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Effect of Sustained Dexamethasone Treatment on Anxiety and Depression-related Behaviors in Pregnant Rats

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Abstract: Dexamethasone, an immunosuppressive drug with 30 times the potency of cortisone, has significant therapeutic potential but may cause adverse effects such as pathological lesions, abortion, and behavioral changes when used at high doses. This study aimed to investigate the optimal dexamethasone dose to positively affect anxiety and depressive behaviors in pregnant rats. A total of 72 female Wistar rats (4 months old, 250±20 g) were divided into four groups: control pregnant, control nonpregnant, pregnant with two dexamethasone doses (625 and 1250 µg/kg body weight), and nonpregnant with the same doses (n=6 per subgroup). Anxiety- and depression-related behaviors were assessed via open-field and forced-swim tests, and blood parameters were assessed. Compared with that of control rats, the immobility period of 125×10 µg-treated rats was shorter, indicating improved behavioral outcomes. However, the 625 µg dose caused mild neural necrosis, thrombotic vasculitis, and spleen infiltration with red blood cells. Mild lymphopenia was observed at this dose compared with that of the controls. Overall, a 625 µg dose administered for 14 days to pregnant and nonpregnant rats was identified as an effective therapy for mitigating anxiety and depression-like behaviors while minimizing adverse effects.
Keywords: Dexamethasone, Immunosuppressive therapy, Anxiety and depression-like behaviors, Lymphopenia

1. Introduction

Over the past decade, immunosuppressive drugs have become pivotal in managing a wide array of medical conditions [1]. Among these, dexamethasone—a synthetic corticosteroid approved by the FDA in 1958—stands out as a highly potent and versatile immunosuppressive agent. With approximately 30 times the potency of cortisone and a prolonged duration of action lasting 2–3 days, dexamethasone is widely employed in clinical practice [2]. Dexamethasone, a potent synthetic corticosteroid with prolonged activity, is widely used in clinical practice to manage inflammatory and autoimmune conditions such as arthritis [3], allergic reactions [4], skin and eye diseases [5, 6], gastrointestinal disorders [7], cancers [8, 9], and immune system dysfunctions [10].

The therapeutic role of dexamethasone gained further prominence during the COVID-19 pandemic because of its ability to modulate angiotensin-converting enzyme 2 (ACE2) receptor pathway, potentially reducing viral entry into host cells and alleviating inflammatory responses associated with severe disease [11–14]. However, while its benefits are well-established, dexamethasone is not without significant adverse effects. Prolonged or high-dose use has been linked to complications such as depression [15,16], ocular hypertension [17, 18], diabetes [19], growth retardation, and pathological lesions, including brain trauma [20] and oxidative stress in resistant arterioles [21]. In addition, dexamethasone has detrimental effects on the thymus and bones [19], further complicating its therapeutic profile.

Pregnancy introduces unique physiological challenges that can amplify or modify the effects of dexamethasone. In animal studies, dexamethasone administration during pregnancy has been associated with adverse outcomes such as increased risk of abortion, fetal growth restriction, and altered maternal metabolic profiles [22,23]. These effects are thought to result from the profound impact of the drug on the hypothalamio-pituitary-adrenal (HPA) axis, which plays a critical role in maintaining pregnancy and regulating stress responses. Dexamethasone therapy may lead to outcomes such as fetal growth restriction, altered maternal metabolic profiles, and immune modulation. Additionally, differential effects on behavior and immune function have been observed in pregnant versus nonpregnant animals, underscoring the influence of reproductive status on the drug's pharmacodynamics.

Understanding the multifaceted effects of dexamethasone,

particularly in the context of pregnancy, is essential for optimizing its therapeutic use while mitigating potential risks. Rats were chosen for this study because they are easier to handle, exhibit less stress, or are more tolerant than are mice [24, 25]. The Wistar strain, which is commonly used in medical research, was selected for its relatively high activity levels [26].

This study aimed to investigate the dose- and duration-dependent effects of dexamethasone on physiological, behavioral, and hematological parameters in pregnant and non-pregnant Wistar rats. The research specifically examines the impact of high and low doses of dexamethasone administered for 7 or 14 days on anxiety- and depression-related behaviors, as well as selected hematological variables. Thus, the treatment window overlaps significantly with the second and third trimesters, allowing the study to examine effects during these critical periods of fetal development. The study's goal was to provide deeper insights into the implications of dexamethasone use during pregnancy and to contribute to a better understanding of its effects on both maternal and non-pregnant physiological and behavioral outcomes.

2. Materials and methods

2.1. Animals and Management

The experiments were carried out at the Experimental Animals Unit, Faculty of Veterinary Medicine, Sohag University, Egypt. Pregnant 4-month-old Wistar rats (7 days of gestational age) were acquired from the Experimental Animals Unit. The study was carried out in accordance with the regulations of the Animal Ethics Committee of Sohag University (Approval number; 2020, 1019 Dec 01). The weights of these rats 250 ± 20 g on average, and the rats were kept under standard environmental conditions (25 ± 2°C; 12:12 h dark/light cycle), and humidity (40–50%) The rats were provided with a typical diet and water that was available as needed [26].

To establish pregnancy in Wistar rats we monitored the rats for mating behavior. If mating occurs, it is often indicated by the presence of a copulatory plug in the female's vagina, which can be checked the following morning. Then we looked for physical signs of pregnancy in the female, such as: Increased body weight, Changes in behavior (e.g., nesting behavior) and Enlarged abdomen and nipples [27].

2.2. Dosing Solutions and Procedures

Dexamethasone was administered continuously via drinking water. The drug was serially diluted to achieve the following concentrations: 625 and 1250 µg/kg body weight. The solution was prepared in drinking water starting on the 7th day of pregnancy, in accordance with previous studies [28,29].

2.3. Experimental Design

As outlined in Table 1, a total of 72 female Wistar rats were randomly allocated into four primary experimental groups: (i) control pregnant rats (n = 6 per group); (ii) pregnant rats treated with dexamethasone at doses of 625 µg/kg and 1250 µg/kg body weight, which were further divided into four subgroups (n = 6 per subgroup); (iii) control non-pregnant rats (n = 6 per group); and (iv) non-pregnant rats treated with dexamethasone at doses of 625 µg/kg and 1250 µg/kg body weight, forming four subgroups (n = 6 per subgroup).

Table 1: Experimental Design

Group	Dose (µg/kg, BWT)	Duration of treatment (Days)	Pregnancy Days (D)	Number of rats
Control Pregnant	0	7	D7 to D14	6
	0	14	D7 to D21	6
Dexamethasone pregnant	650	7	D7 to D14	6
	650	14	D7 to D21	6
	1250	7	D7 to D14	6
	1250	14	D7 to D21	6
Control non-pregnant	0	7	Non-pregnant	6
	0	14	Non-pregnant	6
Dexamethasone non-pregnant	650	7	Non-pregnant	6
	650	14	Non-pregnant	6
	1250	7	Non-pregnant	6
	1250	14	Non-pregnant	6

Table.1 showcased the four primary groups and its subgroups with their doses and the period of oral administration of dexamethasone in the present study. We collected samples on days 14 and 21 of pregnancy, corresponding to 7- and 14-days post-treatment initiation, respectively. This timeline coincided with the end of the second trimester and the completion of the third trimester, following the administration of dexamethasone starting on the 7th day of gestation in pregnant rats. Simultaneously, non-pregnant rats were treated with dexamethasone following the same dosing schedule to serve as comparative controls. Both groups were compared to their respective 0 dexamethasone-treated control groups.

2.4. Behavioral assessment

The assays were conducted on all rats. The behavioral assays were conducted after 7 or 14 days from starting administrating dexamethasone at the 7th days of gestational age rats before the animal sampling.

2.4.1. Forced Swim Test

The forced swim test (FST) was used to assess depressive-like behaviors in rats by measuring escape-related mobility in a water-filled, transparent tank from which escape is impossible. The test was conducted following established protocols to ensure minimal stress and the reliability of results. Each session lasted 6 minutes, with the first 2 minutes used to observe initial active swimming behaviors and the remaining 4 minutes analyzed for immobility, indicative of despair or reduced motivation [31]. All procedures adhered to ethical guidelines for animal research and welfare.

2.4.2. Open Field Test

The open field test is a widely used method for assessing animal behavior in experimental models, providing valuable insights into locomotor activity and emotional responses. Standardized protocols, as outlined in previous studies, were followed to ensure reliability and consistency in behavioral assessments [28]. The test, conducted over a 10-minute duration, allowed for comprehensive observation of the rat's behavior in the open field arena [32]. Parameters measured included total distance traveled, velocity, time spent in the center, number of entries into the center, latency to enter the center, frequency of rearing, latency to first rearing, times of urination, and times of defecation. These metrics collectively offered a detailed evaluation of exploratory behavior, anxiety levels, and general activity.

2.5. Euthanasia

Rats showing clinical signs for two consecutive days were humanely euthanized for physiological and pathological analyses. Euthanasia was performed via cervical dislocation, a commonly used method to ensure quick and humane death [33]. The rats were weighed immediately before euthanasia, and their bodyweight was documented accurately.

2.6. Differential leukocyte count

Blood samples were obtained via cardiac puncture and collected into plain tubes for hematological analysis. Blood smears were prepared on clean glass slides, fixed with absolute methanol for 5 minutes, and stained using freshly diluted Giemsa stain (1:10 dilution with Sorensen buffer, pH 6.8) for 20 minutes. After staining, the slides were rinsed with tap water and air-dried. Differential leukocyte counts (DLC) were performed manually under a light microscope by counting 100 leukocytes per smear. This approach allowed for the identification of leukocyte based on their morphology [34].

2.7. Statistical analysis

Statistical analyses were conducted via GraphPad Prism software. Group comparisons between dexamethasone-treated rats and control rats were performed via two-way ANOVA followed by Tukey's post-hoc test to identify specific differences. The data are presented as the means ± standard deviations (SDs). A significance threshold of $P \leq 0.05$ was applied for all analyses.

3. Results and Discussion

We must point out that a deterioration occurs which leads to death with all the dexamethasone doses that used in this experiment except these doses (1250 µg/kg body weight for 7 days, and 625 µg/kg body weight for both 7 days and 14 days). So we discussed only the results of those doses.

3.1. Effect of dexamethasone treatment on depressive and anxiety-like behaviors

The clinical signs shown by exposed rats were expressed as an increase in mobility period, latency period to enter the center, latency center to 1st rearing, urination times, defecation times; and decrease the total time in center, number of rearing times. As shown in Fig. 1, treatment with dexamethasone at a high dose (125X10 µg) led to a significant reduction in the live body weights of both pregnant and nonpregnant rats after 14 days of continuous treatment (Fig. 1A, B; p<0.001 and p<0.05, respectively). However, this weight-reducing effect was not observed in pregnant rats treated with a lower dose of dexamethasone (650 µg) after 21 days, in contrast to the significant reduction observed in nonpregnant group under the same conditions (Fig. 1A). Owing to the observed mortalities associated with prolonged high-dose dexamethasone treatment, body weight data for both pregnant and nonpregnant rats under these conditions were excluded from analysis (Figure. 1A, B). With respect to the behavioral outcomes assessed via the forced swim test, continuous treatment with dexamethasone significantly reduced immobility, indicating potential antidepressant-like effects. This reduction was observed after both 14 and 21 days of treatment with the 650 µg dose and after 14 days with the 125X10 µg dose. These findings highlight the dose- and duration-dependent effects of dexamethasone on physiological and behavioral parameters, emphasizing its differential impact on reproductive status and treatment regimen.

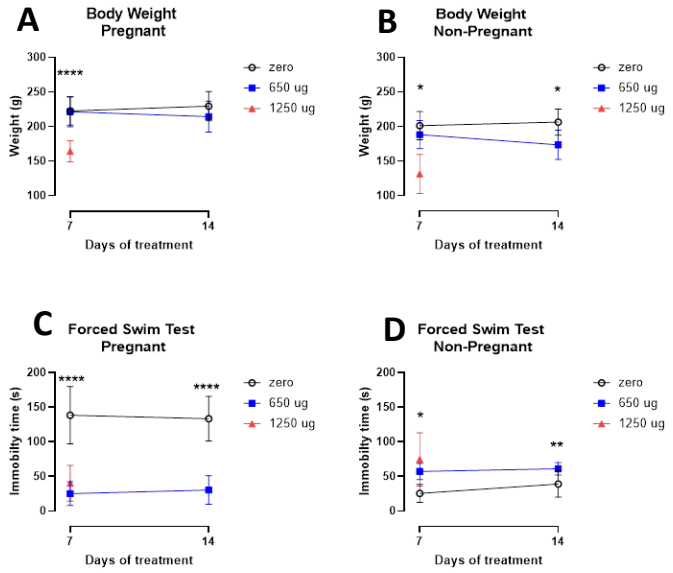


Figure.1. Effects of sustained dexamethasone treatment on body weight and immobility duration in the forced swim test for pregnant and non-pregnant rats. Data were analyzed using two-way ANOVA followed by Tukey's post-hoc test. Results are presented as mean ± SD, with * indicating statistically significant differences at P < 0.05.

Using the open field test, we evaluated the behavioral effects of dexamethasone treatment on pregnant and nonpregnant rats. In pregnant rats, treatment with a low dose of dexamethasone for 14 and 21 days, as well as a high dose for 21 days, resulted in a notable increase in the total time (seconds) spent in the center of the arena and the number of entries into the center (Fig. 2A, C). These increases suggest a reduction in anxiety-like behavior in pregnant rats following these specific treatment regimens. In contrast, such effects were not observed in nonpregnant groups (Fig. 2B, D), indicating potential differences in the behavioral response on the basis of reproductive status. In nonpregnant rats, significant effects of 14-day dexamethasone treatment were observed in significantly reduced the latency to enter the center (Fig. 2F, p<0.05), as did the number of center entries (Fig. 2H, p<0.001) and the number of defecations (Fig. 2K, p<0.001). These changes suggest a mix of stress-related and anxiety-related responses to treatment in nonpregnant rats. Conversely, no significant effects were observed in pregnant rats following 14- or 21-day dexamethasone treatments for parameters such as latency to enter the center, the number of rearing events, the latency to the first rearing, or the number of urinations (Fig. 2G, I, K). Similarly, in nonpregnant rats, there were no significant changes in the time spent in the center, the number of center entries, the latency to the first rearing, or the frequency of urination and defecation (Fig. 2B, H, J, L). These findings highlight that dexamethasone elicits dose-, duration-, and reproductive status-dependent behavioral effects in the open field test. Pregnant rats exhibited signs of reduced anxiety-like behavior under certain treatment regimens, whereas nonpregnant rats displayed mixed responses,

emphasizing the need to consider reproductive state in the interpretation of corticosteroid-induced behavioral changes.

3.2. Effects of dexamethasone treatment on some several hematological indices

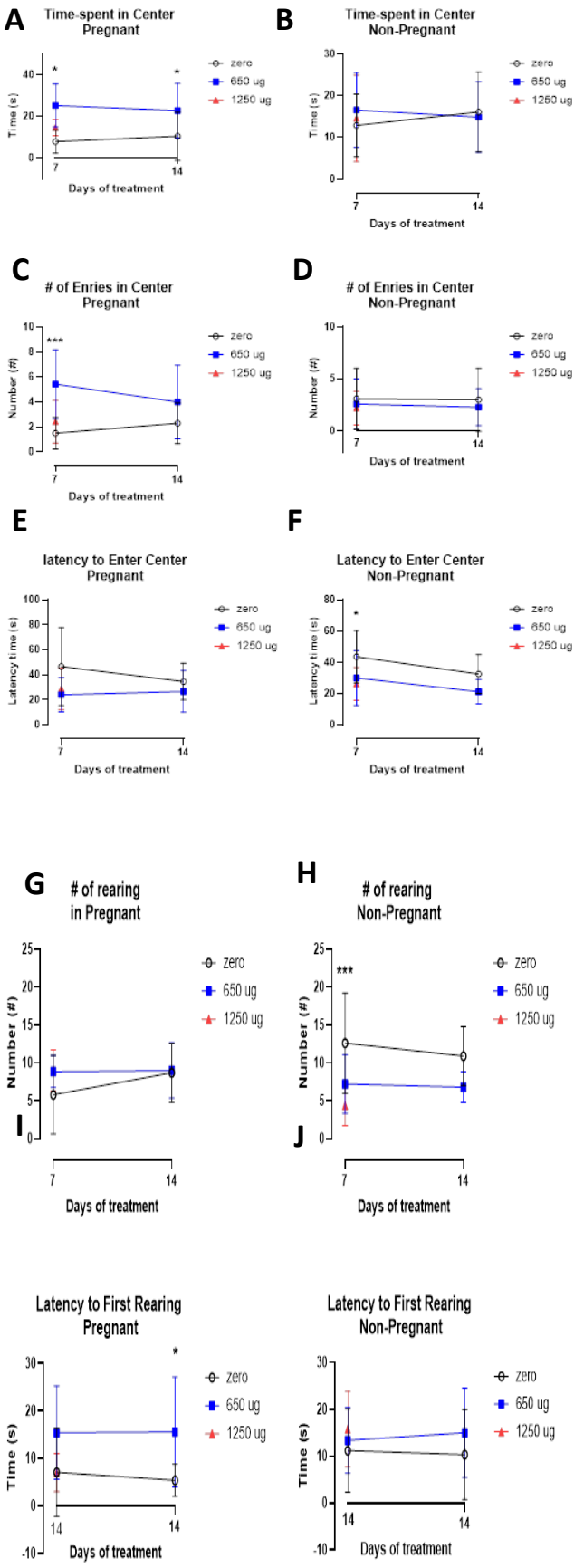
The impact of dexamethasone treatment on hematological parameters was assessed to evaluate stress-related immune changes, as shown in Fig. 3. The neutrophil-to-lymphocyte (N/L) ratio, a widely recognized marker of physiological stress, was calculated on the basis of the percentages of these cell types. Treatment with dexamethasone for both 14 and 21 days led to a notable increase in the N/L ratio, indicating heightened stress levels under these conditions (Fig. 3A, B).

In pregnant rats, 14 days of dexamethasone treatment resulted in a significant reduction in monocyte levels (Fig. 3C, $p<0.05$), suggesting potential suppression of innate immune activity during the early phase of treatment. However, this effect was not observed after 21 days, implying a transient or compensatory immune response over time. Additionally, eosinophil counts were significantly elevated following 14 days of treatment (Fig. 3E, F, $p<0.01$), which may reflect dexamethasone-induced modulation of allergic or inflammatory pathways.

These findings highlight the dose- and duration-dependent immunological effects of dexamethasone treatment, particularly its capacity to increase stress markers such as the N/L ratio and modulate specific leukocyte populations in pregnant rats. This findings underscore the complex interplay between glucocorticoid treatment, immune function, and stress physiology.

ANOVA, followed by Tukey's post-hoc test. Values are expressed as mean ± SD, with * indicating statistically significant differences at $P < 0.05$.

This study provides comprehensive insights into the physiological, behavioral, and immunological effects of dexamethasone treatment, revealing its dose- and duration-dependent effects on body weight, anxiety- and depressive-like behaviors, and hematological parameters in pregnant and nonpregnant rats. Despite its widespread use as a synthetic glucocorticoid in people and experimental animals, dexamethasone has been linked to somewhat significant pregnancy-related adverse effects such as abortion/pregnancy inhibition in some animals. Therefore, this study aimed to optimize dexamethasone treatment in pregnant Wistar rats. Herein, we found that dexamethasone had a significant dose-dependent effect on examined parameters. The observed reduction in body weight in both pregnant and nonpregnant rats following high-dose dexamethasone treatment (125X10 µg) for 14 days aligns with the well-documented catabolic effects of glucocorticoids, which promote protein degradation and lipolysis [35]. Interestingly, pregnant rats treated with a lower dose (650 µg) did not exhibit weight loss after 21 days, unlike their nonpregnant counterparts. This differential response may be attributed to pregnancy-associated hormonal or metabolic adaptations, such as increased progesterone and altered glucose metabolism, which can counteract the catabolic effects of dexamethasone [**36**].



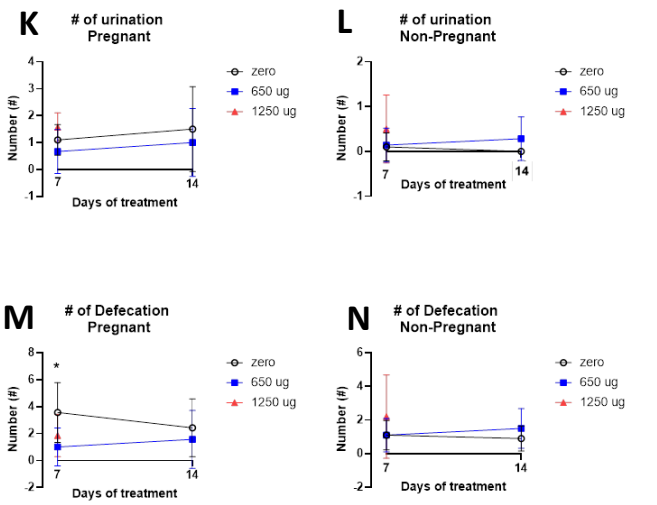


Figure.2 Effects of sustained dexamethasone treatment on behavioral parameters in pregnant and nonpregnant rats in the open field test. Data were analyzed using two-way ANOVA followed by Tukey's post-hoc test. Results are presented as mean ± SD, with * indicating statistically significant differences at $P < 0.05$.

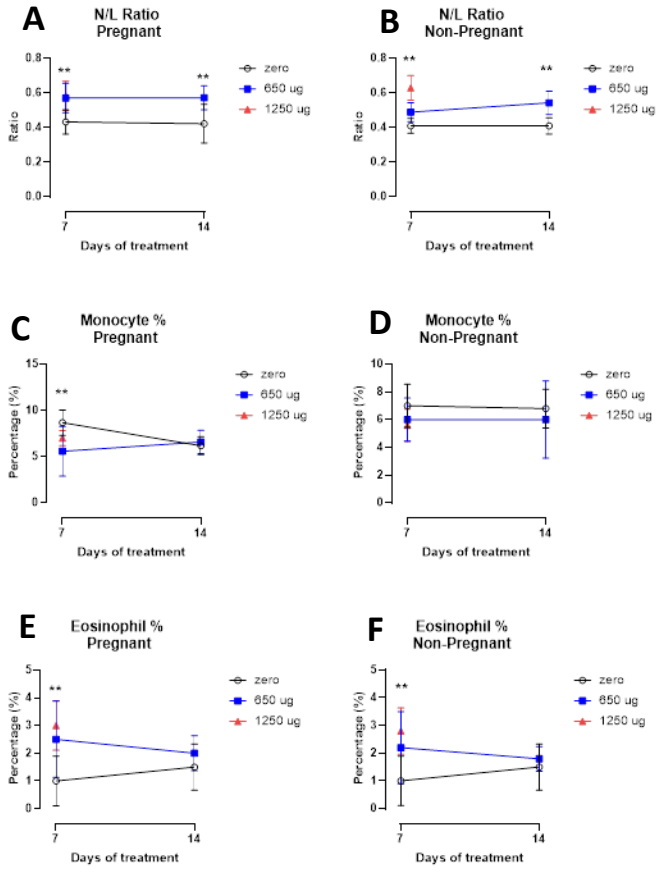


Figure.3 Effects of sustained dexamethasone treatment on hematological parameters in blood samples from pregnant and non-pregnant rats. Data were analyzed using two-way.

Behavioral assessments through forced swim and open field tests revealed significant differences in depressive- and anxiety-like behaviors between pregnant and nonpregnant groups. Reduced immobility in the forced swim test following dexamethasone treatment suggests an antidepressant-like effect, which is consistent with reports of glucocorticoid modulation of the hypothalamic-pituitary-adrenal (HPA) axis and monoaminergic systems [37]. In the open field test, pregnant rats exhibited reduced anxiety-like behaviors, as evidenced by increased time spent in the center and increased center-entry frequency after both low- and high-dose treatments. This finding is in line with studies suggesting that pregnancy-related neuroendocrine adaptations mitigate anxiety responses [38]; conversely, nonpregnant rats display mixed responses, including increased latency to enter the center, reduced center entries, and fewer defecations, indicative of heightened anxiety and stress-related behaviors, which may result from the exacerbated effects of glucocorticoids on the amygdala and prefrontal cortex [37,39].

Hematological analysis revealed that dexamethasone treatment significantly increased the neutrophil-to-lymphocyte (N/L) ratio, a recognized marker of physiological stress [40]. This effect was consistent across doses and durations in both pregnant and nonpregnant rats, underscoring the stress-inducing potential of glucocorticoids [40,41]. Furthermore, the reduction in monocyte levels and increase in eosinophil counts observed in pregnant rats after 14 days of treatment suggest transient immunosuppressive and inflammatory responses, likely mediated by glucocorticoid-driven modulation of cytokine production and leukocyte distribution [42,43]. These effects were not sustained after 21 days, indicating a possible adaptive or compensatory mechanism over prolonged treatment periods.

Overall, these findings demonstrate the multifaceted effects of dexamethasone on body weight, mood-related behaviors, and immune parameters, highlighting the importance of dose, duration, and reproductive status in shaping physiological and behavioral outcomes. This underscores the need for careful consideration of these factors in both experimental and clinical applications of glucocorticoids [44].

In this study, we examined the effects of dexamethasone treatment during pregnancy, focusing on behavioral and hematological changes. Our findings indicate that dexamethasone induces a range of physiological and behavioral alterations, with the severity of these effects being dose- and duration-dependent. Notably, high doses of dexamethasone led to significant reductions in body weight and increased mortality rates, particularly in pregnant and nonpregnant rats treated with higher doses. These findings align with previous research suggesting that dexamethasone treatment can disrupt physiological homeostasis, potentially through modulation of the hypothalamic-pituitary-adrenal (HPA) axis, which regulates stress and immune responses during pregnancy [45].

Behavioral alterations observed in both the forced swim test and the open field test further support the role of dexamethasone in modulating anxiety- and depression-like behaviors. In the forced swim test, a reduction in immobility was noted after treatment with low doses of dexamethasone, which may indicate antidepressant-like effects. This effect was more pronounced after 14 and 21 days of treatment at lower doses, suggesting that prolonged exposure to glucocorticoids may alter emotional

reactivity, particularly in pregnant rats [46].

Furthermore, the open field test revealed that pregnant rats exhibited reduced anxiety-like behavior following specific treatment regimens, characterized by increased time spent in the center of the arena and more frequent entries into the center. In contrast, nonpregnant rats exhibited a mixed response, indicating that reproductive status influences behavioral outcomes in response to dexamethasone [47]. The observed changes in immune function, particularly the elevation in the neutrophil-to-lymphocyte (N/L) ratio, suggest heightened physiological stress in both pregnant and nonpregnant rats treated with dexamethasone. In pregnant rats, the transient suppression of monocyte levels and increased eosinophil counts further highlight the immune-modulating effects of dexamethasone. These immune changes, along with the behavioral alterations, suggest that dexamethasone may exert its effects through complex neuroendocrine pathways, particularly by altering stress-related immune responses and modulating the HPA axis [48].

Limitations and Future Directions

This study focused primarily on continuous treatment effects, and explored the effects of chronic dexamethasone exposure during the second and third trimesters. Although behavioral changes have been documented, the inclusion of a broader array of behavioral and cognitive assessments could provide a more comprehensive understanding of the effects of dexamethasone. Furthermore, research has focused mainly on immune and physiological markers, offering limited insight into the molecular mechanisms underlying these outcomes. While comparisons with control groups were included, incorporating additional stratifications, such as stress-induced models, would enhance the understanding of how dexamethasone impacts different physiological conditions [43]. Future studies should focus on molecular markers, such as cytokines and neuropeptides, to clarify underlying mechanisms and include longitudinal research to assess the long-term effects on maternal and offspring health. Future research should investigate a wider range of dexamethasone doses to refine its optimal therapeutic range, especially during pregnancy. Studies addressing the chronic effects of dexamethasone are also critical for evaluating the risks associated with prolonged use. Expanding this research to diverse animal models could increase the applicability of findings to humans. Molecular investigations into the pathways underlying dexamethasone-induced immunosuppression and behavioral changes are essential for advancing therapeutic strategies [27]. Additionally, exploring the interaction of dexamethasone with stress-induced immune responses and potential drug synergies could provide valuable clinical insights. Finally, using a more extensive suite of behavioral tests would help elucidate the cognitive and emotional effects in treated animals, improving the translatability of these findings [28]. Future studies should focus on molecular markers, such as cytokines and neuropeptides, to clarify underlying mechanisms and include longitudinal research to assess the long-term effects on maternal and offspring health. Investigating these molecular markers will help bridge the gap between observed behavioral changes and underlying neuroendocrine and immune pathways, thereby deepening mechanistic understanding and advancing the clinical application of dexamethasone therapy. Longitudinal studies are also recommended to evaluate the lasting impacts of dexamethasone on maternal well-being and offspring development, providing a deeper understanding of its implications for clinical use.

4. Conclusion

This study demonstrates the dose-dependent effects of dexamethasone on physiological, behavioral, and hematological parameters in pregnant and nonpregnant Wistar rats. The lowest dose (625 µg/kg) showed minimal adverse effects, with less weight loss, milder changes in hematological profiles, and fewer behavioral alterations, suggesting it may be safer than higher doses. In pregnant rats, this dose caused the least disruptions in hematological and behavioral parameters, while the highest dose (125X10 µg/kg) showed relatively mild effects on monocyte counts and neutrophilia. These findings highlight the need for cautious dose selection, particularly during pregnancy, to mitigate dexamethasone's immunosuppressive and behavioral impacts.

CRediT authorship contribution statement:

SGF and MEM jointly developed the hypothesis and concept of the study and contributed to the manuscript's chemistry and materials, as well as technique. For this research and scientific paper, the IFR, FAM, RMA, and ZA-A, are all involved in the experimental procedures and analyses of this study and scientific paper. The MEM was used to rewrite and finalize the manuscript. The final manuscript was read and approved by all of the authors.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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