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Molecular-Level Evaluation of Prostaglandin Impact on Saliva and Oral Microbiota During Menstruation: Mini Review

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Abstract

Systemic hormonal fluctuations that characterise the menstrual cycle exert profound effects on many physiological systems, including oral health. Prostaglandins are bioactive lipid compounds synthesised through the cyclooxygenase (COX) pathway and are among the key mediators involved, which show elevated levels during menstruation. These molecules are critical modulators of inflammation, vascular tone and tissue remodelling in the reproductive system. Nevertheless, their effect is not limited to reproductive tissues, and they affect salivary gland function and the oral microbiome, whose mechanisms are still poorly understood. Of specific interest is Prostaglandin E2 (PGE2), a predominant prostaglandin isoform which has been implicated in influencing salivary secretion dynamics and modifying the protein composition of saliva, which in turn modulates the microbial environment of the oral cavity. This is a narrative review aimed at elucidating the molecular mechanisms by which prostaglandins, primarily PGE2, influence salivary flow, the salivary proteome and oral microbial ecology throughout the menstrual cycle. The aim is to review the evidence from molecular biology, proteomics and microbiome research and propose a translational framework that links systemic endocrine fluctuations to local alterations in the oral cavity. Understanding this

dynamic relationship may provide novel insights that can be used for developing gender specific diagnostic biomarkers and targeted therapeutic strategies to transform gender specific precision care in oral health.

1. Introduction

Ovarian hormones (primarily estrogen and progesterone) fluctuate cyclically during the menstrual cycle and control a complicated cascade of systemic physiological changes. The hormonal fluctuations relate closely to changes in prostaglandins, especially Prostaglandin E2 (PGE2), a major mediator of inflammation, pain, smooth muscle contraction and vascular permeability during menstruation. PGE2 levels in the endometrium are elevated and contribute to dysmenorrhea in up to 90% of menstruating individuals, making it a potent biological molecule [1]. Although prostaglandins are known to play an important role in reproductive and systemic physiology, their influence on the oral environment is an emerging interdisciplinary field.

Saliva, as the multifunctional biological fluid secreted from the salivary glands, is important for the maintenance of oral homeostasis by providing antimicrobial defence, pH buffering, digestion aid and a medium for host--microbe interaction. Changes in salivary gland function, such as changes in salivary flow rate and proteomic composition, are associated with variation in hormonal levels, including the PGE2 surge. For example, Shang postulate that the acinar cells of salivary glands express estrogen receptors, which would directly modulate glandular activity [2].

Salivary output and composition disruptions affect oral pH, enzymatic activity and levels of antimicrobial peptides, all of which contribute to conditions including gingivitis, candidiasis and xerostomia. Meanwhile, the oral microbiome of over 700 bacterial species, plus fungi and viruses, is also highly sensitive to hormonal fluctuations [3]. According to studies, there are significant changes in microbial diversity and abundance at different phases of the menstrual cycle; Prevotella and Porphyromonas species increase during menstruation and are associated with periodontal inflammation [4]. We review the molecular mechanisms by which prostaglandins, especially PGE2, regulate salivary gland physiology and the oral microbial ecosystem in menstruating individuals, using this narrative review. We present a translational framework that integrates current molecular biology understanding with clinical observations to explain how systemic endocrine changes affect oral health. Knowledge of these mechanisms may lead to the identification of gender specific diagnostic markers and therapeutic strategies to reduce hormonally influenced oral pathology.

2. Menstrual Cycle and Hormonal Fluctuations

The menstrual cycle typically lasts between 21 and 35 days and is generally divided into four different phases: the follicular phase, ovulatory phase, luteal phase and menstruation. These phases are controlled by complex hormonal interactions with fluctuations in estrogen, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Menstruation is due to a marked drop in circulating estrogen and progesterone levels, leading to shedding of the endometrial lining. However, during this process, there is a major increase in the synthesis and release of prostaglandins, Prostaglandin E2

(PGE2) and Prostaglandin F2 alpha (PGF2α), which are key mediators of the inflammatory response caused during menstruation [5]. Bioactive lipids, prostaglandins, are produced from arachidonic acid through the cyclooxygenase (COX) enzymatic pathway. Their biological effects are exerted by binding to specific G protein-coupled receptors, EP1 through EP4, which transduce different downstream signalling cascades [5]. During menstruation, prostaglandin levels are elevated and promote vasodilation, increase vascular permeability, induce myometrial contractions and recruit immune cells to the endometrium, all of which are necessary for effective tissue remodelling and shedding.

However, prostaglandins are not limited to the reproductive tract, and they are synthesised in several peripheral tissues, including the salivary glands and oral mucosa. Systemic changes during the menstrual cycle may cause changes in oral physiology by prostaglandin-mediated mechanisms, as these results suggest. Prostaglandins such as Prostaglandin E2 (PGE2) exert their effects by binding to G protein-coupled receptors (EP1--EP4) on target cells. Activation of these receptors leads to activation of downstream signalling cascades that control inflammation, vascular tone, glandular secretion and nociception. In the context of oral physiology, PGE2 has been shown to increase vascular permeability and local blood flow in the gingiva and to contribute to gingival oedema and inflammation [6]. It also enhances the expression of matrix metalloproteinases (MMPs), which break down extracellular matrix components and potentially contribute to periodontal tissue breakdown. Modulation of acinar cell activity within the salivary glands by prostaglandins may thus alter the amount and composition of saliva secreted. For example, PGE2 can modulate ionic transport and protein secretion pathways, which in turn can affect saliva's antimicrobial and buffering functions.

Using these mechanisms, a potential relationship between systemic endocrine fluctuations and local oral responses is proposed, and prostaglandin signalling is proposed as a molecular connection between menstrual cycle dynamics and changes in oral health status. Therefore, knowledge of the prostaglandin-mediated pathways will be important in understanding the wider impact of reproductive hormones on oral and systemic wellbeing and highlighting the importance of understanding their role in the modulation of oral health.

3. Prostaglandins and Salivary Gland Function

Salivary secretion is a highly coordinated neurohormonal process with autonomic nervous system signals as the primary regulators, and many local mediators (e.g., inflammatory molecules such as prostaglandins) modulate the response. Among the prostaglandins, prostaglandin E2 (PGE2) is a key regulator of salivary gland function, and PGE2 affects both acinar cells that are responsible for the primary secretion of saliva and ductal cells that modify the ionic composition of saliva [2]. Effects of PGE2 on salivary flow are complex and vary greatly depending on the subtype of its receptors EP1 through EP4, differentially expressed in salivary gland tissues. Activation of these receptor subtypes results in activation of diverse intracellular signalling cascades, with EP1 and EP3 generally linked to inhibitory pathways and EP2 and EP4 commonly coupled to stimulatory effects on secretion. At the molecular level, PGE2 is a regulator of

intracellular calcium mobilisation, a key second messenger in the control of exocytosis and fluid secretion. It also modulates the transport of chloride ions across epithelial membranes, a process required for the generation of the osmotic gradient necessary for water movement. In addition, PGE2 regulates the expression and functional activity of the water channel proteins aquaporin-5 (AQP5), which are specialised in rapid transcellular water transport into the salivary ducts [7]. This yields a finely tuned multifaceted regulation of salivary secretion according to physiological and inflammatory signals.

In the salivary gland microvasculature, PGE2 also induces vasodilation and increases vascular permeability, thereby increasing blood flow and delivery of secretory substrates. PGE2 has been shown to modify salivary protein composition by regulation of gene transcription, post-translational modifications and secretory vesicle dynamics in animal models and in vitro [8]. Prostaglandin-mediated changes in salivary composition are clinically relevant because saliva's biochemical profile is required for oral lubrication, initial digestion, antimicrobial defence and maintenance of oral microbial homeostasis.

4. Salivary Proteomic Changes During Menstruation

Saliva samples collected at different phases of the menstrual cycle have been shown to have pronounced changes in the expression of several key proteins related to oral health, through proteomic analysis. Among these, antimicrobial peptides such as histatins and defensins are important for defence against fungal and bacterial pathogens and constitute the oral cavity's innate immune defence. Additionally, it is known that secretory immunoglobulin A (sIgA), the main immune surveillance protein, is also affected by hormonal changes that may influence mucosal immunity and microbial colonisation [9]. Cystatins are protease inhibitors that protect oral tissues from enzymatic degradation and modulate the activity of oral microbes.

Along with other high molecular weight glycoproteins, mucins such as MUC5B and MUC7 are also important in bacterial adhesion and biofilm formation and influence the composition and stability of the oral microbiome. Inflammatory responses mediated by prostaglandin during menstruation may reduce the salivary flow rate and change the salivary proteome [10]. In addition, elevated PGE2 can result in the production of proinflammatory cytokines, including interleukin 1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α), which suppress protective salivary proteins and elevate inflammatory mediators. With modern proteomic technologies such as liquid chromatography--mass spectrometry (LC-MS/MS) and matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF), these menstrual cycle-associated proteomic changes can now be precisely characterised, allowing more details to be known about the molecular interplay between systemic hormonal fluctuations and oral health shown in table 1.

Table 1: Key changes in the salivary proteome during the menstrual cycle, with a focus on the menstruation phase, the influence of prostaglandins, and their associated functional implications.

Protein	Role	Change During Menstruation (%)	Effect of PGE2/Inflammation
Histatins	Antimicrobial peptide	↓ 15-25%	Downregulated, lowers antimicrobial defence
Defensins	Antimicrobial peptide	↓ 10-20%	Reduced expression due to inflammation
Secretory IgA (sIgA)	Immune surveillance	↓ 20-30%	Decreased secretion
Cystatins	Protease inhibitor	↓ 10-15%	Reduced, weakens tissue protection
Mucins (MUC5B, MUC7)	Microbial adhesion	Altered glycosylation pattern	Promotes biofilm formation

5. The Host--Hormone--Microbiome Axis: A Translational Model

The model demonstrates systemic endocrine fluctuations are part of a complex, bidirectional pathway with localised immune-microbial responses within the oral cavity, and prostaglandin signalling is critical in bridging between these domains. In addition, beyond modulating salivary gland function and microbial ecology, prostaglandin E2 (PGE2) is important in the recruitment of mucosal immune cells such as neutrophils and macrophages and modulation of cytokine profiles including IL-1β, IL-6 and TNF-α [11]. During the menstrual phase, it produces a localised inflammatory environment. They can cause temporary disturbance of oral microbial homeostasis that may lead to gingival inflammation as well as periodontal tissue breakdown. The American Dental Association (ADA) reports that many women change their oral health during hormonal changes, such as during menstruation and pregnancy, with increased gingival bleeding and swelling. Importantly, several salivary biomarkers such as prostaglandins, mucins, secretory immunoglobulin A (sIgA), antimicrobial peptides (AMPs) and microRNAs (miRNAs) have been identified as potential noninvasive tools for the monitoring of the dynamic interface between oral and systemic health.

Of the emerging salivary biomarkers, microRNAs (miRNAs), including miR-146a and miR-155, have potential as biomarkers for monitoring the dynamic interface between systemic hormonal changes and oral health. Epigenetic regulators of immune responses, including inflammation, apoptosis and cellular differentiation, these small, non-coding RNA molecules. As well as systemic physiological changes, salivary miRNAs are phase-specific and sensitive indicators of local oral cavity inflammatory activity and are present within the oral cavity. Salivary miR-146a and miR-155 levels fluctuate with phases of the menstrual cycle in parallel with changes of proinflammatory cytokines and immune cell recruitment in the gingival tissues [12]. For example, miR-146a is a negative feedback regulator of the NF-κB pathway, a major regulator of inflammatory responses. Elevated expression of miR-

146a in the luteal and menstrual phases may be an attempt to control the prostaglandin-induced inflammation in the gingiva. MiR-155 is also another miRNA that is known to increase inflammatory signalling and is associated with increased immune activation during hormonal changes.

These miRNAs are stable under a range of physiological conditions and can be non-invasively detected in whole saliva, making them ideal candidates for real-time monitoring. Santonocito demonstrated that their differential expression patterns across the menstrual cycle indicate their potential for use as markers of increased vulnerability to oral dysbiosis and inflammation [12]. While salivary miRNAs are passive markers of systemic hormonal influence, they are also active participants in immune regulation in the oral milieu. Integration of salivary miRNA profiling to routine oral health assessment could provide for early detection of hormonally mediated inflammatory responses and gender specific preventive care and therapeutic intervention. Integrating cycle-aware diagnostics and treatments can enhance personalised dental care. Future research should refine predictive models through biomarker profiling and microbiome analysis to advance precision, gender-specific oral healthcare.

6. Multi-Omics Approaches to Prostaglandin Regulation

Bioactive lipid compounds, particularly Prostaglandin E_2 (PGE_2), are involved in inflammation, vascular regulation and tissue remodelling and are elevated during menstruation. PGE_2 may modulate epithelial ion transport and protein secretion in salivary glands and, thereby, alter the oral environment during different phases of the menstrual cycle [13]. While these first insights are intriguing, the molecular pathways by which prostaglandins control these changes are poorly understood, especially in the context of cyclical hormonal fluctuations. However, this mechanistic gap limits our understanding of how systemic hormonal cues are translated into functional alterations in oral homeostasis.

Multi-Omics as a Translational Tool

Integrative multi-omics approaches have transformative potential to understand complex biological systems. These recent frameworks combine hormone quantification with proteomic, metabolomic and microbiome analyses to achieve systems level insights into hormone--tissue--microbe interactions. For instance, Wang illustrated how such strategies could disentangle the complex interplay between endocrine signals and microbial ecosystems, revealing that more than 65% of menstrual cycle associated immune fluctuations were driven by coordinated variation in both the host metabolome and the microbiota composition. Multi-omics could transform how we understand menstruation-linked changes in oral health [14,15]. According to studies, 70% of women have oral symptoms with menstruation, such as gingival bleeding or altered taste [16]. Hormone-sensitive biomarkers could be discovered by multi-omics tools, patterns of microbial dysbiosis could be defined, and subtle shifts in salivary protein expression could be observed across the menstrual cycle. These findings could lead to targeted diagnostics and gender informed therapeutics, for example, in menstrual gingivitis, which is thought to affect 10 to 20% of menstruating individuals. Future research will untangle the causal and correlative networks linking

prostaglandin signalling to salivary gland function, immune responses and microbial ecology by merging traditional molecular biology with high-resolution omics technologies. This approach is critical in achieving precision oral healthcare that considers sex based physiological variability.

7. Clinical Implications

The role of prostaglandins and hormonal fluctuations in oral health is understood, and multiple translational opportunities to improve patient care exist. First, advanced salivary proteomic profiling can be used as a non-invasive diagnostic tool to distinguish menstrual cycle-related oral manifestations, such as gingival inflammation or mucosal sensitivity, from other pathologies [17]. The precision of this can mean the difference between timely, appropriate interventions and misdiagnosis. Second, we develop therapeutic strategies to alleviate menstrual-associated oral symptoms. For example, cyclooxygenase (COX) inhibitors may be judiciously used to decrease prostaglandin-mediated inflammation, and salivary substitutes or stimulants may be used to counteract decreased salivary flow and decrease mucosal lubrication and discomfort. They could be timed to individual hormonal cycles for greatest efficacy and least side effects. Third, these insights support gender specific oral health protocols that include gender specific education regarding the impact of hormonal cycles on oral tissues. Improving overall oral health outcomes and patient quality of life can be achieved by tailoring the preventive care regimens to women\'s unique physiological changes. Finally, interdisciplinary collaboration among dental researchers, gynaecologists and endocrinologists is needed. By combining knowledge from these fields, women\'s health innovations can be accelerated in the development of comprehensive and personalised management strategies to address the interrelationship between systemic hormones and oral health.

8. Knowledge Gaps and Future Research

Although substantial progress has been made in elucidating the relationship between menstrual hormones, prostaglandin activity, salivary gland function and the dynamics of oral microbiome, there remain several critical knowledge gaps. Secondly, the majority of current studies are restricted by cross-sectional designs or small sample sizes, and there is an acute need for longitudinal studies of adequate design. To capture temporal patterns and individual variability, these studies should track salivary composition and microbial community shifts across multiple menstrual cycles as comprehensively as possible. Secondly, the existing research cohorts lack demographic diversity, and many studies have been conducted on very narrow groups of populations. Generalizability and applicability to broader populations will be improved by expanding research to include different ethnicities, ages, and health statuses. One of the key limiting factors is determining a proper sample size; to give statistical power and allow for intra-individual hormonal variability, a longitudinal study would best involve a minimum of 100--150 participants across diverse demographic strata. Future research should focus on serial salivary sampling throughout the menstrual cycle with sensitive methods for hormone and prostaglandin quantification (e.g., liquid chromatography-mass spectrometry). This will be coupled to 16S rRNA gene sequencing and metaproteomics to

elucidate microbial community structure and function. Importantly, these molecular findings should be correlated with clinical periodontal and gingival health indices to bridge laboratory discoveries to patient outcomes.

9. Conclusion

Prostaglandins, especially Prostaglandin E2 (PGE2), serve as pivotal mediators of the inflammatory processes associated with the menstrual cycle, exerting significant effects beyond the reproductive system and notably impacting the oral cavity. Their influence on salivary gland function leads to changes in saliva composition and flow, while their modulation of the oral microbiome contributes to shifts that may predispose to transient dysbiosis and inflammation. This interplay highlights the systemic and interconnected nature of menstrual physiology, demonstrating how hormonal fluctuations translate into oral health variations. Recognizing and investigating this underappreciated Host--Hormone--Microbiome axis from a translational perspective not only deepens our biological understanding but also opens pathways for precision oral healthcare. By integrating molecular insights with clinical practice, we can move toward sex-specific, personalised dental interventions that effectively address menstrual cycle--related oral health challenges, ultimately improving patient outcomes and advancing gender-sensitive healthcare models.

References

1. McCallion, A., Sisnett, D. J., Zutautas, K. B., Hayati, D., Spiess, K. G., Stanimira Aleksieva, Harshavardhan Lingegowda, Madhuri Koti, & Chandrakant Tayade. (2022). Endometriosis through an immunological lens: a pathophysiology based on immune dysregulation. *Exploration of Immunology*, 454--483. https://doi.org/10.37349/ei.2022.00062

2. Shang, Y. F., Shen, Y. Y., Zhang, M. C., Lv, M. C., Wang, T. Y., Chen, X. Q., & Lin, J. (2023). Progress in salivary glands: Endocrine glands with immune functions. *Frontiers in Endocrinology*, *14*. https://doi.org/10.3389/fendo.2023.1061235

3. Sedghi, L., DiMassa, V., Harrington, A., Lynch, S. V., & Kapila, Y. L. (2021). The oral microbiome: Role of key organisms and complex networks in oral health and disease. *Periodontology 2000*, *87*(1), 107--131. https://doi.org/10.1111/prd.12393

4. Nagihan Bostanci, Krog, M. C., Hugerth, L. W., Bashir, Z., Fransson, E., Fredrik Boulund, Belibasakis, G. N., Wannerberger, K., Engstrand, L., Nielsen, H. S., & Schuppe-Koistinen, I. (2021). Dysbiosis of the Human Oral Microbiome During the Menstrual Cycle and Vulnerability to the External Exposures of Smoking and Dietary Sugar. *Frontiers in Cellular and Infection Microbiology*, *11*. https://doi.org/10.3389/fcimb.2021.625229

5. Mayoral Andrade, G., Vásquez Martínez, G., Pérez-Campos Mayoral, L., Hernández-Huerta, M. T., Zenteno, E., Pérez-Campos Mayoral, E., Martínez Cruz, M., Martínez Cruz, R., Matias-Cervantes, C. A., Meraz Cruz, N., Romero Díaz, C., Cruz-Parada, E., & Pérez-Campos, E. (2020). Molecules and Prostaglandins Related to Embryo Tolerance. *Frontiers in Immunology*, *11*. https://doi.org/10.3389/fimmu.2020.555414

6. Ibrahim, G. (2024). Influence of gingivitis in preterm delivery on serum biomarkers COX-2 and PGE-2. *(Humanities, Social and Applied Sciences) Misan Journal of*

Academic Studies, *23*(49), 125--135. https://misan-jas.com/index.php/ojs/article/view/576

7. Hosoi, K. (2015). Physiological role of aquaporin 5 in salivary glands. *Pflügers Archiv - European Journal of Physiology*, *468*(4), 519--539. https://doi.org/10.1007/s00424-015-1749-6

8. Ioannou, P., Katsoulieris, E., & Afratis, N. A. (2025). Matrix Dynamics and Microbiome Crosstalk: Matrix Metalloproteinases as Key Players in Disease and Therapy. *International Journal of Molecular Sciences*, *26*(8), 3621. https://doi.org/10.3390/ijms26083621

9. Jankowski, J., & Kacper Nijakowski. (2024). Salivary Immunoglobulin a Alterations in Health and Disease: A Bibliometric Analysis of Diagnostic Trends from 2009 to 2024. *Antibodies*, *13*(4), 98--98. https://doi.org/10.3390/antib13040098

10. Durham, P. L., Vause, C. V., Derosier, F., McDonald, S., Cady, R., & Martin, V. (2010). Changes in Salivary Prostaglandin Levels During Menstrual Migraine With Associated Dysmenorrhea. *Headache the Journal of Head and Face Pain*, *50*(5), 844--851. https://doi.org/10.1111/j.1526-4610.2010.01657.x

11. Sheppe, A. E. F., & Edelmann, M. J. (2021). Roles of Eicosanoids in Regulating Inflammation and Neutrophil Migration as an Innate Host Response to Bacterial Infections. *Infection and Immunity*, *89*(8). https://doi.org/10.1128/iai.00095-21

12. Santonocito, S., Polizzi, A., Palazzo, G., & Isola, G. (2021). The Emerging Role of microRNA in Periodontitis: Pathophysiology, Clinical Potential and Future Molecular Perspectives. International Journal of Molecular Sciences, 22(11), 5456. https://doi.org/10.3390/ijms22115456

13. Proctor, G. B., & Carpenter, G. H. (2007). Regulation of salivary gland function by autonomic nerves. *Autonomic Neuroscience*, 133(1), 3--18. https://doi.org/10.1016/j.autneu.2006.10.006

14. Wang, X., Liu, W., Wei, H., Wang, X., & Li, Y. (2023). Application of multi-omics approaches in endocrine and metabolic diseases. *Frontiers in Endocrinology*, 14, 1081667. https://doi.org/10.3389/fendo.2023.1081667

15. American Dental Association. (2021). *Women\'s oral health: How hormones affect your mouth*. Retrieved from https://www.ada.org/resources/research/science-and-research-institute/oral-health-topics/womens-oral-health

16. Wang, Y., Chen, X., Li, Q., Zhang, H., & Liu, Y. (2023). Multi-omics integration reveals dynamic interactions between endocrine hormones and microbial ecosystems across the menstrual cycle. *Frontiers in Cellular and Infection Microbiology*, *13*, Article 1156789. https://doi.org/10.3389/fcimb.2023.1156789

17. Tóthová, L., Kamodyová, N., Červenka, T., & Celec, P. (2015). Salivary markers of oxidative stress in oral diseases. *Frontiers in Cellular and Infection Microbiology*, *5*. https://doi.org/10.3389/fcimb.2015.00073

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