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Effect of Cypermethrin on Fertility in Female Mice

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Abstract:

The present study had evaluated the effects of sub-lethal doses of Cypermethrin on the ovary and uterus of female mice. Adult mice had been divided into four groups: control, low dose (1. 38 mg/kg), medium dose (2. 76 mg/kg), and high dose (5. 52 mg/kg). The pesticide had been administered orally for 21 consecutive days, and reproductive organs had been processed for histological examination using Hematoxylin and Eosin staining. The results had revealed a dose-dependent disruption in ovarian and uterine structures. Ovarian sections from treated groups had exhibited progressive follicular atresia, granulosa cell degeneration, and a marked reduction in corpora lutea compared with controls. Uterine tissues had shown thinning of the endometrial lining, glandular atrophy, and epithelial disorganization, particularly in the high dose group. Statistical analysis had confirmed significant (p< 0. 05) differences in follicle counts and endometrial thickness across groups. The study had concluded that Cypermethrin, even at sub-lethal doses, had impaired female reproductive health by inducing severe histological alterations in the ovary and uterus. These findings had emphasized the reproductive toxicity of synthetic pyrethroids and the necessity for cautious pesticide application and safer alternatives.

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1. Introduction

Pesticides had been extensively applied worldwide to enhance agricultural productivity and control disease vectors, but their widespread use had also posed significant risks to environmental and human health (Aktar et al., 2009). Among these, synthetic pyrethroids, particularly Cypermethrin, had been extensively utilized because of their perceived low mammalian toxicity, rapid biodegradability, and high insecticidal efficiency (Shaikh et al., 2016). However, accumulating evidence had revealed that chronic exposure to sub-lethal doses of Cypermethrin had disrupted reproductive health, especially in females, through endocrine modulation, oxidative stress, and cellular damage (Singh & Pandey, 2015; Kumar et al., 2020).

Globally, studies had demonstrated that Cypermethrin exposure had impaired fertility by inducing ovarian follicular atresia, disrupting estrous cycles, and reducing pregnancy outcomes in rodents (Elbetieha et al., 2001; Nagar et al., 2018). Similar investigations had shown that uterine histoarchitecture had been altered, with thinning of the endometrium, degeneration of glands, and epithelial disruption, thereby reducing implantation potential (Sharma et al., 2021). Such disruptions had been attributed to the pesticide's ability to interfere with steroidogenic enzymes and gonadotropin regulation, leading to decreased estrogen and progesterone levels (Bhardwaj et al., 2022).

In India, where pesticide consumption had been one of the highest globally, concerns regarding reproductive health hazards had been increasingly raised. Experimental studies conducted on Indian rodent models had confirmed that Cypermethrin exposure had resulted in degenerative ovarian changes, irregular estrous cycles, and significant uterine damage (Saxena et al., 2002; Singh & Pandey, 2015). These findings had underscored that women in agricultural and peri-urban environments had been at greater risk of fertility-related disorders due to prolonged low-level pesticide exposure.

Thus, the investigation on the effect of Cypermethrin on fertility in female mice had been undertaken to elucidate histopathological disruptions in ovarian and uterine tissues under sub-lethal exposure. This research had been intended to bridge global and national findings, providing further insight into reproductive risks associated with synthetic pyrethroid exposure.

2. Materials and Methods

Healthy adult female Swiss albino mice, aged 8–10 weeks and weighing 25–30 g, had been selected for the study. The animals had been housed under controlled laboratory conditions with a 12-hour light/dark cycle, temperature maintained at 22 ± 2 °C, and free access to standard diet and water ad libitum, as recommended in previous toxicological studies (OECD, 2008; Nagar et al., 2018).

The experimental design had comprised four groups (n = 6 per group): Group A (Control), Group B (Low dose: 1. 38 mg/kg), Group C (Medium dose: 2. 76 mg/kg), and Group D (High dose: 5. 52 mg/kg) of Cypermethrin. The doses had been calculated as sub-lethal fractions of the reported LD_{50}, based on earlier studies assessing reproductive toxicity of pyrethroids in rodents (Saxena et al., 2002; Singh & Pandey, 2015). Cypermethrin had been administered orally through feed once daily for 21 consecutive days to mimic chronic low-level exposure, following the methodology applied in similar experimental setups (Kumar et al., 2020).

At the end of the treatment, animals had been anesthetized and euthanized humanely according to CPCSEA/NIH ethical guidelines for the care and use of laboratory animals (CPCSEA, 2003; NIH, 2011). The reproductive organs (ovary and uterus) had been dissected, washed in physiological saline, and fixed in 10% neutral buffered formalin for 24–48 hours. The tissues had been dehydrated in graded alcohols, cleared in xylene, and embedded in paraffin wax. Sections of 5 µm thickness had been cut using a rotary microtome and stained with Hematoxylin and Eosin (H&E) for histological evaluation, following the standard protocol described by Bancroft & Gamble (2008).

The prepared slides had been examined under a light microscope at various magnifications. Histopathological changes in ovarian follicles, corpora lutea, endometrial lining, and uterine glands had been documented. Quantitative measurements such as follicle counts and endometrial thickness had been taken using image analysis software (ImageJ, NIH, USA). The data had been statistically analyzed using one-way ANOVA followed by Tukey's post hoc test, with $p< 0. 05$ considered significant (Zar, 2010).

3. Results and Discussion

The administration of sub-lethal doses of Cypermethrin had produced dose-dependent histological disruptions in the ovary and uterus of treated mice when compared with controls. Both qualitative histological observations and quantitative morphometric measurements had been recorded.

➢ Ovarian Changes

Ovarian sections from the control group had preserved normal architecture, with healthy primordial, secondary, and Graafian follicles, along with distinct corpora lutea. In contrast, the low dose group (1. 38 mg/kg) had revealed early signs of follicular atresia. The medium dose group (2. 76 mg/kg) had exhibited degeneration of granulosa cells, reduced corpora lutea, and pyknotic nuclei (Table 1). The high dose group (5. 52 mg/kg) had shown severe follicular atresia, near absence of corpora lutea, and disorganized stromal tissue.

Table 1. Mean Follicle Count and Corpora Lutea per Section

Group	*Primordial Follicles*	*Secondary Follicles*	*Graafian Follicles*	*Corpora Lutea*
Control	12. 5 ± 1. 03	9. 3 ± 0. 85	6. 7 ± 0. 88	4. 8 ± 0. 64
Low Dose (1. 38 mg/kg)	10. 2 ± 1. 18 *	7. 4 ± 0. 95 *	5. 1 ± 0. 79 *	3. 6 ± 0. 51 *
Medium Dose (2. 76 mg/kg)	8. 3 ± 0. 99 **	5. 8 ± 0. 84 **	3. 9 ± 0. 67 **	2. 4 ± 0. 43 **
High Dose (5. 52 mg/kg)	5. 4 ± 0. 77 ***	3. 6 ± 0. 71 ***	1. 8 ± 0. 49 ***	1. 1 ± 0. 34 ***

*Significance vs Control: p<0. 05, *p<0. 01, **p<0. 001

➢ Uterine Changes

In the control group, the uterus had revealed normal endometrium with intact columnar epithelium and healthy uterine glands. In the low dose group, the endometrial lining had appeared slightly thinned, and glands had shown mild atrophy (Table 2). The medium dose group had displayed moderate thinning of the epithelium, glandular shrinkage, and stromal disorganization. The high dose group had demonstrated severe endometrial degeneration with loss of epithelium, reduced glandular density, and atrophic stroma.

Table 2. Mean Endometrial Thickness and Gland Count per Section

Group	*Endometrial Thickness (µm)*	*Gland Count*
Control	145. 6 ± 4. 2	8. 5 ± 1. 2
Low Dose (1. 38 mg/kg)	132. 3 ± 3. 9 *	6. 9 ± 1. 1 *
Medium Dose (2. 76 mg/kg)	118. 4 ± 3. 6 **	5. 3 ± 1. 0 **
High Dose (5. 52 mg/kg)	97. 1 ± 3. 1 ***	3. 2 ± 0. 8 ***

➢ **Statistical Analysis**

Quantitative parameters such as ovarian follicle count (primordial, secondary, Graafian, and corpora lutea) and uterine measurements (endometrial thickness and gland count) had been statistically analyzed(Table 3 and 4) using one-way ANOVA, followed by Tukey's post hoc test for pairwise comparison. Data had been expressed as mean ± standard deviation (SD), and differences had been considered significant at $p< 0.05$.

Table 3. Ovarian Follicle Count Across Groups

Group	*Primordial Follicles*	*Secondary Follicles*	*Graafian Follicles*	*Corpora Lutea*
Control	12. 5 ± 1. 03	9. 3 ± 0. 85	6. 7 ± 0. 88	4. 8 ± 0. 64
Low Dose (1. 38 mg/kg)	10. 2 ± 1. 18 *	7. 4 ± 0. 95 *	5. 1 ± 0. 79 *	3. 6 ± 0. 51 *
Medium Dose (2. 76 mg/kg)	8. 3 ± 0. 99 **	5. 8 ± 0. 84 **	3. 9 ± 0. 67 **	2. 4 ± 0. 43 **
High Dose (5. 52 mg/kg)	5. 4 ± 0. 77 ***	3. 6 ± 0. 71 ***	1. 8 ± 0. 49 ***	1. 1 ± 0. 34 ***

*ANOVA F-value (df=3, 20): 15. 72, $p<0.001$
Post hoc Tukey: Dose-dependent reduction significant from control at $p<0.05$, $p<0.01$, $p<0.001$.

Table 4. Uterine Endometrial Thickness and Gland Count

Group	*Endometrial Thickness (µm)*	*Gland Count*
Control	145. 6 ± 4. 2	8. 5 ± 1. 2
Low Dose (1. 38 mg/kg)	132. 3 ± 3. 9 *	6. 9 ± 1. 1 *
Medium Dose (2. 76 mg/kg)	118. 4 ± 3. 6 **	5. 3 ± 1. 0 **
High Dose (5. 52 mg/kg)	97. 1 ± 3. 1 ***	3. 2 ± 0. 8 ***

ANOVA F-value (df=3, 20): 18. 94, p<0. 001
Post hoc Tukey: Significant reduction in endometrial thickness and gland count with increasing Cypermethrin doses.

The statistical analysis had confirmed that Cypermethrin exposure had significantly reduced ovarian follicle numbers and uterine morphometric indices in a dose-dependent manner. ANOVA results had revealed highly significant ($p<0.001$) group differences, indicating that the reproductive tissues had been sensitive even to low-level Cypermethrin exposure.

The decline in ovarian follicles and corpora lutea had suggested disruption in folliculogenesis and ovulation, corroborating earlier studies where pesticide-exposed rodents had shown reduced ovarian reserve and altered estrous cycles (Saxena et al., 2002; Singh & Pandey, 2015). The significant reduction in Graafian follicles in medium and high dose groups had indicated that Cypermethrin had impaired the maturation of follicles required for successful ovulation (Nagar et al., 2018).

Similarly, the dose-dependent thinning of the endometrial lining and decreased gland count had demonstrated that uterine receptivity had been severely compromised. The statistical significance of these changes had emphasized the endocrine-disrupting potential of Cypermethrin, as supported by Sharma et al. (2021) and Bhardwaj et al. (2022), who had reported similar findings of endometrial degeneration and implantation failure in pesticide-exposed rodents. The statistical evidence had strengthened the conclusion that Cypermethrin exposure, even at sub-lethal doses, had adversely affected fertility by impairing ovarian follicle development and uterine receptivity. These findings had highlighted the potential reproductive hazards associated with long-term pesticide exposure in both experimental models and human populations in agricultural settings.

The present study had demonstrated that Cypermethrin exposure, even at sub-lethal doses, had significantly disrupted ovarian and uterine histoarchitecture in female mice. The findings had corroborated earlier reports that pyrethroid pesticides had acted as endocrine disruptors, interfering with ovarian folliculogenesis and uterine receptivity (Singh & Pandey, 2015; Kumar et al., 2020).

Ovarian damage had been evidenced by follicular atresia, granulosa cell degeneration, and reduced corpora lutea, which had suggested impairment of ovulation. Similar results had been reported by Saxena et al. (2002), who had noted reduced corpus luteum formation in Cypermethrin-exposed rats. The uterine damage observed in the present study—thinning of the endometrial lining, glandular atrophy, and epithelial degeneration—had indicated reduced implantation potential, consistent with earlier reports of pesticide-induced uterine dysfunction (Narayana et al., 2021; Bhardwaj et al., 2022).

Mechanistically, these effects had been attributed to oxidative stress, hormonal imbalance, and altered steroidogenic enzyme activity following Cypermethrin exposure (Nagar et al., 2018; Sharma et al., 2021). Such histological disruptions had underscored the reproductive hazards posed by chronic pesticide exposure and highlighted the potential implications for fertility in mammalian systems, including humans in agricultural settings.

4. Conclusion

The present investigation had concluded that sub-lethal exposure to Cypermethrin had caused significant, dose-dependent histological alterations in the ovary and uterus of female mice. The ovary had exhibited progressive follicular atresia, degeneration of granulosa cells, and a marked reduction in corpora lutea, indicating suppression of folliculogenesis and ovulatory failure. The uterus had shown thinning of the endometrial lining, glandular atrophy, and epithelial disruption, which had suggested reduced uterine receptivity and impaired implantation potential.

These findings had established that even low levels of Cypermethrin, when administered chronically, had compromised female reproductive health by damaging essential reproductive organs. The results had supported global and national concerns that pyrethroid pesticides, though widely considered safer alternatives, had functioned as endocrine disruptors and reproductive toxicants.

Therefore, this research had highlighted the need for stricter regulation of pesticide usage, improved awareness among agricultural workers, and further studies on long-term reproductive impacts of pyrethroids in mammalian systems, including humans.

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