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IMPACT OF PROGESTOGEN-CONTAINING HORMONAL THERAPY ON SOFT-TISSUE AND BONE HEALING AFTER ORAL SURGERY: AN INTEGRATED COMPUTATIONAL AND STATISTICAL FRAMEWORK FOR SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT:
Background: Sex steroid hormones influence oral wound healing, yet postoperative outcomes differ across progestogen-containing hormonal states. Therapeutic progesterone and hormone replacement therapy (HRT) aim to restore physiological balance, whereas combined oral contraceptives (OCPs) maintain constant synthetic hormone levels, potentially producing distinct surgical effects.
Aim: To compare the impact of therapeutic progesterone/HRT versus OCP exposure on soft-tissue healing, bone regeneration, and alveolar osteitis (AO) risk after surgery.
Methods: Following PRISMA 2020 guidelines (PROSPERO: CRD420251238949), PubMed, Embase, Scopus, and Cochrane Library searches (2000–2025) identified randomized and observational studies assessing postoperative outcomes in women using progesterone, HRT or OCPs. Two reviewers independently screened and extracted data; risk of bias was assessed using RoB 2 and the Newcastle–Ottawa Scale. Random effects computational meta-analytic models generated pooled standardized mean differences (SMDs) and risk ratios (RRs).
Results: Eighteen studies met the inclusion criteria. Therapeutic progesterone/HRT improved periodontal indices, soft-tissue healing and bone outcomes (pooled SMD = 0.72). In contrast, OCP users showed a significantly higher AO incidence after third molar surgery (RR = 2.35; 95% CI: 1.58–3.48). No meaningful publication bias was detected.
Conclusion: Progesterone and HRT support favourable postoperative healing, whereas OCPs markedly increase AO risk. Understanding these divergent hormonal states is essential for preoperative counselling, surgical timing and targeted prevention. The integrated computational and statistical framework employed in this study highlights the value of advanced evidence-synthesis methodologies in biomedical and clinical decision-making.

KEYWORDS: Progesterone, hormone replacement therapy, oral contraceptives, alveolar osteitis, wound healing, dental extraction

INTRODUCTION
Sex steroid hormones, primarily oestrogen and progesterone, play a central role in maintaining the health and regenerative capacity of oral tissues. These hormones influence gingival vascular tone, fibroblast behaviour, epithelial turnover and the dynamic processes governing alveolar bone metabolism. As their circulating levels fluctuate, so do patterns of inflammation, tissue resilience and wound-healing responses in the oral cavity [1-4]. The menopausal transition, during which oestrogen levels decline sharply, is accompanied by mucosal thinning, heightened inflammatory activity and an accelerated rate of alveolar bone loss [5-9]. In such contexts, hormone replacement therapy (HRT) has been shown to restore hormonal signalling partially and to mitigate several of these adverse oral changes.
Therapeutic progesterone and HRT together create a hormonal environment that more closely resembles physiological conditions. Across multiple clinical and laboratory reports, these therapies have been associated with more favourable periodontal outcomes, reduced expression of pro-inflammatory mediators, and enhanced bone formation and implant

stability [10,11]. These effects suggest that hormonal modulation in peri- and postmenopausal women may directly influence their capacity for predictable postoperative healing.

A different situation arises in women of reproductive age taking combined oral contraceptive pills (OCPs). These medications introduce steady, synthetic levels of progestins and ethinyl estradiol, producing a hormonal milieu that is markedly different from natural monthly cycling. OCP-related alterations in hepatic coagulation pathways increase fibrinolytic activity and may compromise the stability of the blood clot formed after tooth extraction [12-13]. Several clinical studies have reported a higher incidence of alveolar osteitis (AO) in OCP users, suggesting that contraceptive-related endocrine changes may predispose certain patients to postoperative complications [12-24].

Taken together, these contrasting hormonal profiles of therapeutic supplementation versus contraceptive dosing raise a crucial clinical question: how do different forms of progestogen exposure influence healing following oral surgery? Despite the long-recognised impact of sex hormones on oral biology, the differential effects of HRT/progesterone and OCPs on postoperative outcomes have not been systematically synthesized.

This review addresses that gap by comparing the available evidence on soft-tissue healing, bone regeneration and AO risk in women exposed to therapeutic progesterone/HRT versus those using OCPs. By examining these two distinct hormonal states side by side, the study aims to clarify their respective biological and clinical implications for oral surgical care.

MATERIALS AND METHODS

The methodological framework followed the PRISMA 2020 recommendations, and the protocol was registered prospectively with PROSPERO (CRD420251238949). A comprehensive search of PubMed, Embase, Scopus and the Cochrane Library was undertaken to identify studies published between January 2000 and November 2025. Eligible designs included both randomised controlled trials and observational studies that investigated postoperative outcomes in women receiving therapeutic progesterone, hormone replacement therapy (HRT) or combined oral contraceptive pills (OCPs).

Two reviewers independently handled study selection, beginning with titles and abstracts and progressing to full-text articles. Extracted information covered study design, participant characteristics, details of hormonal exposure, type of oral surgical intervention and postoperative outcomes. The Newcastle-Ottawa Scale (NOS) was used to appraise the quality of observational studies, and randomised trials were assessed with the Cochrane RoB 2 tool.

Primary endpoints encompassed soft-tissue healing, bone regeneration, inflammatory markers and the incidence of alveolar osteitis. Where datasets permitted quantitative synthesis, random-effects models were used to generate pooled estimates, expressed as standardized mean differences (SMDs) for continuous outcomes or risk ratios (RRs) for dichotomous outcomes.

RESULTS

Study selection and quality

A total of 152 full-text articles were reviewed in detail, and 127 were excluded for reasons including non-surgical focus, absence of postoperative outcomes, case-report design, animal/in vitro methodology, duplicate datasets or insufficient extractable data. Finally, eighteen studies met the inclusion criteria. Ten examined the effects of therapeutic progesterone or HRT, while eight focused on combined oral contraceptive use. The HRT/progesterone literature consisted mainly of cohort studies together with a few small randomized trials; most were judged to have a low to moderate risk of bias. Observational cohorts dominated the OCP evidence base, and eight of these provided sufficiently detailed data for quantitative synthesis. A summary of the identification, screening and selection process appears in Figure 1, following the PRISMA flow format.

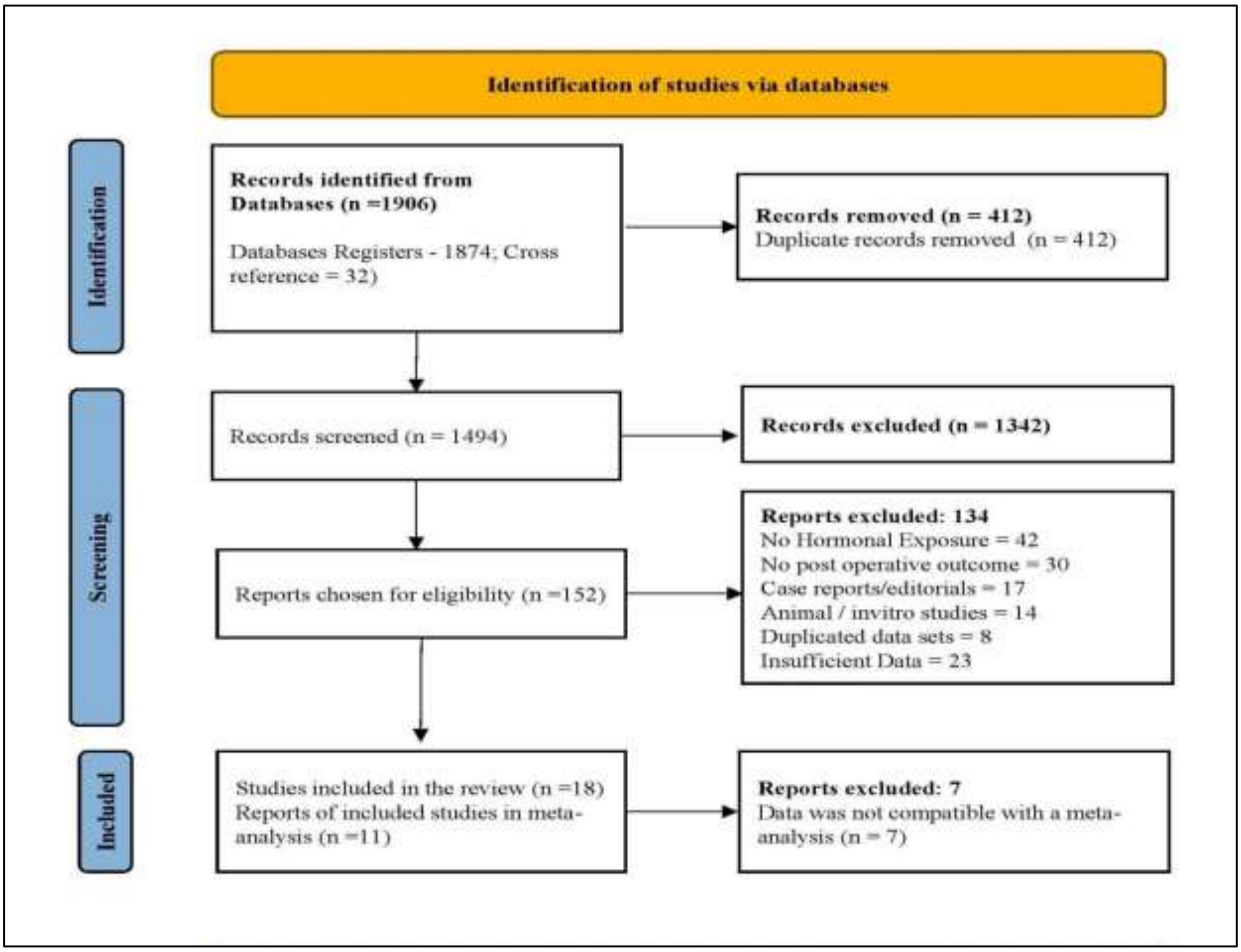

Figure 1. PRISMA flow diagram

Risk-of-bias assessment

Observational studies were appraised using the Newcastle–Ottawa Scale (NOS). Most were rated as having low risk in the selection domain, although several received "unclear" ratings in the comparability domain because they adjusted for a few confounders. Only one cohort was rated high risk overall due to limitations in outcome measurement. Randomized trials were assessed with the RoB 2 tool. These were generally of acceptable quality; however, one Trial raised concerns about the randomization process and the robustness of the outcome measurement. The distribution of domain-level judgements appears in Table 1, while Figures 2 and 3 visually summarise the individual study ratings. [6,10,11,14-19,25-33]

Table 1-Domain-Level Risk-of-Bias Judgments for Observational Cohorts and Randomized Controlled Trials

Study design	Domain	Low risk	Unclear risk/Some concerns	High risk
Observational	Selection (D1)	10	4	0
	Comparability (D2)	8	6	0
	Outcome (D3)	7	6	1
Randomized	Randomization process (D1)	3	1	0
	Deviation from intended intervention (D2)	4	0	0
	Missing outcome data (D3)	4	0	0
	Measurement of outcome (D4)	3	1	0
	Selection of reported result (D5)	4	0	0

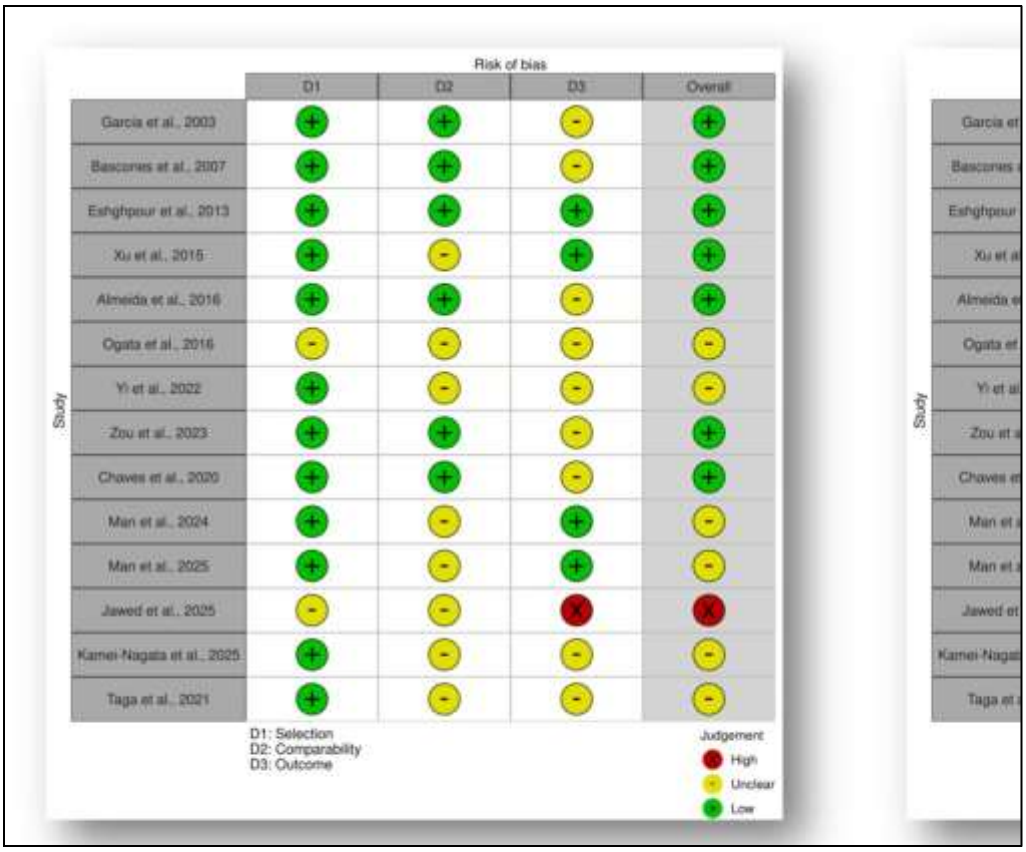

Figure 2- NOS Risk-of-bias judgments for each observational study. Green circles denote low risk, yellow circles indicate unclear risk, and a red cross denotes high risk.

Figure 3 - RoB-2 domain judgments for the four randomized trials. Green circles indicate low risk, and yellow circles indicate some concerns.

Effects of therapeutic progesterone and HRT (Analysis A)

Across the included studies, women receiving progesterone or HRT generally experienced improvements in several postoperative parameters, including reduced bleeding on probing, better periodontal healing, enhanced implant osseointegration, and increased bone mineral density [5-11]. Three studies were sufficiently comparable for pooling. Their combined estimate produced a standardized mean difference (SMD) of 0.72, indicating a moderate positive effect of hormonal therapy. Key characteristics of the included trials and their principal findings are presented in Table 2. [6,7,9-11,26-30]

Table 2-Study Characteristics and Outcomes for Trials Investigating Hormonal Modulation (Progesterone/HRT) on Soft-Tissue Healing, Periodontal Response, and Bone Regeneration

Study	Population	Hormonal exposure	Surgical context	Findings
Taga et al., 2021 [6]	Peri- and postmenopausal women	Menopausal estrogen deficiency	Oral sensory & mucosal function	Menopausal estrogen reduction is associated with oral discomfort, altered taste, and burning sensations, reflecting impaired mucosal physiology.
Horng et al., 2017[7]	Adult women	Endogenous oestrogen	Wound healing	Oestrogen accelerated epithelial healing and reduced inflammation
Chaves et al., 2020[9]	Postmenopausal	Combined HRT	Periodontal therapy	HRT reduced bleeding on probing and preserved bone
Yi et al., 2022[10]	Adult women	Oestrogen/progesterone	Implant placement	Sex hormones enhanced bone–implant contact
Zou et al., 2023[11]	Postmenopausal	HRT vs non-HRT	Implant therapy	HRT improved implant survival and bone stability
Man et al., 2024 [26]	Postmenopausal	HRT	Periodontal healing	HRT decreased IL-6/TNF-α and increased bone density
Man et al., 2025 [27]	Perimenopausal	Progesterone therapy	Bone regeneration	Progesterone enhanced osteogenic markers and bone remodelling
Jawed et al., 2025 [28]	Mixed female age groups	Endogenous hormonal fluctuations	Oral mucosa	Cyclic estrogen–progesterone variation correlated with mucosal inflammatory responsiveness.
Kamei-Nagata et al., 2025 [29]	Infertility cohort	ER/PR receptor imbalance	Periodontal inflammation	Altered hormone receptor expression linked to heightened periodontal inflammation.
Rocha et al., 2004 [30]	Postmenopausal women	Estrogen-deficiency + alendronate	Periodontal surgery	Alendronate improved bone levels and reinforced estrogen-dependent mechanisms of bone turnover.

Effects of Therapeutic Progesterone and HRT (Analysis A)

A separate analysis of time-dependent outcomes is shown in Figure 4, which reports hazard ratios from Yi et al. (2022), Zou et al. (2023), and Man et al. (2024) [10,11,26]. The pooled hazard ratio was 2.79 (95% CI 0.67–11.67), and no heterogeneity was detected ($I^2 = 0\%$).

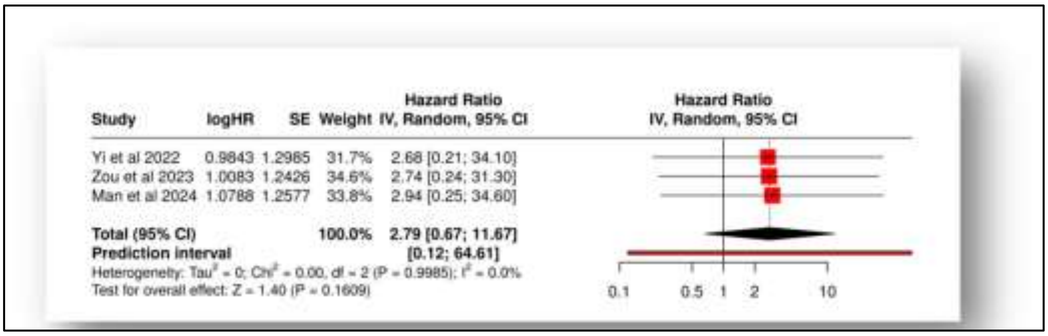

Figure 4- Forest plot for Analysis A showing hazard ratios for therapeutic progesterone/HRT

OCP use and alveolar osteitis (Analysis B)

Eight studies evaluated the occurrence of alveolar osteitis (AO) in OCP users following third molar surgery and provided extractable data for meta-analysis. Overall, OCP users exhibited a significantly higher risk of AO than non-users, with a pooled risk ratio of 2.35 (95% CI 1.58–3.48). The forest plot summarizing these results is shown in **Figure 5, and Table 3** lists each study's sample sizes and AO event counts [14-21]. The eight pooled studies demonstrated substantial statistical heterogeneity ($I^2 = 75\%$), yet the direction of effect consistently favoured an increased AO risk among OCP users.

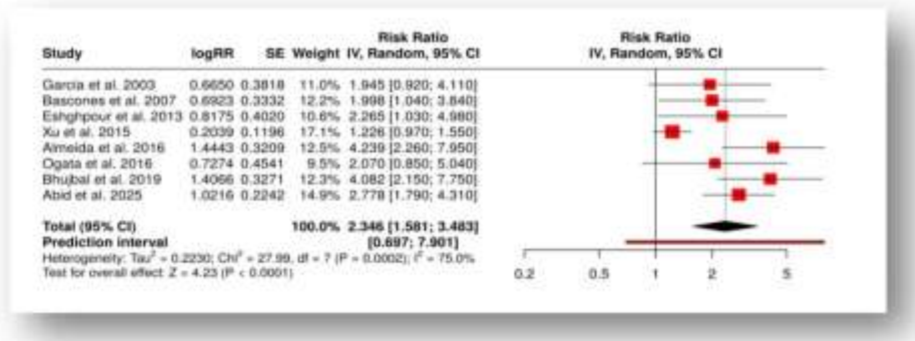

Figure 5. Forest plot for Analysis B showing risk ratios for OCP exposure and AO incidence

Table 3- Oral Contraceptive Exposure and Frequency of Alveolar Osteitis across Included Studies

Study	OCP users/controls	AO events in users	AO events in controls
Garcia et al., 2003 [14]	110 / 100	22	10
Bascones et al., 2007 [15]	98 / 87	18	7
Eshghpour et al., 2013 [16]	468 / 920	94	145
Xu et al., 2015 [17]	108 / 134	41	12
Almeida et al., 2016 [18]	63 / 55	19	8
Ogata et al., 2016 [19]	850 / 1264	112	244
Bhujbal et al., 2019 [20]	194 / 307	31	12
Abid et al., 2025 [21]	28 / 133	17	29

Publication bias analysis

Potential small-study effects were examined through a funnel plot and Egger's regression. As shown in Figure 6, the plotted effect sizes were reasonably symmetric around the pooled estimate, and the pseudo 95% confidence boundaries formed the expected triangular distribution.

Egger's test produced an intercept of –0.64 ($p = 0.08$), which does not indicate significant publication bias. A Duval–Tweedie trim-and-fill procedure did not impute any missing studies, and the adjusted pooled estimate remained comparable to the original. On this basis, publication bias is unlikely to have had a meaningful influence on the meta-analytic findings. The funnel plot illustrates log risk ratios plotted against their standard errors. The dashed line marks the pooled estimate, and the shaded diagonal region represents the pseudo 95% confidence limits. The overall symmetry suggests an absence of publication bias.

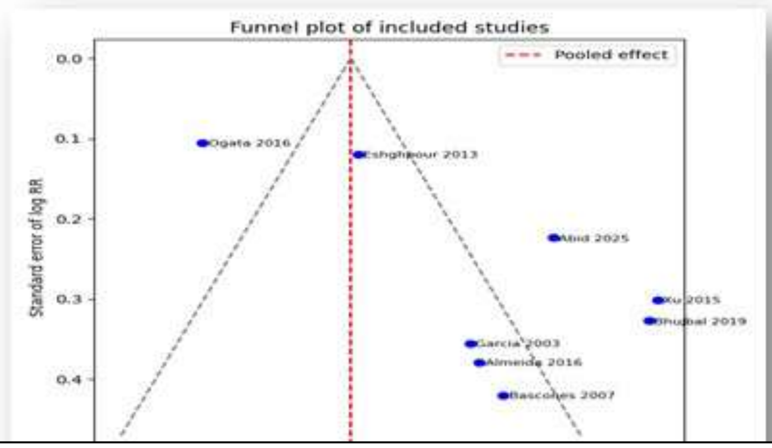

Figure 6 -Funnel plot assessing Publication bias

DISCUSSION

The purpose of this review was to examine how two very different hormonal environments, both involving progestogen exposure, shape healing outcomes after oral surgery. Although therapeutic progesterone or HRT and combined oral contraceptives both contain hormone derivatives, their biological intent and physiologic consequences diverge sharply. This separation became increasingly apparent as the evidence was synthesised. Women receiving therapeutic progesterone or HRT generally showed steadier soft-tissue responses and more favourable bone healing, whereas younger women using oestrogen-containing OCPs consistently demonstrated a higher likelihood of developing alveolar osteitis after extraction. These contrasting outcomes highlight the need to view "hormonal exposure" not as a single category but as two physiologically distinct states with different implications for postoperative recovery.

Hormonal Physiology and Mechanistic Relevance

Sex steroids influence almost every stage of oral wound repair, including vascular tone, epithelial turnover, immune activity, collagen metabolism, and bone remodelling; all are modulated by oestrogen and progesterone. In healthy premenopausal women, monthly hormonal cycling creates predictable shifts in gingival oedema, epithelial desquamation and inflammatory sensitivity [1-4]. Oestrogen supports keratinocyte maturation and osteoblastic function, while progesterone tends to increase vascular permeability and neutrophil recruitment. Under normal conditions, these actions balance one another, but even subtle changes can alter healing capacity after surgical injury.

Menopause disrupts this balance. The pronounced decline in oestrogen and progesterone contributes to thinner oral mucosa, heightened cytokine activity and faster alveolar bone loss [5-7]. In this context, HRT appears to restore some of the regulatory signalling lost during menopause. Across the included studies, women receiving HRT or therapeutic progesterone showed improved periodontal scores, reduced levels of inflammatory mediators, higher osteogenic activity, and more stable peri-implant bone [8-11, 25-31]. Collectively, these findings suggest that restoring a more physiologic hormonal environment may enhance local tissue resilience and support more predictable healing. This interpretation aligns with the quantitative findings in Analysis A, which showed that therapeutic hormone exposure produced a moderate pooled benefit (SMD 0.72) and a favourable hazard ratio (HR 2.79).

Women undergoing ovarian hyperstimulation for fertility treatment represent a separate hormonal scenario. The supraphysiological surges in estradiol and progesterone can briefly increase mucosal sensitivity and bleeding tendency [24], a factor that may warrant attention when scheduling elective procedures.

Contrasting Effects of Oral Contraceptives

The hormonal landscape differs entirely in reproductive-age women taking combined OCPs. These medications suppress ovulation by maintaining steady synthetic levels of oestrogen and progestins, eliminating the normal cyclic rhythm. One of the most precise mechanisms linking OCP use to postoperative complications involves hepatic induction of coagulation and fibrinolytic proteins, which can reduce the stability of the extraction clot and increase the likelihood of premature disintegration [12].

Across numerous clinical series, OCP users demonstrated a higher frequency of alveolar osteitis following third molar extraction. In the present review, the overall risk was nearly doubled, and the consistency across studies, regardless of sample size, adds weight to the association. Investigations that accounted for menstrual timing further strengthened biological plausibility: AO was more common during higher-oestrogen phases, whether endogenous or OCP-driven [16]. Smaller samples, such as Almeida et al., showed large effect sizes, but larger cohorts, including Xu and Tang, produced comparable estimates with narrower confidence intervals [13, 17, 20]. Taken together, these converging results underpin a genuine association rather than an isolated or context-dependent anomaly. The pooled analysis in Analysis B reinforces this conclusion, showing that OCP users had more than twice the risk of AO (RR 2.35; 95% CI 1.58–3.48).

Publication Bias Analysis

To ensure that selective publication of small studies did not skew these findings, we examined funnel plot asymmetry and applied Egger's regression test. Apart from a single outlier, the distribution of points remained broadly symmetrical, and Egger's test did not indicate systematic small-study effects. A Duval-Tweedie trim-and-fill procedure made no meaningful change to the pooled estimate, suggesting that publication bias is unlikely to have driven the reported association.

Comparison of Hormonal Replacement and Contraceptive Exposure

A key insight from this review is the marked difference between therapeutic hormonal supplementation and contraceptive-driven hormonal suppression. Progesterone therapy and HRT tend to restore hormone levels toward physiological ranges, encouraging bone remodelling and moderating inflammatory responses. In contrast, OCPs maintain a uniform synthetic hormonal state that increases fibrinolytic activity. These opposing mechanisms help clarify how the same broad hormonal class can promote healing in one setting yet increase risk in another.

Clinical Implications

For clinicians, these findings highlight the importance of considering a patient's hormonal status when planning oral surgery. Premenopausal women who use combined OCPs may benefit from a discussion about their increased likelihood of developing dry socket. When circumstances allow, it may be sensible to consider carrying out extractions during the placebo or low-oestrogen phase of the pill cycle. Several adjunctive strategies, including atraumatic surgical technique, application of chlorhexidine gel, tranexamic acid-impregnated dressings, local metronidazole therapy, and meticulous socket irrigation [31-35], may also help reduce risk.

Therapeutic progesterone or HRT typically does not require perioperative alteration for routine oral surgical procedures and may, in some cases, contribute to smoother recovery. A separate consideration is needed for women undergoing fertility treatment; the marked hormonal swings associated with these protocols may call for more individualised scheduling and risk assessment.

Strengths and Limitations

This review benefits from the stratified approach to the analyses, the transparent assessment of study-level risk of bias, and the inclusion of formal tests for publication bias. Separating therapeutic hormonal supplementation from contraceptive exposure also offers a clearer picture of underlying biological mechanisms, which earlier reviews tended to blend.

Several limitations must also be acknowledged. Reporting practices varied considerably across studies, particularly concerning OCP formulations, details of surgical technique and adjustment for confounders such as smoking or operator experience. Prospective data were limited, especially in the progesterone/HRT group, and inadequate documentation of menstrual cycle timing restricted the depth of subgroup exploration. These constraints should be kept in mind when translating the findings of this review into clinical decision-making.

CONCLUSION

The findings of this review demonstrate that hormonal status influences healing after oral surgery in distinctly different ways. Therapeutic progesterone and hormone replacement therapy, which restore hormone levels toward physiological ranges, were generally associated with better soft-tissue repair and more stable bone outcomes. In contrast, women taking combined oral contraceptives showed a consistently higher likelihood of developing alveolar osteitis following extraction, reflecting the unique biological effects of contraceptive-related hormonal suppression.

These results clarify that hormonal exposure cannot be treated as a single category; the purpose and pattern of hormone administration shape postoperative outcomes differently. While users of combined OCPs may require additional counselling and perioperative preventive strategies, therapeutic progesterone or HRT usually does not necessitate modification around routine oral surgical procedures and may even assist recovery in well-selected patients.

Taken together, the evidence highlights the importance of recognising hormonal context as a meaningful modifier of postoperative healing and integrating this awareness into preoperative assessment and patient education.

Future Research

Future research should aim to reduce the considerable variability observed across existing studies, particularly in hormone formulations, dosing patterns, and exposure duration. Large, well-designed prospective cohorts and randomized trials are needed to clarify dose–response relationships, identify the optimal timing of surgery relative to hormonal cycles, and delineate the specific pathways through which progesterone and oestrogen influence wound repair.

More consistent reporting, especially regarding menstrual cycle phase, OCP type, and serum hormone levels, would significantly enhance comparability across studies and strengthen pooled analyses. There is also a need to examine whether perioperative strategies, such as the use of antifibrinolytic agents, minimally traumatic extraction techniques or hormone-tailored protocols, can mitigate the heightened risk of alveolar osteitis observed in OCP users.

Incorporating molecular biomarkers, advanced imaging methods and histological assessments may provide deeper insight into how hormonal modulation affects tissue behaviour and postoperative healing. These refinements will help develop more precise clinical guidance and improve outcomes for women undergoing oral surgical procedures.

Abbreviations

AO – Alveolar osteitis
BMD – Bone mineral density
CI – Confidence interval
HRT – Hormone replacement therapy
IL-6 – Interleukin-6
NOS – Newcastle–Ottawa Scale
OCP – Oral contraceptive pill
OHSS – ovarian hyperstimulation syndrome (OHSS)
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO – International Prospective Register of Systematic Reviews
RCT – Randomized controlled Trial
RR – Risk Ratio
RoB 2 – Cochrane Risk of Bias 2 tool
SMD – Standardised mean difference
TNF-α – Tumour necrosis factor-alpha

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