GINGIVAL CREVICULAR FLUID AND PLACENTAL TISSUE LEVELS OF PENTRAXIN-3 AS A POSSIBLE MARKER FOR PRETERM LABOR IN PATEINTS WITH CHRONIC PERIODONTITIS

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Dedication

This work is dedicated to …

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رَب اوزعني ان اشكرَ نعْمَتكَ
التي أنعَمتَ عَليَ وَعَلي وَالدَيَّ
وأن أعمل صالحاً ترضاه
وأصلح لي في ذريتي
إني تُبتُ إليكَ و إني
مِن المُسلِمَين

سورة الأحقاف
(15)

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INTRODUCTION

Pregnancy is normally a healthy physiological procedure that sometimes has opposing outcomes including low birth weight (<2500 grams) and preterm birth (<37 weeks). Preterm birth is now worldwide the second most shared cause of death in children younger than five years after pneumonia. ***(Sanz M,et al.,2013)***

As normal pregnancy progresses, amniotic fluid levels of prostaglandin E2 (PGE2) and inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin 1-β (IL-1-β) are raised until a serious threshold is reached to prompt rupture of the amniotic sac membranes, uterine contraction, cervical dilation and delivery. ***(Haram,et al., 2003)*** Therefore , normal parturition is controlled by inflammatory signaling and this course represents a triggering mechanism that can be controlled by external stimuli including infection and inflammatory stressors. ***(Madianos PN,et al.,2013)***

Adverse pregnancy outcomes (APOs) are usually accompanied with elevated local and systemic inflammatory markers and intrauterine infections. Recent evidence suggests that adverse outcomes are primarily caused by ascending infections from the vagina or cervix or from hematogenous extent from known or unknown non-genital sources. ***(Sanz M,et al.,2013)***

Two major pathways have been recommended to trigger an inflammatory/ immune response and/or suppression of local growth factors in the foetal-placental unit. The direct pathway; where oral microorganisms and/or their components reach foetal-placental unit via hematogenous dissemination from the oral cavity, or oral microorganisms and/or their components reach foetal-placental unit via genitourinary tract. The indirect pathway recommends that inflammatory mediators locally formed in periodontal tissues such as TNF-α and PGE2 circulate and influence the foetal-placental unit, or inflammatory mediators and/or microbial components circulate to the liver, promote cytokine production (e.g. IL-6) and acute phase responses (e.g. C-reactive protein), which then affect the foetal-placental unit. ***(Sanz M,et al.,2013)***

The strongest indication from both animal and human studies supports the idea that periodontal infections provide a portal for hematogenous dissemination of oral microorganisms and their products which extend to the foetal-placental unit. The direct pathway is linked with inflammatory/immune responses in the foetal-placental unit that prompt a range of adverse outcomes, which are reliant on severity of exposure and timing. Lower exposures may prompt hyper contractility of the uterus, cervical dilatation and loss of membrane integrity. Growth restraint and earlier preterm delivery are associated with higher and/or earlier

exposures. Even higher exposures may lead to spontaneous abortion, late miscarriage and stillbirth. ***(Madianos PN, et al.,2013)***

Numerous studies associate a raise in the levels of local and systemic markers of inflammation with APOs. Increased levels of IL-1b, IL-6, PGE2, TNF-α ,foetoprotein and fibronectin in the amniotic fluid have been related with Preterm birth.***(Gursoy, et al.,2010)*** Raised maternal serum levels of pro-inflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF-a, have also been informed to be related with prematurity or low birthweight. ***(Hitti, et al.,2001)*** CRP, which is an acute phase reactant synthesized by the liver in response to pro-inflammatory cytokines, and therefore a marker of systemic inflammation is also reported to be related with preterm birth (PB). ***(Pitiphat, et al., 2005)***

Periodontal diseases are a group of infectious/inflammatory diseases including Gram negative, anaerobic and microaerophilic bacteria that colonize the subgingival area and are the reason for local and systemic rise of pro -inflammatory prostaglandins and cytokine. ***(Smalley JW,1994)***

Evidence shows that periodontal pathogens/byproducts may reach the foetal-placental unit ***(Madianos PN,et al.,2013).*** In this perspective, ***Madianos et al. (2001)*** found that maternal serum IgG specific to oral organisms was related with reduced PB

and increased birth weight. In the presence of maternal oral organisms, the lack of a protective maternal IgG response could elevate foetal exposure which may contribute to a foetal immune response that could result in PB. ***(Madianos, et al.,2001*)**. Periodontal pathogens as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans were found in the placenta of women with PB or pre-eclampsia. ***(Swati,et al.,2012)***

Pentraxins consist of two groups: short pentraxins; C-reactive protein (CRP), serum amyloid P-component (SAP) and long pentraxins; PTX3. Pentraxin3 was recognized in 1990s and is produced by both innate and resident immune cells in peripheral tissues in response to inflammatory signals ***(Bottazzi B,et al., 2006) (Garlanda C, et al., 2009)***. PTX3 has been recommended to have the potential to be a new diagnostic marker for several autoimmune and inflammatory diseases. ***(Ortega-Hernandez O, et al2008). (Pinar G,et al.,2013)*** reported that PTX3 is associated with periodontal tissue inflammation as measured in saliva and serum of chronic and aggressive periodontitits patients.

REVIEW OF LITERATURE

Usually periodontal disease can be classified into two main categories which are gingivitis and periodontitis, the seven forms of destructive periodontal diseases listed as follows: chronic periodontitis, localized and generalized aggressive periodontitis, periodontitis as a manifestation of systemic disease, abscesses of the periodontium, necrotizing ulcerative periodontal disease and combined periodontal-endodontic lesions ***(Armitage, 1999)***

Gingivitis and periodontitis are inflammatory disorders of infectious nature. Plaque-induced gingivitis is an inflammation of the gingiva resulting from bacteria located at the gingival margin, producing change in gingival color and contour, bleeding on probing, increased gingival exudate and lack of attachment and bone loss. ***(Mariotti, 1999)***

Periodontitis in moderate to severe form affects higher incidence in a lot of countries. Thus, hundreds of millions all over the world are affected by such inflammatory diseases, so it is essential that we understand the nature and degree of the risk and start a course of actions to manage it. ***(Brown LJ, et al., 1993)***

A NEW PARADIGM FOR PERIODONTITIS:

Achievements have been made in our understanding of the natural history and pathogenesis of Periodontitis. ***(Offenbacher, et al.1996)(Page RC, et al.1997) (Page RC, et al.1997)***, There has been a paradigm shift in our understanding of the pathobiology of periodontitis .Characteristics of the new paradigm are showed in Figure 1 ***(Page RC, Kornman KS, 1997)***. Periodontitis is an infectious disease caused by a small group of predominantly anaerobic Gram-negative bacteria. Bacteria are critical, but not enough to cause disease; a susceptible host is also necessary and host factors are determinative. It is a family of related diseases that vary in natural history, etiology, disease progression, and response to therapy, but with mutual shared pathways of tissue destruction ***(Page RC, et al., 1997) (Page RC, et al., 1982)*** therefore, ultrastructural characteristics, the histopathological and pathways of tissue destruction. Healing and regeneration are very similar if not identical for all forms of Periodontitis. All forms had similar basic pathologic mechanisms for the observed connective tissue and bone destruction. The proinflammatory cytokines TNF- α, IL-lß, and IFN- γ prompt and improve the production of prostaglandin E2 (PGE2) and matrix metalloproteinases (MMP), and these molecules facilitate destruction of the extracellular matrix of the gingiva , periodontal ligament and resorption of the alveolar bone. The shared events in the pathobiology are influenced by disease modifiers (known as risk