

Oral Alterations in Woman's Reproductive Life Cycle: A Bibliometric Analysis and Systematic Review

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Abstract : The oral tissues exhibit various alterations during every stage of women's reproductive life cycle due to the influence of fluctuating levels of sex hormones. Several confounding factors enhances these hormonal effects. This paper aims to systematically review the scientific literature retrospectively from three different databases namely PubMed, Ebscohost and Google Scholar between Jan 2013 to June 2024 and collect relevant evidence on the oral manifestations during women's reproductive life. We performed PRISMA 2020 protocol and all the 41 included articles were subjected for Bibliometric and scientometric analyses to gather the evidence of oral changes, their etiopathogenesis and their managerial care to sustain the oral health during women's reproductive life cycle.

Keywords: Oral health, pregnancy, puberty, menstruation, oral contraceptives, menopause.

1. Introduction

1.1 Background

The hormonal oscillation in women during her reproductive life cycle has a significant influence in her general as well as on her oral health. These changes are directed by the two important female sex hormones i.e, estrogen and progesterone, that have directional activity on the tissue or have a manipulative action on the local factors to exhibit altered response of the tissue.

Estrogen is vital in development and maintenance of secondary sex characteristics, uterine growth, pulsatile release of luteinizing hormone from the anterior pituitary gland and the development of peripheral and axial skeleton. It is responsible for alterations in blood vessels of the target tissues. Whereas, Progesterone is secreted by the corpus luteum, placenta and the

adrenal cortex. It stimulates production of inflammatory mediators and is involved in bone metabolism.

1.2 Rationale

Women undergo series of biological changes subjected to these hormonal influences during her reproductive life cycle. Puberty, menstruation, pregnancy, oral contraception(OC), menopause and sometimes Hormone Replacement Therapy (HRT) are the vital phases of her reproductive health, where the consequential hormonal alterations in the oral soft tissues are reflected as gingival and periodontal abnormalities. That is because of the presence of receptors for estrogen and progesterone in those oral tissues. Also, there are certain micro-organisms in the human mouth, that produce the enzymes needed for the synthesis and catabolism of these steroid hormones, oestrogen and progesterone. There are exaggerated response of the normal commensals to the local factors like food debris, material alba, plaque and calculus during these phases of hormonal fluctuation.

1.3 Objective

This systematic review aims to summaries the available literature in the scientific database that explains the oral alterations in women during the various stages of her reproductive life cycle.

1.4 Review Questions (RQ)

RQ1. What are the research / publication trends and intellectual structure towards oral alterations in women during different stages of her reproductive life cycle ?

RQ2: What are the anatomical regions/tissues in oral cavity that exhibits changes during women's reproductive phases ?

RQ3. How are the effect of hormonal alterations presented in oral cavity ?

RQ4: How to maintain the health of oral structures during these phases of reproductive cycle?

2. Methodology

A systematic review based on the bibliometric analysis was built to reflect the current trends on this topic in the biomedical literature databases. Bibliometric analysis detects the emerging trend in article, analyses the abundant volume of scientific data and explores the spectrum of specific topic.¹ Whereas Systematic review helps in deciphering the enormous information and compound knowledge available in the scientific platform into clinically applicable details.²

Therefore, a scientometric study to assess the data on oral manifestations in different phases of women's reproductive life cycle was undertaken.

2.1 Search Strategy

The search strategy began by following the PICO framework proposed by Richardson et al. in 1995.³ This is the conceptualized models of clinical question that focus on the precise definition of the patient problem, the required information needed to resolve the problem, and the ability to conduct an efficient search as the skill required for practicing Evidence Based Medicine as recommended by Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) 2020 checklist items; and is represented in represented in Table 1.⁴

Table 1: PICO framework for the focused Clinical Question

| | |
|----------------------------|--------------------------|
| Population | Women |
| Intervention | Sex Hormones in the body |
| Comparison | Normal women |
| Outcome of interest | Oral Alterations |

Our search included retrospective review of electronic databases namely PubMed, Ebscohost and Google Scholar by two authors independently. The published articles between January 2013 to June 2023 were collected. The bibliographic search was done using appropriate keywords, MeSH terms and their combination and checked for its acuteness towards the research questions in their related spectrum. The following were the search strings and keywords used during literature search .

- “Oral changes” OR “oral alterations” OR “Oral manifestations” to include their relative references.

- (Puberty) AND (menstruation / periods/ mensus) AND Preganacy AND (Perimenopause / menopause/post menopause) AND (Oral Contraception) AND (HRT OR Hormone Replacement Therapy) to find all their relative references.

After identifying the relevant key article and related literature, the search strategy was rechecked again to be confirmed by both the authors.

2.2 Inclusion and Exclusion Criteria

Retrieved publications based on the preliminary search were cleaned for suitability based on the following criteria:

Inclusion Criteria:

- Any published studies that are comparative, experimental, case-control, Cohort, Clinical Trials, Cross-Sectional studies, Randomized control trial, case -series, case reports and review articles were included.

- Only available full article were selected for review purpose

- Articles published in english were chosen.

Exclusion Criteria:

Unpublished articles, grey literature, conference proceedings, pilot studies, duplicate records, incomplete reports or data that could not be reliably extracted, abstract-only articles, theses, books and conference papers will be excluded.

2.3 Data Extraction and Analysis

The quantitative evaluation of research topic from the available database were independently done by the two reviewers and were cleaned to extract the included studies. Any disagreements were resolved by discussion and further verification by the third reviewer.

RQ1: Author/s, year of publication, journal, abstract, keywords, citation, research outputs were recorded to analyse the bibliometric entities using VOSviewer version (1.6.19) to perform cluster analysis based on keywords and Co-authorship analysis.

RQ2,RQ3,RQ4: All the articles in the database were scrutinized using the title, abstract and keywords by two reviewers independently. Then the included articles were screened to elicit answers for the research question. Figure 1 describes the eligibility screening process at each stage of search as advised by PRISMA 2020.

Figure 1: Flowchart consistent with PRISMA 2020 statement for systematic reviews.

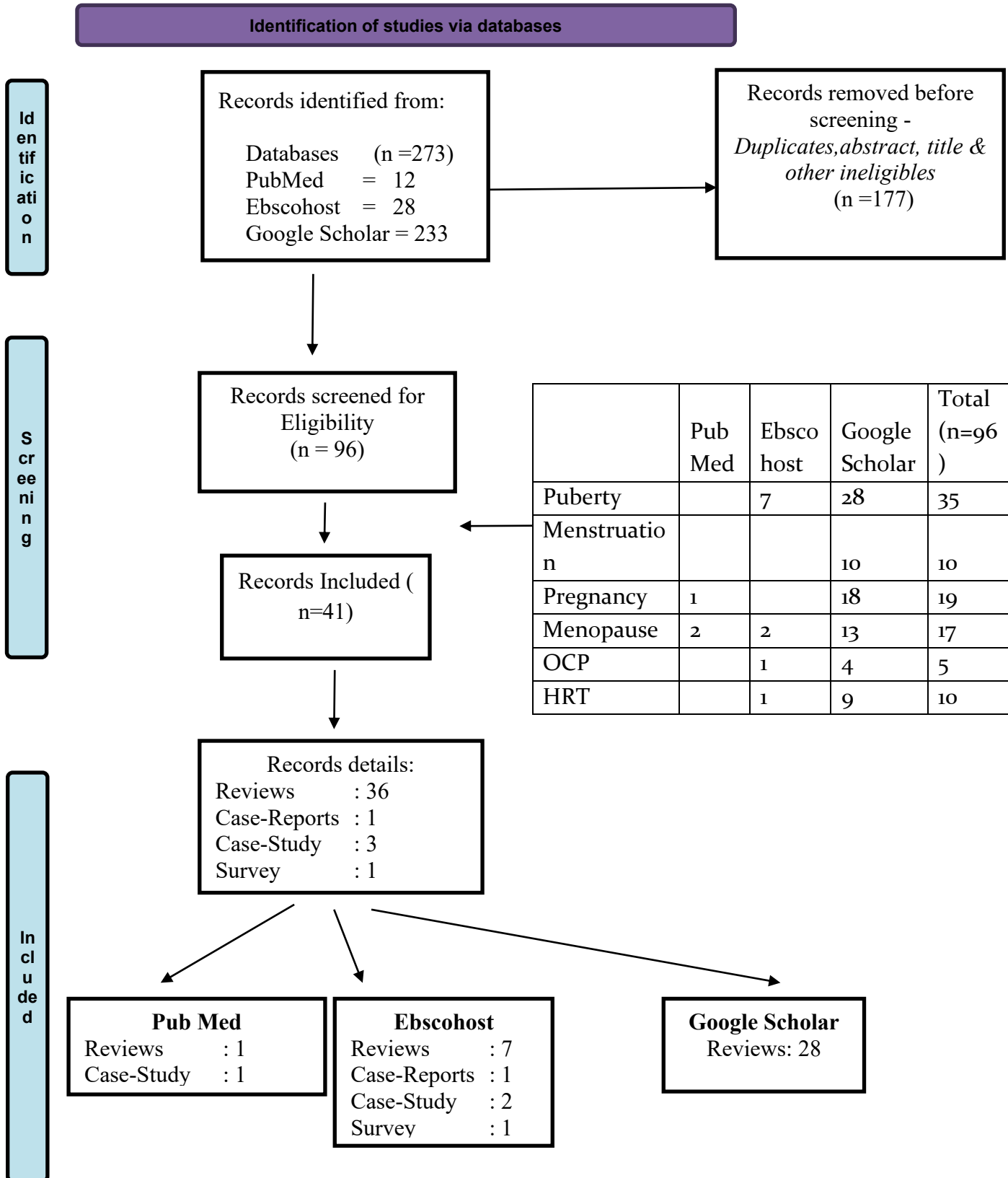
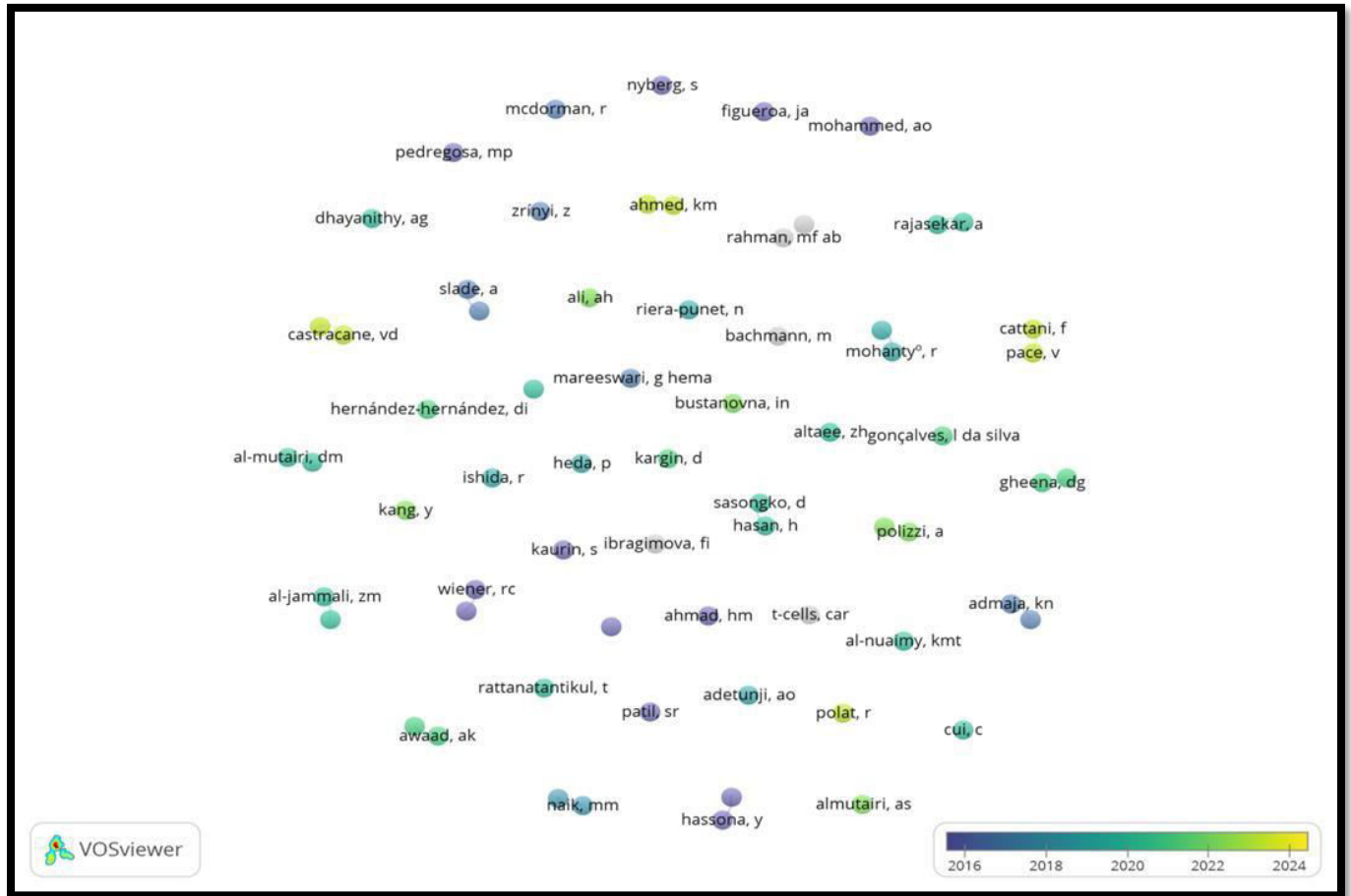


Figure 3: Network mapping of co-authorship citation



4. Discussion

The five phases of women’s reproductive life cycle and their oral implications are reviewed here.

4.1 Puberty

Adolescence is the stage of life between 10-16 years where the body experience dramatic physiological changes. Puberty marks the initiation of these changes from childhood into adulthood.⁵

It is associated with a major increase in the secretions of the sex steroid hormones, progesterone and estrogen in females and its level remains relatively constant thereafter and throughout her reproductive cycle. Studies have reported that there is increased risk and incidence of gingivitis, that is independent of plaque levels during puberty. While few studies correlated gingivitis which increased with the mean plaque levels.⁶

With the onset of puberty, there is increased response of gingival tissues to the subgingivalmicroflora. There is specific altered response of some species of bacteria to the

changing microenvironment of gingival tissues.⁷ There were reported cases of chronic inflammatory marginal and interdental gingiva along with nodular and hyperplastic interproximal papillae in the facial and lingual surfaces. They were erythematous, ballooned, lobulated and retractable.⁸ These were histologically in accordance with inflammatory hyperplasia.⁹ It differed from the other uncomplicated chronic inflammatory gingival enlargement by its degree of enlargement and its tendency of massive recurrence.

Microbially, colonies of *Prevotellaintermedia* (*P. intermedia*), a gram-negative anaerobe and *Capnocytophaga* species, a gram negative bacterium were predominant. These organisms were found to be responsible for increased tendency to gingival bleeding during puberty.¹⁰ It was postulated that there increased proportion is because of there ability to substitute estrogen and progesterone for vitamin K, an essential growth factor for that multiplication.^{11,12}

Management: Gingival enlargement during puberty can be treated by performing scaling and curettage; and removing all sources of food debris, materiaalba, plaque and calculus from the site to minimize gingival irritation.

4.2 Menstruation

The estrogen levels are at peak, two days prior to ovulation (during the proliferation phase) and progesterone secretion reaches its highest concentration after ovulation (during the luteal phase of menstrual cycle) and gradually falls before menstruation, during her monthly menstrual cycle.

Progesterone increases permeability of the microvasculature, altering the rate and the pattern of collagen production in the gingiva, resulting in tooth mobility.¹² Progesterone also increases folate metabolism, stimulates the production of prostaglandins and enhances the chemotaxis of polymorphonuclear leukocytes, thereby significantly causing inflammatory changes in gums, causing swollen and bleeding gingiva, preceding the onset of menstrual flow.¹³ Modulation of Interleukin(IL) -6, as studied by Kenecna et al. during menstrual cycle induced gingival inflammation.¹⁴ Brannstrom and co-workers investigated on peripheral blood levels of cytokines to find TNF(Tumor Necrosis Factor) - α (alpha) as one of the mediator for inflammatory causes in gingiva during menses.^{15,17}

An increase in gingival exudates associated with swollen salivary glands may also be noticed during menses. Increased levels of progesterone can predispose the women to intraoral recurrent aphthous ulcers, herpes labialis lesions and candida infections as a pattern.¹⁴ The lesions appear during the luteal phase of the cycle and heal following menstruation.

Management: Since all these changes are hormonal influenced and as it normalize as the menstruation ends, maintain the regular oral hygiene is advised .

4.3. Pregnancy

The principal estrogen in plasma is estradiol, which is produced by the ovary and the placenta; and progesterone is secreted by the corpus luteum, placenta, and the adrenal cortex.^{18,19} During pregnancy, both of them are elevated due to continuous production by the corpus luteum at the beginning and the placenta afterward. By the end of the third trimester, progesterone and estrogen reach the peak plasma levels of 100 and 6 ng/mL respectively, which are 10 and 30 times the levels observed during the menstrual cycle.²⁰ This period is witnessed with increase in plaque accumulation, gingival exudation, pregnancy gingivitis especially in the anterior teeth and increased population of *P. gingivalis* and *P. intermedia*. Rapidly enlarged, easily bleedable, hyperplastic and nodular tissues called pregnancy tumors or pyogenic granuloma are noticed often in gingival followed by tongue, lips, buccal mucosa and the palate.

Pregnancy is a complex synchronizing phase in a women's life that involves hormonal, metabolic and immunological modulation of the mother and developing foetus that involves resetting and reorganization of oral microbial consortium.²¹ The hormonal alterations, physiological changes and existing oral conditions acts as a confounding factors in influencing the oral environment of a pregnant women. There would be pathological shift of the oral microbiota in terms of structure and function regardless of the gingival status during pregnancy. All these factors effects oral microbial cluster terms of their growth and metabolism, leading to dysbiosis.²²

4.4.(i) Oral bacterial consortium during pregnancy

Although microbial components plays a crucial part in immunological modulation, they themselves undergo immune changes during pregnancy. This immunological alterations during pregnancy to conuter balance two opposing processess :²³

- a. protection against infections to the foetus and/or the child.
- b. preventing foetal rejection by the maternal immune system.

There is abundant change in the oral microbiota at taxonomy level witnessed during pregnancy period. Increased rate of *Prevotella* species has been associated with an increased progesterone or estrogen level. It acts as a substitute for the naphthoquinone requirement of the pathogens and thus as a growth factor for the bacteria.²⁴

The taxa enriched in *Fusobacterium*, *Prevotella*, and *Porphyromonas* species, have been reported to have proteolytic or amino acid degradation properties for amino acid aspartate, glutamate, and tyrosine.²⁵ Deamination of amino acids produces cytotoxic end products, such as short-chain fatty acids, ammonia, and sulphur compounds, which are able to induce tissue inflammation and apoptosis of gingival fibroblasts.²⁶ The oral milieu during pregnancy promotes acquisition of nutrients by microbes to support energy metabolism and this drives bacterial replication within the host.²⁷

Porphyromonas Gingivitis, Tannerellaforstneri, Treponemadenticola and Aggregatibacteractinomycetemcomitans - are the most pathogenic stains of organisms during pregnancy.²⁸ Their colonization and proliferation is conveyed with the release of bacterial proteases eg. Leucotoxins, collagenases, fibrinolysins that damages periodontium.²³ Immunological-inflammatory host response enhances tissue destruction through cell-mediated immunological response, cytokine and prostanoid cascade leading to overproduction of IL -1, IL- 6, TNF- α and Prostaglandin-2. ^{29,30}

Management: Oral hygiene level may influence the speed and efficiency of bacterial replication and is likely to play a detrimental effect on the health of gingiva and periodontium. This draws attention to the importance of oral health maintenance during pregnancy, as women without any prenatal oral conditions are predisposed to the risk of developing overt disease and the ensuing pregnancy complications.

Prenatal health care should include a comprehensive assessment of oral health, which is often overlooked. To prevent the translation of pathogenic microbiome into gingivitis/ periodontitis, pregnant woman should be screened for oral risks, counseled on proper oral hygiene and expected oral changes; and referred for dental treatment, when necessary.

4.4 (ii) Pyogenic Granuloma (PregnancyEpulis Tumor) or Granuloma Gravidarum

Pyogenic granuloma was reported to have developed in upto 5% of pregnancies. Mucosal lesions were present in 44.2% of the pregnant women. A higher incidence of these lesions were seen among pregnant women.³¹ Increased vascularity of the gingiva and local irritants (e.g. trauma or bacterial plaque) contribute to the development of oral pregnancy lesions.³² The prevalence of oral lesions (52.5%) during second and third trimester was comparatively higher than during first trimester (27.5%). This is attributed to the increase in severity of gingival and periodontal changes during second and third trimesters. This is because the gingival and periodontal tissues are more vulnerable to the action of local irritants along with the plasma progesterone and oestrogen levels reaching their peak by the end of the third trimester, the incidence of oral lesions were more.³³ Besides, oestrogen decreases keratinisation and disrupts the effectiveness of the epithelial barrier.³⁴ Periodontal disease is also associated as a risk factor for preterm low birth weight infant. ³⁵

The other common oral lesion seen during first and second trimester was fissured tongue, followed by gingival/mucosal enlargement and melanosis. Fissured tongue was linked with nutritional deficiencies that is often present in early stages of pregnancy.³⁶ These fissures acted as a protective harbour for bacteria to thrive and multiply. Gingival/mucosal enlargements and melanosis was due to transformed hormonal levels during pregnancy. The aphthous stomatitis were seen during first trimester and its pathomechanism during pregnancy is still unidentified, but is often alleys with immunologic factors. ³⁷

Higher prevalence of dental caries and their susceptible in pregnant women is also linked to increased levels of *Streptococcus mutans* and *Lactobacillus*, especially in third trimester of pregnancy; which may be the reason for the higher incidence of dental caries in the third trimester.^{26,38} The dietary changes such as increased consumption of carbohydrates and increased craving for sweets and fast foods affects the susceptibility of pregnant women to dental caries.^{39,40} In addition, increased acidity in the mouth/ saliva, reduction in saliva production, lowered pH of saliva, increased retention of dietary carbohydrates on the tooth surface, that in turn reduces the plaque pH, leading to dental decay.^{41,42,43} Along with changes in dietary habits, pregnant women also experience changes in smell and taste perception. This suggests that pregnant women may dislike the taste of toothpaste and oral mouth-rinse products, especially during the early part of the pregnancy that declines towards the end, to disappear after delivery.^{44,45}

Management: Recognition of early changes during pregnancy and other attributing factors warrants initial and follow up care throughout the period of pregnancy to avoid unforeseen complications towards oral health.

4.5 Menopause

When the ovarian hormones reduce or stops producing hormones in a women, she undergoes through her last phase of reproductive cycle, the Menopause. It is not a disease or disorder, but a normal transition phase. It can be noticed as early as 40 years of age when the estrogen levels slowly decline and levels of Follicle Stimulating Hormone (FSH) and Leutinising Hormone (LH) gradually increase. This can last for few years called 'perimenopause' period. It is a defined period of time beginning with the onset of irregular menstrual cycles until the last menstrual period.⁴⁶ Menopause is defined retrospectively as the time of the final menstrual period, followed by 12 months of amenorrhea. Post-menopause describes the period following the final menses.⁴⁷

Menopause is the permanent cessation of menstruation resulting in the loss of ovarian follicle development.⁴⁸ Post-menopause is the period following the final menses, resulting in irreversible changes in the ovarian and reproductive hormones. The absence of ovarian sex steroids during menopause and period thereafter is the phase of hypoestrogenism which is related to deterioration in gingival and periodontal health, as the receptors of oral mucosa and salivary glands, as well as vaginal mucosa respond in a similar way histologically to oestrogen. There could be neural mechanical or direct effects of the oral tissues due to oestrogen altering the periodontal health.⁴⁸ As the estrogen begins to fall and women notice taste alteration, altered sensitivity to hot and cold, xerostomia, burning sensation in mouth, atrophic gingivitis, paleness and bleeding gums along with reduced salivary flow with an increased incidence of caries and dysestheis, periodontitis and osteoporosis in jaw bones were reported. Estrogen

deficiency also affects the maturation process of the oral mucosal epithelium and can lead to its thinning and atrophy, making it more susceptible to local mechanical injuries, causing change in pain tolerance and problems in the use of removable prosthetic restorations.⁴⁹

Mucosal epithelium during the menopausal period is more vulnerable to infections like candidiasis and other viral infections. Conditions like burning mouth syndrome, oral lichen planus, or idiopathic neuropathy were commonly experienced. Menopausal women with burning mouth syndrome had higher follicle stimulating hormone levels and lower estradiol levels than those without oral symptoms.⁵⁰

Moreover, salivary glands were also hormone-dependent, which leads to changes in saliva secretion and change in its consistency can affect teeth and periodontal tissues, resulting in an increased risk of caries and periodontal disease in menopausal women.^{49, 50} Another common symptom exhibited by menopausal women is dryness of mouth or xerostomia. Saliva acts as a defense mechanism for prevention of caries and reduced salivary flow can encourage oral microbial colonization thus affecting the dental health.⁵¹ Salivary glands contain sex hormone receptors and these hormones have been estimated in the saliva. Salivary flow rates depend upon estrogen status of the individual. Postmenopausal women have low flow rates of saliva than menstruating women.⁵²

During menopause, estrogen deficiency induces cancellous and cortical bone loss in the jaws, leading to penetrative resorption, destruction of local architecture and microfractures in the jaw bone causing periodontal inflammation and loosening of the teeth.⁴⁹ The supportive periodontal tissues of teeth, i.e. gingiva, periodontal ligament, cementum, and alveolar bone will show changes in inflammatory mediators, vascular permeability; and altered growth and differentiation of fibroblasts as a result of sex hormone variations. The estrogen receptors in osteoblasts and fibroblasts of periodontal tissues, which respond to the varying levels of hormones in different stages of reproductive life and thus affects the health of the periodontium.^{53,54} Decreased bone-mineral density of alveolar crest and subcrestal alveolar bone can lead to attachment loss and tooth loss.⁵⁵ Postmenopausal women present with periodontal disease more frequently and in more severe form.

4.6 Oral Contraception and Hormone Replacement Therapy

The commonly used contraceptives during the reproductive age in females are hormonal contraceptives that are available as combination of estradiol and progestin pills (or) just progestinonly pill/ patches. Oral contraceptive pills are the frequently used class of drugs to prevent pregnancy, as it is the commonest, widest and cheapest way of contraception. Globally, around 59 million women are using oral contraceptives. They are utilized in various form. The main operating principle of combined pill is that it inhibits ovulation. Estrogen inhibits pituitary FSH, which will suppress the ovarian follicles development. Whereas, development of LH will be inhibited via the progestogen. Under the influence of high levels of

these sex hormones, defense mechanisms necessary for the maintenance of good oral health may be compromised. The protection of the subgingival environment is reduced and certain types of bacteria are allowed to multiply.

In women under contraceptives, there is hormone induced changes in the bacterial phenotype and there is preferential accumulation. E.g.:There might be 16-fold higher levels of *Bacteroides* species and 2 to 3-fold increase in the incidence of localized osteitis following extraction of mandibular third molars.⁵⁶ There was decreased concentrations of protein, sialic acid, hexosaminefucose, hydrogen, total electrolytes reported. There is also increased secretion of salivary flow and increased gingival fluid volume predisposing to gingivitis.⁵⁷

The estrogen in the oral contraceptives causes variation in the coagulation and fibrinolytic factors leading to a greater incidence of clot lysis. Studies report that women taking oral contraceptives have no increase in the plaque score, but there was shift in the predominant types of the bacterial flora.⁵⁸ Specifically, there was an increase in the populations of *Prevotellamelaninica* and *Prevotella intermedia*.⁵⁹

Progesterone has been shown to affect the permeability of the micro-vasculature in rat gingiva resulting in edema and the increased accumulation of inflammatory cells, thus demonstrating exaggerated reaction of the body to toxins, created from plaque. Furthermore the production of inflammatory cytokines and prostoglandins, which are known mediators of the inflammatory process, has been shown to increase significantly in the presence of high concentrations of estrogens and progesterone.^{60,61} They also alter the immune system, neutrophil chemotaxis and phagocytosis along with antibody and T-cell responses have been reported to be depressed in the presence of high levels of the ovarian hormones.^{62,63}

Estrogen is the main hormone that has an effect on women's bone metabolism. It controls bone remodeling throughout reproductive life in females. The production of many cytokines is inhibited via estrogen, mostly IL, TNF- α . Interleukins are involved in bone resorption by stimulating osteoclast bone formation and osteoclast bone resorption.^{64,65} Temporomandibular joint abnormalities are also been reported in women under hormonal therapy.

The oral soft tissues have a sensitive response to changes in women sex steroid blood levels.⁶⁵ This is reflected as increased pigmentation of the oral mucosa among oral contraceptive user. As the oral contraceptive pills stimulate hyper secretion of Adrenocorticotrophic (ACTH) and melanocyte stimulating hormone.⁶⁶ Apart from this, ulceration and pyogenic granuloma were also reported in higher percentage among oral contraceptive pills user than non-user group.

5. Conclusion

It is evident from this vast review search in the scientific literature that the endogenous female sex hormones play a vital role in modulating gingival and periodontal health in women. Therefore maintaining the oral hygiene is of utmost importance at every stage of her reproductive life cycle, so to combat the altered response to hormonal influence.

Following are some recommendations to maintain the oral health of women during her reproductive life.

1. Daily oral hygiene practices to remove biofilm at and above the gum-line including brushing twice daily with fluoridated toothpaste.
2. Regular dental check-ups and follow-up examinations.
3. Periodic professional cleaning to remove bacterial plaque biofilm for the anatomical areas where toothbrush will not reach.
4. Replacing the toothbrush every 3–4 months (or sooner if the bristles begin to look frayed), along with interproximal teeth cleaning with floss or interdental cleaner and use of medicated mouthwashes.
5. Maintaining a balanced diet, preventive dental care including controlled intake of fermentable carbohydrates.
6. Enough body hydration and stopping the habit of smoking.

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