Original Research Paper

University J Dent Scie 2022; Vol. 8, Issue 4

Comparative Evaluation of C-reactive Protein in Pregnant Women with or Without Periodontitis: A Randomized Control Trial

Abstract:

Background: Serum C-reactive protein (CRP) is non-specific in nature and is seen to be associated with adverse pregnancy outcomes. Thus we aim to compare serum CRP levels in pregnant women with and without periodontitis.

Methods: Group A:- A total of 222 pregnant women aged between 18-45 years were recruited in study and divided into two groups Group A:- Pregnant patient without periodontitis (n=100) and Group B:-Pregnant patient with periodontitis (n=122). Different clinical parameters such as plaque index (PI), gingival index (GI), probing depth (PD) and clinical attachment loss (CAL) were evaluated. A 2 ml of blood sample was taken from antecubital vein for quantative serum CRP analysis.

Results: The mean CRP level in Group B was found to be higher (4.22 ± 2.247 mg/L) than Group A (1.55 ± 0.702 mg/L). In both the groups, statistically significant and positive correlation of PI with GI and CRP level was found ($p < 0.05$). Similarly, in Group B, PI showed a positive correlation with PD &CAL whereas, PD showed a similar correlation with CAL& CRP level was statistically significant. ($p< 0.05$).

Conclusion: Periodontitis influenced the serum CRP levels in pregnant patients representing increased inflammatory burden.

Key-words: Plaque Biofilm, Inflammatory Mediators, C- reactive Protein, Periodontitis, Pregnant Women.

Introduction:

Periodontitis is a chronic inflammatory disease of mixed microbial origin,[1] Somemicro-organisms within the plaque biofilm are more pathogenic and stimulate release of wide varieties of toxins (e.g. endotoxins, lipopolysaccharides etc.). These toxins interact with toll-like receptors present on the surface of neutrophils and monocytes resulting in activation of signal transduction pathways leading to production of cytokines which coordinate local and systemic inflammatory response.[2,3] The cytokines produced, trigger the hepatocytes to release acute phase proteins. The acute phase proteins are the proteins whose serum concentration is altered by at least 25% in response to inflammation and include proteins of complement, coagulation, and fibrinolytic systems.[4] C-reactive protein (CRP) is an extremely sensitive acute phase protein. It isequally distributedin the vascular compartment, whereas its clearanceis mono-exponential with a biological half-life of 19 hours independent of serum concentration or pathophysiological circumstances. Therefore, measurement of CRP is considered as a good marker of disease activity.

Access this article online

Website: www.ujds.in

Quick Response Code

DOI: https://doi.org/10.21276//ujds.2022.8.4.4

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Received : 24 March, 2022, **Published :** 31 Dec., 2022

How to cite this article: Garg, D. K. (2022). Comparative Evaluation of C-reactive Protein In Pregnant Women with or Without Periodontitis: A Randomized Control Trial . UNIVERSITY JOURNAL OF DENTAL SCIENCES, 8(4).

Several studies,[5,6] and systemic review[7] suggest that periodontal infection serves as a pool for micro-organisms, endotoxins, inflammatory mediators such as IL-1β, IL-6, PGE-2 and TNF-α etc. providing hematological translocation of these products to the feto-placental unit. Also, the sex hormonesmay exaggerate the response of gingival tissue to local irritants.[8] Moreover, low grade inflammation is seen to be associated with endothelial dis-function, leading to vascular dysfunction and sub-optimal placental development causing ischemia of placenta which might predispose mothers to increase risk for various pregnancy complications [9] such as fetal growth restrictions, pre-mature rupture of membrane, pre-term birth, low birth weight, and etc. Most evidence in the literature supporting the association between periodontitis and CRP are based on studies in men and non-pregnant women but very limited data is available on pregnant women to the best of our knowledge. Therefore, the present clinical trial was designed to study the association between periodontal discase and CRP levels in pregnant women and to correlate CRP levels with different periodontal parameters.

Material and Methods:

The present randomized observational double blind case controlled clinical trial was conducted in Department of Periodontology & Oral Implantology, Surendera Dental College & Research Institute, Sriganganagar and Department of Obstetrics and Gynecology, Sardar Patel Medical College, Bikaner. The study was carried out as per the declaration of Helsinki (1975), revised in 2013 and was also approved by institutional ethical committee of Surendera Dental College & Research Institute, Sriganganagar, Rajasthan and authenticated by Sardar Patel Medical College, Bikaner to conduct the study at department of Obstetrics and Gynecology. The trial was registered with Clinical Trial Registry of India with number CTRI/2018/08/015497.

The pregnant females with at least twenty teeth present, who belong to age group of 18-45 years and having minimum 4 teeth with one/more site having 4 mm or more probing depth and clinical attachment loss of minimum 2 mm or more with bleeding on probing and interested to participate in the study and submitted the signed written informed consent were enrolled in the study. Subjects having any form of systemic disease, history of periodontal surgery in past 6 months / trauma / resent tooth extraction, patient on antibiotic therapy / anti-inflammatory drugs, tobacco / alcohol users and psychological / sleep disturbances were excluded from the study. Out of enrolled subjects only 100 patients without periodontitis and 122 patients with periodontitis completed the trail. **(Figure:-1)**

Different periodontal parameters such as Plaque Index (PI)by **Silness J. and Loe H. 1964**, Gingival Index (GI) by **Loe H. and Silness J. 1963**, Probing Depth (PD) and Clinical Attachment Loss (CAL) were evaluated. A2 ml blood sample was taken from antecubital vein from each patient of both groups for quantative serum CRP analysis by Erba CRP-Kit.Oral hygiene instructions were given to every subject with demonstration of proper brushing technique. Data obtained was entered in the standard proforma and was subjected to statistical analysis utilizing Arithmetic Mean, ± Standard Deviation, Unpaired't' Test and Pearson Correlation.

Result:

In this study, an attempt was made to evaluate the CRP levels in pregnant women with and without periodontal disease. The mean and standard deviation of PI, GI, PD, CAL and Serum CRP level in Group A were reported to be 0.69 ± 0.465, 0.14 ± 0.349, 2.03 ± 0.171, 0.00 and 1.55 ± 0.702 respectively.(Table 1) Whereas, Group B they were 2.75 ± 0.432, 2.47 ± 0.501, 4.72 ± 0.518, 2.39 ± 0.537 and 4.22 ± 2.247 respectively. (Table 2)

Intergroup comparison of all parameters between Group A and B utilizing unpaired 't' test showed that, the mean difference in PI, GI, PD, CAL and CRP was -2.064, -2.327,-2.691,-2.385 and -2.671 respectively which was statistically significant. (p= 0.000) (Table 3)In Group A, PI showed a

positive correlation with GI and CRP levels (0.270 and 0.435) which was statistically significant ($p < 0.05$). A similar significant correlation (0.177) of GI was found with CRP level (Table 4)In Group B, PI showed a positive correlation with GI, PD, CAL and CRP level (0.230, 0.208, 0.005 and 0.184) and was statistically significant ($p < 0.05$). A similar correlation of PD with CAL & CRP (0.359 & 0.344) and CAL with CRP (0.299) was found to be positive and statistically significant ($p < 0.01$) (Table 5)

Table 1:- Descriptive statistics of parameters of Group-A (Pregnant women without periodontitis.)

Pregnant women without periodontitis [Group A]			
Parameters Evaluated	**Mean**	**Std. Deviation**	**Std. Error Mean**
Plaque Index (PI)	.69	.465	.046
Gingival Index (GI)	.14	.349	.035
Probing Depth (PD)	2.03	.171	.017
Clinical Attachment Loss (CAL)	0.00	0.000	0.000
CRP Level (mg/L)	1.55	.702	.070

Table 2:-Descriptive statistics of parameters of Group B (Pregnant women with periodontitis.)

Pregnant women with periodontitis [Group B]			
Parameters Evaluated	**Mean**	**Std. Deviation**	**Std. Error Mean**
Plaque Index (PI)	2.75	.432	.039
Gingival Index (GI)	2.47	.501	.045
Probing Depth (PD)	4.72	.518	.047
Clinical Attachment Loss (CAL)	2.39	.537	.049
CRP Level (mg/L)	4.22	2.247	.203

Table 3:- Comparison of different parameters among Group A and B utilizing Unpaired 't' Test

Parameters compared	**'t' value**	**Sig. (2-tailed)**	**Mean Difference**
Plaque Index (PI)	-33.965	.000	-2.064
Gingival Index (GI)	-40.676	.000	-2.327
Probing Depth (PD)	-53.856	.000	-2.691
Clinical Attachment Loss (CAL)	-49.061	.000	-2.385
CRP Level (mg/L)	-12.412	.000	-2.671

Table 4:-Correlation between various parameters of Group A utilizing Pearson Correlation.

Group A	**Parameters**		**Plaque Index (PI)**	**Gingival Index (GI)**	**Probing Depth (PD)**	**Clinical Attachment Loss (CAL)**	**CRP Level (mg/L)**
Pregnant women without periodontitis	Plaque Index (PI)	Pearson Correlation	1	.270**	-0.009	.b	.435**
		Sig. (2-tailed)		0.007	0.93		0
	Gingival Index (GI)	Pearson Correlation	.270**	1	-0.071	.b	0.177
		Sig. (2-tailed)	0.007		0.483		0.077
	Probing Depth (PD)	Pearson Correlation	-0.009	-0.071	1	.b	-0.055
		Sig. (2-tailed)	0.93	0.483			0.59
	Clinical Attachment Loss (CAL)	Pearson Correlation	.b	.b	.b	.b	.b
		Sig. (2-tailed)					
	CRP Level (mg/L)	Pearson Correlation	.435**	0.177	-0.055	.b	1
		Sig. (2-tailed)	0	0.077	0.59		
**. Correlation is significant at the 0.01 level (2-tailed).							
*. Correlation is significant at the 0.05 level (2-tailed).							
b. Cannot be computed because at least one of the variables is constant.							

Table 5:- Correlation between various parameters of Group B utilizing Pearson correlation

Group B	**Parameters**		**Plaque Index (PI)**	**Gingival Index (GI)**	**Probing Depth (PD)**	**Clinical Attachment Loss (CAL)**	**CRP Level (mg/L)**
Pregnant women with periodontitis	Plaque Index (PI)	Pearson Correlation	1	.230*	.208*	0.055	.184*
		Sig. (2-tailed)		0.011	0.022	0.544	0.042
	Gingival Index (GI)	Pearson Correlation	.230*	1	0.092	-0.06	-0.1
		Sig. (2-tailed)	0.011		0.315	0.51	0.273
	Probing Depth (PD)	Pearson Correlation	.208*	0.092	1	.359**	.344**
		Sig. (2-tailed)	0.022	0.315		0	0
	Clinical Attachment Loss (CAL)	Pearson Correlation	0.055	-0.06	.359**	1	.299**
		Sig. (2-tailed)	0.544	0.51	0		0.001
	CRP Level (mg/L)	Pearson Correlation	.184*	-0.1	.344**	.299**	1
		Sig. (2-tailed)	0.042	0.273	0	0.001	
**. Correlation is significant at the 0.01 level (2-tailed).							
*. Correlation is significant at the 0.05 level (2-tailed).							
b. Cannot be computed because at least one of the variables is constant.							

Discussion:

CRPlevels may increase to multiple folds in response to wide range of inflammatory stimuli such as infections, hypoxia, trauma etc. In addition, CRP levels may be also influenced by other factors such as pregnancy, high blood pressure, smoking, chronic fatigue, systemic disease, lactation, sleep disturbances etc.[10] It was first discovered by William S. Tillet and Thomas Francis[11] and proved to be a reliable marker of inflammatory burden. Different authors reported association between CRP and preeclampsia,[12] intra uterine growth restrictions,[13] preterm delivery;[14] periodontitis[15,16,17,18,19,20] and periodontitis in pregnant patients.[21,22,23,24] The literature regarding the effect of periodontitis on serum CRP level in pregnancy is limited. Therefore, the present randomized observational trial is designed to compare serum CRP levels in pregnant women with and without periodontitis.

The intergroup comparison of PI, GI, PD and CAL was reported to be statistically significant ($p<.05$) which was in accordance to the reports of Lopez NJ et al,[25] but they evaluated the risk of preterm birth and low birth weight in women with periodontitis. Mean CRP levels in pregnant patients suffering from periodontitis was higher as compare to periodontally healthy pregnant patients that is 4.22 ± 2.247 and 1.55 ± 0.070 respectively which was in accordance to the reports of Sharma A et al,[23] Mannava P et al,[24] and Hortan et al[22] who recorded the median intraquartile readings in healthy, mild periodontitis and moderate to severe periodontitis pregnant patients as well as to the report of Pitiphat W et al[21] who observed the same pattern of median CRP in periodontally disease and healthy pregnant patients.

The association between CRP and periodontitis in pregnancy may or may not be causal. The possible reason of serum CRP elevation may be because of its role in initial host response to injuries, infection, ischemic necrosis or malignancy where it helps to destroy infectious and noxious agents, to remove damage tissue and to repair affected tissue or organ.[26]

On the other hand, CRP could intensify the inflammatory response through compliment activation, tissue damage and stimulation of inflammatory cytokines by monocyte.[27] In pregnancy CRP levels may fluctuate due to wide variety of stimuli occurring during different phases of pregnancy i.e. the implantation of monocyte and macrophage production of interleukin 6 (IL-6),[28] the necrotic process associated with placental aging[29] and progressive increments in the level of estrogen during gestation. Thereby, may arbitrate to the relation between periodontitis and adverse pregnancy outcomes. Moreover, periodontal disease and CRP may share a common risk factors predisposing an individual to hyper inflammatory response.[21]

Looking after the same periodontal phase one therapy was advised to all the patients. Strict oral hygiene maintenance instructions and use of chlorhexidine 0.2% was recommended till the gestation period in order to reduce the inflammatory burden thereby reducing the incidence of adverse pregnancy outcome.

The Intra group correlation comparison between different clinical parameters and serum CRP was observed only in the present trial to the best of our knowledge. Therefore, direct comparison with other trials may not be possible but it can be considered as baseline data for future trials.

Group A showed positive and significant association between PI Vs. GI and CRP. Group B also reported positive and significant correlation between PI Vs. GI and PD whereas, PD Vs. CALwas first reported in the present trial. Positive and significant correlation between PI Vs. CRP, PD Vs. CRP, CAL Vs. CRP was observed in Group B which was in accordance to the reports of Bolla et al[30] but contrary to the report of Bansal T et al[31] but they have evaluated the serum CRP level in healthy, chronic and aggressive periodontitis patients in former and healthy, generalized gingivitis and chronic generalized periodontitis patients in later respectively.

With an increase in mean PI, PD, CAL, we observed an increase in the CRP level in pregnant patient suffering from periodontitis which was partially in accordance to the report of Goyal et al[32] but they have evaluated the PD, CAL and CRPin non-periodontitis, generalized chronic periodontitis and aggressive periodontitis; and Saizberg et al[17] who

evaluated PD, CAL and CRP in localized aggressive periodontitis, generalized aggressive periodontitis and non-periodontitis patient. The outcome achieved may be because i) As the severity and extent of periodontal disease increase, the systemic component of inflammation also increases. This may be seen as increased production of CRP [33] which may further exacerbate under the influence of sex hormones [34]; ii) CRP level may vary in the pregnant subjects,[35] and iii) Increased PD will increase the surface area and volume of the periodontal lesion.[17]

On the basis of overall observations of the trial it was interpreted that plaque is the initiating factor for gingival inflammation which under the influence of endogenous steroid hormones may exacerbate.[34] If not treated, may leads to periodontal tissue destruction either directly by microorganisms or indirectly by interaction with their byproducts or hepatic activation of acute phase reactant such as CRP[36] which further under hormonal influence during pregnancy due to wide variety of stimuli may lead to fluctuations in CRP levels and changes in circulating levels of pro-inflammatory cytokines,[35] which may further induced more inflammation and periodontal destruction.

Conclusion:

It was observed that pregnant patients suffering from periodontitis have elevated CRP levels. But it is very difficult to say whether the fluctuations observed are only due to periodontal destruction, as numerous factors influences the CRP levels. Therefore, CRP levels can only point out present or absence of any systemic / local inflammation, but proves to be of less diagnostic importance in terms of specificity. Still it is suggested that non-surgical periodontal therapy must be implemented as an adjunct to antenatal care, in addition to strict oral hygiene maintenance to reduce the inflammatory burden.

Limitations:

1) Small sample size.
2) Trimesters of the pregnant patient were not noted.
3) Comparison between pre and post-delivery CRP level has not been evaluated.
4) Comparison of pre and post periodontal therapy effect on CRP levels was not evaluated.

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