Archives of Toxicology (2025) 99:4243–4261
https://doi.org/10.1007/s00204-025-04122-z

GENOTOXICITY AND CARCINOGENICITY

Gestational vortioxetine exposure impairs pregnancy outcomes and fetal brain development via modulation of BDNF/Bax-Bcl2/5-HT pathways in rats

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Received: 15 May 2025 / Accepted: 25 June 2025 / Published online: 4 July 2025

Abstract

Pregnancy presents a critical period during which the use of antidepressants requires cautious evaluation, especially due to the high incidence of depression in women of reproductive age. Vortioxetine hydrobromide (VOX), a newer multimodal antidepressant, is increasingly favored for its improved efficacy and tolerability. However, its safety profile during gestation and its potential long-term impact on fetal brain development remain insufficiently explored. This study aimed to assess the reproductive and developmental neurotoxicity of VOX administered at clinically relevant doses during pregnancy using a Wistar rat model. Pregnant dams received daily oral doses of either 1 mg/kg or 2 mg/kg of VOX from gestation day (GD) 6 to 21. On GD 21, the dams were euthanized, and fetuses along with placental tissues were collected for further analysis. Fetal brains underwent morphological, neurochemical, and histopathological evaluations. Exposure to VOX at the higher dose led to significant maternal and fetal toxicity, marked by reduced maternal weight gain, smaller litter sizes, and decreased fetal and placental weights. Notably, adverse neurodevelopmental outcomes were observed, including reduced fetal brain dimensions, cortical and hippocampal thinning, altered levels of brain-derived neurotrophic factor (BDNF), disrupted monoaminergic neurotransmitter levels (serotonin, dopamine, and norepinephrine), elevated apoptotic markers (Bax/Bcl-2 ratio), and increased acetylcholinesterase activity. These findings suggest that prenatal VOX exposure disrupts essential neurodevelopmental pathways, particularly those involving BDNF and monoaminergic signaling, potentially leading to persistent alterations in brain development. This is the first study to systematically demonstrate the developmental neurotoxicity of VOX, emphasizing the urgent need for further investigation into its safety during pregnancy.

Keywords Pregnancy · Vortioxetine · BDNF · Apoptosis · Serotonin · Fetal toxicity · Neurotoxicity

Abbreviations

AD	Antidepressant
SSRIs	Selective serotonin reuptake inhibitors
SNRIs	Serotonin–norepinephrine reuptake inhibitors
5-HT	Serotonin/5-hydroxytryptamine
IUGR	Intrauterine growth restriction
Bax	Bcl-2-associated protein X
Bcl-2	B-cell lymphoma 2 protein
VOX	Vortioxetine hydrobromide
SMS	Serotonin modulator and stimulator
DA	Dopamine
NE	Norepinephrine
AChE	Acetylcholinesterase
BDNF	Brain-derived neurotrophic factor
GD	Gestation day
PFC	Prefrontal cortex
PCL	Pyramidal cell layer
CA	Cornu ammonis
GCL	Granular cell layer
DG	Dentate gyrus
ATI	Acetylthiocholine iodide
RT-PCR	Real-time polymerase chain reaction
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
SEM	Standard error of the mean
ACh	Acetylcholine

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Introduction

Depression is a common complication during pregnancy, affecting approximately 10–20% of expectant mothers worldwide (Gavin et al. 2005; Kessler et al. 2009). Left untreated, maternal depression has been associated with adverse outcomes, including preterm birth, low birth weight, and long-term neurodevelopmental challenges in offspring (Chung et al. 2001; Jahan et al. 2021; Quiñones et al. 2023). Consequently, antidepressant (AD) therapy is often considered essential to safeguard maternal well-being and optimize neonatal health. However, several classes of ADs, notably selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), are known to cross the placental barrier and interfere with fetal neurodevelopment, raising concerns regarding their long-term safety (Rampono et al. 2004; Dubovicky et al. 2017).

The intrauterine environment constitutes a critical determinant of fetal brain development. Throughout gestation, the central nervous system undergoes intricate and highly regulated processes, including neurogenesis, synaptogenesis, and cortical circuit formation (Stiles and Jernigan 2010). These developmental windows are particularly vulnerable to external perturbations, including pharmacological exposures, which can lead to subtle or overt neurodevelopmental deficits with enduring consequences for cognition and behavior.

Among the key modulators of fetal brain development is serotonin (5-hydroxytryptamine, 5-HT), a neurotransmitter essential for neuronal proliferation, migration, differentiation, and synapse formation (Gaspar et al. 2003; Bonnin et al. 2011). ADs that influence serotonergic transmission, particularly SSRIs and related agents, can readily cross the placenta and disrupt fetal serotonergic homeostasis (Oberlander et al. 2008). A growing body of literature indicates that pharmacological interference with 5-HT reuptake during critical stages of prenatal development may increase vulnerability to a spectrum of adverse reproductive outcomes. These include heightened risks of spontaneous abortion, intrauterine growth restriction (IUGR), congenital anomalies—both minor and major—as well as stillbirth (Grote et al. 2010; Oyebode et al. 2012). Further, several studies have reported significant associations between prenatal SSRI exposure and earlier gestational age at delivery, lower neonatal birth weight, and an increase in placental mass compared to unmedicated pregnant populations (Simon et al. 2002; Rotem-Kohavi and Oberlander 2017; Frayne et al. 2018). Notably, fluoxetine—one of the most commonly prescribed SSRIs—has been shown to suppress maternal appetite and limit gestational weight gain, which in turn may adversely impact fetal growth (Chambers et al. 1996; Yonkers et al. 2012; Olivier et al. 2013). Despite these clinical findings, the molecular mechanisms contributing to such growth impairments remain poorly characterized.

Recent prospective studies, encompassing both human cohorts and animal models, have extended these concerns to long-term neurodevelopmental outcomes. SSRIs and SNRIs administered during pregnancy have been linked to alterations in brain structure and delayed developmental trajectories in exposed offspring (El Marroun et al. 2012; Bérard et al. 2017; Chen et al. 2021; Sánchez et al. 2021; Singh et al. 2023; Koc et al. 2023). Previous research on venlafaxine has substantiated these risks through investigations into its developmental toxicity, which led to pronounced cytoarchitectural disorganization in the fetal brain, heightened apoptotic activity, and altered expression of cell death regulators Bcl-2-associated protein X (Bax) and B-cell lymphoma 2 protein (Bcl-2) in neocortical regions including the striatum and hippocampus (Singh et al. 2015, 2022). These findings align with earlier rodent studies, which also demonstrated that perinatal AD exposure disrupts normal brain development and elicits neurotoxic responses (Cabrera-Vera et al. 1997; Sahoo et al. 2010; Smit-Rigter et al. 2012; Svirsky et al. 2016). Furthermore, exposure to fluoxetine during gestation has been shown to induce notable neurochemical disturbances in the developing rat brain (Chen et al. 2021; Bhat et al. 2023).

In response to these concerns, research has increasingly focused on identifying alternative newer serotonergic ADs, especially those with multimodal mechanisms with improved safety profiles for use in pregnancy. Vortioxetine hydrobromide (VOX), a novel AD categorized as a serotonin modulator and stimulator (SMS), exerts its effects through 5-HT transporter inhibition combined with modulation of multiple 5-HT receptor subtypes (5-HT1A agonism, 5-HT3 antagonism, among others) (Baldwin et al. 2016). While VOX offers improved tolerability and cognitive benefits compared to traditional SSRIs, data regarding its safety during pregnancy remain sparse. Recent pharmacovigilance and case reports suggest that VOX exposure during human pregnancy may not substantially elevate risks for major congenital malformations (Shweiki and Diav-Citrin 2021), no adverse developmental effects observed in infants, however, it contributes to the onset of severe neonatal asphyxia (Kiribayashi et al. 2024). A recent preclinical study showed that prenatal and lactational exposure to VOX at higher dose (20 mg/kg) induced anxiety-like symptoms in their offspring (Ergun et al. 2024). This showed the paucity of controlled experimental studies, particularly regarding embryo-fetal development and pregnancy outcomes, highlights a critical knowledge gap.

Building upon our previous findings that prenatal VOX exposure induces increased anxiety-like and

depressive-like behavior, neurodevelopmental delay, mild structural brain abnormalities, and biochemical and neurochemical alterations in young adult offspring (Agrawal et al. 2023; Singh et al. 2024, 2025), we hypothesized that gestational VOX exposure could lead to developmental neurotoxicity via disruptions in monoaminergic, neurotrophic, and apoptotic pathways in fetal brain. Notably, our earlier results demonstrated significant reductions in adult brain length without affecting brain weight, accompanied by altered thigmotactic behavior during cognitive testing—pointing toward subtle, but potentially consequential neurodevelopmental impairments. Despite a rising interest in the neurodevelopmental consequences of prenatal AD exposure, no prior studies have systematically evaluated the impact of VOX on a comprehensive panel of reproductive, fetal growth, and pregnancy outcomes, including neurohistopathological, neurochemical, and apoptotic molecular markers, in a preclinical model.

Given these considerations, the present study systematically evaluated the effects of prenatal VOX exposure on maternal metabolic parameters, pregnancy outcomes, fetal growth indices, brain morphometry, and neurohistological changes. Furthermore, neurochemical markers [5-HT, dopamine (DA), norepinephrine (NE)], acetylcholinesterase (AChE) activity, brain-derived neurotrophic factor (BDNF), and apoptotic regulatory gene expression (Bax and Bcl-2) were assessed to delineate underlying mechanistic pathways. Particular emphasis was placed on identifying disruptions in the BDNF/Bax–Bcl-2/5-HT axis, a signaling pathway critical for neuronal survival and differentiation. Through this comprehensive experimental framework, the study aims to contribute essential insights into the developmental neurotoxicity profile of VOX when administered during gestation.

Materials and methods

Animals and housing conditions

This study was conducted using adult, nulliparous Wistar rats (180 ± 10 g) bred in-house at the Animal Facility of the University of Allahabad. Animals were maintained under controlled laboratory conditions with a 12-h light/dark cycle, ambient temperature of 24 ± 2 °C, and relative humidity of approximately 60%. Standard rodent pellet feed and filtered tap water were supplied ad libitum. Rats were housed in polypropylene cages lined with autoclaved rice husk bedding and acclimatized for 7 days prior to the experiment. All procedures were performed in accordance with institutional ethical guidelines and approved by the Institutional Animal Ethics Committee (IAEC/AU/2019(1)/05), following CPCSEA norms.

Mating and pregnancy confirmation

Female rats in the proestrus phase were housed overnight with sexually mature males at a 2:1 ratio. The presence of spermatozoa in the vaginal smear the following morning was considered indicative of successful mating and designated as gestation day (GD) 0. Sperm positive female rats were randomly assigned to control or treatment groups and housed individually to prevent stress-related interference in gestation.

Drug and dose selection

VOX, a clinically prescribed multimodal AD, was obtained from Lundbeck India Private Limited, Bengaluru, India (trade name Trintellix). Doses were selected based on human therapeutic ranges (5–20 mg/day) which were converted to equivalent rat doses using established conversion methods based on body surface area (mg/m^2) and body weight (mg/kg) (Jang-Woo Shin et al. 2010; Nair and Jacob 2016). Accordingly, two dose groups were established: 1 mg/kg/day and 2 mg/kg/day. The drug was freshly dissolved in distilled water and administered orally via gavage.

Experimental design

Pregnant dams ($n = 6$ per group) were divided into three groups: control (vehicle treated), VOX 1 mg/kg, and VOX 2 mg/kg. From GD 6 to GD 21, animals received daily oral administration of their assigned treatment at a consistent time (9:00–9:30 AM). All doses were adjusted according to maternal body weight recorded on alternate days. On GD 21, all dams were anesthetized with intraperitoneal injection of sodium pentobarbital (30 mg/kg) following the guidelines of the Rat Anesthesia–Analgesia Formulary, 2021. Uterine horns were exposed via uterectomy, and fetuses with placentas were collected for subsequent evaluation. A subset of fetuses from each group was fixed in 10% neutral buffered formaldehyde for histological examination. Additionally, three fetuses per dam were dissected following intracardiac perfusion; their brains were collected, rinsed with saline, and stored at – 20 °C for subsequent neurochemical and biochemical analyses (Fig. 1).

Maternal monitoring

Maternal body weight and food consumption were monitored daily for both control and VOX-treated dams throughout the gestation period (GD 1–21). Data were consistently recorded between 9:00 and 9:30 AM and reported as a 3-day average. Additionally, spontaneous locomotor activity of

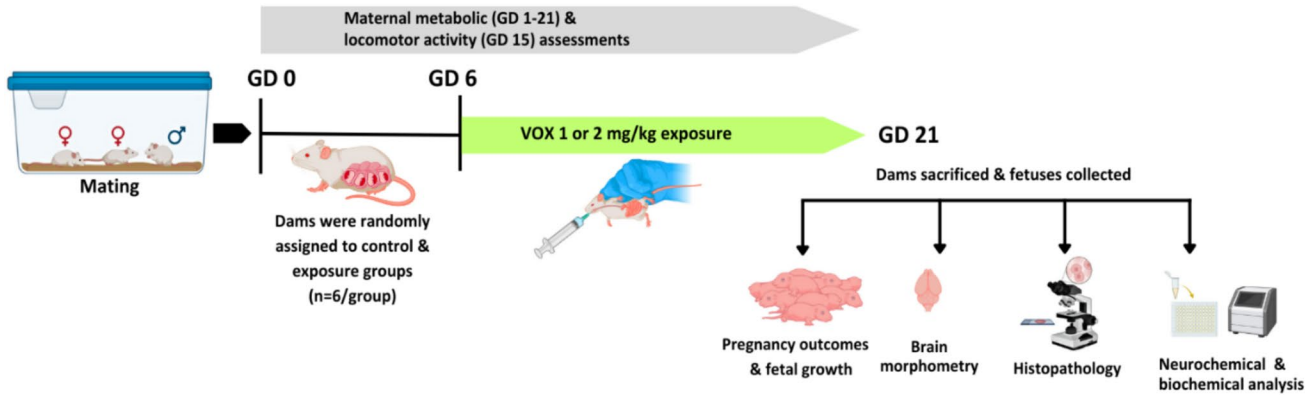

Fig. 1 Schematic diagram illustrating the experimental design

pregnant rats was assessed on GD 15 using an open field apparatus and a digital photoactometer to detect potential drug-induced changes in motor behavior or sedation.

Evaluation of pregnancy and fetal outcomes

Postmortem analysis on GD 21 included examination of uterine horns for the number of implantations, litter size, resorptions, and live and dead fetuses. Uterine horn weight, placental size and weight, and fetal size and weight were also measured for all groups. Fetuses were examined externally to rule out gross morphological anomalies. One fetus per litter was randomly selected for detailed brain analysis to minimize litter effect bias.

Brain collection and morphometry

Brains were carefully dissected from randomly selected fetuses ($n = 6$ brains per group) after removal of olfactory bulbs and brainstem to ensure standardization. Brains were weighed immediately using a digital electronic balance (least count 0.001 g) and their length measured using a millimeter-scale graph paper. Specimens were then fixed in 10% neutral buffered formaldehyde for histological analysis or frozen at – 20 °C for biochemical and neurochemical assays.

Histological analysis of the brain

Fixed fetal brains ($n = 6$ per group) were dehydrated in ascending alcohol series, cleared in xylene, and embedded in paraffin. Coronal sections (8 µm) were cut using a rotary microtome and mounted on poly-L-lysine–coated glass slides. Sections were stained with hematoxylin and eosin (H&E) following the protocol of Suvarna et al. and examined under a bright-field microscope (Suvarna et al. 2019). The "Atlas of prenatal rat brain development" (Altman et al. 1995) was used to identify specific brain regions, i.e., the prefrontal cortex (PFC) and the hippocampus in coronal sections from both control and drug-exposed groups and analyzed with a light microscope. The photomicrographs were captured with an attached digital camera and cortical as well as hippocampal layer thicknesses (total and subregions) were measured using ImageJ software. Neocortical zones, including the cortical plate, intermediate zone, and subventricular zone, and the hippocampal region, including the pyramidal cell layer (PCL) of the cornu ammonis (CA) 1 and CA3 region and the granular cell layer (GCL) of the dentate gyrus (DG) region, were analyzed across five representative sections for each brain per dam ($n = 30$ sections per group).

Neurochemical and biochemical analysis of the brain

Monoamines estimation

Whole brains were homogenized in ice-cold phosphate buffer (0.1 M, pH 7.4), and supernatants were collected after centrifugation. Monoamine levels—5-HT, DA, and NE were estimated using fluorometric methods described by Schlumpf et al., with results normalized to protein content (Schlumpf et al. 1974).

Acetylcholinesterase activity

AChE activity was measured according to Ellman's colorimetric method (Ellman et al. 1961) using acetylthiocholine iodide (ATI) as a substrate and expressed as µmol/min/mg protein. The total protein of each sample was estimated by using Bradford's method (Bradford 1976).

Gene expression analysis

Total RNA was extracted from frozen fetal brains ($n = 6$ per group) using TRIzol reagent (Sigma-Aldrich, India). Purity and concentration were determined spectrophotometrically. cDNA synthesis was performed using a reverse transcription kit (ThermoFisher Scientific, India) following the manufacturer's instructions, and gene expression levels of BDNF, Bax, and Bcl-2 were quantified by SYBR Green-based real-time polymerase chain reaction (RT-PCR) using gene-specific primers (Table 1). For quantitative gene expression, relative mRNA levels of BDNF, Bax, and Bcl-2 were normalized against glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as the internal control, and fold changes were calculated in comparison to the control group using the $2^{-\Delta\Delta Ct}$ method (Wong and Medrano 2005).

Statistical analysis

Statistical comparisons between experimental groups were performed using one-way ANOVA for evaluating neurochemical, biochemical parameters and histomorphometric measurements. Maternal metabolic data were analyzed using two-way ANOVA to account for treatment and day interactions, followed by Tukey's multiple comparisons test for post hoc analysis. All data are expressed as mean ± standard error of the mean (SEM). Statistical analyses were conducted using GraphPad Prism software (version 9.5.1; GraphPad Software, San Diego, CA, USA). A p-value threshold of < 0.05 was considered statistically significant, with significance levels denoted as $*p < 0.05$, $**p < 0.01$, and $\#p < 0.001$.

Table 1 Oligonucleotide primers used in SYBR Green RT-PCR

Gene	Primer sequence (5'–3')	Product length
GAPDH	F- CAACCCAACCCTCAACAGGGA R- TGAAGGGGTCGTTGATGGCAA	179
BDNF	F- AAATAATGTCTGACCCCAGTG R- CTTCATGCAACCGAAGTATG	395
Bax	F- TGGTTGCCCTTTTCTACTTT R- ACCTGAGGTTTATTGGCAC	405
Bcl-2	F- CTTTGAGTTCGGTGGGGTCA R- GCCCAGACTCATTCAACCAGA	168

Results

Effects of VOX exposure on maternal health and metabolic parameters

Daily food consumption and body weight gain

Two-way ANOVA followed by Tukey's post hoc test revealed a statistically significant, dose-dependent decline in daily food consumption among VOX-treated pregnant rats between GD 6 and 21 [F (12, 105) = 2.23, $p < 0.05$]. This reduction in intake was more pronounced in the 2 mg/kg treatment group, which exhibited a marked hypophagic response compared to controls ($p < 0.01$). Correspondingly, maternal body weight gain was also significantly reduced across the treatment groups over the same gestational period, as shown by two-way ANOVA with Tukey's post hoc test [F (12, 105) = 1.90, $p < 0.05$]. The decline in maternal weight was most evident during the later phase of pregnancy (GD 16–21), particularly in the high-dose group, whereas minimal change was observed during GD 13–15. No significant differences in either maternal food intake or weight gain were observed during the pre-treatment period (GD 1–6) between control and VOX-exposed groups, indicating that baseline metabolic parameters were comparable prior to drug administration (Fig. 2).

Maternal locomotor activity

As illustrated in Fig. 3, maternal locomotor activity exhibited a dose-dependent decline in both the open field and photoactometer assessments. Analysis of ambulation scores, reflecting the number of movements across the open field revealed a significant reduction in treated groups compared to controls, with one-way ANOVA followed by Tukey's post hoc test indicating a dose-related suppression in activity [F (2, 15) = 9.47, $p < 0.01$]. A similar trend was observed in the automated photoactometer test, where total activity counts were significantly decreased in VOX-exposed pregnant rats in a dose-dependent manner [F (2, 15) = 6.39, $p < 0.01$]. The decreased maternal locomotor activity was more prominent in the 2 mg/kg VOX treatment group. These findings suggest that VOX may exert a mild sedative or neuromotor-suppressive effect in pregnant dams, particularly at the higher dose.

Effect of VOX exposure on pregnancy outcomes

To obtain six confirmed pregnant rats per group, several sperm-positive females were excluded due to the absence of gestational progression and were classified as pseudopregnancy. The frequency of pseudopregnancy was higher in

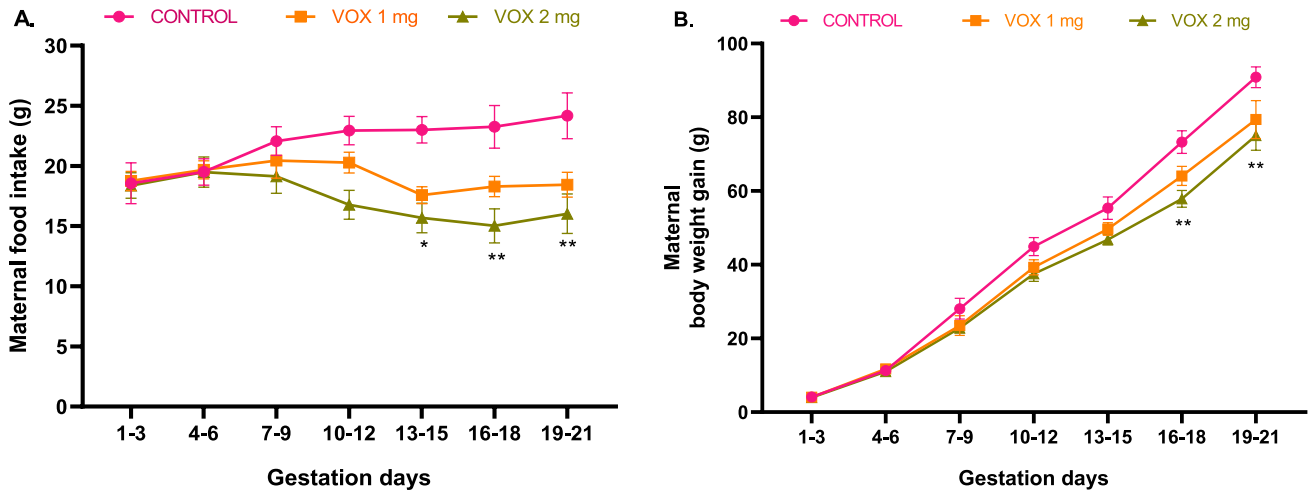

Fig. 2 Effect of VOX (1 and 2 mg) exposure on **A** maternal food intake and **B** maternal body weight gain at different gestational days (GD 1–21). All data represent the mean ± SEM (g) value ($n = 6$ per group). The symbols * and ** indicate significance levels at $p < 0.05$ and $p < 0.01$, respectively, between the control and VOX-exposed groups for a two-way ANOVA followed by Tukey's multiple comparison test

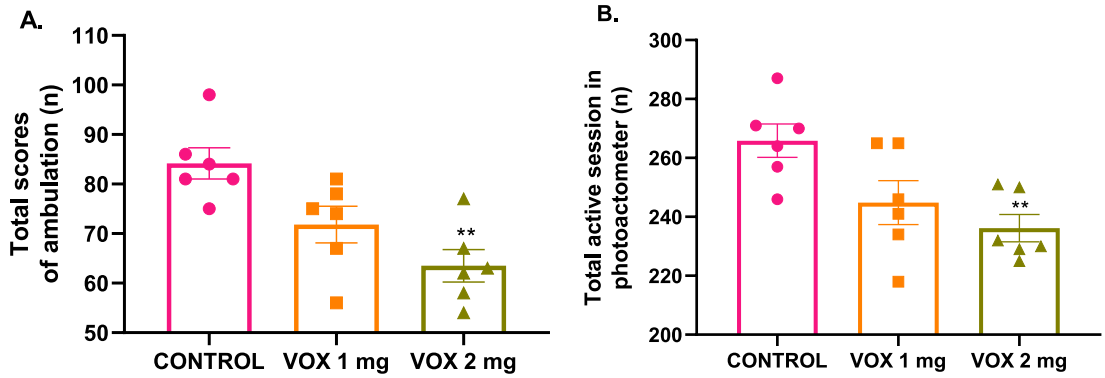

Fig. 3 Effect of VOX (1 and 2 mg) exposure on maternal locomotor activity in **A** open field arena and **B** photoactometer at GD 15. All data represent the mean ± SEM value ($n = 6$ per group). The symbol ** indicates the level of significance at $p < 0.01$ between the control and VOX-exposed groups for a one-way ANOVA followed by Tukey's multiple comparison test

the VOX-treated groups and appeared to increase in a dose-dependent manner rising to 25% and 33.33% in the 1 mg/kg and 2 mg/kg group respectively, compared to 14.29% in the control group (Table 2).

Analysis of implantation outcomes among the confirmed pregnant dams ($n = 6$ per group) revealed a reduction in total implantation sites in both treatment groups relative to controls (Table 2). Furthermore, a significant decrease in litter size was observed with VOX exposure [F (2, 15) = 3.58, $p \leq 0.05$], with reductions of 10.29% in the 1 mg/kg group and 16.18% in the 2 mg/kg group. A corresponding trend was noted in fetal viability, with a dose-related decline in the number of live fetuses and an increase in fetal deaths. However, no physical malformations were seen in fetuses of exposed groups. Uterine horn weight was significantly ($p < 0.05$) reduced only in VOX 2 mg group by 12.27% as compared to control (Fig. 4A).

Additionally, maternal exposure to 1 mg/kg VOX resulted in modest decreases in placental length (9.30%), placental weight (11%), and fetal length (5.02%) and fetal weight (9.92%). These alterations were more pronounced at the 2 mg/kg dose, where placental length and weight were reduced by 13.95% and 18.12%, respectively ($p < 0.05$). Fetal length and weight exhibited a marked decline of 10.04% and 16.48%, respectively ($p < 0.05$). These findings indicate that prenatal VOX administration, particularly at higher doses, negatively impacts both placental morphology and fetal somatic development (Fig. 4B, C and Table 2).

Table 2 Effect of VOX exposure on pregnancy outcomes

Groups	Control	VOX 1 mg	VOX 2 mg	*F* values
No. of dams (n)	6	6	6	–
Pseudo-pregnancy (*n*) (%)	1/7 14.29%	2/8 25%	3/9 33.33%	–
Fertility rate (*n*) (%)	6/7 85.71%	6/8 75%	6/9 66.67%	–
Total no. of implantations (*n*)	68	61	57	–
Total no. of dead fetuses (*n*) (%)	01 (1.47%)	01 (1.64%)	02 (3.51%)	–
Total no. of live fetuses (*n*) (%)	67 (98.53%)	60 (98.36%)	55 (96.49%)	–
Litter size (*n*) (% reduction)	11.33 ± 0.49	10.17 ± 0.40 (10.29%)	9.50 ± 0.56* (16.18%)	F (2, 15) = 3.58; $p \leq 0.05$
Uterus weight (g) (% reduction)	68.52 ± 2.01	63.77 ± 1.74 (6.93%)	60.12 ± 2.55* (12.27%)	F (2, 15) = 3.92; $p < 0.05$
Placenta size (cm) (% reduction)	1.43 + 0.02	1.30 ± 0.07 (9.30%)	1.23 ± 0.04* (13.95%)	F (2, 15) = 4.52; $p < 0.05$
Placenta weight (g) (% reduction)	0.52 ± 0.03	0.46 ± 0.02 (11.00%)	0.43 ± 0.02* (18.12%)	F (2, 15) = 4.19; $p < 0.05$
Fetal body size (cm) (% reduction)	3.98 ± 0.07	3.78 ± 0.09 (5.02%)	3.58 ± 0.10* (10.04%)	F (2, 15) = 5.11; $p < 0.05$
Fetal body weight (g) (% reduction)	5.01 ± 0.12	4.51 ± 0.22 (9.92%)	4.18 ± 0.18* (16.48%)	F (2, 15) = 5.45; $p < 0.05$

The last six rows represent data as mean ± SEM value (n = 6 per group). Symbol * indicates significance levels at $p \leq 0.05$ between the control and VOX-exposed groups for one-way ANOVA followed by Tukey's multiple comparison test. Data in parenthesis of the last seven rows indicate the percentage reduction/increase compared to the control

Effect of VOX exposure on brain morphometry

The fetal brain size was substantially reduced in drug-exposed groups in comparison to the control group (Fig. 4D). One-way ANOVA followed by post hoc Tukey's multiple comparison test revealed that fetal brain size significantly [F (2, 15) = 5.59; $p < 0.05$] reduced in a dose-dependent manner in VOX-exposed groups compared to the control group. The post hoc analysis revealed that fetal brain size was significantly ($p < 0.05$) reduced only at 2 mg dose (14.10%), not at 1 mg dose (7.69%) of VOX-exposed rats as compared to the control rats (Fig. 5A). However, fetal brain weight was found non-significantly [F (2, 15) = 1.40; $p > 0.05$] decreased in both VOX-exposed groups as compared to the control group after one-way ANOVA with post hoc test. The percentile reduction in fetal brain weight was also found to be non-significantly decreased at 1 mg (6.32%) and 2 mg (9.84%) VOX-exposed groups in comparison to the control group (Fig. 5B).

Histological evaluation of the brain

Effect of VOX exposure on the cytoarchitectural pattern and thickness of the prefrontal cortex

Histological evaluation of the PFC in fetal brains prenatally exposed to VOX at relevant doses revealed a significant reduction in total cortical thickness [F (2, 15) = 5.31; $p < 0.05$], displaying a clear dose-dependent trend across treatment groups. Cortical thickness was reduced by 1.55% in the 1 mg group and by 2.67% in the 2 mg group when compared to controls. This reduction in the frontal cortex thickness was largely due to significant thinning ($p < 0.05$) of the cortical plate, encompassing both supra- and infra-cortical layers, as well as the intermediate zone in all VOX-exposed groups. Statistical analysis using one-way ANOVA followed by Tukey's post hoc test confirmed significant decreases in the thickness of the cortical plate layers [F (2, 15) = 3.98; $p < 0.05$] and the intermediate zone [F (2, 15) = 3.73; $p < 0.05$], relative to controls. The most notable alterations were observed in the 2 mg VOX group, indicating a dose-dependent effect on these regions. In contrast, no significant changes were found in the subventricular layer [F (2, 15) = 1.43; $p > 0.05$] (Figs. 6 and 7).

Effect of VOX exposure on the cytoarchitectural pattern and thickness of the hippocampus

Histopathological study of fetal brain prenatally exposed with selected doses of VOX revealed a significant decrease in the thickness of PCL of both the CA1 [F (2, 15) = 3.64; $p < 0.05$] and CA3 [F (2, 15) = 5.53; $p < 0.05$] regions, and insignificant decrease in the thickness of GCL of the DG region [F (2, 15) = 1.45; $p > 0.05$] of the hippocampus compared to the control group after one-way ANOVA analysis. However, post hoc Tukey's multiple comparison test showed a significant decrease by 12.73% and 12.14% in the thickness of PCL of both the CA1 and CA3 regions, respectively, only in the VOX 2 mg group. No significant decrease in the thickness of PCL of both the CA1 (5.98%)

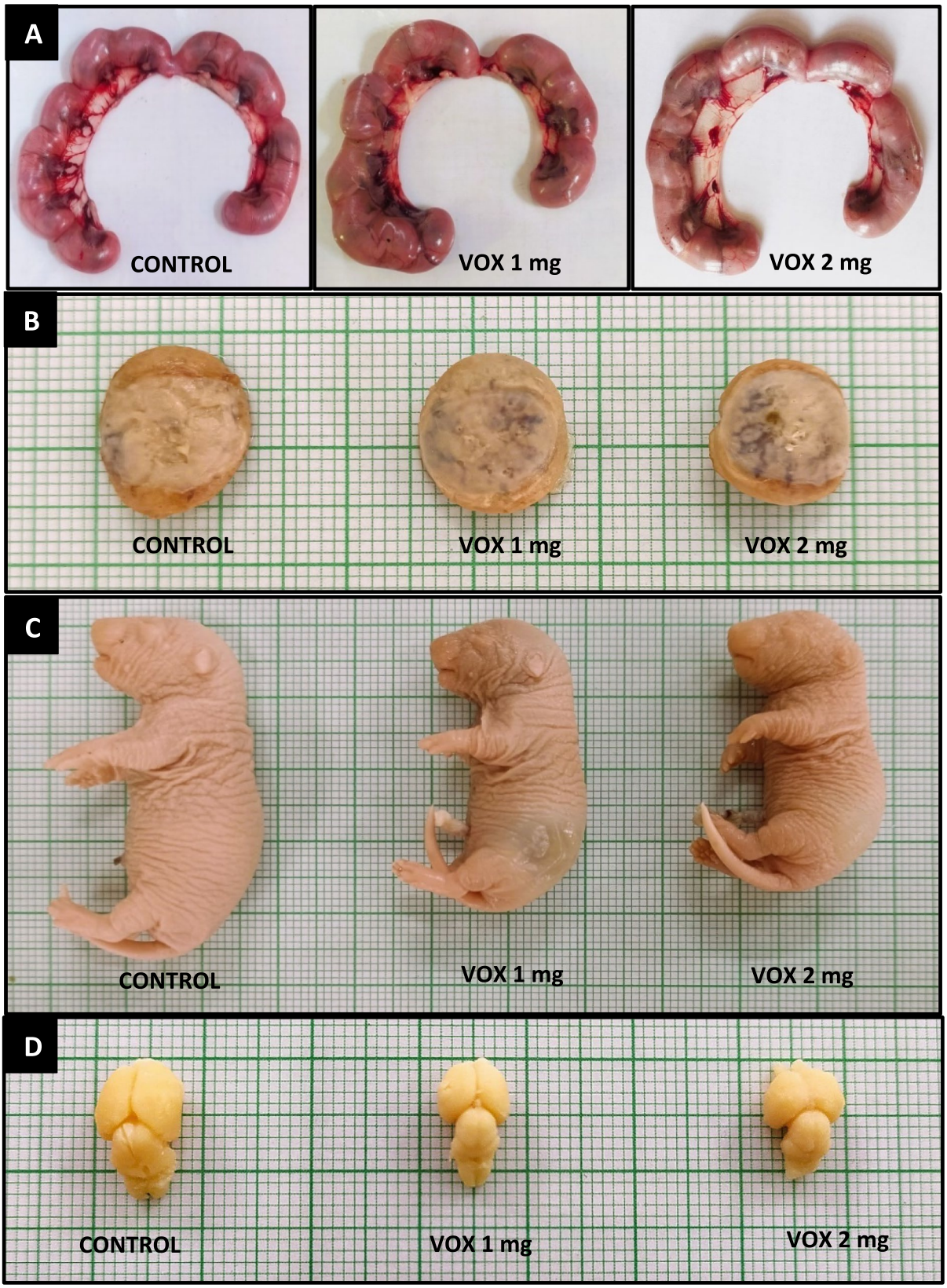

Fig. 4 The representative photographs of **A** uterine horns, **B** dorsal view of the placenta, **C** fetuses, and **D** fetal brains on the 21 st day of gestation in the control and VOX-exposed pregnant rats

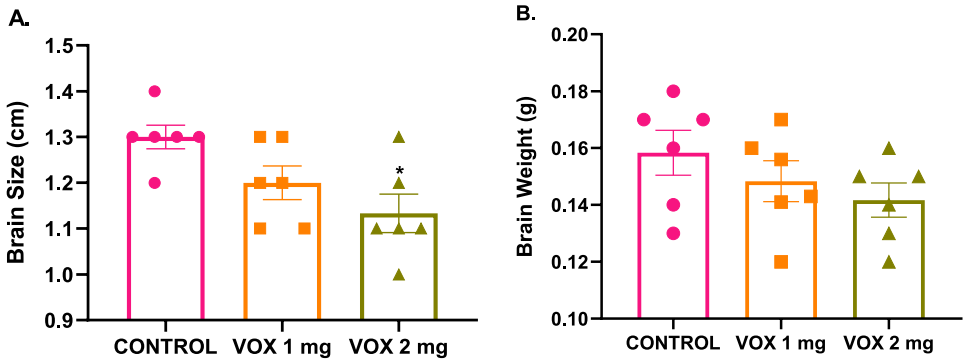

Fig. 5 Effect of VOX (1 and 2 mg/kg) exposure on fetal **A** brain size and **B** brain weight. All data represent mean ± SEM values ($n = 6$ brains/group). Symbol * indicates the level of significance at $p < 0.05$ between the control and VOX-exposed groups for one-way ANOVA followed by Tukey's multiple comparison test

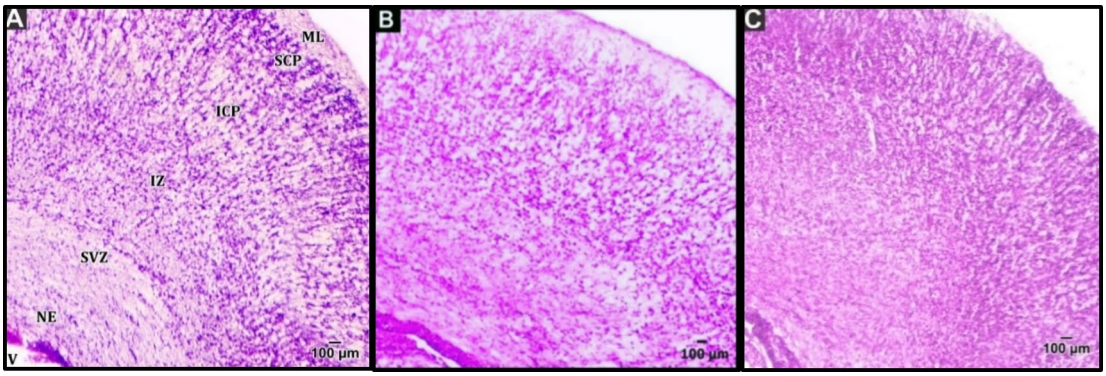

Fig. 6 Neurohistopathological observations of the control and VOX-exposed fetal brains showing cytoarchitectural pattern of the prefrontal cortex (H&E-stained coronal sections); **A** control, **B** VOX 1 mg/kg, and **C** VOX 2 mg/kg (×10). *ML* molecular layer, *SCP* supracortical plate, *ICP* infracortical plate, *IZ* intermediate zone, *SVZ* subventricular zone, *NE* neuroepithelium layer, and *V* ventricle

and CA3 (4.13%) regions were observed in VOX 1 mg-exposed group (Figs. 8 and 9).

Effect of VOX exposure on monoamine neurotransmitter levels in brain

A dose-dependent decline in monoamine neurotransmitter levels was observed in fetal brains following VOX exposure, as determined by one-way ANOVA followed by Tukey's post hoc test. Significant reductions were noted in 5-HT [F (2, 15) = 9.37, $p < 0.01$], DA [F (2, 15) = 9.58, $p < 0.01$], and NE [F (2, 15) = 4.73, $p < 0.05$]. In the group exposed to 1 mg of VOX, levels of 5-HT and DA decreased significantly by 30.53% and 21.27%, respectively ($p < 0.05$), while NE showed a non-significant reduction of 7.14% compared to controls. The 2 mg group exhibited more pronounced declines, with 5-HT and DA levels reduced by 36.64% and 25.78% (both $p < 0.01$), and NE by 10.69% ($p < 0.05$). These findings indicate that prenatal VOX exposure markedly affected 5-HT and DA levels, while NE levels were less consistently altered (Fig. 10A–C).

Effect of VOX exposure on the acetylcholinesterase activity in brain

One-way ANOVA followed by Tukey's post hoc analysis showed a significant dose-dependent increase in total AChE activity in fetal brains of VOX-exposed groups compared to controls [F (2, 15) = 3.97; $p < 0.05$]. Specifically, AChE activity increased significantly by 19.56% in the 2 mg VOX group ($p < 0.05$), while the 1 mg group exhibited a non-significant rise of 6.66% relative to the control group (Fig. 10D).

Effect of VOX exposure on mRNA expression of BDNF in the brain

Prenatal VOX exposure led to a significant reduction in BDNF mRNA expression levels, as indicated by one-way ANOVA followed by Tukey's post hoc test [F (2, 15) = 6.45; $p < 0.01$]. The post hoc analysis revealed a marked decrease of 26.18% ($p < 0.01$) in the 2 mg VOX group, while the 1 mg group showed a non-significant reduction of 13.90% compared to the control group (Fig. 11A).

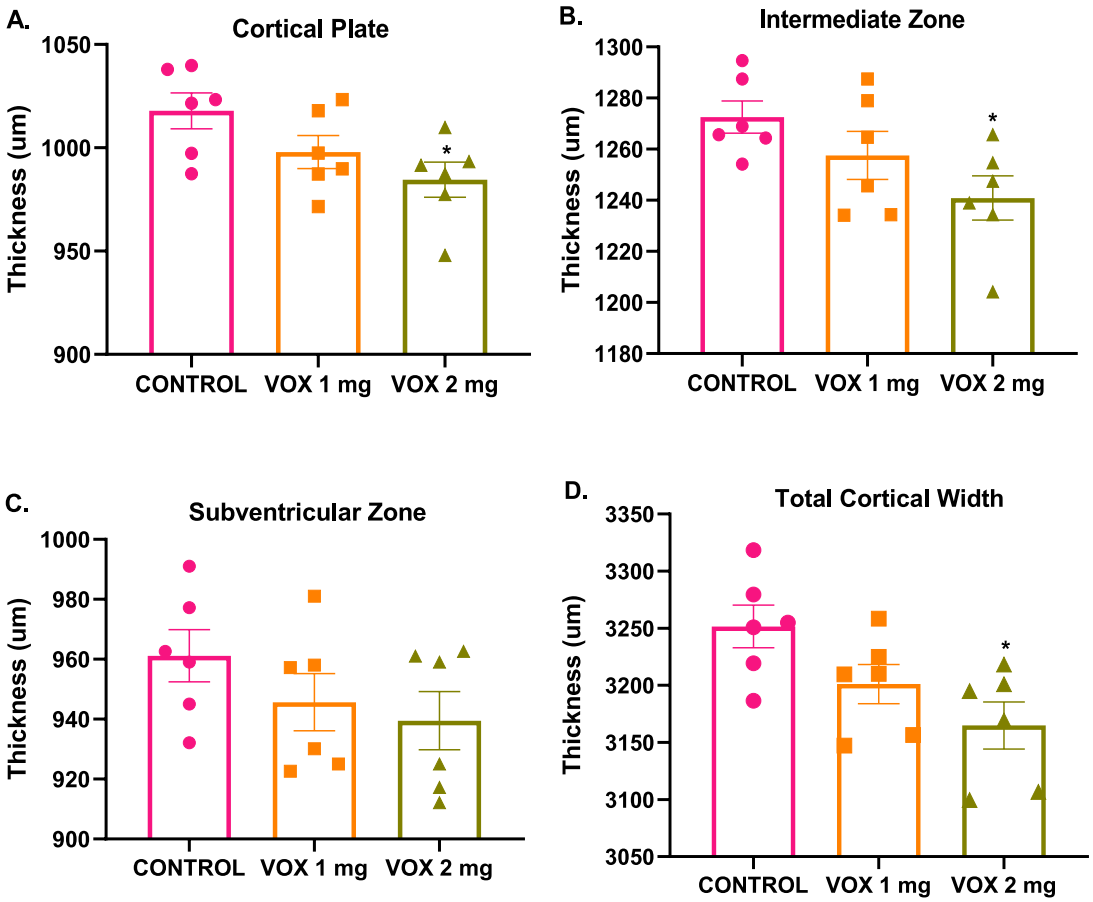

Fig. 7 Effect of VOX (1 and 2 mg/kg) exposure on the thickness of the prefrontal cortex layers. **A** Cortical plate, **B** intermediate zone, **C** subventricular zone, and **D** total cortical width of fetal brains. All data represent the mean ± SEM values (n = 6 brains per group). Symbol * indicates the level of significance at $p < 0.05$ between the control and VOX-exposed groups for a one-way ANOVA followed by Tukey's multiple comparison test

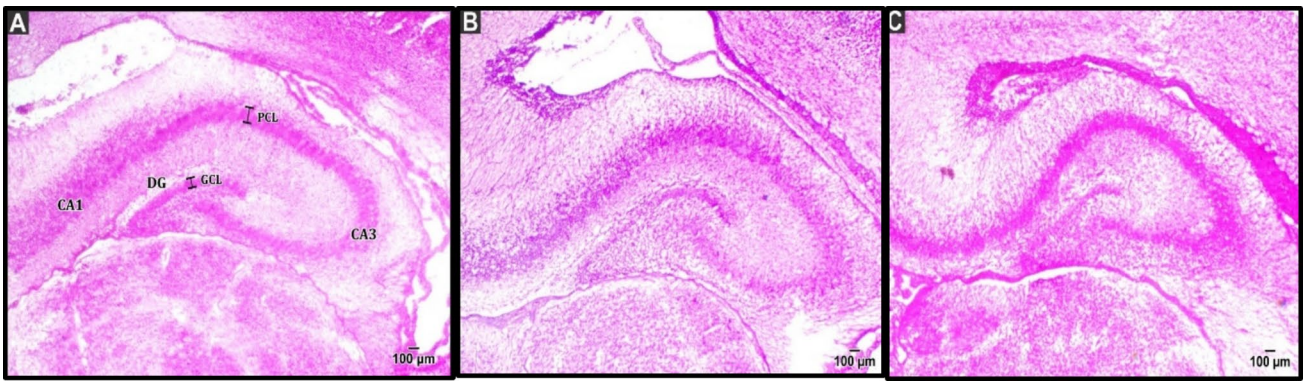

Fig. 8 Neurohistopathological observations of the control and VOX-exposed fetal brains showing cytoarchitectural patterns of the hippocampus (H&E-stained coronal sections). **A** Control, **B** VOX 1 mg/kg, and **C** VOX 2 mg/kg (×10). *PCL* pyramidal cell layer, *CA* cornu ammonis, *GCL* granular cell layer, and *DG* dentate gyrus

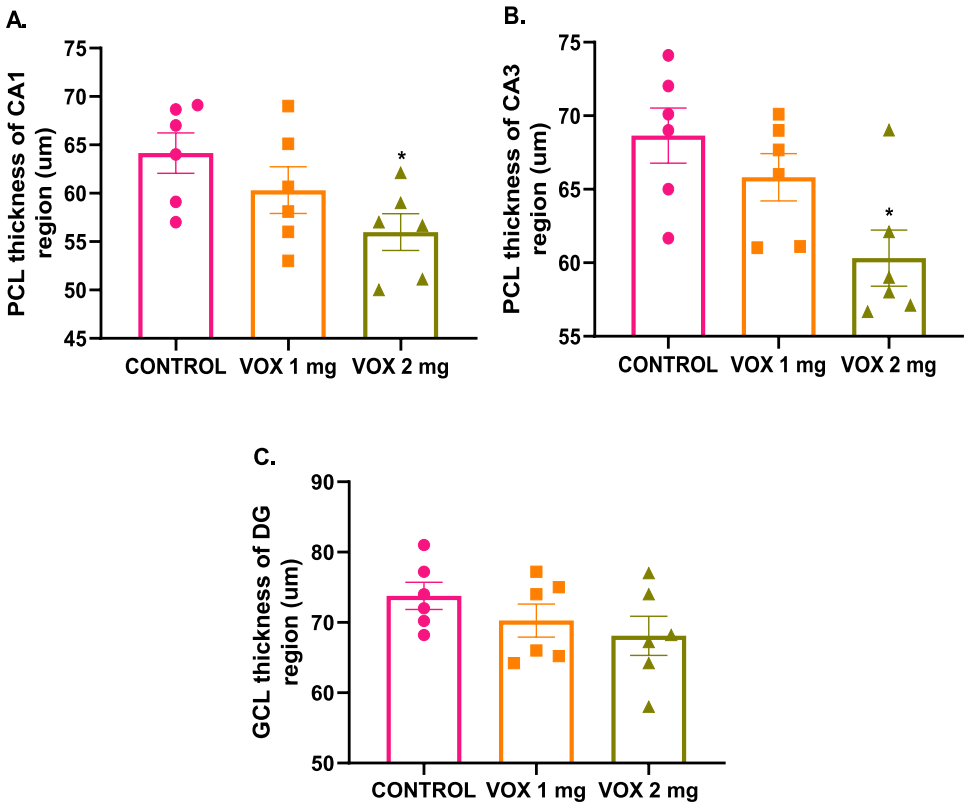

Fig. 9 Effect of VOX (1 and 2 mg/kg) exposure on the thickness of different layers of the hippocampus region of fetal brain; **A** PCL thickness of the CA1 region, **B** PCL thickness of the CA3 region, and **C** GCL thickness of the DG region. All data represent the mean ± SEM values ($n = 6$ brains per group). Symbol * indicates the level of significance at $p < 0.05$ between the control and VOX-exposed groups for a one-way ANOVA followed by Tukey's multiple comparison test

Effect of VOX exposure on mRNA expression of apoptotic genes in brain

One-way ANOVA followed by Tukey's multiple comparison test showed a significant up-regulation of pro-apoptotic gene, Bax [F (2, 15) = 4.62; $p < 0.05$], while significant down-regulation of anti-apoptotic gene, Bcl-2 [F (2, 15) = 5.90; $p < 0.05$], in fetal brains of VOX-exposed groups compared to control group. Tukey's post hoc analysis revealed that, in the 2 mg VOX group, Bax expression was significantly increased by 42.62% ($p < 0.05$), while Bcl-2 expression was significantly decreased by 32.58% ($p < 0.05$) in fetal brains. In contrast, the 1 mg VOX group showed moderate changes in Bax (27.87% increase) and Bcl-2 (21.58% decrease), but these differences did not reach statistical significance. Furthermore, the Bax/Bcl-2 ratio was significantly elevated in VOX-exposed fetal brains compared to controls [F (2, 15) = 7.47; $p < 0.01$], with the most pronounced effect observed at the 2 mg dose (Fig. 11B–D).

Discussion

Understanding the influence of AD use during gestation is essential for evaluating potential risks to both maternal health and fetal development. In this context, the present study examined the effects of clinically relevant doses of VOX on pregnancy and fetal development in rats. At 2 mg/kg, VOX significantly reduced maternal food intake, weight gain, implantation count, litter size, and fetal viability. Fetal and placental growth were also impaired. Neurotoxicity assessments showed reduced brain size, thinner cortical and hippocampal layers, and lower BDNF expression. Biochemical findings revealed decreased AChE activity, altered monoamine levels (5-HT, DA, NE), and imbalanced Bax/Bcl-2 gene expression in fetal brain. Overall, VOX exposure during gestation disrupted fetal brain development, likely via the BDNF/Bax–Bcl-2/5-HT signaling pathway.

This study revealed that daily administration of VOX at doses of 1 and 2 mg/kg during gestation (GD 6–21) led to a dose-dependent decrease in maternal food consumption and weight gain. The reduction was statistically significant at the 2 mg/kg dose, with a greater percentage decline observed in food intake compared to body weight gain. These findings suggest that VOX may induce appetite suppression (satiety) or hypophagia during pregnancy. This effect is consistent with previous reports of reduced appetite and weight changes following treatment with ADs such as fluoxetine, mirtazapine, venlafaxine and vilazodone in both animal and clinical studies (De Oliveira et al. 2004; Singh and Singh 2013; Aggarwal et al. 2016; Agrawal et al. 2024). Although VOX is generally considered weight-neutral in long-term clinical use (Gill et al. 2020; Kukucka et al. 2024), transient reductions in appetite and

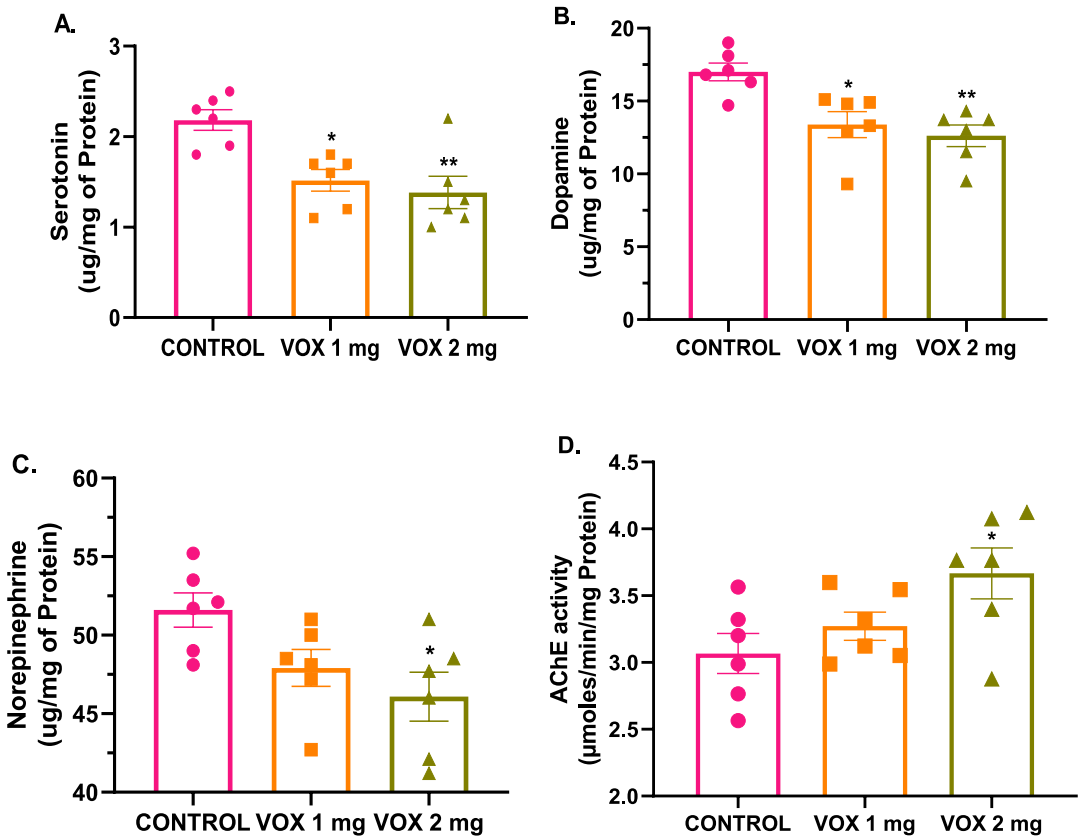

Fig. 10 Effect of VOX (1 and 2 mg/kg) exposure on neurochemical and biochemical levels; **A** 5-HT, **B** DA, **C** NE, and **D** AChE in fetal brain. All data represent the mean ± SEM values ($n = 6$ brains/group). Symbols * and ** indicate the level of significance at $p < 0.05$ and $p < 0.01$, respectively, between the control and VOX-exposed groups for a one-way ANOVA followed by Tukey's multiple comparison test

body weight have been documented, particularly during the early weeks of treatment (Gonda et al. 2019; De Diego-Adeliño et al. 2022).

In animal studies, VOX's serotonergic action may promote satiety through stimulation of 5-HT receptor subtypes such as 5-HT3 and 5-HT1B, which are known to regulate feeding behavior (Magalhães et al. 2010; Voigt and Fink 2015). These receptor-mediated effects may be amplified during pregnancy due to physiological adaptations involving altered hormonal and metabolic states. As such, VOX-induced reductions in food intake and body weight may reflect disrupted energy homeostasis driven by serotonergic activity interacting with pregnancy-specific regulatory mechanisms. The hypothalamus, which integrates peripheral and central signals from molecules such as nesfatin-1, leptin, and agouti-related peptide, plays a central role in feeding regulation (Oh-I et al. 2006). VOX's inhibition of 5-HT reuptake likely influences these hypothalamic pathways, contributing to appetite suppression during pregnancy. Similar mechanisms have been proposed for fluoxetine, which has shown hypophagic effects in rodent models (Yen and Fuller 1992; Halford and Blundell 1996).

Contrastingly, some studies have reported weight gain associated with AD use (Patten et al. 2009; Kivimäki et al. 2010). However, placebo-controlled trials have shown that VOX does not lead to significant weight gain in patients, supporting its classification as weight-neutral during short-term treatment (D'Agostino et al. 2015; Baldwin et al. 2016). To date, no studies have specifically examined VOX's effects on weight in pregnant populations. Nonetheless, the findings from this study align with earlier research on SSRIs and SNRIs, which have demonstrated that appetite suppression—ranging from mild to severe—is a known side effect and may result in significant weight loss depending on dose and duration of exposure (Jackson et al. 1997; Grzeskowiak et al. 2012; Halford et al. 2007). Thus, the hypophagic effects observed in this study may reflect a serotonergic mechanism of appetite suppression triggered by VOX exposure during pregnancy.

The observed weight reduction in pregnant dams exposed to VOX may also reflect side effects such as fatigue and reduced appetite, which are commonly reported with SSRIs (Aggarwal et al. 2016). Furthermore, a significant reduction in locomotor activity was observed in VOX-treated dams in

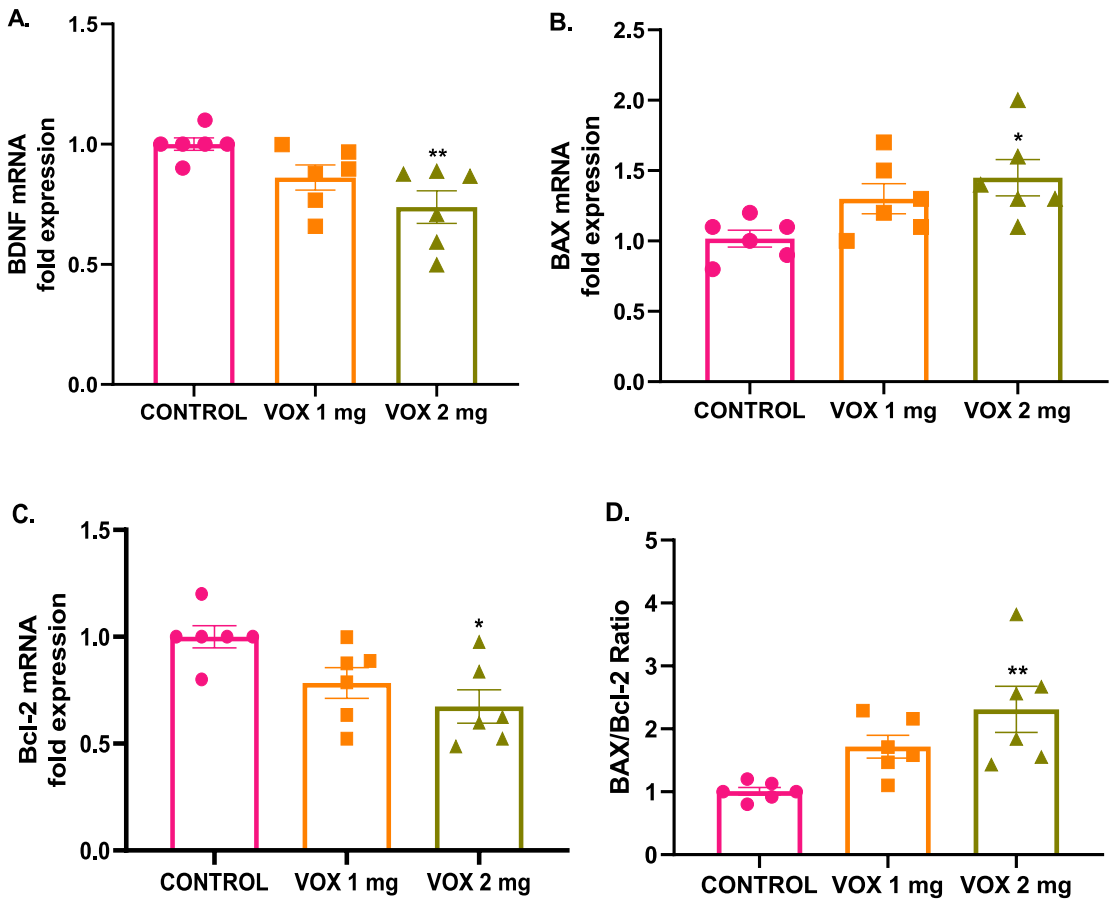

Fig. 11 Effect of VOX (1 and 2 mg/kg) exposure on the mRNA expression of **A** BDNF, **B** Bax, **C** Bcl-2, and **D** ratio of Bax to Bcl-2 in fetal brain. All data represent the mean ± SEM values ($n = 6$ brains per group). Symbols * and ** indicate the level of significance at $p < 0.05$ and $p < 0.01$, respectively, between the control and VOX-exposed groups for one-way ANOVA followed by Tukey's multiple comparison test

both the open field test and photoactometer test, suggesting a mild sedative effect. This sedation may contribute to reduced energy expenditure, further exacerbating appetite loss and weight loss at higher doses. Additional studies in humans and animal models have highlighted that serotonergic ADs may influence energy metabolism and locomotion. VOX has been shown to modulate energy expenditure and activity levels, potentially through its effects on 5-HT and NE pathways (Chen et al. 2018). Similar findings of increased energy expenditure in drug-exposed rats were reported by Li et al., suggesting that metabolic alterations could also play a role in the weight changes observed during VOX exposure (Li et al. 2019). Overall, these findings emphasize the complex interplay between serotonergic modulation, appetite regulation, and energy balance in the context of AD exposure during pregnancy.

Moreover, this study demonstrated a dose-dependent increase in pseudo-pregnancy and significant impairments in embryo-fetal development following VOX exposure, particularly at 2 mg/kg/day. VOX-treated rats exhibited reduced implantation counts, litter size, total live fetuses, and decreased placental size and weight, suggesting implantation failure and impaired placental development. Since VOX administration began on GD-6 (post-ovulation), the reductions are unlikely due to fertilization failure and may instead involve disrupted implantation or early embryonic loss. Potential mechanisms include (1) maternal weight loss-induced metabolic and hormonal disturbances affecting ovarian function (Uphouse et al. 2006), (2) interference with estrogen signaling pathways critical for uterine receptivity (Jacobsen et al. 2015; Hansen et al. 2017), and (3) impaired uterine vascular remodeling and perfusion (Rosenfeld 2020; Levy et al. 2020), which are vital for implantation and placental development (Cartwright et al. 2010). Singh et al. further reported that reduced placental weight may result from impaired trophoblast proliferation, vascularization, and structural alterations, potentially limiting nutrient and oxygen transfer to the fetus prenatally exposed to venlafaxine (Singh et al. 2016). Previous human and animal studies have also linked SSRIs and related ADs to early pregnancy

loss and implantation failure due to altered hormonal signaling, oxidative stress, and disrupted uterine physiology (Bauer et al. 2010; Kjaersgaard et al. 2013; Almeida et al. 2016; Cabrera et al. 2020). Fluoxetine and venlafaxine, for instance, downregulate uterine VEGF expression and other angiogenic factors (Domingues et al. 2022, 2023), mechanisms that may also apply to VOX due to its serotonergic action at 5-HT3, 5-HT1B, and other receptors known to influence reproductive and vascular systems.

The reduction in maternal weight gain may reflect both smaller litter sizes and IUGR. ADs have been associated with IUGR in clinical and experimental settings (Bauer et al. 2010; Müller et al. 2013; Zullino and Simoncini 2018; Bandoli et al. 2020), likely due to impaired uterine blood flow, placental lesions, and altered 5-HT signaling affecting placental function (Rosenfeld 2020). Reduced weight gain and litter size may also indicate early implantation failure or embryonic loss, supported by prior studies linking serotonergic ADs to disruptions in estrogen signaling, vascularization, and oxidative stress (Jacobsen et al. 2015; Hansen et al. 2017). The presence of fully developed dead fetuses in VOX-treated dams raises concerns about delayed parturition or maternal stress contributing to fetal mortality. While these findings support a role for VOX in reproductive and fetal toxicity, caution is needed when interpreting outcomes due to species-specific differences and variability in drug metabolism.

This study also revealed a dose-dependent reduction in fetal and placental size and weight, most pronounced at the 2 mg/kg/day VOX dose, suggesting that placental insufficiency—rather than maternal undernutrition—is a primary driver of fetal growth restriction, which may result from mitotic inhibition, apoptosis, or necrosis in trophoblast cells (Furukawa et al. 2011). Given the placenta's role in regulating 5-HT homeostasis, VOX's inhibition of the serotonin transporter (SERT) may disrupt maternal–fetal 5-HT exchange which is critical for fetal brain development (Bonnin et al. 2011; Hanswijk et al. 2020; Horackova et al. 2021), potentially contributing to placental insufficiency and growth restriction (Velasquez et al. 2013; Rosenfeld 2020). These findings align with prior reports of reduced fetal and neonatal weights following exposure to SSRIs and SNRIs, including fluoxetine, paroxetine, and venlafaxine (Müller et al. 2013; Singh and Singh 2013; Houwing et al. 2019), as well as clinical evidence linking SSRI use to lower birth weights (Kumari et al. 2013; Hutchison et al. 2018). Mechanistically, VOX may block SERT, increasing 5-HT levels that constrict umbilical arteries and impair fetal oxygen and nutrient supply (Okatani et al. 1995).

Furthermore, a significant reduction in brain length ($p < 0.05$) was observed in the VOX 2 mg/kg group, while brain weight showed a non-significant decrease, suggesting mild structural disruption without major impact on brain mass. This reduction likely reflects overall growth retardation, consistent with lower body weights in VOX-exposed offspring. Histological analysis further revealed disrupted neurocytoarchitecture in the PFC and hippocampus, including reduced brain areas and thinner neuronal layers, especially at 2 mg/kg. These morphological abnormalities may stem from impaired neuronal proliferation, migration, or increased apoptosis during critical developmental windows, consistent with prior reports on fluoxetine and venlafaxine (Swerts et al. 2010; Singh et al. 2015; Ahmed et al. 2022). Human imaging studies have also linked prenatal AD exposure to altered brain volume and connectivity (Lugo-Candelas et al. 2018; Koc et al. 2023; Talati 2023). These findings align with previous studies reporting cortical and hippocampal thinning after prenatal AD exposure, including our lab's work showing similar effects with venlafaxine (Singh et al. 2015, 2022; Ahmed et al. 2022). Other reports have found reduced neuronal numbers in frontal lobes with fluoxetine and imipramine exposure (Swerts et al. 2010). Human MRI studies have shown altered brain volumes and connectivity, particularly in the amygdala and insula, in SSRI-exposed infants (Lugo-Candelas et al. 2018; Koc et al. 2023; Talati 2023). Although direct data on VOX-induced neuronal changes are lacking, these results suggest that VOX may share similar neurodevelopmental risks with other ADs.

This study further validated by the quantification of key neurotransmitters, such as 5-HT, DA, and NE, which showed a significant, dose-dependent decrease in fetal brains exposed to 1 mg and 2 mg doses of VOX. Furthermore, the assessment of AChE activity levels revealed a notable increase in fetal brains of exposed groups, implying a corresponding reduction in acetylcholine (ACh) levels (Trang and Khandhar 2023). Post hoc Tukey's multiple comparison analysis showed a significant increase in AChE activity exclusively in the 2 mg/kg VOX dose group, while no such effect was observed in the 1 mg/kg VOX group. AChE is essential for regulating cholinergic neurotransmission, as it hydrolyzes ACh to terminate synaptic transmission and maintain precise cholinergic signaling (Das et al. 2005). The elevated AChE activity in the VOX-exposed groups likely accelerates the breakdown of ACh within the synaptic cleft, reducing its availability for interaction with postsynaptic receptors. This reduction in cholinergic signaling may impair neuronal communication critical for learning and memory processes (Huang et al. 2022).

These monoamines regulate one another, and disruptions in 5-HT signaling can lead to downstream imbalances in DA and NE systems (Bubar et al. 2011), altering neural circuitry related to cognition, emotion, and behavior (Brummelte et al. 2017). Additionally, serotonergic dysfunction may suppress BDNF expression, as observed in VOX 2 mg/kg group, where BDNF mRNA was significantly downregulated. BDNF is essential for neuronal survival, synaptogenesis, and

plasticity, and its reduced expression can impair cortical and hippocampal development (Erickson et al. 1996; Szapacs et al. 2004; Lu et al. 2014). Disruption of the BDNF-5HT feedback loop which normally promotes mutual regulation can compromise both synaptic connectivity and emotional regulation (Martinowich and Lu 2008; Chakraborty et al. 2012; Homberg et al. 2014).

Eventually, VOX exposure induced significant pro-apoptotic changes, with upregulation of Bax and downregulation of Bcl-2, resulting in an increased Bax/Bcl-2 ratio, particularly at the higher dose. This imbalance promotes mitochondrial dysfunction, cytochrome c release, and caspase activation, culminating in apoptosis (Kuwana and Newmeyer 2003; Jarskog et al. 2004). These apoptotic effects likely stem from both monoaminergic dysregulation and oxidative stress (Dong et al. 2009; Subramaniam and Chesselet 2013), as previously reported in SSRI/SNRI studies (Drzyzga et al. 2009; Zhao et al. 2016; Tian et al. 2016; Singh et al. 2022; Bhat et al. 2023). Collectively, these findings indicate that gestational VOX exposure at higher dose (2 mg/kg) disrupts placental function, impairs brain development, alters neurochemical and neurotrophic signaling, and activates apoptotic pathways—mechanistically contributing to long-lasting neurodevelopmental deficits.

Conclusion

Prenatal administration of VOX at a higher dose (2 mg/kg) led to significant embryo-fetal toxicity and compromised fetal brain development, with mechanistic evidence pointing toward disruption of the BDNF/Bax–Bcl-2/5-HT signaling cascade. This dose-dependent neurotoxicity was reflected by a marked decline in 5-HT, DA, and BDNF levels, along with increased Bax expression and an elevated Bax/Bcl-2 ratio, indicating activation of intrinsic apoptotic processes. In contrast, the lower dose (1 mg/kg) produced only modest alterations in these parameters indicating a safer profile during pregnancy. These findings raise important safety considerations for the use higher dose of VOX during pregnancy, emphasizing the need for cautious clinical application. Further comprehensive studies both experimental and clinical are essential to guide the safe use of atypical ADs in maternal mental health care.

Acknowledgements The authors express sincere appreciation to the Head of the Department, University of Allahabad, for providing essential laboratory facilities that enabled the completion of this study. Special thanks are extended to the Head of the Department of Biotechnology, MNNIT, Prayagraj, for granting access to the RT-PCR facility. Gratitude is also due to Dr. Brijesh Kumar Mishra and Dr. Ankit Mishra, Department of Zoology, H. N. B. Government P.G. College, Naini, Prayagraj, for providing access to the light microscopy facility.

Author contributions P.S. carried out experiments, analyzed data, and was responsible for data curation, software analysis, methodology development and funding acquisition. P.S. also wrote the original draft of the manuscript. P.A. contributed to software processing, visualization, and funding acquisition. K.P.S. supervised the study, provided resources and conceptual input, and contributed to manuscript reviewing. The manuscript was reviewed and edited by P.S.

Funding PS was funded by the University of Allahabad, University Grant Commission—Combined Research Entrance Test (UGC-CRET) fellowship [Grant No. 498/RES/19/246], and PA was funded by University Grant Commission-Council of Scientific and Industrial Research (UGC-CSIR) Senior Research Fellowship [Grant No. 964/(CSIR-UGC NET DEC 2017)].

Data availability Derived data supporting the findings of this study are available from the corresponding authors upon request.

Declarations

Conflict of interest The authors report no conflicts of interest that could have influenced the findings or interpretations of this study.

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