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Original Research Article

The Effects of 3,4-Methylenedioxymethamphetamine on Reproductive Hormones, Organ Weight, and Fertility Outcomes in Female Wistar Rats

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ABSRTACT

Hormones play significant role in reproduction, and psychoactive substances such as 3,4-Methylenedioxymethamphetamine (MDMA) can significantly disrupt these hormonal activities. Substance abuse, once considered a male phenomenon, now records increasing women indulgence. MDMA's effects on female fertility remain understudied. This study assessed the impact of MDMA on body and organ weights, hormonal profile, and reproductive outcomes in female Wistar rats. Thirty female rats were divided into three groups (n = 30): Group A (control), Group B (80 mg/kg MDMA), and Group C (160 mg/kg MDMA). Hormonal assays and organ weight were evaluated. Data were analyzed using SPSS version 29.0, with significance at $p \leq 0.05$. Body weight showed no significant differences ($p = 0.21$), but ovarian weight increased in treated groups. Uterine weight was unaffected. Group C showed significant body weight reduction ($p = 0.01$). LH levels declined significantly ($p = 0.02$); FSH and PRL remained unchanged. Group B had elevated progesterone, Group C showed increased estradiol, while testosterone decreased in Group B but increased in Group C. Pregnancy success was 100% in controls, 20% in Group B, and 0% in Group C. MDMA disrupted reproductive hormones and ovarian weight, leading to reduced fertility in female Wistar rats.

Keywords: 3-4 Methylenedioxymethamphetamine, Hormones, Organ Weights, Fertility, Wistar Rats.

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Introduction

Substance and drug abuse remain a significant global health concern, with widespread consequences for individuals and society. The United Nations Office on Drugs and Crime (UNODC) reports that substance abuse plays a significant role in various socio-economic issues, such as escalating healthcare expenses and higher rates of criminal behavior.[1] Historically, drug abuse was regarded as a predominantly male issue, with research and policy interventions largely focused on men. However, recent data reveal a growing trend in substance use among women and the associated health implications.[2] The prevalence of substance abuse among women is increasing. The 2018 Global Burden of Disease (GBD) Study estimated that approximately 46 million women are affected by alcohol use disorders, with the highest rates recorded in Europe.[3] Furthermore, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reports that women constitute about one-quarter of individuals with illicit drug problems in Europe.[2,4] Globally, women account for roughly one-third of drug users, and one in five injecting drug users is female.[5] This trend is concerning, as women often experience distinct health consequences, including menstrual irregularities, fertility disorders, breast cancer, and complications during pregnancy.[6,7]

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In Nigeria, drug abuse is increasingly recognized as a major public health challenge. The 2018 UNODC report revealed that one in seven Nigerians aged 15–60 years had used drugs in the past year, with one in five of those users developing a drug use disorder.[5] Among the frequently misused substances, 3,4-methylenedioxymethamphetamine (MDMA) widely known as Ecstasy or Molly, has become increasingly popular, especially among young people. MDMA is a synthetic psychoactive substance with both stimulant and hallucinogenic effects and is often taken alongside alcohol or cannabis.[8,9]

Despite its growing prevalence, the specific effects of MDMA on female reproductive health remain underexplored. Research has shown that women may be more susceptible to drug-related harm, with gender-specific patterns of addiction and adverse health outcomes.[10] Although MDMA's psychological and physiological effects have been widely studied, there is limited literature on its impact on female reproductive function. This study aims to address that gap by investigating the effects of MDMA on female reproductive health. The findings are essential for informing public health interventions and guiding policies that aim to mitigate the harmful consequences of drug abuse, especially for women who face unique vulnerabilities.

Materials and Methods

Drug and Reagents

The primary drug used in this study was 3,4-methylenedioxymethamphetamine (MDMA), administered orally to female Wistar rats at doses of 80 mg/kg and 160 mg/kg body weight. All experimental animals were bred and maintained in the Animal House of the Department of Anatomy, University of Benin. Standard laboratory equipment included rat feed, precision weighing scales, dissection instruments, tissue preparation devices, and distilled water provided *ad libitum*.

Hormonal assessments were conducted using enzyme-linked immunosorbent assay (ELISA) kits specific for follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), testosterone, progesterone, and estradiol. The kits were procured from Monobind Inc. (Lake Forest, California, USA), and Hormone quantification was performed with a Stat Fax 4200 ELISA Plate Reader. Additional instruments included centrifuges for serum separation, spectrophotometers for biochemical analysis, and IBM SPSS version 29.0 for data analysis.

Animal Care

Thirty adult female Wistar rats (weighing 180–220 g) were procured from the Department of Anatomy Animal House, University of Benin. The animals were acclimated for two weeks under standardized conditions, housed in wire-mesh cages with a 12-hour light/dark cycle, an ambient temperature of 22 ± 2 °C, and 50–60% relative humidity. They had unrestricted access to food and water throughout the study. This acclimatization ensured the animals were physiologically stable and stress-free before experimental procedures commenced.

Experimental Design and Drug Administration

The animals were randomly assigned into three groups, each consisting of 10 rats. Group A served as the control and received distilled water. Groups B and C were administered MDMA orally via gavage at doses of 80 mg/kg and 160 mg/kg, respectively, for a continuous period of 28 days. The median lethal dose (LD_{50}) of MDMA was determined to be 316.2 mg/kg based on Lorke's method.[11] At the end of the treatment phase, five rats from each group were euthanized for the evaluation of body and organ weights and for the collection of blood samples for hormonal analysis. The remaining five rats in each group were retained for mating studies to assess fertility and reproductive outcomes.

Mating Procedure

Following the 28-day treatment period, the remaining female rats were paired overnight with proven fertile, untreated male rats. Mating was confirmed the next morning by the presence of spermatozoa or vaginal plugs in vaginal smears, which marked gestation day one (GD 1). Pregnant rats were monitored for pregnancy success and reproductive parameters.

Hormonal Analysis

Blood was collected by cardiac puncture post-sacrifice and allowed to clot at room temperature. Samples were centrifuged at 3000 rpm for 10–15 minutes. The resulting serum was aliquoted into sterile tubes and stored at −20 °C until analysis. Serum levels of FSH, LH, PRL, testosterone, progesterone, and estradiol were quantified using Monobind ELISA kits, according to the manufacturer's instructions. Samples were brought to room temperature and pipetted into pre-coated microplate wells. Each was run in duplicate alongside a standard calibration curve. After incubation at 37 °C, wells were washed and incubated with horseradish peroxidase-conjugated antibodies. A chromogenic substrate (TMB) was added, producing a colorimetric change proportional to hormone concentration. The reaction was halted using stop solution, and absorbance was measured at 450 nm using the Stat Fax 4200 ELISA reader. Hormone concentrations were calculated from standard curves. Pituitary hormones (FSH, LH, PRL) were expressed in milliunits per milliliter (mU/mL), while steroid hormones (testosterone, progesterone, estradiol) were reported in nanograms per milliliter (ng/mL), per manufacturer standards.

Statistical Analysis

The data were analyzed using one-way analysis of variance (ANOVA), followed by a Least Significant Difference (LSD) post hoc test. Results are expressed as mean ± standard deviation (SD), with statistical significance defined at $p \leq 0.05$. All analyses were conducted using IBM SPSS software, version 29.0.

Ethical Consideration

This study was conducted as part of a doctoral dissertation in the Department of Anatomy, University of Benin. Ethical clearance was granted by the Research and Ethics Committee of the College of Medical Sciences, University of Benin (Approval No.: CMS/REC/2024/620). All experimental procedures involving animals adhered to the guidelines outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals.[12]

Results and Discussion

The analysis of body and reproductive organ weights presented in Table 1 revealed several key findings. There was no statistically significant difference in the final body weight of both treated groups compared to the control group ($p = 0.21$). However, Group C exhibited a statistically significant reduction in weight change ($p = 0.01$), indicating possible systemic toxicity or metabolic disruption due to high-dose MDMA exposure. This reduction in weight change, though not reflected in final body weight, may signal subtle yet impactful physiological stress.

Table 1: Relationship in Pre-gestational Body Weight (n=15)

Test	Group A	Group B	Group C	p-Value
Initial Body Weight	179.40 ± 4.70	198.20 ± 12.43	183.40 ± 3.26	0.24
Ovarian Weight	0.12 ± 0.02	0. 24 ± 0. 02#	0.20 ± 0.04#	0.05*
Uterine Weight	0.18 ± 0.05	0. 36 ± 0.08	0.16 ± 0.06	0.10
Weight Change	19.20 ± 3.21	4.20 ± 1.52	-5.20 ± 7.95#	0.01*
Ovarian-somatic Index	0.06 ± 0.00	0.11 ± 0.01#	0.11 ± 0.02	0.08
Utero-somatic Index	0.08 ± 0.02	0.17 ± 0.03	0.09 ± 0.03	0.15

Note: The results are presented in tables; Data are represented as Mean ± SEM; (+) means weight gain; (-) means weight loss. Group A= control, Group B= 80mg/kg body weight, Group C= 160mg/kg body weight; # = intergroup differences, * = significant differences at $P \leq 0.05$.

Ovarian weights were significantly increased in both Group B and Group C, suggesting possible MDMA-induced ovarian hypertrophy or edema. This finding aligns with the hypothesis that MDMA may interfere with gonadal regulation, possibly through pituitary or hypothalamic disruption. In contrast, uterine weights did not differ significantly across groups, implying that MDMA's effect on the uterus may be less pronounced at the structural level, at least during the pre-gestational exposure window. Furthermore, although the ovario-somatic index and utero-somatic index values were altered, these differences were not statistically significant ($p > 0.05$). This may indicate that, while organ weights increased or decreased, the changes were not sufficient relative to overall body weight to yield meaningful differences in organ-to-body weight ratios. Overall, the findings suggest that high-dose MDMA exposure during the pre-gestational period leads to systemic effects that can influence reproductive parameters, such as ovarian size and body weight regulation. These effects may stem from neuroendocrine disruptions, consistent with existing literature documenting MDMA's impact on energy metabolism, appetite control, and hormonal regulation in rodents.[13,14] As presented in Table 2, exposure to MDMA during the pre-gestational period induced notable alterations in pituitary and ovarian hormone levels in female Wistar rats. Follicle-stimulating hormone (FSH) levels did not differ significantly among the groups ($p = 0.12$), suggesting that early follicular recruitment was not substantially affected by MDMA at the administered doses. In contrast, luteinizing hormone (LH) levels were significantly reduced in both treatment groups ($p = 0.02$), indicating suppression of the hypothalamic-pituitary-gonadal (HPG) axis. This finding is consistent with previous studies demonstrating that MDMA suppresses gonadotropin-releasing hormone (GnRH) expression, leading to downstream reductions in LH and testosterone secretion in rodents.[15] Prolactin (PRL) levels showed no statistically significant change in the treated groups, suggesting that MDMA had minimal influence on

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lactotroph activity or hypothalamic dopaminergic regulation under the conditions of this study. However, progesterone levels were significantly elevated in Group B (p = 0.05), which may indicate preserved or transiently enhanced luteal activity. This elevation may partially account for the 20% pregnancy success observed in this group (Table 3). Conversely, no significant difference in progesterone levels was observed in Group C, possibly reflecting impaired corpus luteum function or luteolysis at higher MDMA exposure.

Table 2: Pre-gestational Stage Hormone Analysis

Hormone	Group A	Group B	Group C	P-Value
FSH (mU/ml)	0.81 ± 0.10	0.60 ± 0.09	0.52 ± 0.05	0.12
LH (mU/ml)	0.51 ± 0.13	0.18 ± 0.06#	0.04 ± 0.04#	0.02*
Prolactin (ng/ml)	0.80 ± 0.02	0.73 ± 0.01	0.82 ± 0.09	0.54
Progesterone (ng/ml)	14.69 ± 0.37	26.54 ± 3.19#	17.09 ± 3.63	0.05*
Estradol (ng/ml)	29.81 ± 2.03	43.52 ± 1.27	141.53 ± 12.35#	0.00*
Testosterone (ng/ml)	1.12 ± 0.14	0.48 ± 0.00#	1.48 ± 0.09#	0.00*

Note: The results are presented in tables; Data are represented as Mean ± SEM; (+) means weight gain; (-) means weight loss. Group A= control, Group B= 80mg/kg body weight, Group C= 160mg/kg body weight; # = intergroup differences, * = significant differences at P ≤ 0.05.

In terms of estrogenic response, estradiol levels were significantly elevated in Group C (p = 0.00), while remaining statistically unchanged in Group B. This rise in estradiol may reflect enhanced aromatase activity or follicular persistence, potentially triggered by altered ovarian steroidogenesis secondary to MDMA-induced neuroendocrine disruption.[16,17] Furthermore, a biphasic response was observed in testosterone outcome. Group B exhibited a significant reduction in testosterone levels (0.48 ± 0.00 ng/mL vs. 1.12 ± 0.14 ng/mL in control), whereas Group C showed a significant increase (1.48 ± 0.09 ng/mL) (p = 0.00). This dual pattern suggests that MDMA may initially suppress androgen production at moderate doses but stimulate androgenic activity at higher doses, possibly through dysregulation of theca cell function or feedback disruption within the HPG axis.[17,18]

Collectively, these findings indicate that MDMA exposure causes dose-dependent and hormone-specific disruptions in female reproductive endocrinology. Suppressed LH, altered progesterone and estradiol levels, and the biphasic testosterone response reflect complex neuroendocrine interference likely to impair ovulation, luteal support, and endometrial receptivity. These findings are consistent with previous studies demonstrating MDMA-induced endocrine dysregulation, oxidative stress,[19] and impaired reproductive function in female rodents.[15,16,17,18]

Table 3 presents the pregnancy outcomes following 28 days of MDMA administration in female Wistar rats. Each group initially comprised five rats designated for mating. In the control group (Group A), all five rats successfully mated and delivered, yielding a total of 42 litters, with 100% pregnancy success. In contrast, only three rats mated in Group B, and among them, only one achieved pregnancy, producing four litters, representing a 20% pregnancy success rate. Group C showed complete reproductive failure, with only two rats mating and none achieving pregnancy or producing litters.

Table 3: Pregnancy Success Rate and Outcomes at pre-gestation stage (n=15)

Parameter	Control	80mg	160mg
Number of female Wistar rats	5	5	5
Number of Dams	5	3	2
Littered Dams	5	1	0
Litter size	42	4	0
Litter weight (g)	5.36±0.10	5.15±0.05	0
% Pregnancy outcomes	100	20	0

Litter weights, presented as mean ± standard deviation, were recorded for the pups in Groups A and B. No gross morphological malformations were observed in the litters across all groups. However, the values reflect average litter weights and reduced litter size in the treated group, further supporting the dose-dependent reproductive toxicity of MDMA. These findings underscore the severe impact of MDMA on female fertility, implantation, and successful gestation. The control group's full pregnancy success contrasts sharply with the impaired reproductive outcomes observed in the MDMA-treated groups. Group B's reduced pregnancy rate and litter size suggest partial implantation failure or early embryonic loss, likely stemming from disrupted luteal support and hormonal imbalance, as previously discussed. The total reproductive failure in Group C, despite evidence of mating, highlights the profound inhibitory effects of high-dose MDMA on conception or early embryogenesis. Such reproductive impairment may be explained by MDMA's ability to disrupt ovarian-pituitary communication, impair uterine receptivity, and increase oxidative stress,[19] all of which are essential for implantation and pregnancy maintenance.[20-22] Recent experimental models support these findings: gestational exposure to MDMA in mice has been shown to cause neonatal growth retardation and reduced pup survival (early postnatal days), accentuating the drug's impact on reproductive success and offspring viability.[23] Additionally, in vitro studies using whole embryo cultures have documented concentration-dependent embryo-toxicity of MDMA and its metabolites, further implicating MDMA in early embryonic impairment.[24] Overall, these outcomes reinforce the hypothesis that MDMA exposure during the pre-gestational period disrupts the hormonal and physiological milieu required for successful mating, implantation, and pregnancy maintenance. The findings align with existing literature indicating that psychoactive substances can impair fertility through endocrine disruption and uterine receptivity deficits.[24] Such effects raise concerns about the reproductive risks of MDMA, particularly with chronic or high-dose exposure in women of reproductive age.

Conclusion

These findings demonstrate that MDMA exposure induces dose-dependent reproductive toxicity, significantly disrupting: Endocrine balance, Follicular development, Ovulation, and Pregnancy success. At higher doses, complete reproductive failure was observed. While MDMA altered ovarian hormone profiles and organ weights, it had minimal impact on overall body weight and prolactin levels. The results emphasize the potential of MDMA to impair female fertility through complex neuroendocrine and gonadal pathways.

Conflict of interest

The authors declare no conflict of interest

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them

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