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Influence of gingivitis in preterm delivery on serum biomarkers COX-2 and PGE-2

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Abstract:

Periodontal disease increases local and systemic inflammatory responses in pregnant women, which may lead to premature delivery. The aim of this study to detect maternal serum levels of Prostaglandin E2 and Cyclooxigenase-2, and evaluate the association between these biomarkers with preterm delivery in pregnant women suffering from gingivitis. A total of 85 pregnant women having gingivitis were divided into three groups; twenty-five preterm-delivery pregnant and thirty full-term delivery pregnant women, in addition to thirty healthy pregnant women with healthy gingiva as a control group. The mean age of patients was (25.07±1.097), (26.12±1.400) years, and (27.73±1.250) years for control group. The blood sample was collected with all participants and the biomarkers cytokines Prostaglandin E2 and cyclooxygenase-2 were detected by enzyme-linked immunosorbent assay (ELISA) kits. The current study showed an increase higher in levels of Prostaglandin E2 and cyclooxygenase-2 in pre-term delivery having gingivitis group followed by full term-delivery pregnant groups having gingivitis compared with a control group, with statistically highly significant differences ($p<0.05$). This finding indicated that the pre-term delivery women higher than full-term-delivery pregnant revealed worsened periodontal health conditions and elevated levels of serum Prostaglandin E2 and cyclooxygenase-2 levels compared with control group.

Keywords: Gingivitis, Periodontal disease, preterm delivery, full term-delivery, Prostaglandin E2, cyclooxygenase-2.

Introduction:

Pregnancy is a physiological process associated with adverse outcomes such as preterm birth (<37 weeks), low birth weight (<2500 grams), or very low birth weight (<1500 grams). The global incidence of preterm delivery is 9.6%, which is equivalent to 12.9 million premature infants (Saini and Walia, 2015). The specific cause of preterm labor often isn't clear. Certain risk factors might increase

the chance of preterm labor, but preterm labor can also occur in pregnant women with no known risk factors (Lockwood, 2019).

Inflammation of soft tissues surrounding the teeth, without loss of attachment, is known as gingivitis. The inflammation of gingiva that is exaggerated during the period of pregnancy is known as pregnancy gingivitis given rise to changes in hormonal levels and in that of life style of a pregnant women. In various previous studies, poor oral health such as periodontitis in pregnant women has been associated with various adverse pregnancy outcomes (Kazem and Mahmood, 2014). Many studies concerned about oral health of pregnant women (Abed and Radhi, 2022). It should be kept in mind that neglecting oral and dental health during pregnancy does not only cause problems such as tooth decay and tooth loss, but may also lead to problems such as premature birth, low birth weight infant, and pre-eclampsia (Yenen and Ataçağ, 2019). In addition to oral health of infants which have all been linked to each other (Abed and Radhi, 2022). Due to hormonal fluctuations during pregnancy, alterations occur in the levels of estrogen and progesterone resulting in tortuous and dilated microvasculature, more permeability of oral blood vessels, and lowering of host immunity, which eventually cause the host to become more vulnerable to oral infections (Talib and Taha, 2024). High levels of estrogen have been found to be associated with occurrence of gingival hyperplasia, gingivitis, pyogenic granulomas, dental caries, and alterations in salivary flow (Abdulbaqi *et al*., 2009).

In a study conducted by Togoo in 2019, around 55.37% of the respondents were unaware about the adverse pregnancy outcome of pregnancy gingivitis and 21.91% believed that it had no such adverse effect, while 13.54% of them reported preterm births as the adverse pregnancy outcome of pregnancy gingivitis (Togoo *et al*., 2019).

It has been hypothesized that the increase of the level of progesterone in circulation stimulates the release of prostaglandin E2 (PGE2) which causes gestational gingivitis. So that more prostaglandins are present at the end of pregnancy than during the first trimester (Mutlak and Yas, 2017).

At the end of a normal term pregnancy (more than 37 weeks) the levels of PGE2 increase until reaching critical levels, which has partial role to start uterine contractions and produces birth (Latorre Uriza *et al*., 2018).

Unfortunately, a local increase in proinflammatory mediators can interrupt this delicate balance; therefore, an inflammatory response stimulated by a local infection (e.g., periodontal disease) under this mechanism would contribute to the premature rupture of membranes and uterine contraction, thereby triggering preterm delivery or spontaneous abortion (Madianos *et al*., 2013). Cyclooxigenase-2 (COX-2) is primarily an inducible enzyme (constitutively expressed in key regions of the body whose expression is activated in a variety of cells in response to cytokines, mitogens, and endotoxins (Talib and Taha, 2022), and it is a rate-limiting enzyme that converts AA to prostaglandin endoperoxide H2 (PGH2) which is an unstable reaction intermediate that is subsequently converted into either prostaglandins (PGs) or thromboxane A2 (Ricciotti and FitzGerald, 2011).

Direct feedback is also observed between COX-2 and its products (Obermajer *et al*., 2011). This feedback plays a dual role in both the proinflammatory and anti-inflammatory processes during pregnancy (Ha *et al*., 2019). In a study by Dahash and Mahmood in 2001, the expression COX-2 is significantly upregulated in inflamed periodontal tissues. Both inflammatory cytokines such bacterial constituents may be responsible for the enhanced COX-2 expression and PGE2 synthesis. Increased level of COX-2 were present in chronically inflamed gingival tissue.

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Prostaglandin production as a result of COX-2 expression is an important factor in the pathogenesis of chronic inflammatory disorders (Dahash and Mahmood, 2019). In addition to a study by Suhandri in and Djanas in 2020 results revealed that there were significant differences in serum cyclooxygenase 2 levels in preterm and term delivery (Suhandri and Djanas, 2020).

Materials and Methods:

-Subjects:

The current study was performed on 55 pregnant women having gingivitis divided into (25) preterm-delivery pregnant and (30) full-term delivery pregnant women and 30 healthy pregnant women (healthy gingiva) as a control group. Study samples were taken from Al-Ramadi teaching hospital for Gynecology and Pediatrics Al-Ramadi, Iraq.

Ethical approval:

The study was conducted out in compliance with the principles established in the "Helsinki" Declaration and was authorized by the College of Dentistry , University of Baghdad's in-house ethics committee. This prospective clinical study summarized only participant-provided clinical data and their clinical samples and did not interfere with the patient's therapy. Thus, this research posed no physical dangers to the participants. In addition, the confidentiality of the participants' information was ensured. The request for exemption from informed consent was submitted, and the exemption was approved.

Inclusion Criteria:

- Pregnant in third trimester months (term > 37 weeks, preterm < 37weeks) (Dahash and Mahmood, 2019).
- Good general health
- 18 – 42-year-old
- Race from Iraq
- Has 20 teeth in oral cavity at least
- Having gingivitis with Pocket depth < 3 mm

Exclusion Criteria:

- Previous periodontal therapy for 3 months
- History of smoking or alcohol drinking.
- Use of antibiotics during the last three months.
- Wearing orthodontic appliances or prosthodontics
- Twin baby pregnancy
- Genital tract infection
- Urinary tract infection
- No systemic or autoimmune disease

Blood Sample Collection:

Five millilitres of venous blood were collected from each subject under aseptic conditions 24 hours before delivery, transferred to a sterile gel tube, and serum was separated by centrifugation at 3000 rpm for 10 min, divided into small aliquots, and stored at -20$_{o}$ C until analysis (Suhandri and Djanas, 2020).

Enzyme-Linked Immunosorbent Assay (ELISA): Detection of pro-inflammatory biomarkers by using Human prostaglandin E2 (PGE2) and cyclooxygenase-2 enzyme immunoassay kit in serum samples.

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Statistical analysis:

In this investigation, SPSS version 26, Microsoft Excel 2010 were employed. To evaluate the difference between groups, using normality tests, the present study's data was carefully examined to determine if it was parametric or non-parametric. As a result, appropriate statistical tests were employed Fisher's exact test, ANOVA test and Person correlation.

Results:

The current study was performed on 55 pregnant women having gingivitis divided into (25) preterm-delivery pregnant and (30) full-term delivery pregnant women and 30 healthy pregnant women with healthy gingiva as a control group. The demographic characteristics of patients group and controls group included in this study are presented in Table 1. The mean age of patients was (25.07±1.097), (26.12±1.400) years, and (27.73±1.250) years for controls group

Table 2: the mean value of age (year) distribution in groups

	Group			
	Full term Mean±SE	Pre term Mean±SE	Control group Mean±SE	Fisher's exact test (***p. value***)
Age (year)	25.07±1.097	26.12±1.400	27.73±1.250	0.296

Clinical periodontal parameters Analysis (Plaque Index (PLI) and Bleeding on probing (BOP):

The mean ±SE values of the percentage of Plaque Index (PLI) in full-term delivery, preterm-delivery pregnant groups having gingivitis and control group were (0.17±0.0299), (0.15±0.018), (0.04±0.004) which is statistically significant different ($p<0.05$). As demonstrated in Table 2.

Table 3 showed the mean±SE value of BOP % in preterm-delivery pregnant groups having gingivitis higher than in full-term delivery group having gingivitis compared with control group, with significant differences ($p<0.05$). The mean±SE was (0.188±0.019), (0.170±0.016), (0.089±0.028), respectively

Table 2: Plaque Index (PLI) in all groups

F =12.380	Group			
Plaque Index (PLI)	Full term Group Mean±SE	Pre term Group Mean±SE	Control Group Mean±SE	ANOVA test (***p. value***)
	0.17±0.0299	0.15±0.018	0.04±0.004	0.0001

Table 3: Bleeding on probing (BOP)% in all groups

F =5.751	Group			
Bleeding on probing (BOP)%	Full term Mean±SE	Pre term Mean±SE	Control Group Mean±SE	ANOVA test (***p. value***)
	0.170±0.016	0.188±0.019	0.089±0.028	0.005

Level of serum PGE-2 (pg/ml):

The results of this study revealed a significant elevation in the mean serum levels of PGE-2 among preterm-delivery pregnant group having gingivitis, the mean±SE value was (94.32±6.84)

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compared to full-term delivery and control group with mean±SE value were (79.49±5.28), (63.55±2.89), (P<0.05), as observed in Table 4.

Table 4: Level of PGE-2 in all groups using ANOVA test

F =9.938	**Group**			
PGE-2	Full term Mean±SE	Pre term Mean±SE	Control group Mean±SE	ANOVA test (***p. value***)
	79.49±5.28	94.32±6.84	63.55±2.89	0.0001

Level of serum COX-2 (pg/ml):

Table 5 showed an increase significant difference in the COX-2 levels in preterm-delivery pregnant group having gingivitis compared with full-term delivery group having gingivitis and control group, the mean±SE value was (2.00±0.41), (0.58±0.09) and (0.96±0.26), (p<0.05) respectively.

Table 5: Level of COX-2 in all groups

F =7.182	**Group**			
	Full term Mean±SE	Pre term Mean±SE	Control group Mean±SE	ANOVA test (p. value)
COX-2	0.58±0.09	2.00±0.41	0.96±0.26	0.001

Discussion:

The present study observed that pregnant women 30 years and above of age could have a greater risk of developing gingivitis. However, this finding corresponds with Usin *et al*. (2013) finding of a prevalence of 22% in pregnant women aged ≥30 years, and for this reason, they suggested that pregnant women aged 30 years could be considered a particular risk group with an increased risk of having an aggravated periodontal status. Similarly, the previous study shows that in patients with periodontitis, this pathogen increases depending on age (Husham and Taha, 2023).

This may, in part, explain the strong relationship between periodontitis and preterm birth in that the prevalence of periodontitis increases with age. In younger women, periodontitis is rather uncommon. Young women may have several other non-dental risk factors that may contribute to giving birth prematurely (Eure *et al*., 2002). The youngest woman (age 18) who delivered preterm also had periodontitis. The other women who delivered preterm were 28 years of age or older (Dörtbudak *et al*., 2005).

The current investigations revealed that plaque was almost similar in three groups. The differences were statistically significant between the two groups. This could be attributed to the negligence of oral health in the total sample and no one had received motivation in plaque control or under an oral health program.

In spite of this, a statistically significant differences were found regarding PLI between the three groups and both study group had a high mean value than that among control groups, therefore adding for hormonal changes during pregnancy. This result in agreement with study of Urbán *et al*. (2005), in which hormonal changes due to increased levels of estrogen and progesterone during pregnancy have a special effect on the periodontium (Al-Naimi, 2009; Tajer and Al-Obaidi, 2013) as a vascular permeability increase in the gingival tissue and as

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consequence, bacteria and/ or their products can diffuse through tissue more readily than normally (Raber-Durlacher *et al*., 2013; Jasim and Taha, 2023).

The present study showed the percent of BOP % in preterm-delivery pregnant groups having gingivitis higher than in full-term delivery group having gingivitis compared with control group, with significant differences ($p<0.05$). It can be concluded from this finding that the pregnant women in this study had suffered from gingivitis conditions in a bad (Al Kuraishy *et al*., 2020).

All periodontal disease indicators examined were higher in the cases with more sites with bleeding on probing, greater gingival recession, and worse PI and BOP values. As noted by Manau *et al*. (2008) the significance of the association between periodontal disease and pregnancy outcomes can be influenced by the definition of periodontal disease employed.

The application of less strict criteria, as well as differences in ethnic background and age among the study populations, may explain higher prevalence of periodontal disease and other oral diseases.

The results of this study revealed a significant elevation in the mean serum levels of PGE-2 among preterm-delivery pregnant group having gingivitis compared to full-term delivery and control group. Actually, PGE2 increase gradually during normal pregnancy and reaches maximum levels at the end of pregnancy. However, Periodontal disease, with its local and systemic bacterial load, can also trigger a systemic inflammatory response with increased inflammatory cytokines (TNF-α, IL-1, and IL-6) and inflammatory mediators (PGE2) to become a risk factor of preterm delivery. PGE2 is positively regulated during preterm delivery; in turn, it is induced by an inflammatory response that promotes the contraction of the uterine smooth muscle (Al Duboni et al., 2012; Li *et al*., 2016). Where cytokines such as IL-1, IL-6, and TNF stimulate the production of prostaglandins in the chorion and exacerbate cervical ripening and uterine contraction, which increase the risk of preterm labour However, although the elevated serum and amniotic levels of these mediators are associated with several adverse outcomes of pregnancy. When analysing PGE2, the present study showed that, as the severity of periodontal disease increased, the levels of PGE2 increased in pregnant women with gingivitis compared with healthy pregnant. These findings are similar to those reported by Konopka *et al*. (2004), who evaluated the relationships among periodontal disease, preterm birth, and low birth weight as well as the levels of PGE2 andIL-1β in the gingival crevicular fluid and those in the blood serum of women with preterm labour and women who gave birth at term. While Deortbudak *et al*. (2005), Hamed *et al*. (2021) reported contradictory evidence by failing to find evidence that the increase of these mediators in gingival crevicular fluid, serum, or amniotic fluid in patients with periodontitis is associated with pregnancy complications. Also, they found that, in the presence of severe and generalized periodontitis, preterm delivery is 3.9 times more likely compared with women with a healthy periodontium.

According to a previous study by Offenbacher *et al*. (1993) elevated PGE2 level in gingival fluid has been reported to identify periodontitis activity and has also been associated with preterm labor.

The animal studies have supported the hypothesis of a significant relationship between an increase in serum PGE2 induced by experimental *Porphyromonas gingivalis* and Escherichia coli infections in pregnant hamsters resulting growth deficit and fetal mortality (Hamed *et al*., 2010). Assuming that the association between periodontitis and preterm has a shared pathogenesis, early periodontal screening could predict/ identify women at risk for premature delivery as a low-cost examination procedure.

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The mechanisms of human preterm labour appear inextricably linked to cytokine biosynthesis by gestational tissues (Mitchell *et al*., 2012). Several causal factors have been related to these pregnancy disorders. Expressions of cytokines and inflammatory mediators, growth factors and proteins related to vascularization, and oxidative stress have been studied in maternal blood (Sert *et al*., 2011; Farhan *et al*., 2022), and the oral cavity (Konopka *et al*., 2004). Inflammatory mediators such as cyclooxygenase-2 (COX-2) are also involved in the induction of parturition, and COX-2 expression is known to increase in foetal membranes at the onset of labour (Slater *et al*., 1999).

The present finding showed an increase significant difference in the COX-2 levels in preterm-delivery pregnant group having gingivitis. But decreased levels in the full term delivery group having gingivitis compared with control group. The increased expression of COX-2 in placental trophoblasts in the cases suggests that a subclinical proinflammatory state at the maternal-foetal interface may have contributed, among other factors, to triggering preterm delivery. This supports the proposition that the regulation of COX-2 in placental membranes may mediate an increase in prostaglandin synthesis, which promotes parturition (Mesa *et al*., 2013).

Therefore, appears reasonable to conclude that the elevated COX-2 level produced by a pro-inflammatory state in the mother may have a negative effect on the pregnancy outcome.

Similar findings were reported in a previous study by Mesa *et al*. (2013), which found a higher expression of COX-2, although not significant, possibly because it was assessed in a semiquantitative manner, unlike in the present quantitative study, in which statistical significance was reached.

Animal studies revealed that maternal infections with periodontal pathogens increase levels of circulating IL-1β, IL-6, IL-8, IL-17, and TNF-α and induce PTB. At the same time in vitro, models showed that periodontal pathogens/ byproducts induce COX-2, IL-8, IFN-γ, and TNF-α secretion and/or apoptosis in placental tissues/cells (Ren and Du, 2017).

Conclusion:

The fact that the levels of PGE2 and COX-2 were higher in subjects with periodontal disease suggests that maternal periodontitis may have an important impact on the inflammatory response expressed in the placenta and foetal conditions. The implication of this is that periodontal disease can induce a primary host response in the chorioamnion, leading to preterm birth. On the other hand, an increase in the concentration of prostaglandin E2 and cyclooxygenase-2 can be considered a predictive value for the presence of inflammation. PGE2 supports acute local inflammation and phagocyte-mediated immunity at the site of pathogen entry, in addition to a specialised role in controlling the potentially harmful activation of CTL-, Th1-, and NK cell-mediated type 1 (cytotoxic) immunity.

Conflict of interest: All the authors declare no commercial or financial conflict of interest.

Funding: The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Ethics statement: The project was approved by the scientific committee at the Basic Science Department/College of Dentistry/ University of Baghdad, on 1/11/2022, and all patients were given a piece of detailed information relating to the study aims and informed consent was signed to represent the patient's acceptance in order to participate in this study.

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التغيرات في مستويات البروستاجلاندين E2 (PGE-2) والمؤشرات الحيوية لإنزيمات الأكسدة الحلقية 2 (COX-2) في مصل النساء الحوامل اللاتي يلدن قبل الأوان والمتأثرات بالتهاب اللثة

شادن هشام مداح غادة ابراهيم طه

المستخلص :

تزيد أمراض اللثة من الاستجابات الالتهابية الموضعية والجهازية لدى النساء الحوامل، مما قد يؤدي إلى الولادة المبكرة .تهدف هذه الدراسة إلى الكشف عن مستويات البروستاجلاندين E2 والسيكلوكسيجيناز-2 في مصل الأم، وتقييم العلاقة بين هذه المؤشرات الحيوية والولادة المبكرة عند النساء الحوامل اللاتي يعانين من التهاب اللثة. تم تقسيم 85 امرأة حامل مصابة بالتهاب اللثة إلى ثلاث مجموعات؛ خمسة وعشرون امرأة حامل في فترة ولادة مبكرة وثلاثون امرأة حامل في فترة ولادة كاملة، بالإضافة إلى ثلاثين امرأة حامل تتمتع بصحة جيدة ولثة صحية كمجموعة ضابطة. كان متوسط عمر المرضى (25.07 ± 1.097)، (26.12 ± 1.400) سنة، و (27.73 ± 1.250) سنة للمجموعة الضابطة. تم جمع عينة الدم من جميع المشاركين وتم اكتشاف المؤشرات الحيوية السيتوكينات Prostaglandin E2 وcyclooxygenase-2 بواسطة مجموعات مقايسة الامتصاص المناعي المرتبط بالإنزيم (ELISA). أظهرت الدراسة الحالية زيادة أعلى في مستويات البروستاجلاندين E2 وcyclooxygenase-2 في الولادة قبل الأوان مع مجموعة التهاب اللثة تليها مجموعات الحوامل بعد الولادة الكاملة المصابة بالتهاب اللثة مقارنة مع مجموعة المراقبة، مع وجود فروق ذات دلالة إحصائية عالية ($P < 0.05$) . أشارت هذه النتيجة إلى أن النساء اللاتي يلدن قبل الأوان أعلى من النساء الحوامل في فترة ولادة كاملة، كشفن عن تدهور ظروف صحة اللثة ومستويات مرتفعة من مستويات البروستاجلاندين E2 في المصل ومستويات إنزيمات الأكسدة الحلقية 2 مقارنة بالمجموعة الضابطة.

الكليمات المفتاحية: التهاب اللثة، أمراض اللثة، الولادة المبكرة، الولادة الكاملة، البروستاجلاندين E2، إنزيمات الأكسدة الحلقية-