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*Original Article*

# Association Between Systemically Healthy Chronic Periodontitis Pregnant Female Subjects and Anemia of Chronic Diseases: A Clinical Study

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**ABSTRACT**

Anaemia of chronic disease (ACD) is the second most common type of anaemia after iron deficiency anaemia. Because of of similar cytokines a role in pathogenesis of ACD and periodontitis, and also the role of periodontitis as a chronic infection, a relationship between these two disease was proposed. As periodontitis is a chronic infectious/inflammatory disease and also various markers of systemic inflammation have been shown to be raised in blood/plasma of periodontitis patients, suggesting that there is chronic immune activation in periodontitis patients. So, periodontitis likewise, other chronic inflammatory disease e.g. rheumatoid arthritis may also can progress towards anaemia (ACD).

**Key words:** Anemia, Chronic Periodontitis, Pregnant Female.

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## INTRODUCTION:

Anaemia can be evaluated by analysing erythrocytes count, Haemoglobin concentration(Hb%)and various red blood cells parameters such as haematocrit, mean corpuscular volume(MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration(MCHC). [1.2]

Present study aimed to assess the various hematological parameters such as : Red Blood cell count (R.B.C count ) Hemoglobin% (Hb%) Erythrocyte sedimentation rate (E.S.R) Hematocrit (HCT) , Mean corpuscular volume (MCV) , Mean corpuscular hemoglobin(MCH) , Mean corpuscular hemoglobin concentration (MCHC) in pregnant subjects with and without chronic generalized periodontitis**.**

## RATIONALE:

### PREGNANCY & PERIODONTITIS

Pregnancy-related changes are most frequent and most marked in gingival tissue. Pregnancy does not cause gingivitis, but may aggravate pre-existing disease. The most marked changes are seen in gingival vasculature.[3]

Pregnancy is accompanied by an increase in the levels of both progesterone and estrogen which, by the third trimester, reaches levels 10-30 times than seen during the typical menstrual cycle. The gingivitis associated with pregnancy has been attributed to increased concentrations of circulating estrogen and/or progesterone.[4]

These hormonal changes induce changes in vascular permeability, leading to gingival edema and an increased inflammatory response to dental plaque. The subgingival microbiota may also undergo changes, including an increase in *Prevotella intermedia*.[5]

**Kolte R A, et.al. ( 2014)** [6] Conducted a study to assess and compare the various blood parameters including hemoglobin ( Hb),total erythrocyte count, total leukocyte count(TLC),bleeding time, and clotting time in healthy subjects and chronic periodontitis patients. They concluded that chronic infections such as periodontitis have systemic effects in terms of blood parameters, indicating a tendency towards anemia.

**Suchetha A et al (2015)** [7] The present study was conducted to evaluate and compare the hematological parameters in periodontally healthy, gingivitis and periodontitis subjects and thereby assess the relationship between anemia and periodontitis. It was concluded from the study that a positive relationship was observed between hematological parameters and severity of periodontal disease, suggesting that like any other chronic disease periodontitis may also leads to anemia.

## ANEMIA IN PREGNANCY

Anemia is one of the most frequent complications related to pregnancy. The anemia is pregnancy is mostly Iron deficiency anemia and Megaloblastic anemia. It is known that there is a larger increase in plasma volume relative to red cell mass in almost all pregnancies, and it accounts for "Physiologic Anemia" The fall in haemoglobin concentration during pregnancy is due to combined effect of haemodilution and negative iron balance i.e as there is marked demand of extra iron during pregnancy specially in the second half. Thus,there always remains a physiological iron deficiency state during pregnancy. [8, 9]

## ANEMIA & PERIODONTITIS

It is accepted that much of the periodontal tissue destruction observed in periodontitis is host-mediated through release of proinflammatory cytokines by local tissues and immune cells in response to the bacterial flora and its products/metabolites, especially LPS. Tumor necrosis factor- α (TNF-α), interleukin-1β (IL-1β) proinflammatory cytokines are most convincing evidence for destruction of the periodontium. These cytokines are significantly elevated in diseased periodontal sites and during periods of active disease/tissue destruction. In term of tissue destructive effects, it's believed that IL-1β recruits inflammatory cells, facilitates polymorphonuclear leukocyte (PMN) priming/degranulation, increases synthesis of inflammatory mediators (prostaglandins)/matrix metalloproteinases (MMP), inhibits collagen synthesis and activates both T and B lymphocytes. TNF-α is a major signal for cellular apoptosis, bone resorption, MMP secretion, intercellular adhesion molecule (ICAM) expression and interleukin-6 production. IL-6, once produced, stimulates formation of osteoclasts, promotes osteoclastic bone resorption and facilitates T-cell differentiation.[8] Also some studies suggested that C-reactive protein level is elevated in chronic periodontal diseaseobserved in other chronic infections and inflammatory conditions.[9]

## THE ANEMIA OF CHRONIC DISEASE[9-13]

Anemia of chronic disease is defined as the anemia occurring in chronic infection, inflammatory conditions or neoplastic disorders that is not due to marrow deficiencies or other diseases, and occurring inspite the presence of adequate iron stores and vitamins.

The characteristic feature of this syndrome is the occurrence of hypoferremia in the presence of ample reticuloendothelial iron stores. As defined, the ACD doesn't include anemias caused by marrow replacement, blood loss, hemolysis, renal insufficiency, hepatic disease, or endocrinopathy, even when these disorders are chronic.

In patients with anemia of chronic disease, the proliferation and differentiation of erythroid precursors—erythroid burst-forming units and erythroid colony-forming units — are impaired and are linked to the inhibitory effects of interferon α, β and γ, TNF-α, and interleukin-1, which influence the growth of erythroid burst-forming units and erythroid colony-forming units.Interferon-γ appears to be the most potent inhibitor, as reflected by its inverse correlation with hemoglobin concentrations and reticulocyte counts.

Moreover, cytokines exert direct toxic effects on progenitor cells by inducing the formation of labile free radicals such as nitric oxide or superoxide anion by neighboring macrophage-like cells.

### Disturbance in iron metabolism / Dysregulation of iron homeostasis

It has been proposed that lack of iron for erythropoiesis contributes to the inadequate marrow response in ACD. Evidence of a functional iron deficiency in this syndrome includes erythrocyte microcytosis, increased FEP, reduced transferrin saturation, and decreased marrow sideroblasts.[9.]

A hallmark of anemia of chronic disease is the development of disturbances of iron homeostasis, with increased uptake and retention of iron within cells of the reticuloendothelial system..

In chronic inflammation, the acquisition of iron by macrophages most prominently takes place through erythrophagocytosis and the transmembrane import of ferrous iron by the protein divalent metal transporter 1 (DMT1). Interferon-γ, lipopolysaccharide, and TNF-α upregulate the expression of DMT1, with an increased uptake of iron into activated macrophages. These proinflammatory stimuli also induce the retention of iron in macrophages by down-regulating the expression of ferroportin, thus blocking the release of iron from these cells. Ferroportin is a transmembrane exporter of iron, a process that is believed to be responsible for the transfer of absorbed ferrous iron from duodenal enterocytes to the circulation.

The role of the liver-produced antimicrobial peptide hepcidin strongly suggests that it is the dominant factor in iron abnormalities of ACD. Hepcidin is an acute-phase-reacting peptide.[10] Urinary hepcidin excretion is strongly correlated with serum ferritin concentration and is markedly elevated in patients with anemia of inflammation compared to iron-deficient patients.[12]

## MATERIALS AND METHODS:

**STUDY DESIGN:** The proposed study was designed as a case control study. The subjects were divided into two groups as per the inclusion and exclusion criteria .

**Group I**: Included pregnant subjects diagnosed with generalized chronic periodontitis having mean probing pocket depth ≥ 4 mm, in atleast 30% sites..

**Group II**: Included periodontally healthy pregnant women with mean sulcus probing depth of ≤ 3 mm ..

**Sample Size:** The sample size of the study consisted of a total of 51 pregnant women, out of which a total of 26 subjects were included as cases and 25 subjects were included as controls as per the inclusion and exclusion criteria of the study.

**INCLUSION CRITERIA:**

- Systemically healthy pregnant women .
- Subjects with minimum of 20 permanent teeth .
- Subjects with age group between 20-30 years.
- Primigravida
- Subjects with Gestational age 17-28 weeks. / second trimester ( 4th month-7th month ) /( nearly 120 days- 196 days of POG )
- Subjects not on Iron supplements.
- ubjects with no history of mechanical periodontal therapy within the last one year before initiation of this study.

**EXCLUSION CRITERIA:**

- Subjects with history of antibiotic intake during pregnancy.
- Other obstetric risk factors like smoking, alcohol consumption, drugs use, etc.
- Subjects already diagnosed with anemia and on medication for the same.
- Subjects who have received blood transfusion.

**INTRA -ORAL EXAMINATION**:

The intraoral examination was performed for recording the following data. Materials and methods used is shown in **colour plate**

**ARMAMENTARIUM** In order to carry out the present study, the following materials and methods were employed:

**MATERIALS**

- Disposable Face mask
- Disposable latex gloves
- Kidney tray
- Plane mouth mirror
- Dental explorer
- Tweezers
- UNC- 15 periodontal probe
- Cotton
- Disposable syringes for blood sample collection (5ml)
- Vials embedded with EDTA for transfer of blood samples
- Vials embedded with sodium citrate for transfer of blood samples
- Westergreen's tube
- Cell Counter for the evaluation of Blood parameters

**INTRA ORAL EXAMINATION** was performed for recording the following data ;

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- **Dentition status**
- **Gingival Index ( Loe H & Sillness)**
- **Probing Pocket ( PPD)** depth measured with UNC-15 periodontal probe (recorded at six sites per tooth).
- **Recession/ Enlargement** measured with UNC-15 periodontal probe (recorded at six sites per tooth).
- **Clinical Attachment level** (recorded at six sites per tooth)

**HEMATOLOGIC EXAMINATION** involved the recording of values of the following parameters;

Red blood cell count ( RBC count) , Hemoglobin %( Hb%), Hematocrit (HCT) & various RED BLOOD CELL INDICES NAMELY ; Mean corpuscular volume ( MCV) Mean corpuscular hemoglobin (MCH),Mean corpuscular hemoglobin concentration . (MCHC)

**INTRA -ORAL EXAMINATION** included recording of following parameters to assess the periodontal status.

**GINGIVAL INDEX (GI ) (LOE AND SILNESS ) ( 1963)[14]**

**TABLE 1:** CRITERIA FOR THE GINGIVAL INDEX SCORING:

| SCORE | CRITERIA |
|---|---|
| 0 | Absence of inflammation/normal gingiva |
| 1 | Mild inflammation, slight change in color, slight edema, no bleeding on probing. |
| 2 | Moderate inflammation, moderate glazing, redness, edema and hypertrophy, bleeding on probing. |
| 3 | Severe inflammation, marked redness and hypertrophy ulceration, tendency to spontaneous bleeding. |

**TABLE 2:** INTERPRETATIONS OF GINGIVAL INDEX SCORES

| Gingival Score | Interpretations |
|---|---|
| 0.1- 1.0 | Mild Gingivitis |
| 1.1- 2.0 | Moderate Gingivitis |
| 2.1- 3.0 | Severe Gingivitis |

**TABLE 3:** ASSESMENT OF PERIODONTAL STATUS PROBING POCKET DEPTH [15]

MEAN POCKET PROBING DEPTH = Sum of the probing pocket depth of all teeth / The total number of surfaces examined

**CLINICAL ATTACHMENT LEVEL [15]**

| CAL (in mm) | Interpretation |
|---|---|
| **<3mm** | mild periodontitis |
| **3-5 mm** | moderate periodontitis |
| **>5 mm** | severe periodontitis |

**Selection of vein site for blood collection**: Median cubital vein is commonly used for the blood collection, if the puncture of this vein is unsuccessful, one of the cephalic or basilica veins may be used. A tourniquet was placed on the arm and the median cubital vein in the antecubital region was palpated.

**HAEMATOLOGICAL PARAMETERS[16]**

With standardized and automated procedures, total numbers of erythrocytes count (RBC Count), hemoglobin concentration (Hb), packed cell volume (PCV), mean corpuscular volume of erythrocytes (MCV), the mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). The erythrocyte sedimentation rate (ESR) was determined according to standardized Wintobe procedures.

1. **BC count:** The normal range of red blood cells for normal pregnant female in 2nd trimester along with the normal reference range of an adult male and Non pregnant female and are listed .
2. **aemoglobin concentration (Hb%):** The normal range of haemoglobin concentration for normal pregnant women in 2nd trimester and of an adult male and female are listed in table
3. **acked cell volume (PCV)/ HCT: P**CV refers to the volume of RBC as a percentage of total blood volume. The normal reference range of PCV or hematocrit (Hct) for pregnant women in 2nd trimester and of an adult male and female are listed in table - Clinical significance of PCV values in detection of anemias. PCV is reduced in anaemia and raised in polycythemia and dehydration.
4. **Determination of erythrocyte indices:**
   The erythrocyte indices are calculated from- haemoglobin concentration, PCV values and total erythrocyte count. Three indices commonly calculated are-
   i. ean corpuscular volume (MCV)
   ii. ean corpuscular haemoglobin (MCH)
   iii. ean corpuscular haemoglobin concentration (MCHC)

   These values give quantitative information about the red blood cell.

   i. **ean corpuscular volume (MCV):**
   MCV is the average volume of a single RBC and is expressed in fl. The normal reference range of MCV for adults is listed in table -3. It was calculated as follows:

   ii. **ean corpuscular haemoglobin (MCH):**
   The mean corpuscular hemoglobin, or "mean cell hemoglobin" (MCH), is the average mass of hemoglobin per red blood cell in a sample of blood. It is expressed in Pico gram (pg). It is diminished in microcytic anaemias, and increased in macrocytic anaemias.

   iii. **ean corpuscular haemoglobin concentration (MCHC):**
   The **mean corpuscular hemoglobin concentration (MCHC)** is a measure of the concentration of hemoglobin in a given volume of packed red blood cell. The normal reference range for both the males and females. Are shown in Table ; . It is diminished ("hypochromic") in microcytic anaemias, and normal ("normochromic") in macrocytic anemias (due to larger cell size, though the haemoglobin **amount** or MCH is high, the concentration remains normal).
   MCHC = haemoglobin in grams per 100ml of blood / Volume of packed cells in ml. /100ml of blood

5. **rythrocyte sedimentation rate (ESR):** To measure ESR, anticoagulated blood is placed in an upright tube, known as a Wintrobe tube. After the erythrocytes were allowed to settle under gravity for one hour, the distance between the surface meniscus and the upper limit of the erythrocyte column was recorded in millimeters. The normal range for pregnant women in 2nd trimester along with normal reference of an adult male and female are listed in table-3.

**TABLE 4:** HAEMATOLOGICAL REFERENCE VALUES FOR NORMAL ADULTS:-[17]

| Haematological variables | Normal reference range | Second half pregnancy | Significance |
|---|---|---|---|
| **Red blood cell count**<br><br>**Non Pregnant Female**<br><br>**Male** | <br><br>4-5 million /cu mm<br>4.5-5.5 million/cu mm | 3.8 5 million /cu mm | RBC count decreases in anemias<br>It also permits to calculate MCV and MCH values. |
| **Haemoglobin**<br>Female<br>**Male** | 12-16gm/100ml<br>14-18 gm/100ml. | 11.5-12.5gm /100 ml | Haemoglobin concentration decreases in anemia. |
| **Packed cell volume**<br>Male<br>Female<br>**Pregnant female** | 42 to 52%<br>36 to 48% | 33-36 | PCV % help in detection of anemia. Its value decreases in anemia |
| **Mean corpuscular volume (MCV)**<br>Male & Female<br>Pregnant female | 92±9 fl | 75-95 | MCV normal value seen in normocytic anemias.<br><br>MCV value increases in macrocytic anemias<br><br>MCV value decreases in microcytic anemias |
| **Mean corpuscular haemoglobin (MCH)**<br>Male and Female<br>Pregnant female | 29.5±2.5 pg. | 26-31 | MCH normal value seen in normochomic anemias.<br><br>MCH value decreases in hypochronic anemias.<br><br>MCH value increases in macrocytic anemias. |
| **Mean corpuscular haemoglobin concentration (MCHC)**<br>**Male & Female** | 32 to 36% | 30-35% | MCHC value decreased in hypochromic anemias<br><br>MCHC value increases in spherocytosis |
| **Erythrocyte sedimentation (ESR) Wintobe tube method**<br>Male<br>Female | 0-9 mm/after 1 hour<br>0-20 mm/after 1 hour | | ESR increases in any condition causing an increase in fibrinogen or globulins such as chronic infection like tuberculosis<br>Inflammatory conditions like rheumatoid arthritis, rheumatic fever, myeloma, etc. |

The study comprised of 51 systemically healthy pregnant subjects in the age group of 20-30 years and they were divided into two groups as follows:

The subjects were divided in to;

Group I (Cases ) : Pregnant subjects ( n=26) with generalised chronic periodontitis with Average PPD of >=4mm ,reporting for treatment at rhe department of Obstetrics and gynecology, People's college of Medical Sciences and Hospital, Bhopal.

**Group II (Control)** : Pregnant subjects (n= 25) with periodontally healthy pregnant subjects .

The following clinical parameters were recorded for the selected patients.

1. Gingival Index (GI) (Loe and Sillness 1963)
2. Probing Pocket depth (PPD)

3. Clinical Attachment level (CAL )

Hematological parameters like Hb%,RBC, HCT, MCV,MCH,MCHC along with different clinical parameters in various groups were subjected to statistical analysis

**TABLE 5:** COMPARISON OF MEAN-- GINGIVAL INDEX (GI), PROBING POCKET DEPTH (PPD), CLINICAL ATTACHMENT LEVEL (CAL) IN THE STUDY POPULATION , ACCORDING TO CASES AND CONTROL

| | GROUP | MEAN | STD. DEVIATION | P VALUE | RESULT |
|---|---|---|---|---|---|
| GI | CASE<br>CONTROL | 1.5550<br>.0000 | 0.26192<br>.00000 | <0.0001 | S |
| PPD | CASE<br>CONTROL | 4.1477<br>1.3544 | 0.11518<br>0.24185 | <0.0001 | S |
| CAL | CASE<br>CONTROL | 4.1646<br>1.3572 | 0.10588<br>0.23795 | <0.0001 | S |

**TABLE 6 :** DISTRIBUTION OF, MEAN HB , RBC & HCT IN THE STUDY POPULATION ACCORDING TO CASES AND CONTROL

| | GROUP | MEAN | STD. DEVIATION | P VALUE | RESULTS |
|---|---|---|---|---|---|
| HB | CASE<br>CONTROL | 10.5192<br>11.4320 | 0.88950<br>1.08617 | 0.002 | (S) |
| RBC | CASE<br>CONTROL | 3.6523<br>3.8772 | 0.61960<br>0.42332 | 0.138 | |
| HCT | CASE<br>CONTROL | 29.6462<br>31.4300 | 4.15964<br>2.80988 | 0.080 | |

**TABLE 07:** DISTRIBUTION OF MCV, MCH , MCHC IN STUDY POPULATION ACCORDING TO CASES AND CONTROL

| | GROUP | MEAN | STD. DEVIATION | P VALUE | RESULTS |
|---|---|---|---|---|---|
| MCV | CASE<br>CONTROL | 80.8538<br>81.8920 | 8.18800<br>7.98253 | 0.649 | NS |
| MCH | CASE<br>CONTROL | 29.0223<br>29.6520 | 3.66309<br>2.10953 | 0.458 | NS |
| MCHC | CASE<br>CONTROL | 35.8512<br>36.3040 | 3.24994<br>2.52776 | 0.582 | NS |

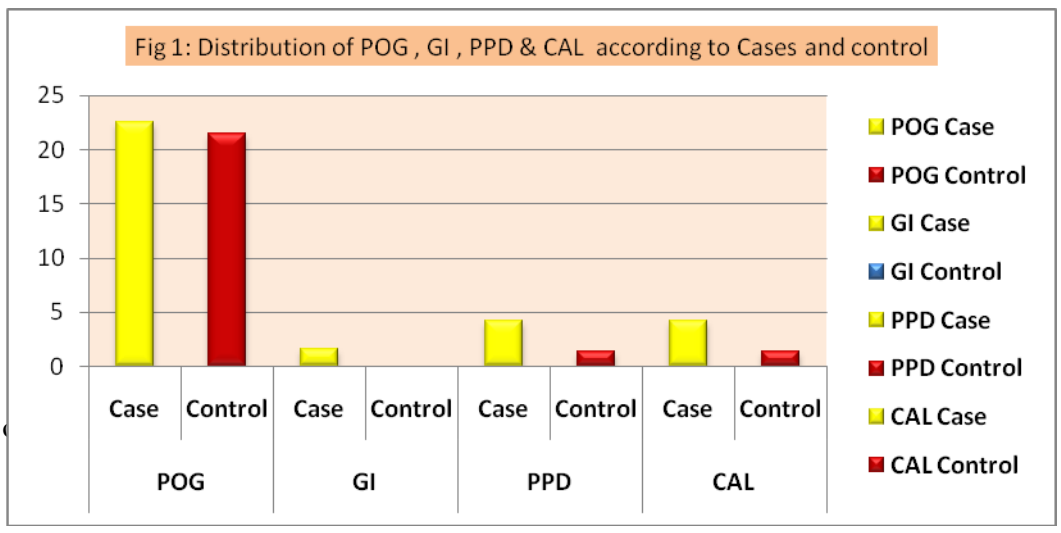

**Fig 02:** ARMAMENTARIUM FOR RECORDING CLINICAL PERIODONTAL PARAMETERS


**Fig 03:** ARMAMENTARIUM FOR BLOOD SAMPLE COLLECTION FOR CRP & VARIOUS HEMATOLOGICAL PARAMETERS

## RESULTS

The mean **GI** score in Group I (cases ) was 1.5550 ± SD 0.26192, ( Moderate gingivitis) in controls Group II, the mean GI score was (0.0233 ± 0.02142 ).The difference was found to be statistically significant.

The mean PPD score in Group I (cases) was 4.1477 ± 0.11518 ,the mean PPD in Group II (controls ) was 1.3544+ 0.24185.The difference was found to be statistically significant.

The mean clinical attachment level in Group I (cases) was 4.1646 ± 0.10588 and in Group II controls ) was found to be 1.3572 ± 0.2379 . The difference was found to be statistically significant.

The results also showed that the levels of hemoglobin, RBC and HCT were less and ESR was significantly raised in cases group as compared to controls.

These findings may be related to elevated levels of pro - inflammatory cytokines in plasma of periodontitis patients suppressing erythropoiesis. These observations were in accordance with the study by Hutter (2001) which provides evidence that the periodontitis , like other chronic conditions, may tend towards anemia .

## DISCUSSION

Periodontal disease has a proven relationship with several systemic conditions like Cardiovascular disease, diabetes mellitus, obesity and stroke.

One of the lesser documented association Hs been the inter relationship between periodontal disease and anemia.

Anaemia in pregnancy has been defined by criteria from the Centers for Disease Control and Prevention (CDC) as a haemoglobin level of less than 11 g per dL during the first and third trimesters and less than 10.5 g per dL during the second trimester.[16]

Overall data analysis of our study showed that pregnant women with periodontitis had significantly lower Mean-

hemoglobin content, low red blood cell count, low hematocrit values as compared to healthy pregnant women of control group. Whereas the various red cell indices: Mean corpuscular hemoglobin(MCH), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin concentration(MCHC) was comaparable among both the groups and was with in the normal refrence range during second trimester of pregnancy. { ( MCH = 26-31 gms, MCV= 75-95 um3, MCHC=30-35 %0} Thus giving a picture of Norrmocytic, Normochromic Erythrocytes".

There is disproportionate increase in plasma volume, RBC volume and hemoglobin mass during pregnancy. In addition, there is a marked demand of extra iron during pregnancy specially in the second half. Even an adequate diet cannot provide the extra demand of iron. Thus, there always remains a physiological iron deficiency state during pregnancy.

Significant deficiency of iron leads to characteristic" Hypochromic, Microcytic Erythrocytes[16] on peripheral blood smear in pregnancy.

## CONCLUSION:

In conclusion, these findings may suggest the understanding that periodontal infection may contribute to a systemic inflammatory burden in otherwise healthy individuals as a positive CRP levels were found to be present in periodontitis cases & the relation between periodontitis and hematological parameters like HB,RBC count, Hct, MCV, MCH, MCHC were also found to be positively co related.

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