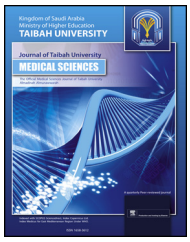
Journal of Taibah University Medical Sciences (2023) 18(6), 1376–1383

Taibah University

Journal of Taibah University Medical Sciences

www.sciencedirect.com



Original Article

Interleukin 1 beta and its association with the periodontal health of pregnant women

Nawal K.B. El Hassan, MD [a] and AbdelRahman M. Ramadan, PhD [b,*]

[a] *Department of Periodontics, Faculty of Dental Medicine and Surgery, El Razi University, Khartoum, Sudan*
[b] *Department of Oral and Basic Clinical Sceinces, Ibn Sina National College for Medical Sciences, Jeddah, KSA*

Received 16 February 2023; revised 18 April 2023; accepted 12 May 2023; Available online 23 May 2023

المخلص

أهداف البحث: تم التخطيط للدراسة لقياس مستويات السيتوكين (آي إل-1) في الأمصال و "جي سي إف" للنساء الحوامل المصابات بإلتهاب اللثة ومقارنتها مع السيدات الحوامل المطابقات اللواتي لديهن دواعم صحية.

النتائج: بالنسبة للتحليل الإحصائي، تم إجراء اختبارات ت لعينات مستقلة لتوزيع مستويات المصل و "جي سي إف" و آي إل-1 في مجموعات الدراسة والمراقبة. تم إجراء اختبار ارتباط بيرسون أيضا بين المعلمات اللثوية والمصل ومستويات "جي سي إف" آي أل-1 بيتا. تم تعيين القيمة ب عند ≥0.05 لجميع المقارنات. كانت هناك زيادة كبيرة في آي إل-1 بيتا و "جي سي إف" لمجموعة الدراسة. أيضا، كان هناك ارتباط إيجابي كبير بين مستويات آي أل-1 بيتا العالية ومستويات جيوب اللثة و فقدان التعلق السريري في "جي سي إف" لمجموعة الدراسة.

الاستنتاجات: تقدم الدراسة أدلة إضافية لدعم الفرضية القائلة بأن التهاب اللثة، الذي يتم قياسه من خلال فحص جيوب اللثة وفقدان التعلق السريري، يمكن أن يؤدي إلى زيادة مستويات آي إل-1 بيتا في السائل اللثوي العنقي للنساء الحوامل المصابات بأمراض اللثة النشطة أثناء الحمل. يمكن أن يؤدي هذا إلى الانتقال العابر للكائنات الفموية إلى مركب الرحم والمشيمة، مما قد يؤدي إلى الالتهاب أو الإجهاد التأكسدي في وقت مبكر من الحمل. في نهاية المطاف، يمكن أن يتسبب ذلك في تلف المشيمة ويؤدي إلى مقدمات الارتعاج والولادة المبكرة وانخفاض الوزن عند الولادة.

الكلمات المفتاحية: إنترلوكين -1 بيتا؛ أمراض اللثة؛ الحمل؛ السودان

Abstract

Objectives: In this study, we measured and compared serum and gingival crevicular fluid (GCF) levels of interleukin 1 beta (IL-1β) in pregnant women with periodontitis and pregnant women with a healthy periodontium. We also determined the prevalence of periodontitis among pregnant women attending Omdurman Midwifery Hospital.

Materials: This was a hospital-based clinical study and laboratory investigation using ELISA tests of 80 pregnant women in the third trimester conducted at the Omdurman Midwifery Hospital in Khartoum, Sudan. The study group consisted of 50 women while the control group consisted of 30 women.

Results: Independent samples t-tests were used to compare serum and GCF levels of IL-1β between the study and control groups. Pearson's correlation analysis was also used to compare gingival parameters and IL-1β levels in the GCF. For each comparison, the p-value was fixed at 0.05. The GCF in the research group showed a considerable increase in IL-1β levels. There was also a strong positive association between high IL-1β levels in the research group's GCF and probing pocket depth (PPD) and clinical attachment level (CAL) levels.

Conclusions: Our study provides further evidence that periodontitis, as measured by a PD ≥4 mm and a CAL ≥3 mm, is associated with an increased level of IL-1β in the GCF of pregnant women with active periodontal disease during pregnancy and may include the transient translocation of oral organisms to the utero-placental unit, inciting placental inflammation or oxidative stress early in pregnancy, ultimately resulting in placental damage and clinical manifestations.

* Corresponding address: Ibn Sina National College, Department of Oral and Basic Clinical Sciences - Division of Periodontics, Al Mahjar Street, Al Mahjar Dist, Jeddah, KSA.
E-mail: dramaramadan@gmail.com (A.M. Ramadan)

Peer review under responsibility of Taibah University.

ELSEVIER Production and hosting by Elsevier

 https://doi.org/10.1016/j.jtumed.2023.05.012

Keywords: Interleukin-1 beta; Periodontal disease; Pregnancy; Sudan

Introduction

Periodontitis is a common chronic infectious inflammatory condition affecting the periodontium. Gingivitis is the first sign of periodontitis; without intervention this can progress to periodontitis which causes the loss of connective tissues and alveolar bone.[1] Periodontitis is a specific response to acknowledged subgingival periodontal pathogens that are insufficient to cause disease progression unless an associated inflammatory response occurs in susceptible hosts.[2]

The bacterial insult caused by bacterial virulence factors, such as collagenases and leucotoxin, can directly destroy host tissues or by a response to the pathogenic biofilm which activates the host's inflammatory cells, including neutrophils and macrophages. These inflammatory cells release effector molecules, such as prostaglandin E2, interleukin 1 beta (IL-1β), and tumour necrosis factor-alpha (TNF-α), to destroy host tissues in an indirect manner. In addition, these effector molecules activate the autocrine and paracrine inflammatory cells through chemotactic mechanisms to modulate the inflammatory process.[2,3] IL-1β is a noteworthy pro-inflammatory cytokine that is known to play a role in the pathogenesis of periodontitis. IL-1β has been shown to regulate inflammatory mediators, break down osteoclasts, and activate matrix metalloproteinases (MMP).[4,5]

Pregnancy is a normal physiological process that significantly impacts women of childbearing age and can manifest orally as dental caries and various forms of periodontal disease, particularly gingivitis.[6] In addition, there is a 10-fold increase in progesterone levels during pregnancy and a 30-fold increase in oestrogen levels than during a menstrual cycle.[7] Gingival inflammation is caused by increased levels of progesterone, which increase vascular permeability, gingival enlargement, crevicular fluid levels, and prostaglandin production. Furthermore, probing pocket depths (PPDs) may increase during pregnancy without a change in the level of clinical attachment. Furthermore, other physiological changes may occur during pregnancy, including microbial species, immune response, and cell metabolism.[6,8–11]

Miller's classical theory of 'focal infection' contributed to the assumption that the foci of oral infection, such as periodontitis, may trigger systemic inflammatory responses and affect the mechanism and course of numerous systemic diseases, including vascular disease, cardiovascular disease, cerebrovascular disease, athermanous diseases, bacterial pneumonia, diabetes mellitus, osteoporosis, or cause adverse pregnancy outcomes.[12]

According to recent research, the haematogenous spread of known periodontal pathogens and their products, or the release of pro-inflammatory mediators from periodontal infection sites into the foetal membranes, placenta, and amniotic cavity, may result in a pathological process that could result in adverse pregnancy outcomes.[13,14]

While researchers agree that there is a deterioration in periodontal health status during pregnancy, some studies have demonstrated no association between periodontal health status and adverse prenatal outcomes.[15] In contrast, numerous studies have identified adverse pregnancy outcomes, such as preterm birth, the restriction of foetal development, low birth weight, or pre-eclampsia. These studies have emphasised the significance of studying the cytokines associated with pregnant women and periodontitis in comparison with women with a healthy periodontium. A possible link between adverse pregnancy outcomes and periodontitis has been suggested.[14,16–21] These are leading global prenatal problems that are associated with significant public health implications because their prevalence has not been reduced despite numerous prevention efforts. Both bacterial vaginosis and intra-uterine infections are well-known risk factors, although distant infections can result in premature births, even in subclinical cases.[22]

Since 1996, several studies have reported a close link between adverse pregnancy outcomes and periodontitis.[17–19] A theoretical model could emerge that proposes a link between maternal inflammatory periodontal conditions and foetal growth. Nonetheless, more research is needed to confirm or reject this association. The virulence factors of putative periodontal microorganisms residing within periodontal pockets can produce a localised host-immune response in the periodontal tissues that leads to the synthesis of antibodies, pro-inflammatory cytokines (lL-1β and TNF-α) and prostaglandin (PG).[23–25]

Because periodontal disease is a chronic and subclinical infectious condition, numerous studies have reported that it may trigger systemic inflammatory responses that increase the risk of adverse pregnancy outcomes.[14,21]

Adverse pregnancy outcomes have all been linked to periodontal disease. For example, pre-eclampsia, an adverse pregnancy outcome, is thought to be caused by an exaggerated systemic inflammatory response (including endotoxin, inflammatory cytokines, and oxidative stressors) and their release into the maternal–foetal circulation during pregnancy.[17,26] The Introduction of these vascular stressors may initiate the development of pre-eclampsia in pregnant women.[27] In addition, significant evidence suggests that periodontal pathogens enter the bloodstream regularly[8,9] and that infected tooth-supporting tissues can act as a pool of metabolites for periodontal pathogens increase both local and systemic levels of the inflammatory factors PGE2 and TNF and other cytokines.[9,28]

In this study, we aimed to compare the profiles of cytokines in pregnant women with periodontitis to those of pregnant women without periodontitis by assessing lL-1β cytokine levels in sera and gingival crevicular fluid (GCF).

Materials and Methods

This was a hospital-based cross-sectional study conducted at the Omdurman Midwifery Hospital (OMH), Khartoum, Sudan. The study was based on clinical and laboratory investigations and compared the cytokine profiles of pregnant women with and without periodontitis.

An introductory letter outlining the study's purpose and importance was sent to the OMH authorities. The study population was all pregnant women attending the antenatal clinic at the OMH. From an initial total of 118 female patients who were randomly examined, only 80 patients who fulfilled the inclusion criteria and were willing to participate were subsequently invited to participate.

The participants were aged between 18 and 45 years of age and had a confirmed intrauterine pregnancy. Periodontitis was defined by a PPD of ≥4 mm and a clinical attachment level (CAL) of ≥2 mm. We excluded pregnant women who had concomitant chronic conditions such as hypertension or diabetes mellitus, as well as women who were taking medications, current antimicrobial therapy, or who had received periodontal therapy in the previous 6 months.

Eligible participants were divided into a study group of 50 subjects and a control group of 30 subjects. Prior to clinical examination, participants were verbally informed of the study's objectives and methodology before being asked to sign a formal consent form. The principal investigator thoroughly examined all participants using a standard, plain dental mirror and a graduated University North Carolina (UNC) No. 15 periodontal probe.

The periodontal clinical parameters were evaluated by the Gingival Index (GI),[25] the Plaque Index (PI),[26] the PPD,[27] CAL,[27] the degree of recession,[28] the degree of tooth mobility,[29] and the furcation involvement.[30]

A certified laboratory technician was assigned to extract 5 mL of blood through venepuncture from each participant's antecubital vein. The blood samples were transferred into the blood containers; this allowed us to acquire GCF. Three paper points (size 55) were gently placed for 30 s into the mesiobuccal, midbuccal, and distobuccal sulci of the lower first molar for each participant. The paper points were then carefully removed using tweezers and placed in a sterile vial to subsequently assay the GCF.

All blood and GCF samples were transported to the Institute of Endemic Diseases laboratories at the University of Khartoum in an ice container for subsequent analysis. The blood samples were centrifuged for 5 min at 12,000 RPM. The extracted serum and the sterile container holding the paper points were kept at −20 °C until analysis. The vials were allowed to thaw to room temperature before being analysed, and cytokine IL-1β levels in both the sera and GCF were then measured using the sandwich ELISA technique.

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 18.0. The independent samples t-test was used to compare IL-1β levels in the serum and the GCF between the control and study group. In addition, Pearson's correlation test was also performed between the gingival parameters and IL-1β levels in the serum and the GCF. For all comparisons, $p < 0.05$.

Results

We conducted a hospital-based, cross-sectional, study based on clinical and laboratory data acquired from the Omdurman Midwifery Hospital in Omdurman, Khartoum, Sudan. We aimed to compare the levels of IL-1β in pregnant women with periodontitis to pregnant women without periodontitis. Following initial interviews with 118 female patients, a final total of 80 participants were randomly chosen and divided into two groups. The study group featured 50 subjects and the control group featured 30 participants. Mean age in the study group was 28.6 ± 5.1 years and the mean age in the control group was 26.1 ± 5.1 years.

In the control group, 24 (80%) of the participants were housewives, two (6.7%) were employees, and four (13.3%), were students. In the study group, 39 (78%) of the participants were housewives, while 11 (22%) were employees (Table 2).

The mean GI score in the case group was 0.63 ± 0.43; this compared to zero in the control group. The mean PI scores in the case and control groups were 0.54 ± 0.39 and 0.47 ± 0.46, respectively.

The mean PPD in the study group was 0.63 ± 0.37 mm; in the control group, the mean PPD was zero. Similarly, the mean gingival recession (R) in the study group was 0.11 ± 0.17 mm; in the control group, R was zero. Similarly, the mean CAL was 0.71 ± 0.40 mm and zero in the study group and control group, respectively. None of the teeth showed furcation involvement or mobility.

The mean number of removed teeth in the study group was 1.3 ± 1.46; this compared to 1.61 ± 2.11 in the control group. The mean number of restored teeth in the study group was 0.23 ± 0.56; this compared to 0.22 ± 0.72 in the control group (Table 1). Only the GCF showed a statistically significant difference in the independent samples t-test between the study and control groups ($p < 0.05$) (Figure 1).

Pearson's correlation analysis demonstrated a statistically significant difference between serum IL-1β levels and the degree of recession in the study group (0.363); this compared to 0.000 in the control group (Table 2). Similarly, a statistically significant difference was observed between the GCF IL-1β and PPD in the study group (0.307); this compared to 0.000 in the control group. A statistically significant correlation was detected between GCF IL-1β levels and the CAL in the study group (0.288); this compared to 0.000 in the control group (Table 2).

Table 1: Distribution of participants according to age, occupation, and oral hygiene frequency.

Participant distribution	Age $\overline{X}$ (±SD) years	Occupation of the participants			Oral hygiene frequency		
		Housewife N (%)	Employee N (%)	Student N (%)	Once a day N (%)	Twice a day N (%)	Three times and more N (%)
Study (N = 50)	28.6 (±5.7)	39 (78%)	11 (22%)	0 (0%)	8 (16.0%)	24 (48.3%)	18 (36.0%)
Control (N = 30)	26.1 (±5.1)	24 (80%)	2 (6.7%)	4 (13.3%)	1 (3.3%)	20 (66.7%)	9 (30%)
Total (N = 80)		63 (78.8%)	13 (16.3%)	4 (5%)	9 (11.3%)	44 (55.0%)	27 (33.8%)

$P \leq 0.05$ is significant.

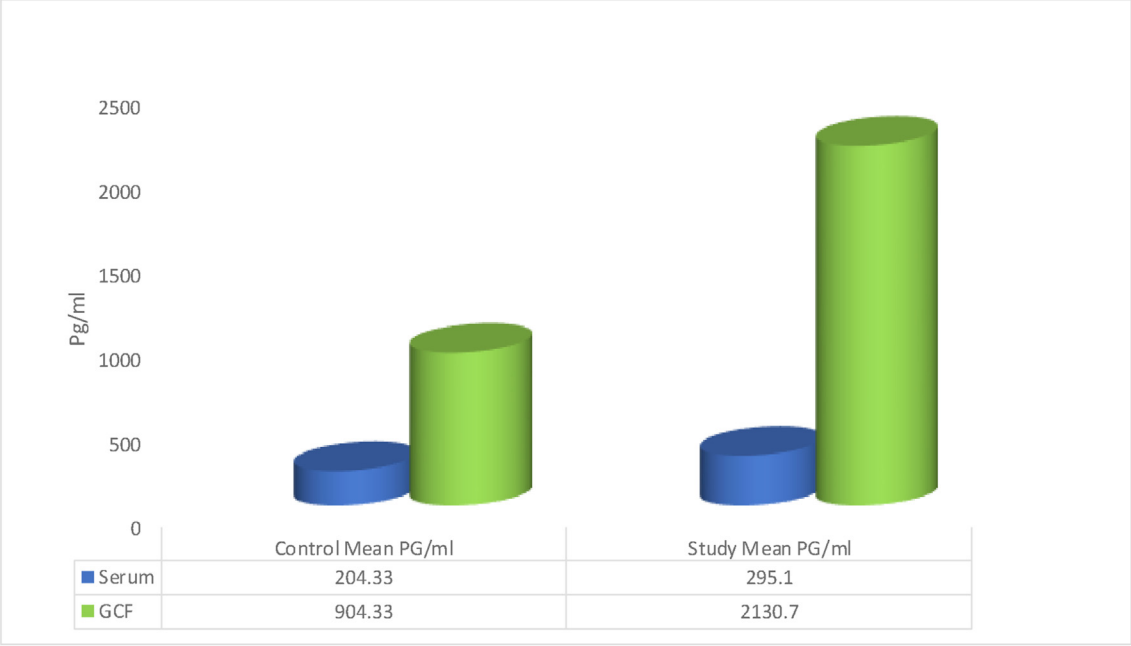


Figure 1: The mean distribution of IL-1β in the serum and GCF of the study and control groups.

Table 2: IL-1β levels in the serum and GCF in the study and control groups and their relationships to gingival and periodontal indices.

Variable	Serum		GCF	
	Study	Control	Study	Control
	Pearson correlation	Pearson correlation	Pearson correlation	Pearson correlation
PI	0.177	0.007	0.121	0.174
GI	0.188	–	0.124	–
PPD	0.138	–	0.307*	–
R	0.363*	–	0.143	–
AL	0.21	–	0.288*	–

*$P < 0.05$.

Discussion

There have been extensive studies on the periodontal health of pregnant women; findings from such studies have been controversial.[31–35] Studies have also demonstrated that the oral tissues of diverse ethnic populations can be affected during pregnancy.[36] Periodontal disease is not caused by pregnancy; rather, it aggravates an existing periodontal condition. During pregnancy, gingivitis is thought to be caused by a plaque biofilm influenced by systemic immunosuppressive factors, with symptoms appearing in the second trimester.[15]

A link between periodontitis progression and IL-1β levels has been detect in the GCF and serum by numerous studies.[23,33] Nonetheless, few studies have attempted to identify associations between symptoms of increased gingivitis during pregnancy and changes in the local immune system.[31,34]

Systemic factors, the progression of periodontitis, and interleukin levels are all known to affect the periodontal health of pregnant women. As a result, in the current study, we used ELISA tests to determined IL-1β levels in pregnant women with periodontitis can compared these levels with pregnant women with a healthy periodontium.

As described by Faizuddin et al.,[37] differences in IL-I levels can be attributed to differences in plaque accumulations or plaque-induced consequent inflammation. Furthermore, studies suggest that continuous or excessive cytokine production, such as IL-1β, can be used as a clinical marker of the severity of periodontitis.[9] IL-1β affects numerous cells, including the fibroblasts, chondrocytes, bone cells, neutrophils, and lymphocytes, implying that in periodontitis, periodontal destruction and repair may be associated with IL-1β.[4,38–40] Moreover, gingivitis and/or periodontitis may be linked to the GCF levels of IL-1β, TNF-α, and PGE2.[41,42]

In the present study, we demonstrated a statistically significant difference in the GCF as the level of IL-Iβ increased . Our findings in the study group mirror those of Cekici et al., who concluded that the local pattern of cytokines in periodontal tissues influences the severity and rate of progression of periodontal disease and an increase in inflammatory response.[5]

In another study, Tymkiw et al. revealed that the GCF of periodontitis subjects possessed significantly higher levels of the pro-inflammatory cytokines interleukins lL-1α, IL-1β, IL-6, and lL-12 when compared with healthy control subjects and concluded that those with periodontitis had a distinctive chemokine profile.[43]

Cytokines have been shown to influence the inflammatory process. In a previous study, Canakci et al. reported that infections are a significant risk factor for the pathogenesis of pre-eclampsia and periodontal disease.[21] Moreover, these authors observed that the study group expressed high levels of IL-1 and concluded that the elevated risk of severe pre-eclampsia in pregnant women was associated with periodontal disease.[44]

The periodontium is highly vascular; this phenomenon is considered to represent a source of systemic inflammatory mediators.[14] In another study, Kampits et al. reported significantly higher serum levels of several inflammatory mediators (IL-1β, IL-2, IFN-1, and TNF-α) in periodontitis subjects than in healthy controls; these effects were attributed to the periodontal reservoir present in the foetal–placental unit.[45,46]

In the present study, we demonstrated a significant relationship between periodontitis and increased IL-1β levels; this may give rise to an adverse pregnancy outcome. This finding mirrored previous results by Mega et al. who concluded that periodontal diseases in pregnant women cause a significant rise in the risk of subsequent adverse pregnancy outcomes.[47]

In their comprehensive review, Puertas et al. concluded that reduced periodontal health status in pregnant women is associated with adverse pregnancy outcomes.[48] Furthermore, other studies have also suggested a possible correlation between a higher risk of adverse pregnancy outcomes and periodontal disease; these previous studies determined that additional studies with large, well-designed, multicentre trials are needed. Furthermore, these authors concluded that the available literature does not clinically associate periodontal disease or periodontal therapy with specific undesirable pregnancy outcomes.[49,50]

In the current study, we further demonstrated a marked statistical correlation between serum levels of IL-1β and gingival recession in pregnant women with periodontitis, a finding that was also highlighted by Radnai et al., who used gingival recession and PPD to evaluate periodontitis and identify a statistically significant association.[51]

In addition, we identified a significant statistical relationship between GCF IL-1β levels and PPD and CAL in pregnant women with periodontitis. In a previous study, Anil et al. reported similar findings in that there was a relationship between adverse pregnancy outcomes and periodontal disease.[36] Offenbacher et al.,[52,53] and Turcu-Duminică et al.[54] have all demonstrated a significant association between CAL and periodontitis.

The current study is consistent with the findings of Mokeem et al., who used PPD to conclude that pregnant females with periodontal disease were 4.21-fold more likely to develop adverse pregnancy outcomes than women with a healthy periodontal status.[55] Radnai et al.[51] also used PPD as a marker of periodontitis to demonstrate a significant statistical association. Moliterno et al.[56] and Jarjoura et al.[57] used PPD and CAL as periodontal parameters of periodontitis and demonstrated a significant statistical association. Uwambaye et al. using the CAL and Vidhale et al. using the PI, CAL and PPD assessed periodontitis[58] while Walia et al., used similar periodontal parameters; these studies concluded that periodontal disease was a possible risk factor for adverse pregnancy outcomes.[59] As periodontitis parameters, PPD and R, also demonstrated a significant statistical association.[60]

In contrast, some of the findings of this study contradicted those reported previously. For example, Meqa et al. used PPD to appraise periodontitis and found no evidence of a link between adverse pregnancy outcomes and periodontal disease.[61] In another study, Ren used PI, PPD, CAL, IL-1β and TNF-α polymorphism to evaluate periodontitis and found no evidence for a statistically significant difference in the presence of IL-1β b+ allelic variants between the study and control subjects.[12] In addition, Ren used PI, PPD, and CAL to assess periodontitis and concluded that periodontitis was not a demonstrable risk factor for adverse pregnancy outcomes.[12]

Conclusions

The present study substantiates the idea that periodontitis, as evaluated by a PPD ≥4 mm, a CAL ≥2 mm, and associated with a high level of lL-1, may be associated with a poor pregnancy outcome and is further supported by a strong positive connection with high levels of IL-l, PPD, and CAL in the GCF of the study group.

Study recommendations

We recommend that a randomised clinical trial should be performed with an appropriate follow-up period so that the specific relationship between IL-1β and periodontitis can be investigated. Efforts should also be made to establish a dental clinic in maternal hospitals for periodical dental check-ups and to provide periodontal education as an aspect of the prenatal care given to attending pregnant women. This will help to demonstrate to patients and staff that there is a possible association between pregnancy and periodontal status.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The study was funded by the authors.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

The Sudan Medical Specialization Board Research Ethics Committee (SMSBREC) approved this study.

Authors contributions

The author(s) attest that all persons designated as authors are qualified for authorship and that the article has been checked for plagiarism. If plagiarism is discovered, all authors will be held equally responsible and subject to the journal's subsequent sanctions. NKE conceived and designed the study, conducted the research, provided research materials, collected and organised the data, and assisted with logistics. AMR conducted research, provided research materials, collected and organised the data, analysed and interpreted data, and wrote the initial and final draft. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Acknowledgements

The authors are grateful to Professor Mouawia Mohammed (The Endemic Disease Health Institute at the University of Khartoum) for his technical assistance. We would also like to thank the Omdurman Midwifery Hospital. We also thank Dr Asim Sati for statistical support.

References

1. Flemmig TF. Periodontitis. **Ann Periodontol 1999**; 4(1): 32–38. https://doi.org/10.1902/ANNALS.1999.4.1.32.
2. Dosch M, Gerber J, Jebbawi F, Beldi G. Mechanisms of ATP release by inflammatory cells. **Int J Mol Sci 2018**; 19. https://doi.org/10.3390/ijms19041222.
3. Szondy Z, Sarang Z, Kiss B, Garabuczi É, Köröskényi K. Anti-inflammatory mechanisms triggered by apoptotic cells during their clearance. **Front Immunol 2017**; 8: 909. https://doi.org/10.3389/fimmu.2017.00909.
4. Silva N, Abusleme L, Bravo D, Dutzan N, Garcia-Sesnich J, Vernal R, et al. Host response mechanisms in periodontal diseases. **J Appl Oral Sci 2015**; 23(3): 329–355. https://doi.org/10.1590/1678-775720140259.
5. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. **Periodontol 2000 2014**; 64(1): 57–80. https://doi.org/10.1111/prd.12002.
6. Togoo RA, Al-Almai B, Al-Hamdi F, Huaylah SH, Althobati M, Alqarni S. Knowledge of pregnant women about pregnancy gingivitis and children oral health. **Eur J Dent 2019**; 13(2): 261. https://doi.org/10.1055/S-0039-1693236.
7. Draper CF, Duisters K, Weger B, Chakrabarti A, Harmes AC, Brenna L, et al. Menstrual cycle rhythmicity: metabolic patterns in healthy women. **Sci Rep 2018**; 8:14568. https://doi.org/10.1038/s41598-018-32647-0.
8. Mishra P, Marawar PP, Mishra S. A cross-sectional, clinical study to evaluate mobility of teeth during pregnancy using periotest. **Indian J Dent Res 2017**; 28(1): 10–15. https://doi.org/10.4103/IJDR.IJDR_8_16.
9. Starzyńska A, Wychowański P, Nowak M, Sobocki BK, Jereczek-Fossa BA, Słupecka-Ziemilska M. Association between maternal periodontitis and development of systematic diseases in offspring. **Int J Mol Sci 2022**; 23(5): 2473. https://doi.org/10.3390/IJMS23052473.
10. Yang I, Claussen H, Arthur RA, Hertzberg VS, Geurs N, Corwin EJ, et al. Subgingival microbiome in pregnancy and a potential relationship to early term birth. **Front Cell Infect Microbiol 2022**: 556. https://doi.org/10.3389/FCIMB.2022.873683.
11. Morelli EL, Broadbent JM, Leichter JW, Thomson WM. Pregnancy, parity and periodontal disease. **Aust Dent J 2018**; 63(3): 270–278. https://doi.org/10.1111/ADJ.12623.
12. Ren H, Du M. Role of maternal periodontitis in preterm birth. **Front Immunol 2017**; 8(Feb): 139. https://doi.org/10.3389/FIMMU.2017.00139.
13. Miller WD. The microorganism of the human mouth. In: König GK, editor. *The local and general diseases which are caused by them [Internet]*. Kruger; 1973. https://doi.org/10.1159/000394885. I–xx.
14. Bui FQ, Almeida-da-Silva CLC, Huynh B, Trinh A, Liu J, Woodward J, et al. Association between periodontal pathogens and systemic disease. **Biomed J 2019**; 42(1): 27–35. https://doi.org/10.1016/J.BJ.2018.12.001.
15. Zi MYH, Longo PL, Bueno-Silva B, Mayer MPA. Mechanisms involved in the association between periodontitis and complications in pregnancy. **Front Public Health 2015**; 290: 2. https://doi.org/10.3389/fpubh.2014.00290.
16. Abati S, Villa A, Cetin I, Dessole S, Lugliè PF, Strohmenger L, et al. Lack of association between maternal periodontal status and adverse pregnancy outcomes: a multicentric epidemiologic study. **J Matern Neonatal Med 2013**; 26(4): 369–372. https://doi.org/10.3109/14767058.2012.733776.
17. Daalderop LA, Wieland BV, Tomsin K, Reyes L, Kramer BW, Vanterpool SF, et al. Periodontal disease and pregnancy outcomes: overview of systematic reviews. **JDR Clin Transl Res 2018**; 3(1): 10–27. https://doi.org/10.1177/2380084417731097.
18. Erchick DJ, Khatry SK, Agrawal NK, Katz J, Leclerq SC, Rai B, et al. Risk of preterm birth associated with maternal gingival inflammation and oral hygiene behaviours in rural Nepal: a community-based, prospective cohort study. **BMJ Open 2020**; 10(8). https://doi.org/10.1136/BMJOPEN-2019-036515.
19. Gomes FI, Aragão MG, Barbosa FC, Bezerra MM, de Paulo Teixeira Pinto V, Chaves H. Inflammatory cytokines interleukin-1β and tumour necrosis factor-α - novel biomarkers for the detection of periodontal diseases: a literature review. **J Oral Maxillofac Res 2016**; 7(2).
20. Nuriel-Ohayon M, Neuman H, Koren O. Microbial changes during pregnancy, birth, and infancy. **Front Microbiol 2016**; 7: 1031. https://doi.org/10.3389/fmicb.2016.01031.
21. Wu M, Chen SW, Jiang SY. Relationship between gingival inflammation and pregnancy. **Mediators Inflamm 2015**; 2015: 623427. https://doi.org/10.1155/2015/623427.
22. Fettweis JM, Serrano MG, Brooks JP, Edwards DJ, Girerd PH, Parikh HI, et al. The vaginal microbiome and preterm birth. **Nat Med 2019**; 25(6): 1012–1021. https://doi.org/10.1038/s41591-019-0450-2.
23. Latorre Uriza C, Velosa-Porras J, Roa NS, Quiñones Lara SM, Silva J, Ruiz AJ, et al. Periodontal disease, inflammatory cytokines, and PGE 2 in pregnant patients at risk of preterm delivery: a pilot study. **Infect Dis Obstet Gynecol 2018**; 2018. https://doi.org/10.1155/2018/7027683.
24. Gesase N, Miranda-Rius J, Brunet-Llobet L, Lahor-Soler E, Mahande MJ, Masenga G. The association between periodontal disease and adverse pregnancy outcomes in Northern Tanzania: a cross-sectional study. **Afr Health Sci 2018**; 18(3). https://doi.org/10.4314/ahs.v18i3.18.
25. Löe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. **Acta Odontol Scand 1963**; 21(6): 533–551. https://doi.org/10.3109/00016356309011240.
26. Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. **Acta Odontol Scand 1964**; 22(1): 121–135. https://doi.org/10.3109/00016356408993968.
27. Glavind L, Löe H. Errors in the clinical assessment of periodontal destruction. **J Periodontal Res 1967**; 2(3): 180–184. https://doi.org/10.1111/J.1600-0765.1967.TB01887.X.

28. Miller PD. A classification of marginal tissue recession. **Int J Periodontics Restor Dent 1985**; 5(2): 8–13.
29. Textbook of Periodontia. In: *Textbook of Periodontia*; 1950. p. 150.
30. Glickman I. Prevention, diagnosis, and treatment of periodontal disease in the practice of general dentistry. In: *Clinical periodontology*. 4th ed. 1972. pp. 242–245. Philadelphia.
31. Komine-Aizawa S, Aizawa S, Hayakawa S. Periodontal diseases and adverse pregnancy outcomes. **J Obstet Gynaecol Res 2019**; 45(1): 5–12. https://doi.org/10.1111/jog.13782.
32. González-Jaranay M, Téllez L, Roa-López A, Gómez-Moreno G, Moreu G. Periodontal status during pregnancy and postpartum. **PLoS One 2017**; 12(5):e0178234. https://doi.org/10.1371/JOURNAL.PONE.0178234.
33. Boggess KA, Urlaub DM, Moos MK, Polinkovsky M, El-Khorazaty J, Lorenz C. Knowledge and beliefs regarding oral health among pregnant women. **J Am Dent Assoc 2011**; 142(11): 1275. https://doi.org/10.14219/JADA.ARCHIVE.2011.0113.
34. Lasisi TJ, Abdus-salam RA. Pregnancy-induced periodontal inflammation: influence of salivary cytokines and antimicrobial proteins. **Saudi Dent J 2018**; 30(4): 306–311. https://doi.org/10.1016/j.sdentj.2018.07.001.
35. Hartnett E, Haber J, Krainovich-Miller B, Bella A, Vasilyeva A, Lange Kessler J. Oral health in pregnancy. **J Obstet Gynecol Neonatal Nurs 2016**; 45(4): 565–573. https://doi.org/10.1016/j.jogn.2016.04.005.
36. Anil S, Al Rowis RM, Chalisserry EP, Chalisserry VP, AlMoharib HS, Al-Sulaimani AF. Oral health and adverse pregnancy outcomes. In: Anil S, Al Rowis RM, Chalisserry EP, Chalisserry VP, AlMoharib HS, Al-Sulaimani AF, editors. *Emerging trends in oral health sciences and dentistry*; 2015. pp. 632–662. https://doi.org/10.5772/59517.
37. Faizuddin M, Bharathi SH, Rohini NV. Estimation of interleukin-1beta levels in the gingival crevicular fluid in health and in inflammatory periodontal disease. **J Periodontal Res 2003**; 38(2): 111–114. https://doi.org/10.1034/j.1600-0765.2003.01649.x.
38. Otenio CCM, Fonseca I, Martins MF, Ribeiro LC, Assis NMSP, Ferreira AP, et al. Expression of IL-1, IL-6, TNF-α, and iNOS in pregnant women with periodontal disease. **Genet Mol Res 2012**; 11(4): 4468–4478. https://doi.org/10.4238/2012.September.20.3.
39. Silva de Araujo Figueiredo C, Gonçalves Carvalho Rosalem C, Costa Cantanhede AL, Abreu Fonseca Thomaz ÉB, Fontoura Nogueira da Cruz MC. Systemic alterations and their oral manifestations in pregnant women. **J Obstet Gynaecol Res 2017**; 43(1): 16–22. https://doi.org/10.1111/jog.13150.
40. Martínez-García M, Hernández-Lemus E. Periodontal inflammation and systemic diseases: an overview. **Front Physiol 2021**; 12: 1842. https://doi.org/10.3389/FPHYS.2021.709438/BIBTEX.
41. Gupta G. Gingival crevicular fluid as a periodontal diagnostic indicator- II: Inflammatory mediators, host-response modifiers and chair side diagnostic aids. **J Med Life 2013**; 6(1): 7–13.
42. Bibi T, Khurshid Z, Rehman A, Imran E, Srivastava KC, Shrivastava D. Gingival crevicular fluid (GCF): a diagnostic tool for the detection of periodontal health and diseases. **Molecules 2021**; 26(5). https://doi.org/10.3390/MOLECULES26051208.
43. Tymkiw KD, Thunell DH, Johnson GK, Joly S, Burnell KK, Cavanaugh JE, et al. Influence of smoking on gingival crevicular fluid cytokines in severe chronic periodontitis. **J Clin Periodontol 2011**; 38(3): 219–228. https://doi.org/10.1111/j.1600-051X.2010.01684.x.
44. Canakci V, Canakci CF, Yildirim A, Ingec M, Eltas A, Erturk A. Periodontal disease increases the risk of severe pre-eclampsia among pregnant women. **J Clin Periodontol 2007**; 34(8): 639–645. https://doi.org/10.1111/J.1600-051X.2007.01105.X.
45. Kampits C, Montenegro MM, Ribeiro IWJ, Furtado MV, Polanczyk CA, Rösing CK, et al. Periodontal disease and inflammatory blood cytokines in patients with stable coronary artery disease. **J Appl Oral Sci 2016**; 24(4): 352. https://doi.org/10.1590/1678-775720160082.
46. Liu X, Li H. A systematic review and meta-analysis on multiple cytokine gene polymorphisms in the pathogenesis of periodontitis. **Front Immunol 2022**; 12: 713198. https://doi.org/10.3389/FIMMU.2021.713198/FULL.
47. Penova-Veselinovic B, Keelan JA, Wang CA, Newnham JP, Pennell CE. Changes in inflammatory mediators in gingival crevicular fluid following periodontal disease treatment in pregnancy: relationship to adverse pregnancy outcome. **J Reprod Immunol 2015**; 112: 1–10. https://doi.org/10.1016/J.JRI.2015.05.002.
48. Puertas A, Magan-Fernandez A, Blanc V, Revelles L, O'Valle F, Pozo E, et al. Association of periodontitis with preterm birth and low birth weight: a comprehensive review. **J Matern Fetal Neonatal Med 2018**; 31(5): 597–602. https://doi.org/10.1080/14767058.2017.1293023.
49. Bobetsis YA, Graziani F, Gürsoy M, Madianos PN. Periodontal disease and adverse pregnancy outcomes. **Periodontol 2000 2020**; 83(1): 154–174. https://doi.org/10.1111/PRD.12294.
50. da Silva HEC, Stefani CM, Melo N DeS, de Lima LAA, Rösing CK, Porporatti AL, et al. Effect of intra-pregnancy nonsurgical periodontal therapy on inflammatory biomarkers and adverse pregnancy outcomes: a systematic review with metaanalysis. **Syst Rev 2017**; 6: 197.
51. Radnai M, Gorzó I, Urbán E, Eller J, Novák T, Pál A. Possible association between mother's periodontal status and preterm delivery. **J Clin Periodontol 2006**; 33(11): 791–796. https://doi.org/10.1111/j.1600-051X.2006.00986.x.
52. Offenbacher S, Lieff S, Boggess KA, Murtha AP, Madianos PN, Champagne CM, et al. Maternal periodontitis and prematurity. Part I: Obstetric outcome of prematurity and growth restriction. **Ann Periodontol 2001**; 6(1): 164–174. https://doi.org/10.1902/ANNALS.2001.6.1.164.
53. Offenbacher S, Boggess KA, Murtha AP, Jared HL, Lieff S, McKaig RG, et al. Progressive periodontal disease and risk of very preterm delivery. **Obstet Gynecol 2006**; 107(1): 29–36. https://doi.org/10.1097/01.AOG.0000190212.87012.96.
54. Turcu-Duminică Ana, Silvia Dumitriu Anca, Paunica Stana, Gică Corina, Botezatu Radu, Gică Nicolae, et al. Periodontitis as a potential risk factor for premature delivery. **J Mind Med Sci 2021**; 8(1). https://doi.org/10.22543/7674.81.P2733.
55. Mokeem SA, Molla GN, Al-Jewair TS. The prevalence and relationship between periodontal disease and preterm low birth weight infants at King Khalid University Hospital in Riyadh, Saudi Arabia. **J Contemp Dent Pract 2004**; 5(2): 40–56. https://doi.org/10.5005/JCDP-5-2-40.
56. Moliterno LFM, Monteiro B, Da Silva Figueredo CM, Fischer RG. Association between periodontitis and low birth weight: a case-control study. **J Clin Periodontol 2005**; 32(8): 886–890. https://doi.org/10.1111/J.1600-051X.2005.00781.X.
57. Jarjoura K, Devine PC, Perez-Delboy A, Herrera-Abreu M, D'Alton M, Papapanou PN. Markers of periodontal infection and preterm birth. **Am J Obstet Gynecol 2005**; 192(2): 513–519. https://doi.org/10.1016/J.AJOG.2004.07.018.
58. Vidhale P, Puri S, Bhongade ML. A relationship between maternal periodontal disease and preterm low birth weight: a cross-sectional study. **Clin Epidemiol Glob Health 2020**; 8(4): 1152–1154. https://doi.org/10.1016/J.CEGH.2020.04.007.
59. Walia M, Saini N. Relationship between periodontal diseases and preterm birth: recent epidemiological and biological data.

Int J Appl Basic Med Res. 2015; 5(1): 2. https://doi.org/10.4103/2229-516X.149217.

60. Uwambaye P, Munyanshongore C, Rulisa S, Shiau H, Nuhu A, Kerr MS. Assessing the association between periodontitis and premature birth: a case-control study. **BMC Pregnancy Childbirth 2021**; 21(1): 1–9. https://doi.org/10.1186/S12884-021-03700-0/TABLES/3.
61. Meqa K, Dragidella F, Disha M, Sllamniku-Dalipi Z. The association between periodontal disease and preterm low birthweight in Kosovo. **Acta Stomatol Croat 2017**; 51(1): 33. https://doi.org/10.15644/ASC51/1/4.

How to cite this article: El Hassan NKB, Ramadan AM. Interleukin 1 beta and its association with the periodontal health of pregnant women. J Taibah Univ Med Sc 2023;18(6):1376–1383.