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A Randomized Clinical Case-Control Study On The Effects Of Ovulation Induction During Infertility Treatment On Gingival Inflammation

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ABSTRACT

Background: Exogenous sex hormones used in ovulation induction for infertility treatment may influence gingival health. This study evaluated changes in gingival inflammation among women receiving ovulation induction therapy.

Methods: A 6-month case-control prospective parallel design study using purposive non-probability sampling was conducted on 49 women (20–35 years). Test groups received clomiphene citrate (CC) alone, CC+FSH, or CC+HMG. Controls received no induction drugs. Clinical indices—Plaque Index (PI), Gingival Index (GI), and modified Sulcus Bleeding Index (mSBI)—were recorded monthly. Statistical analysis included descriptive (frequency), inferential (mean, standard deviation, ANOVA) methods using SPSS v17.0. One-way ANOVA and post hoc tests were used for group comparisons.

Results: GI and mSBI significantly increased in the test groups—especially in CC+HMG—compared to controls, despite similar PI scores ($p < 0.05$). Test Group I showed GI increases by months 1, 3, and 4, while Group III showed consistent GI and mSBI increases from months 3 to 6. Age and baseline PI, GI, and mSBI values showed no significant intergroup differences, indicating homogeneity at start.

Conclusion: Ovulation induction, particularly CC+HMG, significantly aggravates gingival inflammation. Periodontal monitoring is essential during infertility treatment.

Keywords: *Gingival inflammation, ovulation induction, infertility, clomiphene citrate, gonadotropins*

1. INTRODUCTION

Periodontal endocrinology is an emerging field that explores the influence of systemic hormones, particularly sex steroid hormones, on the periodontium [1]. While their classical roles are associated with reproductive tissues, recent findings have extended their significance to oral tissues.[2] Estrogen and progesterone receptors are expressed in gingival fibroblasts, endothelial cells, and keratinocytes, making gingiva highly responsive to hormonal changes [3,4]. Fluctuating hormone

levels, such as those during puberty, menstrual cycles, pregnancy, or menopause, have been shown to affect vascular permeability, immune modulation, and subgingival microbial composition, leading to increased gingival inflammation [5,6,7].

Research has demonstrated that estrogen enhances nitric oxide-mediated vasodilation and increases capillary permeability through the release of inflammatory mediators, while progesterone may suppress protective immune responses by affecting neutrophil chemotaxis and T-cell function [8,9]. These mechanisms render periodontal tissues more susceptible to inflammatory insults under hormonal influence.

Ovulation induction therapy, commonly employed in infertility treatment, relies on exogenous administration of hormones like clomiphene citrate (CC), follicle-stimulating hormone (FSH), and human menopausal gonadotropin (HMG) [10,11]. Although widely studied for their effects on reproductive outcomes, their implications for gingival health remain underexplored.[12] Previous studies such as those by Haytac et al. and Gursoy et al. indicated a significant increase in gingival inflammation and bleeding upon administration of ovulation drugs, independent of plaque levels [13,14].

The present study was designed to evaluate the periodontal effects of commonly used ovulation induction protocols in women undergoing infertility treatment. It aimed to assess changes in plaque levels, gingival inflammation, and bleeding on probing, using validated indices such as PI, GI, and mSBI, and compare them with a healthy control group.

2. MATERIALS AND METHODS

Overview of Autism Spectrum Disorder

Study Setting and Design:This multicentre, randomized, case-control, prospective parallel design study was conducted over six months at the Department of Periodontics, Sri Ramakrishna Dental College & Hospital and Iswarya Women's Hospital & Fertility Centre, Coimbatore. Ethical approval was obtained, and informed consent was secured from all participants.

Sample:
A total of 49 female patients aged 20–35 years were recruited.

- Inclusion criteria: ≥25 natural teeth, women aged 20–35 years.
    - *Test group:* Women undergoing infertility treatment.
    - *Control group:* Women not undergoing infertility treatment.
- Exclusion criteria: Systemic diseases (e.g., diabetes), recent antibiotic/anti-inflammatory use, recent periodontal therapy, severe periodontal conditions, and reproductive disorders (e.g., PCOS, amenorrhea).

Study Groups:

- Control group: 15 patients.
- Test group (n = 34):
    - *Group I (n=15):* Clomiphene citrate 50 mg twice daily (Day 2–5 of cycle).
    - *Group II (n=7):* Clomiphene citrate + 150 IU FSH (Day 2–5 and 9,11); 3 patients excluded due to drug change.
    - *Group III (n=15):* Clomiphene citrate + 150 IU HMG (Day 2–5 and 9,11).

Armamentarium:
Mouth mirror, William's probe, dental explorer, tweezer, sterile cotton pellets, gloves, surgical mask, head cap.

Gingival Examination:

Conducted monthly for six months by a single examiner on the 14th day of each menstrual cycle (baseline excluded if on 14th day).

- Parameters recorded:
    - Plaque Index
    - Gingival Index
    - Modified Sulcus Bleeding Index

Statistical Analysis

SPSS v17.0; One-way ANOVA and Tukey post hoc. $p < 0.05$ = significant.

3. RESULTS

This prospective case-control study involving 49 women assessed the impact of ovulation induction on periodontal health using PI, GI, and mSBI indices. Groups were comparable in age ($p = 0.211$) and baseline clinical indices (PI: $p = 0.561$; GI: $p = 0.441$; mSBI: $p = 0.306$), confirming group homogeneity.

Across all months, Plaque Index (PI) remained stable with no significant differences between or within groups ($p > 0.05$), indicating consistent oral hygiene.

Gingival Index (GI) revealed significant increases:

- Group I (CC): Significant rise at months 1, 3, 4 compared to control ($p < 0.05$). [Table 1]
- Group III (CC+HMG): Consistently elevated GI from months 3 to 6($p < 0.05$). [Table 3]

Modified Sulcus Bleeding Index (mSBI):

- Group III showed significant increases from months 4 to 6 ($p < 0.05$).

Post hoc comparisons indicated:

- GI: Significant between control and Groups I & III.
- mSBI: Significant between control and Group III.

Within-group comparisons:

- Group I: GI significantly increased from baseline to 3rd month ($p < 0.05$).
- Group III: Both GI and mSBI increased from baseline to 5th month ($p < 0.05$).
- Group II and Control: No significant within-group changes. [Table 2]

Supporting data and statistical outcomes are summarized in the sections that follow.

Table 1. Overall comparisons of test group I (ANOVA)

		Sum of Squares	df	Mean Square	F	Sig.
PI	Between Groups	0.147	4	0.037		
	Within Groups	1.729	48	0.036	1.021	0.406
	Total	1.876	52			
GI	Between Groups	1.600	4	0.400		
	Within Groups	3.800	48	0.079	5.053	0.002*
	Total	5.400	52			
mSBI	Between Groups	0.036	4	0.009		

	Within Groups	0.694	48	0.014	0.615	0.654
	Total	0.729	52			

Table 2. Overall comparisons of test group II (ANOVA)

		Sum of Squares	**df**	**Mean Square**	**F**	**Sig.**
PI	Between Groups	0.108	2	0.054		
	Within Groups	0.124	6	0.021	2.607	0.153
	Total	0.232	8			
GI	Between Groups	0.168	2	0.084		
	Within Groups	0.164	6	0.027	3.064	0.121
	Total	0.332	8			
mSBI	Between Groups	0.016	2	0.008		
	Within Groups	0.141	6	0.024	0.350	0.718
	Total	0.157	8			

Table 3. Overall comparisons of test group III (ANOVA)

		Sum of Squares	df	Mean Square	F	Sig.
PI	Between Groups	0.201	6	0.0333		
	Within Groups	3.058	70	0.044	0.766	0.599
	Total	3.258	76			
GI	Between Groups	1.374	6	0.229		
	Within Groups	4.518	70	0.065	3.549	0.004*
	Total	5.892	76			
mSBI	Between Groups	1.303	6	0.217		
	Within Groups	2.369	70	0.034	6.415	0.000*
	Total	3.672	76			

4. DISCUSSION

Hormonal fluctuations during critical periods in a female's life such as puberty, pregnancy, and menopause significantly impact the periodontium. Sex steroid hormones, including androgens, estrogens, and progesterone, play a crucial role in maintaining homeostasis and modulating inflammatory processes throughout the body. Biochemical and immunological evidence implicates these hormones in the etiology of inflammatory gingival diseases, as periodontal tissues—including endothelial cells, gingival epithelium, connective tissue, periodontal ligament, bone, and cementum—respond to changing steroid hormone levels [15]. During times of marked hormonal fluctuation, such as puberty or pregnancy, the periodontium becomes more reactive, often manifesting as acute inflammatory responses. Elevated levels of sex steroid hormones, whether endogenous or exogenously administered, may adversely affect gingival tissues.

This study investigated the effects of exogenously administered ovulation induction drugs on gingival tissues in women undergoing infertility treatment. Three treatment protocols were assessed: clomiphene citrate (CC) alone; CC combined with follicle stimulating hormone (FSH); and CC combined with human menopausal gonadotropins (HMG). The clinical periodontal parameters measured were plaque index (PI), gingival index (GI), and modified sulcus bleeding index (mSBI), recorded from baseline (before treatment) up to six months.

The study employed a case-control prospective parallel design. Group I (CC alone) included 15 patients initially, receiving 50 mg CC twice daily on days 2–5 of the menstrual cycle; Group II (CC + FSH) had 7 patients with the same CC regimen plus 150 IU FSH intramuscularly on days 9 and 11; Group III (CC + HMG) comprised 15 patients treated with CC and 150

IU HMG on days 9 and 11. Patient numbers decreased over time due to drug protocol changes or pregnancy achievement.

Within Group I (CC alone), PI and mSBI changes from baseline to the 4th month were not statistically significant ($p=0.406$ and $p=0.654$, respectively), but GI showed significant increase at the 3rd month ($p<0.05$). Comparison to controls revealed statistically significant GI differences at months 1 and 3 only, with no significant changes in PI or mSBI. These findings align with Haytac et al. who reported increased gingival inflammation in patients using CC over three cycles despite similar plaque levels [16].

In Group II (CC + FSH), no significant changes in PI, GI, or mSBI were observed within the group or compared to controls from baseline to the 2nd month ($p>0.05$). This contrasts with Haytac et al., who found significant gingival inflammation in similar treatment groups, likely due to the smaller sample size in the present study [16].

For Group III (CC + HMG), PI remained statistically unchanged ($p=0.599$) up to the 6th month, while GI and mSBI significantly increased ($p<0.05$). GI scores were significant up to the 5th month but not the 6th month, likely due to reduced sample size. Similarly, mSBI increased significantly up to the 5th month but not the 6th. Compared to controls, GI was significantly higher at months 3–6, and mSBI was significant at months 4–6, while PI showed no significant difference. These results corroborate Haytac et al., demonstrating increased gingival inflammation without a corresponding increase in plaque in patients on CC + HMG [17].

The study suggests that prolonged exposure to exogenous sex steroid hormones during infertility treatment exacerbates gingival inflammation, likely due to sustained elevated hormone levels affecting periodontal tissues similarly to endogenous fluctuations seen in puberty, pregnancy, and menopause [18,19]. Consequently, rigorous oral hygiene and professional prophylaxis are essential during infertility therapy. Additionally, maintaining periodontal health is critical even after conception, as it may influence successful fetal implantation [20].

Future research incorporating analyses of gingival crevicular fluid, serum, and subgingival microbiota could further elucidate the mechanisms by which exogenous sex steroid hormones affect periodontal tissues.

5. CONCLUSION

Bacterial plaque is the primary cause of periodontal disease, but systemic factors like sex steroid hormones also modify its prevalence, progression, and severity. Significant hormonal changes occur during puberty, the menstrual cycle, pregnancy, and menopause, which are associated with increased gingival inflammation due to alterations in gingival tissue and microbial environment.

This study evaluated the effects of ovulation induction drugs on gingival inflammation in 49 women aged 20–35 undergoing infertility treatment. The test groups were: clomiphene citrate (CC) alone (15 patients), CC combined with follicle stimulating hormone (FSH) (4 patients), and CC combined with human menopausal gonadotropins (HMG) (15 patients). A control group of 15 women not receiving ovulation drugs was included. Clinical parameters—Plaque Index (PI), Gingival Index (GI), and modified Sulcus Bleeding Index (mSBI)—were measured at baseline and monthly on the 14th day of the menstrual cycle for six months.

Results showed statistically significant increases in GI in groups treated with CC alone and CC+HMG, while mSBI increased significantly in the CC+HMG group. Despite similar plaque levels across groups, gingival inflammation and bleeding on probing were elevated in patients receiving exogenous sex steroid hormones.

The findings indicate that ovulation induction drugs influence periodontal tissues, highlighting the need for thorough periodontal assessment and care during infertility treatment. Further research is needed to fully understand hormonal effects on the periodontium.

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