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The Relationship between Periodontal Status and Pre–Eclampsia among Pregnant Ladies in Khartoum State, Sudan

Abubakr Omar Mohamed Abdelsalam[1]*, Alharith Haider Hamadalanil[2]

*[1]Department of Periodontology, Faculty of dentistry, Misurata University, Misurata, Libya
[2]Department of Periodontology, Faculty of dentistry, University Khartoum, Khartoum, Sudan
*Corresponding Author Email: aseelwazeer@gmail.com

Abstract Pre-eclampsia is a vascular disorder of pregnancy characterized by blood pressure and proteinuria and it is a major cause of maternal and perinatal mortality and morbidity worldwide. Several studies have suggested an association between periodontal diseases and pre-eclampsia. The aim of this study was to determine possible relationships between periodontal diseases and pre-eclampsia in Sudanese case control population at Khartoum hospitals, gynaecology departments. A total 100 cases and 100 controls were recruited in the study (200 women in total). A case control study was conducted with 100 cases (pre-eclamptic women with blood pressure $\geq$ 140/90 mmHg and proteinurea $\geq$ 300 mg/ 24 hours after 20 weeks of gestation) and 100 controls (non-pre-eclamptic healthy pregnant women who delivered singleton infant). Periodontal indices were used including plaque index, gingival index, probing pocket depth and clinical attachment loss using University of Michigan probe with William's markings. Associated risk factors for pre-eclampsia were recorded in the questionnaire. Insignificant association was found between periodontal disease and pre- eclampsia, but significant association with regard to severity of periodontal disease with P-value 0.000 after adjustment for some risk factors. this study concluded that a poor periodontal health status of a mother might be possible risk factors for pre-eclampsia.

Keywords Periodontitis, Pre-eclampsia, Risk Factor, Pregnancy

Introduction

Oral cavity cleanliness was practiced since early ages. This is implied upon by oral hygiene practices by the Sumerian of some 3000 years BC. Their decorated gold tooth picks that was found in their excavations in Mesopotamia suggesting an interest in cleanliness of the month. This indicates that the oral cavity is considered as an entrance to the body by early civilizations, and hints that oral manifestations accompany many systemic diseases. The oral cavity is a remarkably forgiving environment in which to operate, because of its excellent blood supply and it contains many organs such as, tongue, teeth and peridontium ...etc [1]. The periodontium comprises the gingiva, the periodontal ligament, the root cementum and the alveolar bone. The main function of the peridontium is to attach the tooth to the bone tissue of the jaws and to maintain the integrity of the surface of the masticatory mucosa of the oral cavity [2]. Periodontal disease is a chronic destructive inflammatory disease affecting the tooth supporting tissue (periodontium) and is one of the most prevalent chronic infections in humans. The disease is caused by dental plaque; a biofilm in which gram-negative anaerobic microorganisms dominate. Plaque-associated periodontal diseases can be divided into gingivitis and periodontitis [3]. Gingivitis refers to an inflammatory state of the gingiva with no loss of the periodontal attachment fibers or alveolar bone. In

perioodontitis, progressive destruction of collagen fibers and supportive bone structures occurs. Periodontitis is the most prevalent disease affecting alveolar bone in mankind [4]. If the severe form remains untreated it would lead to tooth loss in 10-15% of adults and it is more common in males. Periodontal disease is initiated by oral microorganisms, but it is believed that the severity of periodontal breakdown is orchestrated by the inflammatory response of the host. It has been proposed that, daily episodes of bacteraemia or dissemination of bacterial endotoxin originating from the periodontal focus may induce systemic activation of the inflammatory response [5]. Bacteria and bacterial endotoxin in the systemic circulation may induce pro- inflammatory cytokine production. The cytokines activate inflammatory cells and endothelial cells and may result in endothelial dysfunction. There are many conditions occurring in the body that result from destruction caused by the inflammatory response; among which is pre- eclampsia [6]. Pre-eclampsia is a maternal multiple-organ disease that manifests clinically in the second half of pregnancy by the appearance of hypertension and proteinuria. The pathogenesis is not completely understood, but it is generally accepted that endothelial dysfunction of the maternal vascular system plays a key role in the clinical manifestations of the disease. It is most likely the result of a generalized inflammatory response including activation of inflammatory and endothelial cells. Women with diseases associated with chronic low-grade inflammation such as diabetes mellitus, hypertension, obesity and arterial diseases at an increased risk of developing pre-eclampsia and because periodontal disease is also associated with low-grade inflammation, it can be hypothesized that patients with periodontal disease have an increased risk of developing pre-eclampsia. Pre-eclampsia is a threatening condition for both the mother and the foetus [7]. It is a common obstetric syndrome affecting about 7-10% of pregnant women and remains one of the two most common causes of maternal mortality in developed countries. Despite of intense efforts being done to find mechanisms and modes that induce pre-eclampsia no specific etiological factor has been identified so for. The known risk factors for pre-eclmapsia include prim parity multi gravidity, obesity, renal disease, uterine malformation, fetal hydrops, elevated serum lipid ratio, no prenatal care and diabetes [8]. Numerous studies suggest that periodontal disease, as a source of subclinical and persistent infection may induce systemic inflammatory response that increases the risk of adverse pregnancy outcomes including pre-eclampsia. So, Pre-eclampsia is a serious condition which may affect pregnant ladies and their fetuses. Recently several studies have shown that pre-eclamptic women have a higher prevalence of periodontitis and periodontal destruction [9, 10]. In the light of the above mentioned facts, this study is designed to investigate the periodontal status and its severity in pre-eclamptic women and trying to discover any possible association between pre-eclamptic women and periodontal disease among the pregnant subjects in Khartoum state maternity hospitals (Omdurman Maternity Hospital, Department of Obstetrics & Gynaecology of Khartoum Teaching Hospital and Soba University Hospital).

Materials and Methods

Study design - case control hospital based study.

Study area - Omdurman Maternity Hospital and Departments of Obstetrics and Gynaecology of Khartoum North Teaching Hospital and Soba University Hospital.

Sample size - Two hundred cases (100 cases and 100 controls).

The statistical calculation should be: level of significance 0.05, study power 90%, ratio of samples (cases: controls) is 1:1 and estimated Odds Ratio is 2.85.

Study population

Study group

Hundred pregnant pre-eclamptic women aged 15 - 45 years, (with blood pressure ≥ 140 /90 mm Hg and proteinurea ≥ 300 mg /24h after 20 weeks of gestation), will be examined at the above-mentioned hospitals in Khartoum State.

Control group

Hundred non pre-eclamptic healthy pregnant women who delivered a singleton infant at term will be enrolled; they will be selected from the same maternal hospital with the same age.

Inclusion criteria

For study group

1. Willingness of the patient to participate in the study.
2. Non smoker status.
3. Normal response to glucose testing.
4. No history of recent infections.
5. Absence of uterine contractions.
6. Diagnosed patients with 15-45 years old after 20 weeks of gestation.
7. Only partially or fully dentate patients (at least 8 teeth excluding 3rd molar).

For control group

1. Willingness to participate in the study
2. Absence of pre-eclampsia.
3. Age group (15-45) years old
4. Only partially or fully dentate patients (at least 8 teeth excluding 3rd molar.

E

xclusion criteria

History of periodontal treatment within last 3 month. History of taking antibiotic. Any condition that modify periodontal tissue status e.g. diabetes mellitus, smoking, aggressive periodontitis.

Plan for data collection

Data collection techniques & dental examination

Oral examination for patients with pre-eclampsia and the control group will be performed by one examiner (Alharith). All present teeth will be examined at six sites (mesiobuccal, mid buccal, distrobuccal), (mesiolingual, mid lingual, distolingual) for presence of bacterial plaque using plaque index (PI), the gingival inflammation using gingival index (GI), probable pocket depth (PPD) and clinical attachment loss (CAL). The periodontal condition was further stratified by severity according to the criteria used by Boggess et al. Periodontal health was defined as the absence of ≥4mm PPD. Mild periodontal disease was defined as 1-15 tooth sites with ≥4mm PPD and bleeding on probing (BOP). Severe periodontal disease was defined as >15 tooth sites with ≥4mm PPD and BOP [11 - 14].

Questionnaire

All study subjects will be interviewed by the investigator using a structured questionnaire to ensure comparability between the cases and control groups. The questionnaire is divided into sections; the first section contains the background variables of: age of participant in years, years of education. The second section gathers information about the history of pregnancy and includes gravidity measured as the number of times that a woman has been pregnant, parity measured as the number of times that she has given birth to a fetus with a gestational age of 24 weeks or more, regardless of whether the child was born alive or was stillborn, gestation defined as the period of time between conception and birth during which the fetus grows and develops inside the mother's womb and measured in weeks from the first day of the woman's last menstrual cycle to the current date, and the participants body weight in the 3rd trimester measured in Kg. The third and last part of the questionnaire comprises of social habits and prenatal care.

Data collection tools

University of Michigan probe with Williams's markings and a dental mirror will be used in a day light under strict infection control measures.

Plan for data analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 11. Chi-square analyses will be used to test the group differences in categorical variables and student t-test will be used to test the group differences in continuous variables. Correlation analysis will be performed to analyze the relationship between periodontal disease and pre-eclampsia. The odds ratios (OR) and 95% confidence intervals (95% CI) will be obtained to indicate the association between periodontal disease as a risk factors and pre-eclampsia.

For all statistical tests, two-sided type I error probability = 0.05 will be considered as the level of significance.

Ethical Considerations

The ethical clearance will be obtained from Faculty of Dentistry, U of K. All study participants will have the free will to participate in the study and a written consent form will be obtained from all participants to include their names and signatures. The collected data will be kept and dealt with in a secure and professional manner to keep the confidentiality of the participants.

Results

A total of 100 cases and 100 controls were enrolled in this study (A total of 200 women). The results revealed that that distribution between cases and controls were equal in age with mean and standard deviation (33.11 ± 6.36) for cases and (31.62 ± 7.59) for controls with P-value 0.133, the distribution was equal in education with mean and standard deviation (14.46 ± 2.64) for cases and (15.01 ± 2.68) for controls with P-value 0.054. Distribution was also equal in parity with 100% for cases and 100% for controls. Distribution was equal in prenatal care as well with 91.1% for cases and 81.2% for controls with P-value 0.065. The distribution was equal too in start of prenatal care with mean and standard deviation (10.58 ± 0.65) for cases and (10.67 ± 0.70) for controls with P- value 0.400. Significant difference in the distribution was found between the cases and control groups regarding gravity with mean and standard deviation (3.60 ± 1.83) for cases and (2.97 ± 1.41) for controls with P- value 0.006. Significant distribution was found also in gestation with mean standard deviation (30.40 ± 1.20) for cases and (29.46 ± 1.78) for controls with P- value 0.000. Significant difference was also seen in body weight with mean and standard deviation (70.69 ± 7.15) for cases and (65.79 ± 5.19) for controls with P-value 0.000. Table 1 displays the previously mentioned facts: with Comparative statistics:

Table 1: Baseline comparison in personal characteristics between pre- eclamptic cases and normotensive controls

Description	Pre-eclamptic cases (N = 100)	Normotensive cases (N = 100)	P-value
Age (mean ± SD)	33.11 ± 6.36	31.62 ± 7.59	0.133[a]
Years of education (mean± SD)	14.46 ± 2.64	15.01 ± 2.68	0.054[b]
Parity (Yes) [no %]	101 (100.0%)	100 (100.0%)	NA
Gravity (mean ± SD)	3.60 ± 1.83	2.97 ± 1.41	0.006[a]
Gestation (wks) (mean ± SD)	30.40 ± 1.20	29.46 ± 1.78	0.000[a]
Body weight in the 3rd trimester (kg)(mean ± SD)	70.69 ± 7.15	65.79 ± 5.19	0.000[c]
Prenatal care (Yes) [no %]	92 (91.1%)	82 (81.2%)	0.065[c]
* Starts of prenatal care	10.58 ± 0.65	10.67 ± 0.70	0.400

[a]Independent sample t-test, [b]Mann-whitney U-test, N.A: Non applicable

[c]Fisher's exact test * Cases n = 92, controls n = 82

Periodontal disease was diagnosed in terms of gingivitis and periodontitis, prevalence of gingivitis was 58.4% in cases and 52.5% in controls and these findings were statistically insignificant with P-value 0.479, whereas the prevalence of periodontitis was 34.7% in cases and 32.7% in controls and these findings were statistically insignificant with P-value 0.882. This indicated that, there was no association in the prevalence of gingivitis and periodontitis. Assessment of pre-eclampsia as a risk factor for gingivitis and periodontitis revealed that pre-eclampsia is not a risk factor with 0.79, 95% CI 0.45 – 1.37 for gingivitis and 0.92, 95% CI 0.51-

1.64 for periodontitis. On the other hand, significant association was found in the severity of both gingivitis and periodontitis, gingivitis was furtherly classified into mild 31.7% in cases and 0.0% in controls, moderate 26.7% in cases and 41.6% in controls and severe 0.0% in cases and 10.9% in controls with P-value 0.000 while periodontitis was classified as well into mild 7.9% in cases and 0.0% in controls, moderate 0.0% in cases and 21.8% in controls, severe 26.7% in cases and 10.9% in controls with P- value 0.000. Table 2 displays the above-mentioned facts. Periodontal parameters were measured using average Plaque Score, Plaque Index (PI) according to criteria of Loe and Silliness 1967, probing pocket depth (PPD) and clinical attachment loss (CAL) according to criteria of the US public health service, national center for health statistics 1965. The mean and standard deviation for the average plaque score was found to be statistically significant (P-value 0.000) whereas insignificant association was found among the following: Plaque index (P-value 0.571), average gingival score (P-value 0.749), average probing pocket depth and clinical attachment loss with P-value 0.234 for both. Table (3) displays the above-mentioned findings:

Table 2: Comparison in periodontal disease status between pre-eclamptic cases and normotensive controls

Description	Pre-eclamptic cases (n = 100)	Normotensive controls (n = 100)	P-value	Odds ratio (95% CI)
Prevalence of gingivitis	59 (58.4%)	53 (52.5%)	0.479[a]	0.79 (0.45-1.37)
Prevalence of periodontitis	35 (34.7%)	33 (32.7%)	0.882[a]	0.92 (0.51-1.64)
Degree of gingivitis				
Mild	32 (31.7%)	0 (0.0%)		
Moderate		42 (41.6%)	0.000[b]	NA
Severe	27 (26.7%)	11 (10.9%)		
Degree of periodontitis				
Mild	8 (7.9%)	0 (0.0%)		
Moderate		22 (21.8%)	0.000[b]	NA
Severe	0 (0.0%)	11 (10.9%)		
Prevalence of gingivitis	59 (58.4%)	53 (52.5%)	0.479[a]	NA
Prevalence of periodontitis	35 (34.7%)	33 (32.7%)	0.882[a]	NA

Table 3: Baseline comparison in dental and periodontal parameters between pre-eclamptic cases and normotensive controls

Description	Pre-eclamptic cases (n = 100)	Normotensive controls (n = 100)	P-value
Total no. of teeth (mean ± SD)	31.76 ± 0.43	32.00 ± 0.00	0.000[a]
Average plaque score (mean ± SD)	0.65 ± 0.67	0.34 ± 0.33	0.000[a]
Plaque index			
No accumulation [no (%)]	42 (41.6%)	47 (46.5%)	0.571[b]
Light accumulation [no (%)]	59 (58.4%%)	54 (53.5%)	
Average GI Score (mean ± SD)	0.69 ± 0.72	0.84 ± 0.85	0.749 [a]
Average PPD Score (mean ± SD)	1.24 ± 1.90	1.32 ± 1.91	0.234 [a]
Average CAL Score (mean ± SD)	1.51 ± 2.34	1.20 ± 1.81	0.234 [a]

[a]Mann-Whitney U-test; [b]Fisher's exact test

Bivariate correlation shows the crude correlation co-efficient between cases and controls, while partial correlation shows the adjusted correlation co-efficient after controlling for gravity, gestation and body weight in the 3rd trimester. The correlation was found to be significant at the 0.01 level for prevalence of periodontitis, degree of gingivitis, degree of periodontitis and extent of periodonitis. Table 4 and table 5 show these findings.

Table 4: Disease status Vs study sample (Pre-eclamptic cases and normotensive controls bivariate correlation)

Description	Correlation	P-value
Prevalence of gingivitis	- 0.060	0.398[a]
Prevalence of periodontitis	- 0.021	0.767[a]
Degree of gingivitis	0.126	0.073[a]
Degree of periodontitis	- 0.054	0.445[a]
Extent of gingivitis	- 0.060	0.398[a]
Extent of periodontitis	- 0.026	0.0767[a]

n = 200; [a]Spearman correlation test; significance level P ≤ 0.05

* Correlation is significant at the level 0.01 level (2-tailed)

Table 5: Periodontal disease status Vs study sample (pre-eclamptic cases an normotensive controls) partial correlation: (Controlling for gravity, gestation and body in 3rd trimester)

Description	Correlation	P-value
Prevalence of gingivitis	0.073	0.305[a]
Prevalence of periodontitis	0.207[(*)]	0.003[a]
Degree of gingivitis	0.301[(*)]	0.000[a]
Degree of periodontitis	0.192[(*)]	0.007[a]
Extent of gingivitis	0.073	0.305[a]
Extent of periodontitis	0.207[(*)]	0.003[a]

n = 200, Spearman correlation test, significance level P ≤ 0.05, [(*)]Correlation is significant at the 0.01 level (2-tailed)

Discussion

A total of 200 women were recruited in this study. Prevalence of PE for the year 2011 or any other previous years in Khartoum State Hospitals (specially Omdurman Maternity Hospital as it is considered as one of the biggest referred gynaecological center in the state). Prevalence would not be achieved because of difficulty in getting the information from pregnant suffering from this condition, however almost all women who came with PE during this study period and matched the eligibility criteria were included in the case group. A total of 100 cases and 100 controls were enrolled in this study. Insignificant association between periodontal status and PE in this case-controls study was found. Adjustment for risk factors was done to clearly overview the relationship between periodontal status and PE and to avoid any biases that may confound the relationship. So, after adjustment of these factors; gravity, gestation and body weight significant correlation existed. Also, significant correlation was found with regard to the severity of the periodontal disease [15]. The results of these investigations disagree with results of studies by Canakci et al., 2004 [16]; Contreras et al., 2006 [17]; Kunnen et al., 2007 [18]; Siqueira et al., 2008 [19]; Nabet et al., 2010 [20] and Shetty 2010 [21], as all these studies support the association between the periodontal status and PE. On the contrary, the findings of this study supports other studies that suggest there is no significant association between the periodontal status and PE such as Castaldia et al., 2009 [22]; Khadir et al., 2006 [23]; Lohsoonthorn et al., 2009 [24] and Srinivas et al., 2009 [25]; Canakci et al., 2007 [26]. Fatherly stratified the severity of periodontal disease, as it is done in our current study, he recorded significant correlation between the severity of periodontal disease and PE after he adjusted for some risk factors like body weight. Siqueira and colleagues found an association between periodontitis and PE before matching, the association remained significant even after matching for risk factors regarding age ≥30 years, chronic hypertension, prenatal care [27 – 29]. However, when probing pocket depth (PPD) and clinical attachment loss (CAL) were tested with cut-off points of ≥ 5 or ≥ 7 mm, the ORs for PE were not significant indicating that periodontal break down in itself was not associated with PE. These findings agree with the results of our current study. Shetty et al., 2010 [21] carried the most recent case control study the sample size of control was more than the cases 100 and 30 respectively, after adjustment for maternal age, body weight,

occupation, education and income, he found an association both at enrolment and delivery as well. Khader et al., 2006 [23] disagree with Shetty's study, Khader study ensured also non-smoking and non-alcohol drinking women as same as in our current study. After controlling for maternal age, parity and body mass index (BMI), he found no statistical difference between case and control. Lohsoonthorn et al., 2009 [24] also disagree with Shetty's study in spite of adjusting for maternal age, parity and BMI, but unlike Khader et al., 2006 [23] Lohsoothorn included smoking and alcohol use, however still there was no association between periodontal disease and PE which supports our current study. Castaldia et al., 2006 [22] and Srinivas et al., 2009 [25] carried a cross-sectional and a cohort studies respectively, but both found no association between periodontal disease and PE while Boggess et al., 2003 [30] reported an association with a cohort study. In the current study, periodontal disease was diagnosed as periodontitis when at least 8 teeth excluding 3^{rd} molar are present and these teeth show one more sites with $\geq$ 4 mm PPD and bleeding on probing (BOP). So, the difference in the findings between studies may be because there is no association in fact or there is difference in the diagnostic criteria for periodontitis or the association took place due to presence of other factors (environmental or genetic). The periodontal parameters used in our current study included plaque index (PI), gingival index (GI), PPD, and CAL, all showed insignificant association between periodontal disease and PE with P-values 0.571, 0.749, 0.234 and again 0.234 respectively. And these findings agree with the findings reported [31] but disagree with the findings recorded [32] who found significant association between periodontal disease and PE. Significant association was found with regard to the average plaque score with P-value 0.000 and also high significant recorded in terms of severity of periodontal disease with P- value 0.000. This supported by a study performed by Canakci et al., 2007 [26], but contradicted by another study carried by Lohsoonthorn et al., 2009 [24]. The similarity of PI and GI of both group's case and control would suggest that, the amount of periodontal destruction in pre-eclamptic cases could be attributed to other factors [33–34]. Both diseases are characterized by increased secretion of pro-inflammatory mediators which may explain why an association between the two diseases does exist [35 - 37]. The result of this study may provide and additional evidence that pregnant women with periodontal disease are at risk for developing PE and the necessity for prospective intervention attempts are required to rule out whether periodontal infection is a real risk factor for PE. One of the limitations is the variety in clinical disease definitions for periodontal disease.

Conclusion

The purpose of this study was to find out the possible relationship between this disease and PE. The study provided no association between periodontal disease prevalence and PE, but provided a positive correlation between severity of periodontal disease and PE.

Recommendations

The periodontal status of pre-eclamptic women should be carefully taken care of. Necessity for close co-operation between obstetrician and dentists should be considered. As far as possible, and from preventive oral health programs, women should receive supportive periodontal treatment to prevent future deterioration. Encouragement for further researches and studies to be carried out in the future.

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References

[1]. Philstorm, B.L., Michalowicz, B. S and Johnson N.W. (2005). Periodontal disease. *Lancet*, 366, 1809-1820.

[2]. Katz, J., Peretz, B., Sgan-Cohen, H. D., Horev, T., Eldid. (2000). Periodontal status by CPTIN and associated variables in an Israeli permanent force military population. *Journal of Clinical Periodontology*, 27:319-324.

[3]. Offenbacher, S., Barros, S. P., Beck, J. D. (2008). Rethinking periodontal inflammation. *Journal of periodontology*, 79, 1577-1584.

[4]. Geerts, S. O., Nys, M., De M. P., Charpentier, J., Albert, A. R., Legard, V. & Rompen, E. H. (2002). Systemic release of endotoxin induced by gentle mastication: association with periodontitis severity. *Journal of periodontology*,. 73: 73-8.

[5]. Loose, B. G. (2005). Systemic Markers of inflammation in periodontitis. *Journal of periodontology*, 76:2106-15.

[6]. Scanapieco, F. A. (2004). Periodontal inflammation: from gingivitis to systemic disease? *The compendium of continuing Education Dentistry*, 25: 16-25.

[7]. Amar, S., Gokce, N., Morgan, S., Lankideli, M., Van Dyke, T. E. & Vita J. A. (2003). Periodontal disease is associated with brachial artery endothelial dysfunction and system inflammation. *Arterioschlerosis, thrombosis and vascular biology.* 23: 1245-9.

[8]. Tonetti, M. S., D' Ainto, F., Nibale, L., Donald, A., Storry, C., Parker, M., Sovan, I., Hingorani, A. D., Vallance, P. & Deanfield, J. (2007). Treatment of periodontitis and endothelial function. *New England Journal of Medicine*, 356: 911-20.

[9]. Higashi, Y., Goto, C., Jitsuiki, D., Umenoura, T., Nishioka, K., Hidaka, T., Takemoto, H., Nakamura, S., Saga, J., Chayama, K., Yoshixomi, M. & Tagushi A. (2008). Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. *Hypertension*, 51: 446-53.

[10]. Piconi, S., Trabattoni, D., Luraghi, C., Perilli, E., Borelli, M., Pacei, M., Rizzardini, G., Lattuada, A., Bray, D. H., Catalano, M., Sparaco, A. & Cleric, M., (2008). Treatment of periodontal disease results in improvement in endothelial dysfunction and reduction of the carotid intima-media thickness. *The FASEB Journal*, 23: 1196-1204.

[11]. Buduneli, N., Bayles, H., Budnneli, E., Turkoglu, O., Kose, T., Dohlen, G. (2005). Periodon tal infectious and preterm low birth weight: case-control study *Journal of Clinical Periodontology* 32, 174-81.

[12]. Redman, C. W., Sargent, I. L. (2004). Pre-eclampsia and systemic inflammatory response. *Neurology*, 24, 565-70.

[13]. Roberts. J. M. and Gammil H. S. (2005). Pre-eclampsia: recent insights hypertension, *Journal of Clinical Periodontology*, 46, 1243-1249.

[14]. Rodie, V. A., Freeman, D. J., Sattar, N. and Green, I. A. (2004). Pre-eclampsia and cardiovascular disease metabolic syndrome of pregnancy. *Atherosclerosi*, 175, 189-202.

[15]. Duckitt, K., Harrington, D. (2005). Risk factors for pre-eclampsia at antenatal booking: Systematic review of controlled studies. *British Medical Journal*, 330: 565-7.

[16]. Canakci, V., Canakci, C. F., Canakci, H., Canakci, E., Cicek, Y., Ingec, M., Ozgoz, M., Demir, T., Dilziz, A., Yagiz. (2004). Periodontal disease as a risk factor for pre- eclampsia: a case-control study. *Australian and New Zeland Journal of Obstetrics and Gynaecology* 44, 568-73.

[17]. Cntreras, A., Herrera, J. A., Soto, J. A., Arce, R. M., Jaramillo, A. & Botero, J. E. (2006). Periodontitis is associated with pre-eclampsia in pregnant women. *Journal of Periodontology*, 77:182-8.

[18]. Kunnen, A., Baleauw, J., Van Doormaal, J. J., Van Pampus, M. G., Van der schans, C. P., Aarnoudse, J., G., Van Winkelhoff A.J., & Abbas, F. (2007). Women with a recent history of early onset pre-eclampsia have a worse periodontal condition. *Journal of Clinical Periodontologdy*, 34: 202-7.

[19]. Siqueira, F. M., Cota, L. O., Costa, J. E., Haddad, J. P., Lana, A. M., & Costa F.O., (2008). Maternal periodntitis as a potential risk variable for prec-eclampsia: a case-control study. *Journal of periodontology*, 79: 207-15.

[20]. Nabet, C., Lelong, N., Colombier, M. L., Sixou, M., Musset, Goffinet, F., & Kaminski, M. (2010). Maternal periodontitis and the causes of pre-term birth: the case control Epipap study. *Journal of Clinical Periodontology*, 37: 37-45.

[21]. Shetty, M., Shetty, P. K., Ramesh, A., Thomas, B., Prabbu, S. & Rao, A., (2010). Periodontal disease in pregnancy is a risk factors for pre-eclampsia. *Acta Obstetrica et Gynaecologica Scandinavica*, 89: 718-21.

[22]. Castaldi J.L., Bertin M.S., Gimenez F. & Lede R., (2006). Periodontal disease: is it a risk factor for premature labour, low birth weight or pre-eclampsia? *Revista panamericana de salud publica*, 19: 253-8.

[23]. Khader Y.A., Jibreal M., Al-Omiri M., & Amarin Z, (2006). Lack of association between periodontal parameters and pre-eclampsia. *Journal of periodontology, 77*: 1681-7.

[24]. Lohnsoonthoran, V., Kungsadalpipob, K., Chanchareansook, P., Limpangsanurak S., Vanichjakvong, O., Sutdhibhisal, S., Sookprone C., Wongkittikraiwan, N., Kamol Pornwijit, W., Jantarasangaram S., Manotaya S., Siwawej, V., Barlow, W. E., Fitzpatrick, A. L., Williams, M. A, (2009). Maternal periodontal disease and risk of pre-eclampsia: a case control study. *American Journal of Hypertension*, 22: 457-36.

[25]. Srinivas, S. K., Sammel, M. D., Stamilio, D. M., Clothier, B., Jeffcoat, M. K., Parry, S., Macones, G. A., Elovitz, M. A., & Metley, J. (2009). Periodontal disease an adverse pregnancy outcomes: is there an association? *American Journal of Obstetrics and Gynaecology*, 200: 497-498.

[26]. Carreiras, M., Montagnani S., Layrisse Z., (2002). Pre-eclampsia: a multi-factorial disease resulting from the interaction of the feto-maternal HLA genotype and HCMV infection. *American Journal of reproductive immunology*, 48: 176-83.

[27]. Darmochwal, Kolarz, D., Rlonski, J., Leszczynska-Gorzela, B., Oleszczuk, J. (2002). The expressions of intracellular cytokines in the lymphocytes of pre-eclamptic patients. *American Journal of Reproductive immunology*, 48: 381-386.

[28]. Von Dedelszen, P., Magee, L. A. (2002). Could an infectious trigger explain the differential response of the shared placental pathology of pre-eclampsia and normotensive intrauterine growth restriction? *Act Obstetricia et gynecologica scandinavica*, 81: 642-448.

[29]. Erkkola, R. (1997). Can pre-eclampsia predicted an prevented? *Acta Obstetricia et gynecologica scandinavica*, 76 (suppl. 164): 98-100.

[30]. Boggess, K A, Lieff, S., Murtha A P, Moss K, Beck J, Offenbacher S, (2003). Maternal periodontal disease is associated with an increased risk for pre-eclampsia *Obstetrics and gynaecology*, 101, 227-31.

[31]. Odegard R.A., Nilson S.T., Austgulen R, (2000). Pre-eclampsia and fetal growth. *Obstetrics and Gynaecology* 96, 950-5.

[32]. Riche, E. L., Boggess, K. A., Lieff, S., Murtha, A. P., Auten, R. L., Beck, J.D., Offenbacher, S. (2002). Periodontal disease increases the risk of pre-term delivery among pre-eclampsia. *Annals of periodontology* 7: 95-101.

[33]. Bobetsis, Y. A., Barros, S. P. & Offenbacher, S. (2006). Exploring the relationship between periodontal disease and pregnancy complications. *Journal of the American Dental Asociation.* 137(suppl.10): 7S-13S.

[34]. Shub A, Swain, J. R., Newnham, J. P. (2006). Periodontal disease and adverse pregnancy outcomes. *The Jouranl of Maternal–Fetal and Neonatal medicine*, 19, 521-528.

[35]. Xiong, X., Ruekens, P., Fraser, W. D., Beck, J., Ofenbaker, S. (2006). Periodontal disease and pregnancy outcomes; a systemic review. *British Journal of obstetrics and Gynecology*, 113, 135-43.

[36]. Oettinger-Barak, O., Barak, S., Ohel, G., Ottinger, M., Kreutzer, H., Peled, M. (2005). Severe pregnancy complications (Pre-eclampsia) is associatyed with greater periodontal destr uction. *Journal of Periodontology*, 76: 134-7.

[37]. Canakci, V., Canakci, C. F., Yildirim, A., Ingec, M., Eltas, A., & Erturk, A., (2007a). Periodntal disease increases the risk of severe pre-eclampsia among pregnant women. *Journal of Clinical Periodontology.* 34: 639-45.