COMPARATIVE ANALYSIS OF INTERLEUKIN-11 LEVELS IN PREGNANT AND NON-PREGNANT WOMEN WITH AND WITHOUT PERIODONTITIS

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Abstract

Aim: The aim of the study is to asses the levels of interleukin -11 in pregnant and non-pregnant women with and without chronic periodontitis.
Material and Methods: A total of 60 systemically healthy patients aged 18-40 years were included in the study. Subjects were classified into four groups based on probing pocket depth and pregnancy status. Other clinical parameters such as plaque index, gingival bleeding index and oral hygiene index were recorded. Gingival crevicular fluid from these patients was collected using micro-capillary pipettes and the concentrations of IL-11 in the samples were determined using Quantitive ELISA.
Results: The levels of Interleukin -11 was highest in pregnant healthy women compared to pregnant chronic periodontitis patient and non pregnant healthy and chronic periodontitis patients
Conclusion: The concentration of IL-11 was found to be significantly higher in healthy individuals and pregnant women, as compared to non-pregnant women. Due to its anti-inflammatory properties, IL-11 is believed to have a protective effect against chronic periodontitis, and can therefore be considered a potential biomarker for the assessment of periodontal disease activity.

Keywords: IL-11, pro-inflammatory cytokines, endometrium,pregnancy, gingivitis, periodontitis

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1. Introduction

Periodontitis is a multifactorial chronic inflammatory disease characterized by destruction of supporting tissues of the teeth. Periodontal alterations have been demonstrated to occur in women during three stages of life: puberty, pregnancy, and menopause. Both puberty gingivitis and pregnancy gingivitis can develop into periodontitis if left untreated. Similar to non-pregnant women, bacterial plaque causes gingivitis in pregnant women. The clinical situation is altered by pregnancy, which amplifies the gingival reaction to plaque.

During pregnancy, the severity of gingivitis develops from the second or third month onward, becomes severe by the eighth month, and then declines by the ninth month. As long as the local factors continue, the gingiva does not recover to its healthy state. Pregnancy gingivitis, if left untreated, can result in premature, low birth weight babies or preterm labour as well as periodontitis.

Cytokines are thought to be crucial in the development, progression, and host modulation of periodontal disease. When there is periodontal inflammation, the balance between pro-inflammatory and anti-inflammatory cytokine activity determines the severity, duration, and resolution of the inflammation.[1]

By reducing the generation of pro-inflammatory cytokines and causing less damage to periodontal tissue, IL-11 is crucial in the control of immune response. As pro-inflammatory cytokines like IL-1, TNF, IL-6, IL-12, and nitric oxide are inhibited by IL-11. Based on the limited scientific evidence, there is a basic understanding that periostin is downregulated in the presence of chronic inflammatory periodontal disease and TNF-α modulates the expression of periostin **Burra Naga Radhika, Deva Priya Appukuttan et al 2019**.[2] Different mesenchymal cells, including bone marrow stromal cells, lung fibroblasts, and osteosarcoma cells, produce IL-11, with expression depending on the cell being either transcriptionally or post-transcriptionally regulated. TREM-1/DAP12 signalling pathway promotes the synthesis of inflammatory cytokines like IL-1β, TNF-α, IL-6, IL-8. **Kumar G, Ponnaiyan D et al 2020**[3]This study highlights the significance of IL 11, which is crucial for the prevention and resolution of pregnancy-related inflammation

2. Materials and Methods

A total of 60 women participated in the study, out of which 30 pregnant women in their second trimester were recruited from the outpatient department of voluntary health service, Taramani. Thirty patients were recruited from the department of Periodontology ,SRM dental college, approved from the IRB. Subjects were classified into four groups based on the clinical parameters such as plaque index, gingival index, bleeding on probing, probingpocket depth and pregnancy status.Gingival crevicular fluid samples were collected from maxillary teeth of all subjects to reduce the possibility of contamination with saliva. Chosen site for collection for GCF has been isolated with cotton rolls. Verbal and written consent was obtained from the patients after explaining the procedure and willingness to participate in the study .The study was approved by the ethical committee,

Selection Criteria:

Inclusion Criteria:

Systemically healthy patients in the group between 18-40 years who had not received any antibiotic therapy and periodontal therapy in the last 6 months having a minimum number of 20 teeth were included in the study.

Exclusion Criteria:

Post menopause women, women using oral contraceptives, hormonal replacement therapy, smokers, chronic inflammatory diseases, and patients with acute infections.

Group I: (Healthy Control)

Consists of 15 subjects with clinically healthy periodontium with no evidence of periodontal disease.

Group Ii: (Women with Chronic Periodontitis)

Consists of 15 subjects with clinical signs of inflammation and periodontal pocket.

Group Iii: (Pregnant Women in Second Trimester with Chronic Periodontitiis)

Consists of 15 subjects with clinical signs of inflammation and periodontal pocket.

Group Iv: (Pregnant Healthy/ Pregnant Women In Second Trimester Without Chronic Periodontitis) Consists of 15 subjects with no clinical signs of inflammation and periodontal pocket.

Clinical parameters to be assessed are oral hygiene index- simplified that include oral hygiene index, plaque index, gingival index, papillary bleeding index, probing pocket depth.

Procedure for collection of GCF:[4]

Subjects selected for the study were made to sit comfortably in an upright position on the dental chair with proper illumination. Based on periodontal status the site with maximum probing depth in the maxillary teeth was selected for sampling. The site to be sampled was isolated with cotton rolls and air dried. Supragingival plaque was carefully removed. Crevicular fluid was obtained by placing 1-5 micro

litre calibrated volumetric micro-capillary pipettes at the gingival margin. A standardized volume of 1 micro litre of crevicular fluid was collected by placing the tip of the pipettes extra crevicular. Crevicular fluid contaminated by blood or saliva were discarded. Samples were stored at -80 degree Celsius and were assayed for IL-11 concentrations by using quantikine human IL_11 Elisa kit. This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for IL-11 has been pre coated onto a microplate. After washing away any unbound enzyme reagent a substrate solution is added to the wells. Colour develops in proportion to the amount of IL-11 bound in the initial step. The colour development is stopped and the intensity of the colour is measured.

Assay procedure:

All the reagents and samples are brought to room temperature before use and prepared for the assay. Add 100µl of standard, control, sample per well. The plate was covered and incubated for 2 hours at room temperature(18-25 degree Celsius). The plate was gently tapped to ensure thorough mixing done. The cover was removed and plate was washed four times using the wash µbuffer. 200µ*l* of Il-11 conjugate was added to all the wells. The plate was securely covered with a plate sealer and incubated for 2 hours at room temperature. The plate was washed 4 times followed with addition of 200µl substrate solution to each well. The plate was incubated for 30 minutes at room temperature. The enzyme substrate reaction was stopped quickly by pipetting 50µl stop solution to each well the colour in the wells changed from blue to yellow. The optical density of each well was determined within thirty minutes using a microplate Reader set to 450nm as the primary wave length. The levels of IL-11 in the samples were estimated using the standard curve. IL-11 concentration obtained in pg/ml.

3. Results

Table 1 : Intra comparison of OHI S revealed significant difference between group 4 compared with group 2 and group 3 (P<0.0001), group 2 compared with group 1 and group 4 (P<0.0001). No statistical difference was observed between group 4 with group 1 at 95% confidence level.

(I)Group	(J) Group	Mean Difference	Std Error	Sig
Healthy Patients	Chronic Periodontitis	-1.0147	.1061	.000
Pregnant Chronic	Periodontitis	-.7813	.1061	.000
	Pregnant Healthy	-.0680	.1061	.918
Chronic Periodontitis	Healthy Patient	1.0147.	.1061	.000
	Pregnant Chronic Periodontitis	.2333	.1061	.136
	Pregnant Healthy	.9467	.1061	.000
Pregnant Chronic Periodontitis	Healthy Patient	.7813	.1061	.000
		-.2333	.1061	.136
	Chronic Periodontits	.7133	.1061	.000
	Pregnant Healthy			
Pregnant Healthy	Healthy Patients	.0680	.1061	.918
	Chronic Periodontits	-.9467	.1061	.000
	Pregnant Chronic Periodontitis	-7133	.1061	.000

Table 2: Intra comparison of plaque index showed significant difference between group 1 compared with group 2, group 3 (P<0.0001), group 2 compared with group 1, group4 (P<0.001). Group4 compared with group 1 (P<0.46). No statistical difference was observed between group 2 when compared with group 3 at 95% confidence interval .

(I)Group	(J) Group	Mean Difference	Std Error	Sig
Healthy Patients	Chronic Periodontitis	-.86800	.07395	.000
Pregnant Chronic	Periodontitis	-. 69467	.07395	.000
	Pregnant Healthy	. 19867	.07395	.046
Chronic Periodontitis	Healthy Patient	.86800	.07395	.000

Pregnant Chronic Periodontitis Pregnant Healthy	.17333 1.06667	.07395 .07395	.100 .000
Pregnant Chronic Periodontitis Healthy Patient Chronic Periodontits Pregnant Healthy	.69467 -.17333 .89333	.07395 .07395 .07395	.000 .100 .000
Pregnant Healthy Healthy Patients Chronic Periodontits Pregnant Chronic Periodontitis	-. 19867 -1.06667 -.89333	.07395 .07395 .07395	.046 .000 .000

Table 3: Intra group comparison of Gingival bleeding index revealed significant difference was observed in group 1 compared with group2 and group 3 (P<0.001), group2 compared with group1 (P<0.001) and group(P< 0.013). No significant difference was observed between group when compared between group 4 when compared between group 1 and group 2 at 95% interval

.(I)Group (J) Group	Mean Difference	Std Error	Sig
Healthy Patients Chronic Periodontitis Pregnant Chronic Periodontitis Pregnant Healthy	-.35533 -. 62533 . 16200	.08551 .08551 .08551	.001 .000 .046
Chronic Periodontitis Healthy Patient Pregnant Chronic Periodontitis Pregnant Healthy	.35533 .27000 .19333	.08551 .08551 .08551	.001 .013 .120
Pregnant Chronic Periodontitis Healthy Patient Chronic Periodontits Pregnant Healthy	.62533 .27000 .46333	.08551 .08551 .08551	.000 .013 .000
Pregnant Healthy Healthy Patients Chronic Periodontits Pregnant Chronic Periodontitis	.16200 -.19333 -.46333	.08551 .08551 .08551	.242 .120 .000

Table 4. Il-11 Concentrations Showed Significance Difference Between Group4 Compared With Group 1 (P<0.004), Group 2 (P<0.003) And Group 4 Compared With Group3 (P<0.037). No Statistical Significance Was Observed Between Group 2 Compared With Group 1and Group 3

(I)Group (J) Group	Mean Difference	Std Error	Sig
Healthy Patients Chronic Periodontitis Pregnant Chronic Periodontitis Pregnant Healthy	6.002600 -51.745933 -224.94967	62.640142 62.640142 62.640142	.001 .000 .046
Chronic Periodontitis Healthy Patient Pregnant Chronic Periodontitis Pregnant Healthy	-6.002600 -57.748533 -23095227	62.640142 62.640142 62.640142	.001 .013 .120
Pregnant Chronic Periodontitis Healthy Patient Chronic Periodontits Pregnant Healthy	51.745933 57.748533 -173.20373	62.640142 62.640142 62.640142	.000 .013 .000

Pregnant Healthy Healthy Patients Chronic Periodontits Pregnant Chronic Periodontitis	224.949667 230.952267 173.203733	62.640142 62.640142 62.640142	.004 .003 .037

4. Discussion

Scientific evidence has emerged in the field of periodontology linking periodontitis to a person's overall health. Chronic periodontitis is characterized by inflammatory destruction of connective tissue loss of periodontal attachment and resorption of alveolar bone **Page and kornman1997.[5]** The destruction of the periodontium occurs due to release of toxic products from the pathogenic plaque bacteria and is compounded by the host response elicited against these bacteria and their products.

Research has demonstrated that the host response to periodontal infection results in the local production of cytokines and biological mediators such as prostaglandins and interleukins as well as the systemic production of serum antibodies.

Cytokines are considered to play an important role in the initiation, progression and host modulation of periodontal disease **Birkedal- Hansen et al 1993,Steven B. Mizel 1989.[6]** The intensity, duration and resolution of inflammation depend on shifting the balance between the activities of pro-inflammatory and anti inflammatory cytokines during periodontal inflammation. IL-11 is a multifunctional cytokine derived from primate stromal cell line (pu-34) and later from human MRC_5 cell line. The intensity, duration, and resolution of inflammation depend on shifting the balance between the activities of proinflammatory and anti-inflammatory cytokines during the periodontal inflammation. IL-11 has been shown to inhibit IL-1β, TNF-α, IL-6, and downregulated LPS-induced cytokines throughout the inhibition of NF-κB expression *in vitro*.[7]

The emergence of sex specific relationships and the associations between periodontitis and certain systemic disorders have prompted researches to investigate the possibility of association between periodontitis and specific women's health issues.

Changes in hormone levels such as those that occur during puberty, menstruation, pregnancy and menopause as well as those that occur with the use of hormone supplements(including oral contraceptives) have long been associated with the development of gingivitis. **Samant. A et al 1976 O.Niel et al 1979.[8] Ojanatko-Harri AO et al 1991.[9] Tillakaratne et al 2000. [10]**

Estrogen , progesterone and chorionic gonadotropin (during pregnancy) affect the microcirculatory system by increasing vascular permeability and vascular proliferation.[11]

This pattern of gingivitis appears to follow the normal cycle of hormonal changes and may be seen with varying degrees of significance. Perhaps even greater importance than the above changes, however is the shift in microbiota, which has been documented during these hormonal changes **Laurence M. Adriaens et al 2009.[12]**

The current study attempted to quantify IL-11 to evaluate its role in periodontal diseases in women with pregnancy. Gingival crevicular fluid was taken from patients categorized into healthy (1), chronic periodontitis(2), pregnant chronic periodontitis (3), and pregnant healthy(4). IL-11 concentration was assayed using Quantikine human IL-11 ELISA KIT. Clinical parameters like calculus, plaque, probing depth, gingival bleeding and gingival inflammation were assessed.

The average mean of gingival bleeding index and gingival index were found to be elevated in pregnant chronic periodontitis patients followed by chronic periodontitis compared to other groups. This present study agrees with the studies of **Samant. A et al 1976, O.Niel et al 1979.[8] Ojanatko-Harri AO et al 1991.[9]Tillakaratne et al 2000.**[10]

The current study shows, IL-11concentration presented an average mean concentration of 45.01± 31.02ng/ml for group 1, 39.01±9.03ng/ml for group296.75± 168.6ng/ml for group 3 and 269.96± 297ng/ml for group 4. IL-11 concentrations showed statistical difference between group 4when compared with group 1($P<0.0004$), group2 ($P< 0.003$), and group 3 ($P<0.037$) where group 3 had lesser significance compared to the other two groups. No statistical difference was observed when group 2 was compared with group 1 and group 3.

The present study indicated elevated concentrations of Il-11 in GCF of pregnant women with healthy periodontium compared to pregnant women with chronic periodontitis and healthy women when compared to women with chronic periodontitis. This correlates with previous periodontally diseased sites. Il -11 plays an important role during the early years of pregnancy , such as differentiation of endometrial stromal cells into deciduous cells which is crucial for embryo implantation and placentation **Karpovich N et al 2005.[13]** Increased plasma levels of Il-11 have been reported during early pregnancy Which could be speculated to be a cause in the elevated levels of IL-11 in the GCF of pregnant women.

Though IL-11 plays an important role in the modulation of immune response via the reduction of pro inflammatory cytokine production and periodontal tissue damage It has also been shown to be osteopromotive, stimulating the osteoblastic differentiation of periodontal ligament cells mainly through the synthesis of type I collagen and possibly by the induction of tissue inhibitor of metalloproteinase-I**.** Anti inflammatory effects of IL-11 is well documented in various studies on inflammatory diseases.

5. Conclusion

To conclude IL-11 concentration increased substantially in health and pregnant women relative to non pregnant women. Since IL-11 is an anti inflammatory cytokine it could play a protective role in periodontitis . thus IL-11 could be used a biomarker for periodontal disease activity

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Conflicts of interest:
There are no conflicts of interest

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