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Pregnancy-Related Effects on Oral Wound Healing and Implant Osseointegration

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Abstract

The purpose of the study was to assess the impact of pregnancy on the healing of oral wounds and the early implant osseointegration in a rabbit model. Rabbits were randomly allocated into pregnant and non-pregnant control, extraction, and immediate implant placement groups. Clinical healing was measured at days 3, 7, 14 and 28. Epithelialization, collagen deposition, angiogenesis and inflammatory response were assessed through histological analysis. The resonance frequency analysis (RFA) was used to measure the stability of implants and the histomorphometric bone-to-implant contact (BIC) was measured. The level of oxidative stress was measured by spectrophotometric methods such as malondialdehyde (MDA) and glutathione peroxidase (GPx). Throughout all groups, progressive healing of wounds was observed over time, and full mucosal cover was noted in all groups at day 14. Implant stability and BIC values increased significantly during the healing period ($p < 0.001$). The highest MDA levels were observed on day 3 and gradually declined over time, whereas GPx activity peaked on day 14 before returning toward baseline values. Significant differences were observed between pregnant and non-pregnant groups in most evaluated parameters ($p < 0.05$), indicating that pregnancy influenced healing dynamics and early implant osseointegration. Within the limitations of this experimental rabbit model, pregnancy appeared to influence oral wound healing and early implant osseointegration through modulation of angiogenesis, immune response, and oxidative stress regulation. These findings highlight the importance of systemic physiological conditions in peri-implant healing dynamics.

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Introduction

Healing of oral wounds is a complicated and highly controlled biological procedure that consists of a series of events comprising inflammation, proliferation and remodeling of tissues. It is controlled by dynamic interactions of epithelial cells, fibroblasts, osteoblasts, immunomediators and vascular elements. The success of osseointegration in implant dentistry is not only determined by the local surgical conditions, but also by the systemic physiological factors, which affect bone remodeling, angiogenesis and immune homeostasis [1,2].

Pregnancy is a special systemic condition that is characterized by significant hormonal, vascular and immunological changes. Inflammatory processes and endothelial permeability, as well as an immune-tolerant environment via immune pathway manipulation, are affected by increased levels of estrogen and progesterone [3,4].

Hormonal variations have been associated with alterations in soft tissue repair, bone turnover, and regenerative capacity. Surgical interventions such as tooth extraction are associated with tissue trauma and inflammatory responses that may influence healing outcomes [5]. The control of bone remodeling, that is the process whereby bone is continuously remodeled throughout life, is also crucial for the process of healing of the tissues surrounding the implant and for the early physiological changes induced by estrogen, which can stimulate the

osteoblastic activity and implant fixation. Simultaneously, oxidative stress is an obligatory part of the healing process: reactive oxygen species are involved in initiating inflammatory responses, and antioxidant mechanisms like glutathione peroxidase aid in keeping the oxidative damage under control and allow healing processes [2,6,7].

Importantly, few experimental studies have simultaneously evaluated soft tissue healing, implant stability, bone-to-implant contact, and oxidative stress biomarkers within a controlled pregnancy model. Moreover, direct comparative evidence between pregnant and non-pregnant conditions remains limited and incompletely understood, particularly in integrated experimental designs [1,8].

Therefore, this study aimed to evaluate the effect of pregnancy on oral wound healing and early implant osseointegration in a rabbit model, using a comprehensive approach that integrates clinical, histological, histomorphometry, and biochemical assessments. Few studies have simultaneously evaluated clinical healing, implant stability, bone-to-implant contact, and oxidative stress in pregnancy-associated implant healing models.

Materials and Methodos

This was a controlled experimental in vivo study designed to evaluate the effect of pregnancy status (pregnant vs. non-pregnant) on oral wound healing and early implant osseointegration in a rabbit model. The research was comparative in nature and involved clinical, histological, histomorphometric, and biochemical measurements at specified intervals of healing.

Ethical approval for the experimental animal study was granted by the Institutional Animal Care and Use Committee (IAC of experimental animals) (Approval No. 126/2025). The experimental study was carried out in such a way to minimize possible discomfort or pain to animals, and the study was designed according to the three R's (Reduce, Refine and Replace) and kept to a minimum number of animals possible.

Animals were randomly allocated into six experimental groups (n = 6 per group):

- Group I: Pregnant control (no surgical intervention)
- Group II: Pregnant extraction
- Group III: Pregnant extraction with immediate implant placement
- Group IV: Non-pregnant control (no surgical intervention)
- Group V: Non-pregnant extraction
- Group VI: Non-pregnant extraction with immediate implant placement

Animals in the extraction and implant groups were further evaluated at different healing time points (days 3, 7, 14, and 28).

Pregnancy of the animals was confirmed by controlled mating as well as by regular checks of the animals by a veterinarian. To minimize physiological variations of early- and late- term pregnancy, surgery was performed in the mid-gestational period of pregnancy of the animals. Six animals were included in each experimental group. Clinical healing and implant stability were longitudinally evaluated in the same animals throughout the study period. For histological and biochemical analyses, two animals from each group were sacrificed at days 7, 14, and 28.

All surgical procedures were performed under general anesthesia using ketamine (35 mg/kg, intramuscular) and xylazine (5 mg/kg, intramuscular).

Atraumatic extraction of the maxillary premolar was carried out using a minimally invasive technique to preserve the surrounding bone and soft tissue.

In the implant groups, commercially pure titanium implants (Dentium®, South Korea; sandblasted acid-etched surface; 2 mm diameter × 6 mm length) were immediately placed into the extraction sockets following a standardized drilling protocol under copious saline irrigation. Controlled insertion torque was applied to achieve primary implant stability. The resorbable sutures (5-0) were used to close the surgical sites.

Surgical treatment was followed by analgesic (meloxicam, 0.2 mg/kg subcutaneously) and infection prevention (enrofloxacin 5mg/kg subcutaneously) drugs.

The efficacy of clinical healing was evaluated at days 3, 7, 14, and 28 depending on: wound closure, edema, erythema, and signs of infection. The progression of healing was assessed qualitatively with the parameters of epithelialization and inflammation resolution.

Stability of implants was determined through resonance frequency analysis (RFA) at 3-, 7, 14, and 28 days. The values of implant stability quotient (ISQ) were noted.

Tissue samples were processed and analyzed for re-epithelialization, inflammatory cell infiltration, neovascularization, and collagen deposition and maturation.

Histological assessment was performed using a semi-quantitative scoring system. All histological sections were evaluated by a blinded examiner to minimize observational bias. Tissues were analyzed for degree of inflammation, neovascularization, collagenization and for degree of tissue maturation. All the above parameters were scored on a four-point scale from 0 to 3. 0 = absent, 1 = mild, 2 = moderate, 3 = severe/intense. Bone-to-implant contact (BIC) was determined by histomorphometry. BIC was calculated as a percentage of BIC of the total surface area of the implants using ImageJ software.

Extraction and peri-implant sites were homogenized tissue samples that were collected at days 7, 14 and 28 and evaluated on oxidative stress parameters malondialdehyde (MDA), indicator of lipid peroxidation, and glutathione peroxidase (GPx), a marker of antioxidant activity.

Measurements were performed using standard spectrophotometric methods.

The obtained values were normalized to total protein content and expressed as GPx (U/mg protein) and MDA (nmol/mg protein).

Data analysis was performed by means of IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). All data from the experiments were presented as mean values ± standard deviation (SD). The data was checked for normal distribution using the Shapiro-Wilk test. The two-way ANOVA was used to test the effect of pregnancy status, of healing time and of their interaction on the analyzed parameters. If there were any significant main or interaction effects, the variables were compared between the groups using the Tukey's test. The repeated measures from the same animals were analyzed using the repeated-measures two-way ANOVA. In addition to p-values, the partial eta squared (η^2) and 95% confidence intervals (95% CI) of the significant effects were calculated to assess the magnitude and the precision of the found differencese.

Results

There were no postoperative complications in all animals, and they survived the surgical operations. Partially wound closure and mild edema as well as erythema were seen at day 3 in both pregnant and non-pregnant groups. By day 7, progressive epithelialization occurred and full coverage of the mucosa by day 14. The normal mucosal architecture was recovered by day 28.

Healing progression appeared more advanced in the pregnant groups, with earlier inflammatory resolution and improved tissue organization compared with non-pregnant animals.

There was an increased implant stability with time in both non-pregnant and pregnant groups ($p < 0.001$). Nevertheless, much greater values of implant stability quotient (ISQ) were found in the pregnant group at all periods ($p < 0.05$).

Data are presented as mean ± SD. Statistical analysis was performed using two-way ANOVA followed by Tukey's post hoc test. Differences were considered statistically significant at $p < 0.05$.

Two-way ANOVA found that there was a significant impact of pregnancy status, time, and their interaction on the measured parameters ($p < 0.05$).

Bone-to-implant contact (BIC) values progressively increased throughout the healing period in both experimental groups. The pregnant group indicated considerably high values of BIC at all the time points that were assessed in comparison to the non-pregnant group ($p < 0.05$).

The GPx activity significantly improved with time in both groups ($p < 0.001$) and was highest on day 14. The pregnant group demonstrated significantly higher GPx activity compared with the non-pregnant group ($p < 0.05$), indicating an enhanced antioxidant response.

At day 3 MDA was the highest and it reduced considerably over time in both groups ($p < 0.001$). The level of MDA in the pregnant group was significantly lower than non-pregnant group ($p < 0.05$) indicating less oxidative stress.

Effect size for the given data was quantified and depicted as partial eta squared (η^2). Cohen (1977, 1988) defined the following thresholds for sample sizes of this order for the partial eta squared: An η^2 of 0.01 corresponds to a small effect, 0.06 corresponds to a moderate effect and 0.14 corresponds to a large effect. For the present data 95% Confidence Intervals were calculated as well.

The histological parameters of healing tissue of pregnant animals were in an earlier phase of the inflammatory resolution process and there was a higher degree of collagenization, and mature tissue formation compared with the parameters of non-pregnant control animals.

The inflammatory response to cellular infiltration was observed at early times in both groups, but in the pregnant group, inflammation was resolved earlier. This reaction can also be affected by the trauma connected to surgeries during extraction (Salih et al., 2021). Histological differences between groups were interpreted within the limitations of semi-quantitative tissue assessment.

On day 28, the pregnant group exhibited a good organization of bone formation and had more bone-to-implant contact, as compared to the non-pregnant group which exhibited relatively retarded maturation (Table 6).

The analysis of the two-way ANOVA showed that the variables of pregnancy status, time, and their interaction had significant effects on the level of implant stability, bone-to-implant contact and oxidative stress indicators ($p < 0.05$).

Discussion

This experimental study aimed to find out the effects of physiological and hormonal changes of pregnancy on oral wound healing and the early phases of implant osseointegration. Pregnant animals and their non-pregnant counterparts were included in the study. The results of the study revealed positive correlation between pregnancy and healing. The findings of the study related to the implant stability, bone to implant contact and the degree of tissue organization and oxidative stress of the early peri-implant wound of pregnant animals were superior to those of the non-pregnant animals. These findings support the hypothesis of the study that the hormonal and immunological changes of pregnancy affect the healing of the peri-implant tissue.

The pattern of healing that was observed adhered to the classical stages of inflammation, proliferation and remodeling but the processes proceeded and were more intense in one group than in the other. In the current research, the pregnant group had the more developed healing properties, such as earlier epithelialization, better tissue organization and bone formation. These results indicate that physiological modifications in the biological environment during pregnancy alter the system to bias tissue repair and regeneration. This aligns with the prior data that structures changes in pregnancy due to the hormonal and vascular adaptations may affect the process of tissue healing [3,4].

However, pregnancy-associated hormonal changes may exert both beneficial and adverse effects depending on local and systemic inflammatory conditions.

During the healing period. The values for the pregnant animals showed a significant increase in the ISQ values throughout the whole measuring period. The same applies for the non-pregnant animals. As already mentioned, the stability of an implant is determined by the process of healing of the soft tissues as well as the process of remodeling of the bone. As a result of the healing process an increased formation of peri-implant bone takes place. The above-mentioned biological positive effect of the hormonal changes during pregnancy (estrogen related) most likely caused the higher values for the pregnant animals rather than a negative effect [2,9].

The percentages of the bone-to-implant contact (BIC) of the test groups increased with the healing times but were always higher in the pregnant group. The BIC parameter measures the degree of a direct contact or integration of a structure (in this case the bone) with an implant in the surrounding bone. Thus, it can be stated that the bone of a woman in her increased physiological increased physiological activity during pregnancy gets matured faster in contact with an implant. Increased angiogenesis, the deposition of the extracellular matrix and increased vascular permeability are possibly the main factors for the enhanced bone growth around an implant of a woman in the state of pregnancy. Similar results have been reported in several studies. It is the process of vascularization and the activity of cells which are of major importance for a successful process of osseointegration [10,11].

Oxidative stress markers followed a time-dependent course during wound healing. In the first phase of the repair process, the peak of MDA levels resulted from the acute inflammatory response to tissue damage caused by the surgical procedure. The subsequent peak of GPx activity indicated the beginning of the specific antioxidant defense. MDA levels as well as GPx activity were found to be decreased in wound healing of pregnant compared to non-pregnant animals. In general, the animals of the pregnant group showed a balanced oxidative state during tissue repair. The maintenance of a stable oxidative state within tissue repair is crucial for the protection of cellular structures, for the control of the signaling of the acute inflammatory response and for angiogenesis and collagen maturation [6,7].

The histological examination of healing in pregnant animals went through the different phases of healing, it was noted that in comparison to the non-pregnant animals the transition to the proliferative healing phase occurred earlier. Please note that this study was of a purely descriptive nature and therefore must be treated with caution [3,4]. The study has limitations, as it only included an investigation of the early stages of the healing process, osseointegration, and the long-term phase with respect to the implant's stability and functional loading. In addition, the number of animals included in the study was small, and an experimental model was used. Thus, future studies should include the assessment of the bone-remodeling process and the related inflammatory process by using molecular markers, as well as well as a long-term functional assessment to clarify the effect of pregnancy on the implant's healing process.

Some physiological changes that occur during pregnancy could influence the oral wound healing as well as the early tissues surrounding the dental implant. These changes include the hormonal, the immune as well as the antioxidant changes that are made to cope with the increased oxidative stress during this period. The above factor should therefore be taken into consideration when assessing the early wound healing of oral tissues that have been subjected to dental implant surgery.

Conclusion

The aim of the present experimental study was to assess the effects of pregnancy on oral wound healing as well as on early implant

osseointegration in rabbits. The possible involvement of several parameters, including angiogenesis, immune response and oxidative stress, was considered. The results of the study on pregnant rabbits indicated higher values of implant stability, bone-to-implant contact and a more favorable profile of oxidative stress parameters. The study provided evidence that the changes in the general physiological state could affect peri-implant healing during the healing period when compared to the data obtained from the non-pregnant animals. Therefore, systemic physiological alterations during pregnancy may influence peri-implant tissue healing responses.

Study Limitations

There are several limitations in this study. The study period was not long enough to complete the healing process and to study the initial phase of osseointegration. Also, there were no histological photographs of some of the experimental groups at the different stages of healing.

Further studies incorporating molecular biomarkers and long-term functional assessment are recommended to better clarify the biological effects of pregnancy on peri-implant healing. Long-term functional follow-up studies are still required to better understand the underlying biological mechanisms.

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Table 1. Implant stability (ISQ values).

Time (Days)	Pregnant (Mean ± SD)	Non-pregnant (Mean ± SD)	p-value
Day 3	52.3 ± 3.1	49.8 ± 2.9	0.041
Day 7	58.7 ± 2.8	55.2 ± 3.0	0.036
Day 14	64.5 ± 3.4	60.3 ± 3.1	0.028
Day 28	71.2 ± 2.6	66.8 ± 2.9	0.021

Data are presented as mean ± SD. Statistical analysis was performed using two-way ANOVA followed by Tukey's post hoc test. Differences were considered statistically significant at $p < 0.05$.

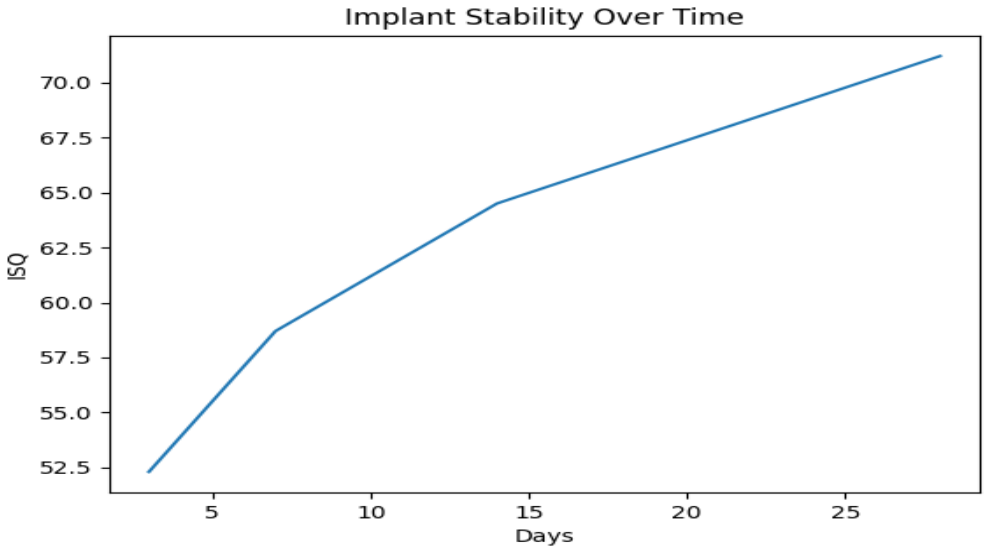

Figure 1. Temporal changes in implant stability quotient (ISQ) values during the healing period in pregnant and non-pregnant groups.

Table 2. Bone-to-implant contact (BIC%).

Time (Days)	Pregnant (%)	Non-pregnant (%)	p-value
Day 7	30.5 ± 4.2	26.9 ± 3.8	0.032
Day 14	54.8 ± 5.1	49.6 ± 4.7	0.027
Day 28	72.3 ± 4.6	66.1 ± 4.3	0.019

Data are presented as mean ± SD. Statistical analysis was performed using two-way ANOVA followed by Tukey's post hoc test. Differences were considered statistically significant at $p < 0.05$.

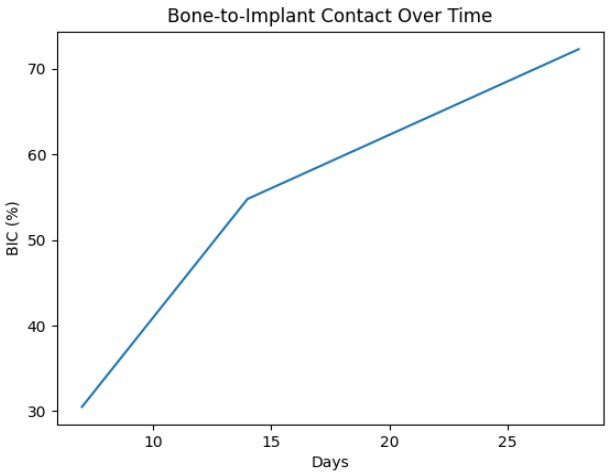

Figure 2. Progressive increase in bone-to-implant contact (BIC%) during the healing period in pregnant and non-pregnant groups.

Table 3. Marks of oxidative stress (GPx and MDA).

Time	GPx Pregnant	GPx Non-pregnant	p-value	MDA Pregnant	MDA Non-pregnant	p-value
Day 3	12.4 ± 1.5	10.8 ± 1.4	0.039	5.8 ± 0.7	6.5 ± 0.8	0.044
Day 7	18.9 ± 1.8	16.7 ± 1.6	0.031	4.2 ± 0.6	4.9 ± 0.7	0.037
Day 14	24.6 ± 2.1	21.8 ± 1.9	0.025	3.1 ± 0.5	3.8 ± 0.6	0.029
Day 28	13.2 ± 1.4	11.5 ± 1.3	0.034	2.6 ± 0.4	3.2 ± 0.5	0.033

Data are presented as mean ± SD. Statistical analysis was performed using two-way ANOVA followed by Tukey's post hoc test. Differences were considered statistically significant at $p < 0.05$.

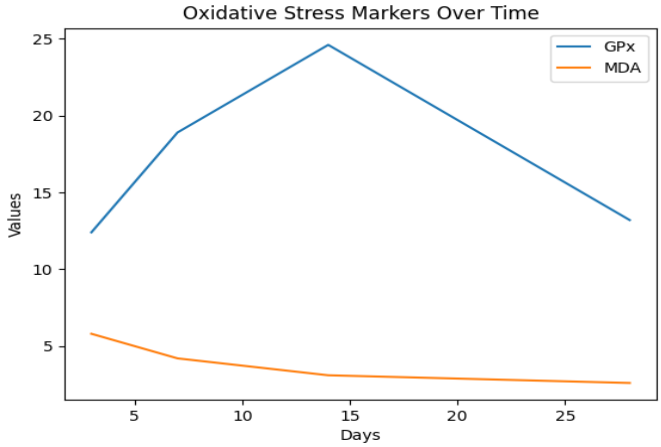

Figure 3. Temporal alterations in oxidative stress markers (GPx and MDA) during oral wound healing and early implant osseointegration.

Table 4. Two-way ANOVA analysis of the effects of pregnancy status, healing time, and their interaction on implant stability, bone-to-implant contact, and oxidative stress markers.

Parameter	Source of Variation	F-value	p-value
ISQ	Pregnancy status	8.42	0.011
	Healing time	46.31	<0.001
	Interaction	4.27	0.018
BIC	Pregnancy status	7.95	0.014
	Healing time	52.74	<0.001
	Interaction	3.88	0.026
GPx	Pregnancy status	6.73	0.021
	Healing time	39.18	<0.001
	Interaction	4.01	0.022
MDA	Pregnancy status	7.26	0.017
	Healing time	41.92	<0.001
	Interaction	3.74	0.031

Table 5. Effect size and confidence interval analysis of major study outcomes.

Parameter	Mean Difference	95% CI	Effect Size (η^2)	Interpretation
ISQ	4.1	1.2 – 6.8	0.34	Moderate-to-large
BIC	5.6	2.1 – 8.9	0.38	Large
GPx	2.4	0.9 – 4.0	0.29	Moderate
MDA	-0.8	-1.4 – -0.2	0.26	Moderate

Table 6. Semi-quantitative histological scores during healing in pregnant and non-pregnant groups.

Group	Day	Inflammation Score	Collagen Deposition	Angiogenesis	Tissue Maturation
Pregnant	7	2.8 ± 0.4^{a}	1.9 ± 0.3^{b}	2.6 ± 0.5^{a}	1.7 ± 0.4^{b}
Non-pregnant	7	3.0 ± 0.0^{a}	1.3 ± 0.4^{c}	1.8 ± 0.4^{b}	1.1 ± 0.3^{c}
Pregnant	14	1.4 ± 0.5^{c}	2.7 ± 0.4^{a}	2.9 ± 0.3^{a}	2.5 ± 0.5^{a}
Non-pregnant	14	2.1 ± 0.4^{b}	2.1 ± 0.5^{b}	2.2 ± 0.4^{b}	1.9 ± 0.4^{b}
Pregnant	28	0.6 ± 0.5^{d}	3.0 ± 0.0^{a}	2.3 ± 0.5^{b}	3.0 ± 0.0^{a}
Non-pregnant	28	1.2 ± 0.4^{c}	2.4 ± 0.5^{b}	1.9 ± 0.3^{b}	2.3 ± 0.5^{b}

p-values (Two-way ANOVA)

Parameter	Pregnancy Status	Healing Time	Interaction
Inflammation	0.018	<0.001	0.027
Collagen deposition	0.011	<0.001	0.021
Angiogenesis	0.024	<0.001	0.034
Tissue maturation	0.009	<0.001	0.018

All parameters were calculated as the mean value ± standard deviation. Histological findings were rated in a semi quantitative fashion using a four point-scale from 0 points (absent) to 3 points (severe/intense). Data were analyzed by two-way ANOVA and subsequently by Tukey's test of comparison of means. Within each graph the superscript letters in each column indicate significant differences between groups as well as between timepoints ($p<0.05$).