

# Evaluation of the effect of various types of stress on fertility in wistar rats- An Experimental Study

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## ABSTRACT

**Background-** Stress is a well-established factor that negatively influences reproductive health in both humans and animals. This study investigates the impact of various stressors like restraint and immobilization, noise, cold exposure, and post-surgical stress on fertility in Wistar rats.

**Objective:** To evaluate the effect of different types of stress on fertility parameters in Wistar rats.

**Methods:** Male and female Wistar rats were divided into five groups: restraint/ immobilization stress (2 hours/day), noise stress (1 hour/day of loud sound), cold stress (2 hours/day at 4°C), post-surgical stress and a control group without stress. The following reproductive parameters were monitored: estrous cycle regularity, mating behavior, pregnancy rate, litter size and histopathological changes. Statistical analysis was performed using one-way ANOVA.

**Results:** The control group showed normal estrous cycles and high pregnancy rates.

All types of stress significantly impaired fertility compared to the control group ( $p < 0.001$ ). Restraint and immobilization delayed estrous cycles and reduced pregnancy rates, noise stress led to irregular cycles and fewer pregnancies, cold exposure resulted in delayed conception and smaller litter sizes, post-surgical stress caused less reproductive disruption and less effect on fertility.

**Conclusion:** Exposure to various types of stress markedly disrupts reproductive function in Wistar rats, highlighting the importance of stress control in laboratory animal welfare and reproductive studies.

**Keywords:** Stress, Fertility, Wistar rats, Restraint stress, Noise stress, Cold exposure

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## INTRODUCTION

Stress is an unavoidable factor in modern life directly or indirectly affecting the overall health and well-being(1). With the computerization, increase in the sedentary life style shows direct correlation with the infertility in male and female(2).The impact of stress on fertility is a multifaceted issue, influenced by numerous physiological, psychological, and environmental factors. Stress can be categorized into different types, including psychological, physical, and environmental stress, each potentially affecting reproductive health through different mechanisms(3). Psychological stress, often induced by factors such as isolation or social defeat, can lead to alterations in hormonal balance, particularly involving the hypothalamic-pituitary-gonadal (HPG) axis(4).Physical stress, such as forced exercise or restraint, can result in the

release of stress hormones like cortisol, which can directly impact reproductive tissues and processes(5). Environmental stressors, including noise, temperature extremes, and exposure to toxins, can disrupt the delicate balance of endocrine functions necessary for reproduction(6).

The World Health Organization (WHO) has identified infertility as a significant public health concern, with an estimated 60 to 80 million couples worldwide affected by this condition(7). Data from the Indian Census (1981, 1991, 2001) indicate a rising trend in infertility rates among reproductive-age couples, with the prevalence increasing from 13% in 1981 to 16% in 2001 among ever-married women(8).While biological factors remain the primary contributors, various social, health-related, and lifestyle elements also negatively influence reproductive

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potential(9). Increasing evidence suggests that lifestyle choices significantly influence overall health and quality of life (QoL), with numerous lifestyle-related risk factors being strongly linked to disruptions in reproductive function, potentially leading to infertility (4).

Prolonged exposure to stress has been linked to a wide range of pathophysiological changes, impacting behavioral responses, immune system function, neural communication, and cardiovascular health. It also contributes to the onset of chronic mood disorders, including anxiety and depression(10).

This study aims to evaluate the effects of various types of stress on fertility in Wistar rats, providing insights into the specific mechanisms and potential therapeutic targets for mitigating stress-induced reproductive dysfunction. Understanding relationships between stress and infertility in a controlled animal model will contribute to the broader knowledge necessary for developing interventions to improve fertility outcomes in stress-affected populations.

### Materials and Methods

Wistar rats of either sex (10 males and 40 females) were used for the study. The animals were housed in polypropylene cages and autoclaved rice husk was serve as the bedding material. The animal room were maintained under controlled environmental conditions with a temperature of  $25 \pm 3$  °C, relative humidity of  $60 \pm 5\%$ , and a 14-hour light/10-hour dark cycle. Additionally, 10% air exhaust was maintained in the air conditioning system to ensure adequate ventilation. A standard rodent diet procured from Pranav Agro was to animals daily at 10:00 AM and remained consistent throughout the study duration. Drinking water (aqua) was made available at all times. All experimental procedures were carried out strictly in adherence to the guidelines established by the Committee for the Control and Supervision of Experiments on Animals (CCSEA).

**Estrous cycle:** Vaginal smears were collected daily in the morning from each animal in order to assess the estrous cycle. To collect the sample, 0.1 ml of normal saline (NaCl 0.9%) was gently introduced into the vaginal opening of the female rats and then same is aspirated back using a sterile dropper. Smear of vaginal fluid was prepared and examined under a microscope at 10x and 40x magnification. From the presence of cells like epithelial cells, cornified cells and leukocytes the phase of the oestrus cycle was identified. The female rats with regular estrous cycle were included in the study (11).

### Groups

Rats were divided into five groups 10 rats in each group (8 Females and 2 Males).

### Stressors Used

**Restraint and immobilization stress-** Restraint stress induced by placing animals in ventilated cylindrical tubes for a duration of 120 minutes, limiting head and body movement(12) This method generates both physical and psychological stress, with minimal adaptation over time(13). The animal were immersed in cold water (40C for 30 min) and again back to the normal temperature, results from abrupt drops in environmental temperature, which activate the thermoregulatory center and the hypothalamic-pituitary-adrenal (HPA) axis, triggering a stress response(14). Such temperature shifts are commonly used in laboratory settings to simulate stress conditions in experimental animals (15). Noise-induced stress models mimic conditions similar to those experienced by humans who are frequently exposed to high-intensity, potentially harmful noise in modern environments. In this model, stress is induced using loudspeakers (15 W) connected to a white noise generator emitting frequencies ranging from 0 to 26 kHz, positioned approximately 30 cm above the animal cage. The animals were exposed to the noise repeatedly (2 hours/day)(16). In post surgical stress model surgical incision was taken under all aseptic precaution on abdominal area and leprothomy done. Post operative analgesic and antibiotic were given for 3 days. This process generates physiological changes that correlate with stressful states (17).

All the animals were exposed to the stressors as per the respective groups for the period of 15 days. Two females from each group were sacrificed on day 16 and uterus were removed. Weight of the uterus was taken and sent for histopathological changes. 6 Females from each group after blood withdrawal under ketamine anesthesia were kept for mating with the stress exposed males to assess the effect on the reproductive outcome, litter size, weight and general parameters of the fetus.

### Parameters assessed-

- Oestrus cycle
- Reproductive hormone levels (e.g., FSH, LH, estradiol, progesterone)
- Post stress exposure fertility
- Ovarian histology

### Hormone estimation

The levels of FSH, LH, estradiol, and progesterone were measured using the enzyme-linked immunosorbent assay (ELISA) technique. All samples were analyzed in duplicate to ensure the accuracy and reliability of the results.

### Statistical Analysis

Statistical analysis was carried out using GraphPad Prism 6.0 software (GraphPad Software, San Diego, CA, USA). Analysis was done with ANOVA followed by Dunnett's

test. All the data expressed as the mean±SD and p<0.05 was considered as significant.

**RESULTS**

**Effect of Stress on Estrous Cycle**

All stress-exposed groups exhibited significant alterations in estrous cycle patterns compared to controls. The

**restraint stress group** showed prolonged diestrus phases and irregular cycling. Similarly, **cold exposure** led to extended metestrus and diestrus stages. The **noise-stressed group** displayed the most pronounced disruption, with many animals showing persistent estrus or anestrus conditions.

**Table 1: Effect of Stress on Estrous cycle Phases duration in different experimental groups during study period**

	Control	Restrain	Cold	Noise	Surgery
<b>Cycle Length (days)</b>	4.5 ± 0.3	6.2 ± 0.5	5.8 ± 0.4	6.5 ± 0.5	5.6 ± 0.2
<b>Proestrus Duration (days)</b>	1.0 ± 0.1	1.2 ± 0.2	1.8 ± 0.1	1.2 ± 0.2	1.8 ± 0.1
<b>Estrus Duration (days)</b>	1.0 ± 0.1	1.3 ± 0.2	0.9 ± 0.1	1.5 ± 0.2	1.2 ± 0.1
<b>Metestrus Duration (days)</b>	1.1 ± 0.1	1.8 ± 0.1	1.5 ± 0.1	1.9 ± 0.1	1.1 ± 0.1
<b>Diestrus Duration (days)</b>	1.4 ± 0.2	1.9 ± 0.3	1.6 ± 0.2	1.9 ± 0.3	1.5 ± 0.2
<b>Cycle Regularity</b>	Regular	Irregular	Slightly Irregular	Irregular	Regular

Vaginal smear cytology was used daily to determine cycle phases. Changes in cycle length or irregularity indicates hormonal imbalances caused due to the stress.

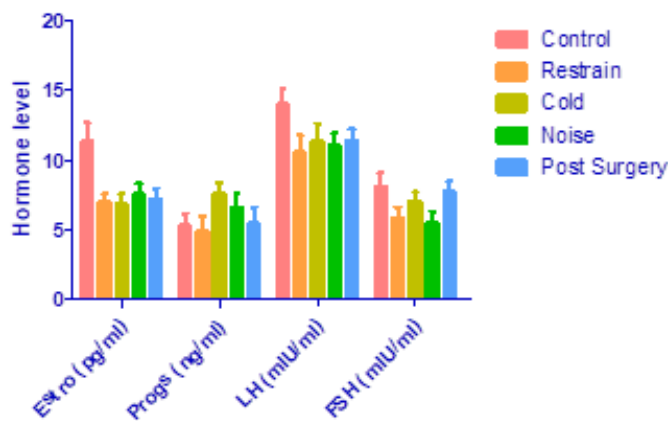
**Table 2: Effect of Stress on Estrous cycle Pattern.**

Groups	Average cycle length (days)	% irregular Cycles	Dominant Phase observed
Control	4.5	10	Normal
Restrain stress	6.2	60	Prolonged Diestrus
Cold stress	5.8	55	Prolonged Metestrus
Noise stress	6.5	70	Persistane Estrus
Post surgery stress	5.2	40	Anestrus

Exposure to different stress paradigms led to distinct alterations in the estrous cycle patterns of female rats. In the restraint stress group, a significant disruption of normal cyclicity was observed, characterized by a prolonged diestrus phase and reduced occurrence of proestrus. The cold stress group showed marked suppression of estrous cyclicity, with several animals exhibiting complete cycle arrest or persistent diestrus and Metestrus. Similarly, animals subjected to noise stress

displayed irregular cycles with shorter durations of estrus and prolonged metestrus and diestrus phases. In contrast, the post-surgical stress group exhibited a transient disruption in the estrous cycle, with a temporary extension of diestrus or delayed onset of estrus observed during the immediate postoperative period. However, most animals gradually resumed normal cycling within 7 to 10 days post-surgery.

**Effect if various types of stress on Female sex hormones**



**Figure 1: Serum Reproductive Hormone Levels across the groups**

Exposure to various stressors led to notable changes in reproductive hormone levels. When compared to the non-stressed control group, all stress-exposed animals exhibited a **significant reduction in serum estradiol and**

**luteinizing hormone (LH) levels (p < 0.01)**, indicating a suppression of normal reproductive hormonal activity. The **cold stress group**, in particular, showed a **moderate increase in progesterone levels**. Additionally, **follicle-**

stimulating hormone (FSH) levels were considerably lower in animals subjected to **restraint and noise stress**.

These hormonal imbalances are consistent with the observed disturbances in estrous cycle patterns.

**Table 3.** Reproductive outcome at the end of the study across groups.

Groups	Pre-exposure fertility	Pre-exposure fertility
1. Control	12.40	11.16
2. Restrain & Immobilization stress	10.83	6.83
3. Cold stress	11.66	6.33
4. Noise stress	13.16	7.83
5. Post surgery stress	12.83	11.33

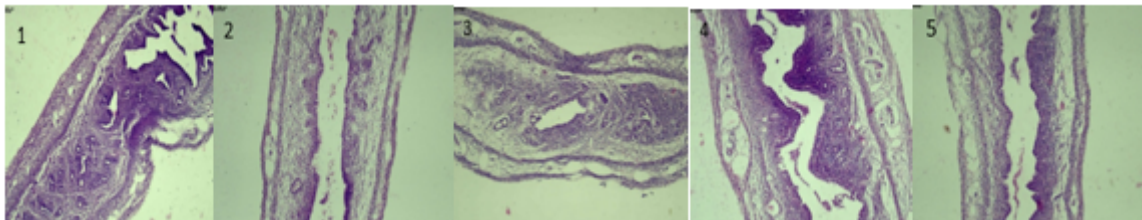
At the end of the experimental period, reproductive outcomes were assessed across all study groups. The control group exhibited normal reproductive parameters, including regular estrous cycles, successful mating and full-term pregnancies with healthy litter sizes.

In contrast, animals in the exposed to restrain, cold and noise stress group showed significant alterations in reproductive performance. These included irregular estrous cycles, delayed mating, reduced conception rates and a lower number of pregnancies carried to term. Additionally, the average litter size was significantly reduced compared to the control group ( $p < 0.01$ ) and incidences of stillbirths were observed in these groups.

Animals with post operative stress, however, demonstrated a partial restoration of reproductive outcomes. Estrous cyclicity showed improvement and pregnancy rates increased compared to other stress group.

**3] Histopathological Examination:**

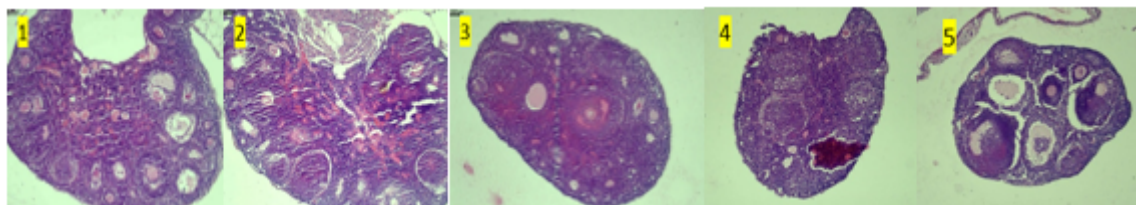
Microscopic observation-Microscopic examination of uterus and ovaries sample from different groups showed atrophy of ovarian stroma with multiple cysts with haemorrhages and atrophy of uterus with loss of endometrial glands except in control group.



**Figure 1.** Uterine histology under H&E stain showing morphological changes.

Effect of different types of stress on Uterine morphological changes under 40X, H & E (hematoxylin and eosin staining) Stain. 1 Control: Uterus: showing normal endometrium, myometrium and uterine glands. 2 Restrain Stress: Uterus: Showing atrophy and loss of uterus glands and muscle, mild. 3. Cold Stress: Uterus:

Showing atrophy and loss of uterus glands and muscle, mild. 4: Noise Stress: Uterus: Showing atrophy and loss of uterus glands and muscle, mild. 5: Post Surgery Stress: Uterus: Showing atrophy and loss of uterus glands and muscle, mild.



**Figure 2.** Ovarian histology under H&E stain showing morphological changes.

Effect of different types of stress on Ovarine morphological changes under 40X, H & E (hematoxylin and eosin staining) Stain. 1 Control: Ovaries: showing normal ovarian stroma, medulla, follicles. 2 Restrain Stress: Uterus: Showing atrophy of ovarian stroma with multiple cysts with haemorrhages, minimal. 3: Cold Stress: Ovaries: Showing atrophy of ovarian stroma with multiple cysts with haemorrhages, minimal. 4: Noise

Stress: Ovaries: Showing atrophy of ovarian stroma with multiple cysts with haemorrhages, minimal. 5: Post Surgery Stress: Ovaries: Showing atrophy of ovarian stroma with multiple cysts with haemorrhages, minimal. 40X, H & E Stain

Histological analysis revealed notable structural changes in the ovaries of stressed rats

**In Restraint stress** follicular atresia, with fewer antral follicles and increased stromal fibrosis was observed. **Cold stress** resulted in reduced corpus luteum numbers and degenerative changes in granulosa cells. The **noise-stressed group** showed enlarged, cystic follicles and disrupted folliculogenesis and **Surgical stress** led to inflammatory infiltration and marked disruption of ovarian architecture.

Among all stressors, **restraint and noise stress** produced the most profound impact on fertility markers, including estrous irregularities and histological damage. **Surgical stress** had the least hormonal impact but showed notable physical disruption in ovarian tissues.

## DISCUSSION

Stress represents a multifaceted physiological and psychological response to environmental or internal stimuli and has been implicated in the dysregulation of several biological systems, including reproductive function (18). The underlying mechanisms through which stress exerts its effects on fertility are intricate, involving the activation of neuroendocrine pathways such as the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the HPA axis results in increased glucocorticoid secretion, primarily cortisol in humans and corticosterone in rodents, which can exert suppressive effects on the hypothalamic-pituitary-gonadal (HPG) axis. This suppression impairs the release of key reproductive hormones, thereby influencing gametogenesis and overall fertility (19,20).

Moreover, stress is often accompanied by oxidative stress and inflammatory responses, both of which can detrimentally impact gonadal tissues and compromise the structural and functional integrity of reproductive organs (21). These physiological alterations can impair oocyte maturation, ovulation, and implantation, ultimately reducing reproductive success.

In the present study, we investigated the reproductive consequences of different stress paradigms, namely restraint and immobilization, noise exposure, cold (low temperature) stress, and post-surgical stress in female Wistar rats. Each of these stressors represents distinct physical or environmental challenges and was evaluated for its impact on estrous cyclicity, conception rates and reproductive outcomes.

Restraint and immobilization are commonly used experimental stressors that restrict physical movement, thereby inducing psychological and somatic stress. These conditions have been shown to alter circulating levels of stress-responsive hormones such as corticosterone and prolactin, both of which are closely linked to reproductive endocrinology (22). Previous studies have reported that restraint stress in rodents leads to disrupted estrous cycles, reduced ovulation frequency, and delays in mating

success, largely through dysregulation of the HPA axis (23).

Our findings support this evidence, with the restraint-stressed group showing significant reductions in fertility parameters, including conception rates and litter sizes. (Table 1, Figure 1) Chronic exposure further appeared to impact gonadal steroidogenesis, potentially through glucocorticoid-mediated inhibition of gonadotropin-releasing hormone (GnRH) secretion.

Exposure to low ambient temperatures poses a substantial metabolic challenge, activating thermoregulatory mechanisms such as vasoconstriction and shivering. These processes increase the animal's energy expenditure and provoke neuroendocrine changes, particularly through increased corticosterone release and altered thyroid hormone levels (24). Such endocrine disruptions can impair ovarian function and interfere with the timing and quality of ovulation. In this study, the intensity of estrous cycle disruption was most pronounced in cold stress, rats exposed to cold stress demonstrated decreased fertility (Table 3), marked by fewer pregnancies and compromised reproductive performance followed by restraint and noise stress, while post-surgical stress resulted in comparatively milder and reversible changes.

These effects are consistent with previous findings suggesting that cold stress can disturb reproductive cycles and lower fecundity in laboratory animals and also to delayed conception and smaller litter sizes, suggesting impairment in both ovulation and implantation (25).

In contemporary environments, noise pollution has emerged as a prevalent stressor. Chronic noise exposure activates the HPA axis, leading to sustained elevations in stress hormones, which can influence reproductive hormone balance (26). Our study revealed that rats subjected to continuous noise exhibited extended estrous phases (Table 1) and reduced mating success, indicating disruptions in hormonal cyclicity (Figure 2) and reproductive behavior (Table 3). These observations mirror earlier research demonstrating that noise stress negatively affects reproductive physiology by altering estrogen and progesterone levels and impairing mating efficiency (27).

Surgical interventions introduce both physical trauma and subsequent physiological stress due to tissue injury and the activation of immune-inflammatory pathways. These acute stress responses can affect reproductive organs by disrupting ovarian steroidogenesis and uterine receptivity (28). In our study, post-surgical stress led to minimal effect on the oestrus cycle and reproductive outcome, indicating that acute, controlled stress might exert a milder effect. These outcomes are in line with studies that associate surgical trauma with temporary infertility,

likely due to altered levels of reproductive hormones and increased systemic inflammatory markers(29).

Histological analysis of ovarian tissues in stressed rats revealed distinct structural alterations associated with different stressors. Restraint stress led to pronounced follicular atresia, a reduction in antral follicles and increased stromal fibrosis, indicating impaired follicular development and diminished ovarian reserve. Cold stress resulted in a decreased number of corpus lutea and degenerative changes in granulosa cells, suggestive of disrupted luteinization and potential luteal phase deficiency. In the noise-stressed group, enlarged cystic follicles and disrupted folliculogenesis were observed, closely resembling features of polycystic ovarian morphology. Surgical stress, while exhibiting the least hormonal impact, caused notable physical disruption, including inflammatory cell infiltration and architectural damage. Among all groups, restraint and noise stress produced the most profound effects on ovarian function, as evidenced by significant estrous cycle irregularities and histological damage(30).

## CONCLUSION

The findings of this study provide compelling evidence that different types of stress have significant and often detrimental effects on fertility in Wistar rats. Restrain and immobilization stress, noise stress, cold stress, and post-surgery stress all result in disturbances to the reproductive system, manifesting as altered estrous cycles, reduced mating success and decreased fertility. These findings suggest that psychological stressors exert a more detrimental influence on reproductive health than physical or environmental stressors, with potential implications for stress-induced infertility.

Future research needed to explore the long-term effects of chronic stress on reproductive health and investigate the potential for interventions to mitigate these negative outcomes, such as pharmacological treatments or behavioral therapies aimed at stress reduction.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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