrhagic necrosis giving rise to elevated enzyme levels.[13] These microhaemorrhages may then coalesce to give rise to a subcapsular haematoma that causes epigastric pain. Similarly brain undergoes changes like edema, hyperaemia, infarcts, thrombosis and haemorrhage. The CNS manifestations of preeclampsia include seizures, blindness or unconsciousness. In retina there could be localized vascular spasm, generalized narrowing, haemorrhage and papilloedema.[10]

Vasospasm and hypovolaemia compromise the uteroplacental perfusion. In pregnancy the trophoblasts erode into the maternal blood vessels and form the uteroplacental bed. But in preeclampsia this process is incomplete causing the intact maternal blood vessels to respond to any circulating vasoconstrictor substances compromising the placental blood flow and in the long run leading to intrauterine growth restriction.[10]

Prostaglandins - The Key factor in Preeclampsia:

In preeclampsia there is an imbalance in the levels of prostacyclin and thromboxane A2. The level of latter is much more than the former.[14] Prostacyclin is vasodilatory, uterus relaxing, platelet deaggregating substance as opposed to thromboxane A_2, the actions of which are just the opposite. Preeclampsia has elevated thromboxane A_2 levels leading to proteinuria, decreased glomerular filtration rate and altered liver function.[14]

Oral Infection contributing towards Preeclampsia - Recognising the new risk factor :

Periodontal disease is the most common chronic gram negative anaerobic infection. Periodontium affected with the periodontal disease act as a toxic reservoir of pathogenic gram negative bacteria. The toxins produced by the bacteria attack the gums, ligaments and bone surrounding the teeth to produce infected pockets that are similar to large infected wounds in the mouth.[15] These bacteria gain access to the bloodstream and travel throughout the body; they even enter the cervix causing increase in prostaglandin E2 in the placenta.[16] Fluid that bathes the tooth at the gingival margin, known as gingival crevicular fluid, often contains inflammatory mediators and the oral pathogens associated with periodontitis. The mechanisms underlying this destructive process involve both direct tissue damage resulting from plaque bacterial products, and indirect damage through bacterial induction of the host inflammatory and immune responses. While periodontitis is a chronic, local oral infection, there is evidence that both local and systemic inflammation may occur.[15]

The biological mechanisms involve bacterially induced activation of cell mediated immunity, which lead to production of cytokines, Tumor Necrosis Factor(TNF)-ά synthesis and release of prostaglandins. During normal pregnancy, when the intraamniotic levels are reached, cervical dilatation and delivery are induced. Abnormal production of these mediators during the pregnancy in the setting of infection triggers preterm labour and low birth weight. Cytokines like Interleukins (IL)-1, IL-6 and TNF-ά can cross human fetal membranes. Active periodontal disease during pregnancy may have transient translocation of oral organisms to the ultra placental unit, inciting placental inflammation or oxidative stress early in pregnancy which may ultimately produce placental damage and clinical manifestations of preeclampsia.[17] Subgingival microorganisms like Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola occur more frequently or in higher levels in periodontitis sites.[18] Bacteria known as Fusobacterium nucleatum has been linked with adverse pregnancy outcomes. Since Fusobacterium nucleatum is associated with periodontal infection rather than genital or uterine infections, it is hypothesised that the infection does not enter the womb by an ascendant route coming through the genital tract; rather it enters the mother's bloodstream making way down from the oral cavity.[19] The virulence factors of P.gingivalis have been linked to various complications in pregnancy outcome and pathogenesis of atherosclerosis.[19] This gram negative periodontal pathogen found in periodontal disease may find its way into the patient's bloodstream through oral hygiene procedures or even chewing.[18] The cysteine proteinases produced by *P.gingivalis* termed "gingipains" have deleterious effects in activating coagulation factors and platelet aggregation and in altering the cytokine response in human umbilical-vein-endothelial cells.[20] Other virulent factors

like fimbriae and lipopolysaccharides that can activate spleen cells and peripheral blood monocytes, resulting in the release of proinflammatory cytokines like IL-1, IL-6 and TNF-ά.18 T.forsythia possesses virulence traits, including the production of LPS and a trypsin like protease as well as the ability to penetrate and induce apoptosis in host cells.[21] This may explain the possible mechanisms of *P.gingivalis* and *T.forsythia* virulence factors involved in preeclampsia development.[18]

Endothelial cell dysfunction is the key feature of preeclampsia, potentially explaining the multiorgan nature of the disorder. This dysfunction is demonstrated by the structural changes in the placental bed and uterine boundary vessels and the high maternal blood levels of markers of endothelial damage like fibronectin, Von Willebrand factor, endothelin, tissue plasminogen activator and thrombomodulin.[22] Endothelial cell dysfunction may be because of increase in oxidative stress due to reduced placental perfusion. Placental ischemia is a common feature of preeclampsia and enhances the synthesis of inflammatory cytokines like TNF-ά which induces oxidative damage.[23] Under hypoxic conditions free radicals of oxygen are formed that can stimulate lipid peroxidation of free fatty acids, leading to the injury of endothelial cells.[24] The consequence of this oxidative stress includes activation of microvascular coagulation, increased capillary permeability and the production of lipid-laden macrophage foam cells, which are the characteristic features of atherosis. Acute atherosis, the placental lesion of preeclampsia shares a similar pathology, pathogenesis (inflammation) and clinical setting (endothelial cell damage) with atherosclerosis. It is characterised by infiltration of the perivascular spaces by mononuclear cells, an accumulation of lipid-laden macrophage foam cells and lipoprotein deposition.[19] Increased plasma levels of free 8-isoprostane, a marker of lipid peroxidation and a potent vasoconstrictor, have been found in preeclamptic women.[25] It is also found that periodontal disease is a vascular stressor as evidenced by increase in serum levels of soluble intercellular adhesion molecules.[26]

Periodontal disease may burden pregnant women systemically with endotoxin, inflammatory cytokines and oxidative stressors at the maternal-fetus interface.[18] It is suggested that oral infection could also be an important trigger of the chronic inflammatory response that characterizes preeclampsia and could also initiate the preeclamptic process by increasing the risk for acute uteroplacental atherosis.[27]

Conclusion:

Association between preeclampsia and chronic periodontal diseases should be interpreted with prudence, as the aetiology of both events is likely multifactorial. Various longitudinal and cross-sectional studies in future are necessary to further elicit the role of periodontal infection in preeclampsia. It is important to emphasize that primary health care services must be able to diagnose and control periodontal disease during pregnancy. Managing periodontal disease may represent a novel strategy to reduce the incidence and/or complications from this pregnancy hypertensive disorder. Thus periodontal treatment during pregnancy could be one of the future aspects in giving better prenatal care.[1]

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