

Risks and benefits of prenatal exposure to antidepressants: Neurobiological mechanisms and clinical evidence

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Abstract. This review summarizes current evidence on how maternal stress, depression, and antidepressant treatment during pregnancy influence offspring neurodevelopment. We focus on neurobiological mechanisms linking maternal and fetal brains, particularly interactions between monoaminergic systems and the brain-derived neurotrophic factor (BDNF)-tyrosine kinase receptor B (TrkB) signaling axis. Preclinical studies demonstrate that maternal stress during gestation alters the activity of offspring monoaminergic neurons and associated neuroplasticity pathways. Prenatal stress typically reduces serotonergic neuronal firing while enhancing catecholaminergic transmission, whereas pregestational stress may produce opposite neurophysiological effects. These changes are accompanied by behavioral alterations, including increased anxiety- and depression-like behavior. Clinical studies indicate that maternal stress and depression are associated with structural and functional brain alterations in offspring, particularly within the amygdala-hippocampal network involved in emotional regulation. Prenatal antidepressant exposure may modify these outcomes, with effects varying according to drug class, timing of exposure, and maternal clinical status. Although some studies report mild perinatal effects such as earlier delivery or lower birth weight, many associations between prenatal antidepressant exposure and neurodevelopmental disorders appear to be largely explained by underlying maternal psychiatric conditions. The available evidence highlights the complex interaction between maternal mental health, neurotrophic signalling, and monoaminergic neurophysiology in offspring brain development.

Key words: Maternal stress — Prenatal depression — Prenatal antidepressant treatment — Corticosteroids — Monoamines — BDNF

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BDNF, brain derived neurotrophic factor; CNS, central nervous system; CSF, cerebrospinal fluid; CS, corticosteroids; CRH, corticotropin-releasing hormone; CYP, cytochrome P450; DD, depressive disorder; DRN, dorsal raphe nucleus; GRs, glucocorticoid receptors; HPA, hypothalamic-pituitary-adrenal; LPS, lipopolysaccharide; MIA, maternal immune activation; PPD, postpartum depression; SLC6A4, serotonin transporter gene; TrkB, tyrosine kinase B; VTA, ventral tegmental area.

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Introduction

Even though the pathophysiology of depression is not completely understood, multiple lines of evidence suggest the involvement of corticosteroids, central monoamines, such as serotonin (5-HT), noradrenaline, and dopamine, and neurotrophins, such as brain derived neurotrophic factor (BDNF; Fig 1) (Dremencov et al. 2003, 2021; Pavlovicova et al. 2015; Grinchii et al. 2018; Tseilikman et al. 2020; Paliokha et al. 2022; Singh et al. 2022). Central monoamines are fundamental in emotions. Thus, 5-HT plays a key role in anxiety and impulsivity, noradrenaline is primarily responsible for alertness, energy, and dopamine-for reward and motivation. The imbalance within the monoaminergic circuits results in depressive symptoms, such as anxiety, fatigue, and anhedonia (Stahl 2008).

Monoamines closely interact with the trophic factors of the CNS, such as BDNF. Monoamines stimulate BDNF expression in the brain, *via* several mechanisms involving G-protein coupled receptors (GPCRs), cyclic adenosine monophosphate (cAMP) and intracellular calcium (Ca^{2+}) signaling (Dremencov et al. 2003; Pavlovicova et al. 2015). BDNF, in turn, stimulates the expression of VGF (non-acronymic), *via* a mechanism involving tyrosine kinase

B (TrkB) receptors. Finally, the C-terminal of the VGF transcript, TLQP-62, putatively acts back on 5-HT neurons and stimulates central 5-HT transmission *via* a mechanism which is not yet known. Decreased monoaminergic neurotransmission may result in decreased activity of the BDNF-TrkB-VGF-TLQP-62 axis (Licznernski and Duman 2013; Zanos et al. 2018), and *vice versa* (Dremencov et al. 2021). When monoamines are putatively responsible for the depressed mood, decreased BDNF signaling might be behind the organic CNS abnormalities associated with chronic depression, such as decreased amygdaloid volume (Nolan et al. 2020) and hippocampal volume (Warner-Schmidt and Duman 2006), reduced size of the dendritic trees of the pyramidal neurons (Duman and Li 2012), and reduced density of the dendritic spines (Dremencov et al. 2003; Licznernski and Duman 2013; Pavlovicova et al. 2015).

Chronic and/or severe stress is one of the main risk factors for depression. A key component of stress is the release of the corticosteroids, such as corticosterone in rodents or cortisol in primates, from the adrenal cortex to the circulating blood. Corticosteroids reach the CNS and activate the glucocorticoid receptors (GRs) therein. Glucocorticoid receptors in the dorsal raphe nucleus (DRN) and ventral tegmental area (VTA) are interacting with the serotonergic-

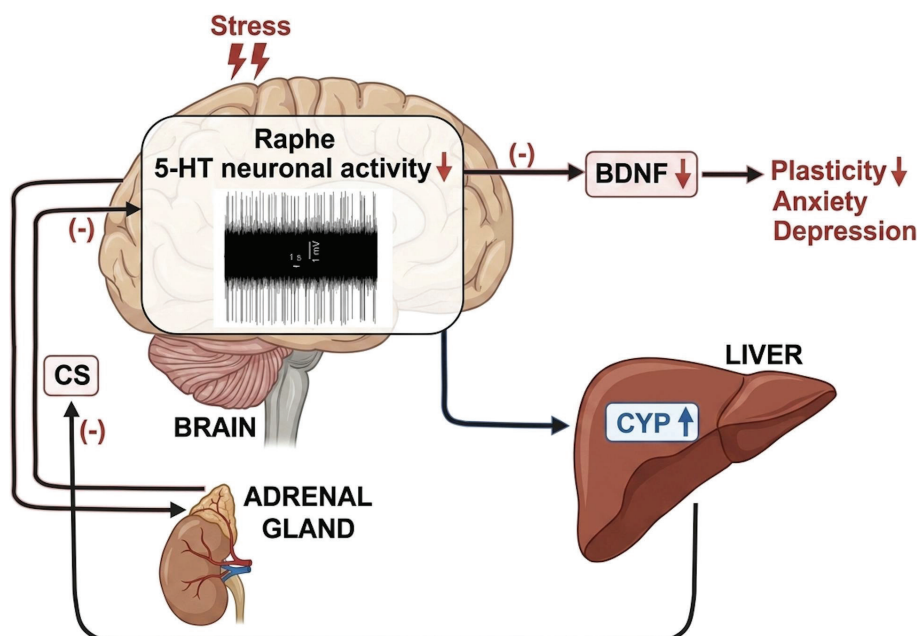


Figure 1. Putative mechanisms underlying pathophysiology of depression and related mood and anxiety disorders. Stress leads to an increase in corticosteroids (CS), leading to decreased excitability of the raphe nuclei serotonin (5-HT) neurons. Decreased 5-HT transmission triggers compensatory mechanisms, such as increased metabolism of CS by the enzymes of the cytochrome P450 superfamily (CYP). *In lieu* of the properly functioning compensatory mechanisms, stress-induced decrease in 5-HT neuronal activity leads to decreasing expression of the brain-derived neurotrophic factor (BDNF), resulting in decreased neuroplasticity, anxiety, and depression. The figure was prepared using illustrations (brain, adrenal gland, and liver) from Servier Medical Art (<https://smart.servier.com>) licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>). The original materials were adapted, including modification of colors.

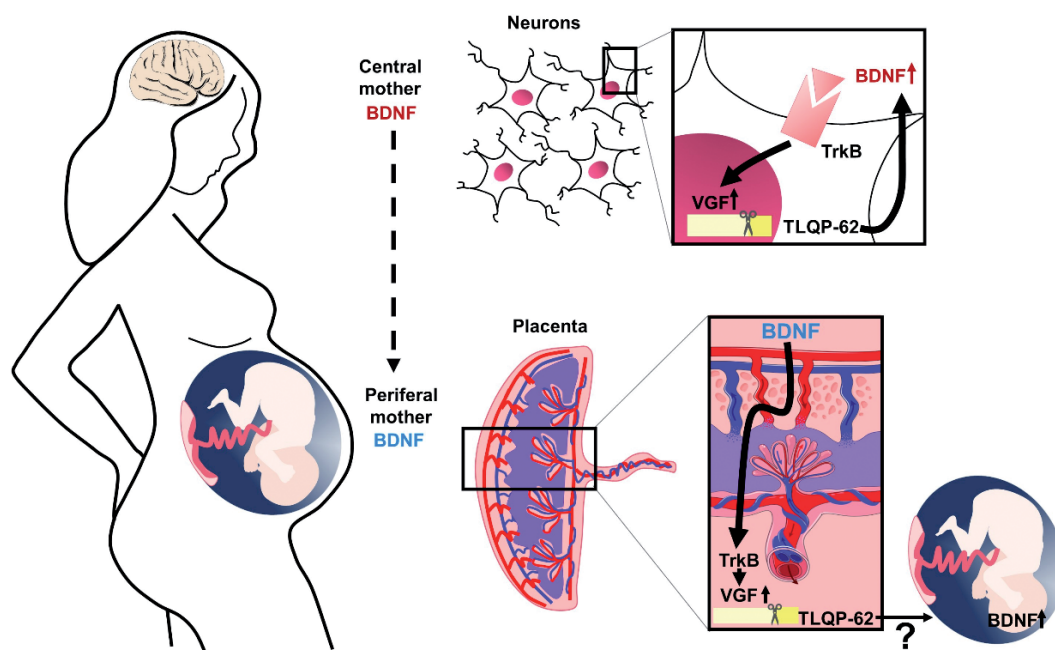


Figure 2. Putative interaction between maternal and embryonal brain derived neurotrophic factor (BDNF)-tyrosine kinase receptor B (TrkB)-VGF-TLQP-62 signaling axes. The figure was prepared using illustrations (brain, fetus in the uterus, and inset of placenta) from Servier Medical Art (<https://smart.servier.com>) licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>). The original materials were adapted, including modification of colors.

1A (5-HT_{1A}) (Wang et al. 2012; Grinchii et al. 2018) and dopaminergic-2 (D₂) (Peng et al. 2021; Paliokha et al. 2022) receptors, increasing their affinity to 5-HT and dopamine, respectively. This sensitization of the inhibitory autoreceptors is likely to lead to decreased central 5-HT and/or dopamine neurotransmission after exposure to the stressor(s).

After chronic exposure to the stressor(s), two alternative scenarios may happen. Under the first scenario, an adaptive mechanism based on the increased glucocorticoid metabolism, resulting in decreased circulating glucocorticoid concentrations (Tseilikman et al. 2019; Sarapultsev et al. 2020) and increased excitability of 5-HT neurons (Dremencov et al. 2022), is developed. Alternatively, *in lieu* of these adaptive changes, prolonged suppression of the CNS monoaminergic tone may lead to decreased BDNF and depressive-like behavior (Tseilikman et al. 2019; Ullmann et al. 2019).

Interestingly, pregnancy *per se* is linked with decreased plasma BDNF concentrations (Lommatzsch et al. 2006; Christian et al. 2016). When pregnancy is associated with stress and/or depression, decrease in circulating BDNF becomes more robust (Singh et al. 2022). Decreased peripheral BDNF in pregnant women has been considered a biomarker for the maternal (e.g., prenatal and postnatal/postpartum depression) (Singh et al. 2022), as well as with embryonal (e.g., low weight at birth) pathologies (Christian et al. 2016).

BDNF-TrkB-VGF-TLQP-62 axis interconnecting maternal and embryonal brains

The primary location of BDNF synthesis, as well as the primary arena of its action is the CNS. Nevertheless, this peptide has also been detected in the circulating blood. BDNF enters the circulation with the cerebrospinal fluid (CSF) drained into the circulation, and it is also produced by thrombocytes, monocytes, and vascular endothelium. Peripheral BDNF plays a role in female reproduction. For instance, it is involved in folliculogenesis, embryo implantation, and placenta development (Singh et al. 2022).

Even though the maternal BDNF is unlikely to pass the placenta (Dingsdale et al. 2021), TLQP-62, because of its lower molecular weight, may cross it. Alternatively, since TrkB receptors are also expressed in the fetal part of the placenta bathed in maternal blood (Mayeur et al. 2010), maternal BDNF may induce embryonal VGF expression *via* their activation. VGF was indeed detected in the placenta (Tesfaye et al. 2023). Peripheral BDNF, VGF, and TLQP-62 are unlikely to pass the blood-brain barrier (BBB) in adults. However, since the BBB is not fully formed until birth (Saili et al. 2017), peripheral embryonal BDNF, VGF, and/or TLQP-62 can enter the brain and reinforce their own expression therein (Fig. 2).

Studies in animal models support the hypothesis that maternal and embryonal BDNF systems are interconnected.

It was reported that the maternal immune challenge with polyriboinosinic-polyribocytidilic acid (poly I:C) in rats led to decreased BDNF levels in the placenta and foetal liver and spleen (Gilmore et al. 2005). Another study reported decreased brain BDNF levels in adult offspring of dams experienced immune challenge with lipopolysaccharide (LPS) (Lin and Wang 2014).

Early life stress and trauma can have lasting effects across generations through epigenetic modifications of key neurodevelopmental genes like BDNF and its receptor TrkB. Stress-induced glucocorticoids can suppress BDNF expression through DNA methylation, leading to persistent gene silencing (Cosi et al. 1993). Studies in neonatal rats have shown that exposure to early life stress and elevated cortisol

results in reduced BDNF mRNA levels in both hippocampus and cortical regions (Roceri et al. 2004).

Binding to glucocorticoid receptors in cells, cortisol influences gene expression and induces both genomic and nongenomic effects crucial for neonatal adaptation (Mitre-Aguilar et al. 2015). Glucocorticoids are essential steroid hormones produced by the adrenal cortex and regulated by the hypothalamic-pituitary-adrenal (HPA) axis. They play key roles in glucose regulation, development, metabolism, neurobiology, and apoptosis. Widely used in medicine, glucocorticoids are valued for their anti-inflammatory, immunosuppressive, and apoptosis-inducing effects, especially in treating cancers like leukemia and lymphoma (Yudt and Cidlowski 2002). Cortisol, a glucocorticoid released from the adrenal cortex, surges in fetal plasma near term, acting as a key maturation trigger that prepares fetal tissues, like lungs, liver, and kidneys, for life outside the womb (Fowden 1995).

Maternal stress alters offspring behavior and excitability of monoamine-secreting neurons *via* BDNF and/or glucocorticoid-mediated mechanism(s)-preclinical evidence

As was mentioned in the Introduction, the interaction between the excitability of monoaminergic, and specifically 5-HT neurons, and expression of BDNF, is putative reciprocal. It is well established that 5-HT induces BDNF expression, and BDNF may in turn stimulate 5-HT neurons, *via* the VGF/TLQP-62 mediated mechanism. Since maternal and embryonal BDNF signaling might be interconnecting, decrease in maternal BDNF may lead to the reduced 5-HT neurotransmission not only in the maternal, but also in the offspring brain. Attenuated firing activity of 5-HT neurons of DRN in the offspring of dams exposed to the different types of stressors during gestation, such as restraint (Oosterhof et al. 2016) or immune challenge by LPS (Csatlosova et al. 2021), was indeed reported. With respect to catecholaminergic neurons, the effects of prenatal restraint and immune challenge were however different. Maternal restraint led to increased excitability of noradrenergic, as well as dopaminergic neurons (Oosterhof et al. 2016), while maternal immune challenge stimulated dopaminergic neurons only. Furthermore, the stimulatory effect of the maternal immune challenge on dopaminergic neuronal firing activity was observed only in male, but not in female offspring (Csatlosova et al. 2021) (Fig. 3).

Decreased excitability of 5-HT neurons is consistent with the increased anxiety and depressive-like behavior observed in the offspring of the dams stressed during the gestation. Thus, offspring of the dams experienced immune challenge during the gestation had reduced locomotion in the open field test, increased anxiety evaluated by the elevated plus maze

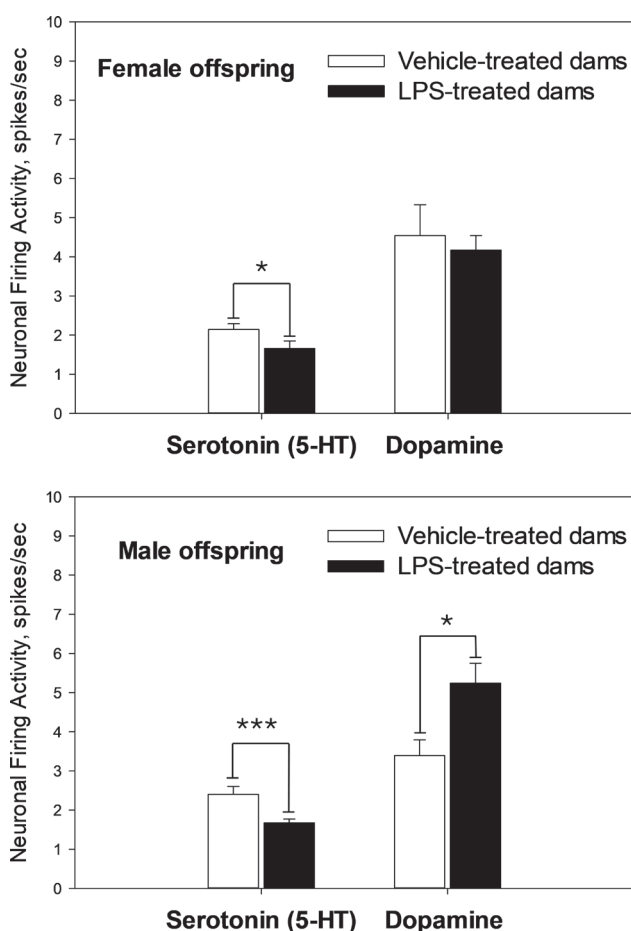


Figure 3. Effects of the immune activation with lipopolysaccharide (LPS) in gestating rats on the excitability of serotonin (5-HT) neurons of the dorsal raphe nucleus (DRN) and dopamine neurons of the ventral tegmental area (VTA) in female (A) and male (B) offspring. The effect of the maternal LPS was statistically significant ($p < 0.001$, two-way analysis of variance: ANOVA); * $p < 0.05$ and *** $p < 0.001$, Bonferroni *post-hoc* test. According to (Csatlosova et al. 2021).

(EPM) test (Enayati et al. 2012), and higher novelty-induced hypophagia (Lin et al. 2012). Furthermore, offspring of the LPS-treated dams showed higher immobility and reduced swimming and climbing time during the forced swim test (FST). This depression-like behaviour, detected by the FST, was reversed by chronic fluoxetine treatment (Lin and Wang 2014).

Similarly to the immune challenge, maternal restraint stress also led to the depressive-like behaviors in offspring, such as increased immobility and decreased climbing. These behavioral alterations were however observed only in male, but not in female offspring (Iturra-Mena et al. 2018).

Maternal immune challenge and restraint stress had also altered BDNF and corticosteroid signalling in the offspring. As it was already stated in the previous paragraph, maternal immune challenge led to decreased brain BDNF expression in the offspring (Lin and Wang 2014). Restraint stress during the gestation had led to the decreased brain BDNF levels in the offspring brain as well (Weston et al. 2014). The molecular mechanism underlying decreased BDNF levels in the offspring of prenatally stressed dams, at least in the case of the restraint stress, might be a decrease in the activity and expression of tissue plasminogen activator (tPA), a key serine protease involved in the extracellular conversion of pro-BDNF to the mature BDNF protein (Weston et al. 2014). Remarkably, the effects of the immune challenge and restraint stresses during the gestation on the reactivity of the HPA axis were opposite. Prenatal restraint was reported to blunt (Iturra-Mena et al. 2018), and prenatal LPS to enhance (Lin et al. 2012; Zager et al. 2014) glucocorticoid response to the acute stressors in the offspring. The recent findings from our laboratory suggest that corticosteroids-induced inhibition of 5-HT neurons in the offspring of maternal immune activation (MIA) dams was stronger, comparing to the controls (Dremencov et al. 2025).

Interestingly, when the maternal exposure to the stressors was pregestational, the effects of these stressors on the excitability of monoaminergic neurons in the offspring were completely distinctive. In two different studies (Grinchii et al. 2024; Paliokha et al. 2026), a stimulatory effect of pregestational maternal chronic unpredictable stress on the excitability of 5-HT neurons was observed. Regarding dopaminergic neurons, recent data from the authors' laboratory suggests that pregestational stress decreases their phasic or burst-like mode of firing (Paliokha et al. 2026). Unlike prenatal stress, pregestational stress did not affect the offspring anxiety as a single main factor in a statistically significant way. However, when the effect of pregestational stress was assessed in interaction with other factors, such as sex and prenatal antidepressant treatment, a slight anxiogenic effect of pregestational stress was detected (Viñas-Noguera et al. 2022; Grinchii et al. 2024).

Studies in animals show that maternal stress exposure results in dysregulated offspring HPA axis activity and

various behavioural abnormalities including anxiety, depression, and cognitive deficits (Van den Hove et al. 2006). Thirty-day-old pups from stressed mothers showed significantly elevated serum corticosterone levels, increased DNA methylation of BDNF and TrkB genes, and reduced expression of these proteins in the hippocampus compared to control pups. Male offspring from stressed mothers specifically exhibited heightened anxiety-like behaviors compared to controls, demonstrating sex-specific effects of maternal stress on behavioural outcomes (Niknazar et al. 2017). Maternal stress during late gestation programs long-term cognitive vulnerabilities by causing a persistent ~45% reduction in hippocampal neurogenesis across all ages and blocking learning-induced neurogenesis in the dentate gyrus, resulting in impaired spatial learning and memory in offspring (Lemaire et al. 2000). Early life stress through 24-hour maternal deprivation on postnatal day nine in rat pups leads to reduced expression of BDNF in the adult hippocampus, along with impaired BDNF regulation in response to acute stress. These changes in rats emerged specifically in adulthood and were largely restricted to the hippocampus, suggesting that early adverse experiences can program lasting region-specific changes in plasticity-related molecules that may increase vulnerability to psychiatric disorders (Roceri et al. 2002).

Summarizing the data from the preclinical studies in animal models, it can be suggested that the maternal stress altered the firing rate and/or excitability pattern of monoaminergic neurons in the offspring. Simultaneous alteration of the BDNF and glucocorticoid signaling pathways suggested their linkage with the maternal stress-induced changes in the offspring catecholaminergic neurotransmission. When the dams experienced the stress prenatally, an inhibitory effect on 5-HT and stimulatory effect on catecholaminergic neurons was observed. Pregestational stress, *vice versa*, led to the stimulation of 5-HT and inhibition of dopamine neurons. It is possible that the inhibitory effect of the prenatal stress on the offspring 5-HT neurons is responsible, at least in part, for the anxiety and depressive-like behavior in the offspring of the stressed dams. The stimulatory effect of the maternal stress on monoaminergic neurons might be, *vice versa*, an adaptive/compensatory mechanism designated to diminish the negative effects of the maternal stress on the offspring brain.

Effects of maternal stress and depression on anxiety and depression in offspring: clinical observations

As it was already mentioned above, there is ample preclinical evidence that the interaction of stress, cortisol, growth factors, and depression in a pregnant woman can alter the condition of the offspring. Clinical studies support this paradigm

as well. Thus, it has been shown that women exposed to stress had shorter gestations, significant fetal growth retardation and developmental defects, and a decrease in head circumference. The risk of spontaneous abortion and premature birth has also increased (Coussons-Read 2013). Stress in the body can cause changes in the HPA axis by increasing the production of corticotropin-releasing hormone (CRH) (Herman et al. 2016). CRH increasing during pregnancy can be a node of other interactions. First, stress, CRH and cortisol as components of stress reaction system can be triggers of depressive disorder (DD) (Reul and Holsboer 2002; Fuchs and Flügge 2004; Dziurkowska and Wesolowski 2021). Second, increased stress-dependent release of CRH leads to disruption of the foetal HPA axis, which may lead to its future imbalance (Parker and Douglas 2010; Coussons-Read 2013). Third, its effect on the BDNF system (Porter and O'Connor 2022). BDNF plays an important role in the development of DD. There is good evidence that BDNF may decrease in women during pregnancy, and this is a physiological effect (Singh et al. 2022). However, HPA imbalance can lead to increased cortisol levels, which in turn leads to decreased BDNF levels (Costa et al. 2019). Since BDNF plays a critical role in the formation, protection, metabolism and development of neurons, its improper functioning can disrupt these processes. Moreover, BDNF itself affects the development of the placenta, and its deficiency leads to pathology of the placenta and, consequently, malnutrition of the foetus (Antonakopoulos et al. 2018). Fourth, HPA axis disturbances lead to immune imbalance, altering inflammatory status affects all body systems. And, naturally, this contributes to the development of DD, for example, a shift in tryptophan metabolism towards kynurenine and further glutamatergic hyperactivation (Kruse et al. 2019).

Taking all of the above into account, it would be fair to extrapolate all these effects on offspring. Indeed, children whose mothers suffered from DD were often diagnosed with affective disorder, which confirms the validity of our statement (Urizar and Muñoz 2022). Understanding how problems that occur in utero in offspring can affect their lives after birth requires a comprehensive approach. First, we need to focus on the anatomical changes of the offspring after birth. It was found that amygdala volume was larger in girls but not in boys (Jones et al. 2019). Hippocampal volume remained slower in the first six months after birth, and hippocampal volume remains smaller in the first 2–6 weeks (Wen et al. 2017; Groenewold et al. 2022).

Microstructural changes are associated with a decrease in fractional anisotropy and axial diffusivity in the right amygdala in newborns (Rifkin-Graboi et al. 2013) and an increase in mean diffusivity in the left amygdala in a boy (Hashempour et al. 2023). Both studies show evidence of white matter abnormalities in the amygdala. Also, there is evidence of disturbances in the brain connectivity. In neonates, there

is an inverse correlation between stress symptomatology and functional connectivity, indicating decreased coactivation and weakened connections in limbic architecture, particularly between the amygdala and hippocampus. This attenuation manifests itself as impaired connectivity in core regions involved in emotion regulation and social-emotional processing, including the bilateral hippocampus, posterior cingulate cortex, and orbitofrontal cortex (Qiu et al. 2015; Scheinost et al. 2016). Female juveniles show increased negative amygdala connectivity with sensory processing areas, along with decreased connectivity with cortico-striatal circuits, potentially influencing emotional and cognitive developmental trajectories. During childhood, these disruptions in connectivity culminate in amygdala hyperreactivity, indicating increased emotional reactivity that can impact behavioural outcomes and mental health (Soe et al. 2018; Donnici et al. 2021). Taken together, these results shed light on the profound and lasting influence of maternal stress and depression during pregnancy on the ontogeny of neural networks essential for emotional regulation and cognitive functioning in the offspring.

As we mentioned before there are multiple lines of evidence that maternal stress has neurobehavioral consequences for offspring. Externalizing behaviors, such as aggression and defiance, are associated with maternal depression, highlighting the significant influence of maternal mood disorders on behavioural outcomes (Sandman et al. 2015; Hay et al. 2020). Executive function impairments, including inhibitory control and visuospatial working memory, indicate gender-specific vulnerabilities to maternal psychological conditions (Buss et al. 2011). There exists a broad association between maternal depression and mental health issues in offspring across various developmental stages, suggesting a pervasive and long-term psychological impact (Urizar and Muñoz 2022). Elevated maternal cortisol levels, indicative of stress and depression, are associated with affective problems in girls, revealing a biochemical pathway through which maternal conditions affect offspring (Buss et al. 2012). Adolescent offspring exhibit increased depressive symptoms, with changes in fronto-temporal cortical thickness from early childhood potentially mediating this relationship, underscoring the developmental continuity of maternal depression's effects (Duan et al. 2019). Furthermore, adult offspring demonstrate mood disturbances, marked by increased cortical gyrification and a brain age gap, reflecting enduring neurodevelopmental changes tied to maternal anxiety and depression (Klein et al. 2014), collectively highlighting the critical need for addressing maternal mental health to mitigate its extensive impact on child development.

Thus, maternal stress is closely associated with changes in the HPA axis. The functioning of this system changes, leading to changes in the BDNF and monoamine system. Impaired

function of this factor in the mother during pregnancy leads to maternal depression and delayed foetal development. Signs of malnutrition and hypoxia are noted. The offspring also undergo changes. The greatest changes are observed in the amygdala and hippocampus. Microstructural changes in the amygdala, as evidenced by changes in fractional anisotropy, axial diffusivity, and mean diffusivity, indicate white matter abnormalities. Functional connectivity studies show decreased coactivation and weakened limbic connections, particularly between the amygdala and hippocampus, leading to impaired emotion regulation and socioemotional processing. These impairments extend to gender-specific executive function vulnerabilities and increased emotional reactivity, leading to amygdala hyperactivity in childhood. In addition, maternal psychological distress is associated with a spectrum of neurobehavioral outcomes, including externalizing behaviour, executive dysfunction, mental health problems across developmental stages, and mood disturbances in adult offspring. These findings highlight the profound and lasting impact of maternal mental health on children's emotional and cognitive development, highlighting the need for interventions to combat maternal stress and depression.

Prenatal stress exposure, especially in early pregnancy, has profound long-term effects: infants show delayed maturation, impaired cognitive performance, and disrupted emotional regulation, while school-age children exhibit reduced brain volume in learning and memory regions. Maternal endocrine alterations during stressed pregnancies simultaneously affect both mother and child, leading to decreased stress responses, altered memory function, and increased postpartum depression risk, ultimately impacting child development and mother-child relationships (Sandman et al. 2012).

Postpartum depression (PPD), affecting 10–20% of women after childbirth, involves complex interactions between hormonal systems during pregnancy and after delivery. During pregnancy, the maternal HPA axis undergoes significant changes due to the presence of the placenta, which functions as a temporary endocrine organ. The HPA axis plays a crucial role in PPD risk, supported by three key findings: excessive stress triggers 85% of depression cases, HPA axis dysregulation is a hallmark feature of major depression, and pregnancy fundamentally alters maternal HPA axis function (Glynn et al. 2013). In a recent study examining stress-related factors and fetal neurodevelopment, maternal depressive symptoms and lower socioeconomic status were found to be significantly associated with elevated BDNF levels in cord blood serum at birth. The study demonstrated positive correlations between fetal BDNF and both maternal depressive symptoms ($r = 0.398$, $p = 0.022$) and household crowding ($r = 0.526$, $p = 0.002$), with these associations persisting after controlling for potential confounders ($\beta = 0.404$, $p = 0.041$ and $\beta = -0.562$,

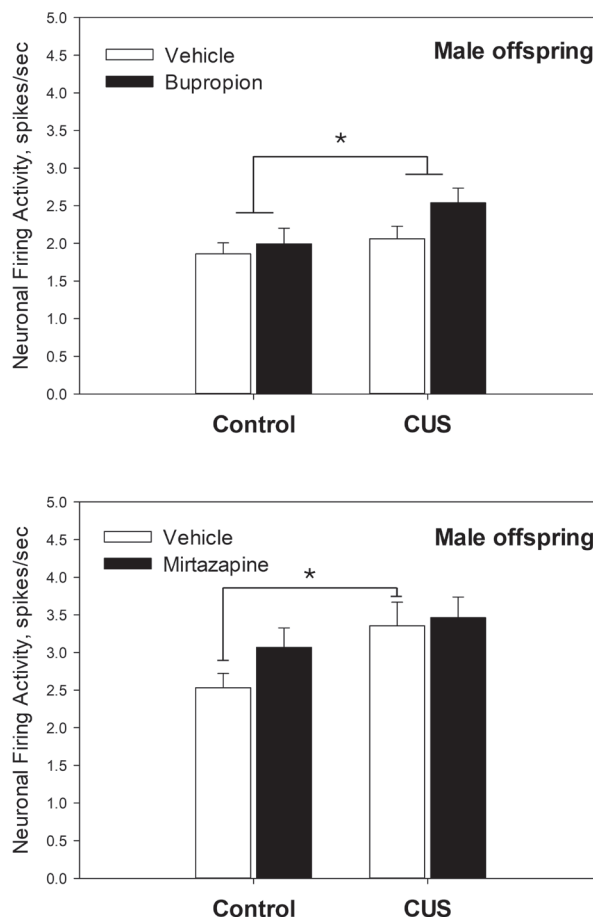


Figure 4. Effects of the pregestational chronic unpredictable stress (CUS) and prenatal treatment with bupropion (A) or mirtazapine (B) on the excitability of serotonin (5-HT) neurons of the dorsal raphe nucleus (DRN) in male offspring. The effects of the maternal CUS ($p < 0.05$) and offspring sex ($p < 0.001$) were statistically significant (three-way analysis of variance: ANOVA). In females, no effect of the maternal CUS was observed (not shown); * $p < 0.05$ and *** $p < 0.001$, Bonferroni *post-hoc* test. According to (Paliokha et al. 2026).

$p = 0.027$, respectively). Notably, fetal BDNF levels showed no significant relationship with newborn anthropometric measurements, suggesting that early BDNF alterations may be specifically linked to maternal stress factors rather than physical growth parameters (Lamadé et al. 2024a).

In a study of 37 mother-newborn pairs undergoing elective cesarean section, higher glucocorticoid levels in amniotic fluid strongly correlated with increased fetal BDNF at birth ($r = 0.745$, $p < 0.001$), while lower birth weight and head circumference were inversely associated with fetal BDNF levels ($r = -0.519$, $p < 0.001$ and $r = -0.508$, $p = 0.001$, respectively), suggesting potential adaptive or compensatory mechanisms in fetal neurodevelopment (Lamadé et al. 2024b).

Prenatal antidepressants alter the effect of maternal stress on the offspring neurophysiology and behavior: preclinical data

It was reported that prenatal treatment with the selective 5-HT reuptake inhibitor (SSRI) fluoxetine led to anhedonia in adult offspring (Gallo et al. 2023). A later study from the same group demonstrated that adolescent offspring of the dams exposed to fluoxetine had stronger response to acute restraint stress and increased glucocorticoid signaling (Gallo et al. 2024). A study from another laboratory showed that prenatal fluoxetine had an anxiogenic effect on male, but not female offspring (Linhares et al. 2022).

With respect to the highly selective SSRI escitalopram, the effect of its prenatal exposure on the offspring behavior depends on the time of its administration. Thus, escitalopram administration to gestating rats during the first trimester of the gestation led to higher behavioral flexibility and lower anxiety-like behavior. When escitalopram was administered during the last trimester, it induced slight pro-compulsive behavioral effect in offspring (Bezenah et al. 2023). Prenatal treatment with the racemic citalopram, however, did not have effect on the offspring behavior, neither did it corrected behavioral (increased anxiety) and neurochemical (decreased 5-HT transmission) abnormalities induced by prenatal stress (Zohar et al. 2016).

Singh and co-authors recently reported that the treatment of the gestating rats with two antidepressant drugs, the 5-HT reuptake inhibitor and 5-HT_{1A} partial agonist vilazodone, and dual 5-HT and noradrenaline reuptake

inhibitor, 5-HT_{3/7} and β_1 -adrenergic antagonist, 5-HT_{1A} agonist and 5-HT_{1B} partial agonist vortioxetine, both induced anxious and depressive-like behavior in offspring. The behavioral abnormalities were accompanied by reduced 5-HT, noradrenaline, and dopamine concentrations in the prefrontal cortex (Singh et al. 2024). With respect to the dual 5-HT and noradrenaline reuptake inhibitor venlafaxine, it was reported that its prenatal administration reduced anxiety and depressive-like behavior in rats (Bogi et al. 2018).

It has been reported in our previous studies that the prenatal treatment with the catecholamine releaser bupropion (Grinchii et al. 2024) and 5-HT_{2A/2C/3} and α_2 -adrenergic antagonist mirtazapine (Paliokha et al. 2026), reversed the anxiogenic effect of the maternal pregestational stress on the offspring. Both drugs also enhanced the mean spontaneous firing activity of 5-HT neurons in the offspring brain (Fig. 4). Furthermore, prenatal mirtazapine reverses pregestational CUS-induced decrease in hippocampal BDNF protein expression in female offspring (Fig. 5) (Paliokha et al. 2026). Considering the fundamental roles of 5-HT and BDNF in anxiety, the reduced anxious behavior in rats prenatally administered bupropion or mirtazapine is likely to be explained by a 5-HT-related mechanism.

Tianeptine is an unconventional antidepressant with mechanisms involving opioid receptor agonism and glutamate pathways (Nishio et al. 2024). In a study conducted on tianeptine, while the drug did not affect Fos immunoreactivity, it modulated GR immunoreactivity in a region-specific manner, sometimes counteracting the effects of acute stress and maternal separation (MS) in the hippocampus and amygdala. Behaviourally, tianeptine reversed the anxiety-like effects induced by MS or chronic stress, suggesting that early adversity modifies stress responses that tianeptine can partially normalize (Trujillo et al. 2016).

Effects of prenatal antidepressants on the offspring mental health: clinical evidence

Research has shown that prenatal exposure to antidepressants can influence early sensory processing capabilities in infants. Hunter et al. (2012) found that infants exposed to maternal anxiety without antidepressants exhibited diminished sensory gating, a critical attentional process. However, antidepressant exposure during pregnancy mitigated these deficits, suggesting a potential neuroprotective effect. This improvement may be attributed to different cholinergic mechanisms influenced by antidepressant treatment.

The association between prenatal antidepressant exposure and neurodevelopmental outcomes such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) has sparked considerable debate. Sujan et al. (2019) highlighted that observed associations could

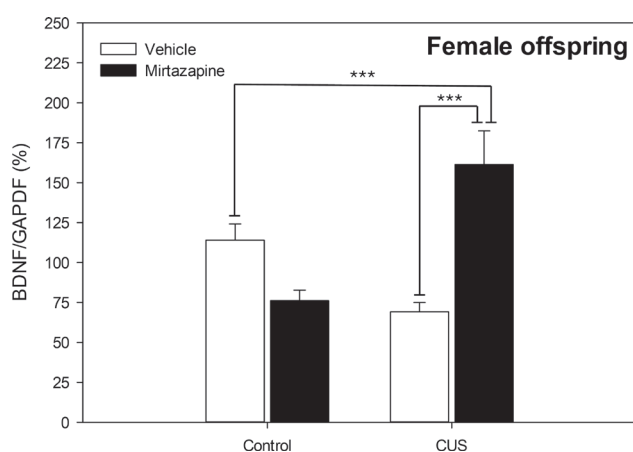


Figure 5. Effects of the pregestational chronic unpredictable stress (CUS) and prenatal treatment with mirtazapine on the brain derived neurotrophic factor (BDNF) expression in female offspring. The interaction between the effects of the maternal CUS and mirtazapine was statistically significant ($p < 0.001$; three-way analysis of variance: ANOVA); *** $p < 0.001$, Bonferroni *post-hoc* test. According (Paliokha et al. 2026).

often be attributed to confounding factors like maternal psychiatric conditions and genetic predispositions, rather than direct causation. Observational studies indicate that maternal mood disorders may play a more critical role than the antidepressant exposure itself. Additionally, prenatal exposure to SSRIs has been linked to changes in brain morphology that persist through childhood. Koc et al. (2023) reported that children exposed to SSRIs showed reduced grey matter, particularly in the corticolimbic circuits responsible for emotional regulation. These brain changes continued from childhood into adolescence, raising questions about the long-term developmental implications and their effects on cognitive and emotional processing.

Simon et al. (2002) conducted studies that showed prenatal antidepressant use, especially SSRIs, was associated with earlier delivery and reduced birth weight, although these differences did not contribute to congenital malformations or developmental delays. For instance, SSRIs were linked to a 0.9-week reduction in gestational age, and a 175-gram decrease in birth weight. These findings point to potential perinatal complications but not significant congenital anomalies. Figueroa (2010) assessed the risk of ADHD in children prenatally exposed to antidepressants, finding that exposure to certain medications, such as bupropion, increased the likelihood of ADHD. However, exposure to SSRIs did not show the same significant association. This suggests that the type of antidepressant plays a role in the risk profile for neurodevelopmental disorders.

Longitudinal assessments of children exposed to prenatal SSRIs indicate potential changes in executive function. Dhaliwal et al. (2020) found that these cognitive changes might be modulated by genetic factors, particularly variations in the serotonin transporter gene (SLC6A4). Children with specific alleles demonstrated varied resilience to maternal depressive symptoms, suggesting that genetic predisposition significantly influences developmental outcomes. Oberlander and colleagues (Oberlander et al. 2006) highlighted that prenatal exposure to SSRIs could lead to neonatal complications, including respiratory distress and feeding issues. Even after accounting for maternal illness severity, SSRIs were associated with a higher incidence of these neonatal issues. These findings underscore the importance of weighing potential neonatal risks against the benefits of maternal mental health treatment. Another study (Malm et al. 2016) indicated that children exposed to SSRIs during pregnancy had an increased risk of developing depression in adolescence. However, links to ASD or ADHD were less pronounced, suggesting that while there may be some increased risk for certain psychiatric conditions, the broader spectrum of neurodevelopmental disorders may not be significantly affected by SSRIs. Studies consistently emphasize that maternal mental health is a significant confounding factor in research on prenatal antidepressant exposure. Hagberg and colleagues (Hagberg et

al. 2018) found that after adjusting for maternal depression, the association between antidepressant use and ASD risk diminished, suggesting that maternal mental illness, rather than antidepressant exposure itself, is a crucial determinant. Sibling-controlled studies by Brandlistuen et al. (2015) demonstrated that prenatal antidepressant exposure was specifically linked to increased anxiety symptoms in children, even after controlling for maternal and familial factors. This association was not observed for other behavioural problems, highlighting a specific risk profile related to anxiety.

Hanley et al. (2013) reported significant findings indicating that infants prenatally exposed to SSRIs scored lower on the gross motor, social-emotional, and adaptive behaviour subscales of the Bayley Scales of Infant Development. These developmental delays were not attributed to maternal depression, suggesting a direct impact of the antidepressants. The mechanism underlying SSRI exposure impacts the serotonin system, which is pivotal in brain development processes such as synaptogenesis and neuronal differentiation (Hunter et al. 2012; Millard et al. 2017), who highlighted that early exposure could disrupt serotonin signalling, potentially influencing neurodevelopmental trajectories. This mechanism underscores the importance of understanding how prenatal SSRI exposure may alter early brain development (Millard et al. 2017).

On the other hand, while concerns exist regarding the potential adverse effects of prenatal antidepressant use, untreated maternal depression poses substantial risks. Davalos et al. (2012) noted that maternal mental health stability is critical for child development, and in some cases, antidepressant treatment may indirectly benefit the child by alleviating maternal depression. The long-term effects of prenatal SSRI exposure vary significantly among individuals. Rotem-Kohavi and Oberlander (2017) pointed out that these differences can be attributed to genetic and environmental factors, emphasizing the need for personalized risk assessments and further research. Rommel et al. (2020) conducted a meta-analysis that revealed significant associations between prenatal antidepressant exposure and various outcomes, but most associations diminished when adjusting for confounding factors such as maternal mental health severity. This highlights that maternal mood disorders are a major determinant in assessing risks and outcomes related to antidepressant exposure.

Conclusions

The effect of antidepressant treatment during pregnancy is significantly influenced by several factors, including the timing of administration, the maternal mental and physiological state, and the pharmacodynamics of the specific antidepressant. By carefully considering and combining these variables, clinicians

can develop a clearer understanding of the potential impact of antidepressant therapy on offspring health and development.

The gestational period during which antidepressants are administered plays a pivotal role in shaping their effects on offspring. Early exposure, particularly in the first trimester, is associated with critical neurodevelopmental processes such as neuronal differentiation and synaptogenesis. For example, escitalopram administered during early pregnancy has been linked to improved behavioral flexibility and reduced anxiety-like behaviors in animal models, while late administration showed slight pro-compulsive effects (Bezenah et al. 2023). Similarly, prenatal fluoxetine exposure at critical developmental stages has been associated with increased glucocorticoid receptor signaling and heightened stress responses in offspring (Gallo et al. 2024). These findings underscore the importance of tailoring the timing of treatment to minimize adverse outcomes.

The maternal condition – both psychological and physiological – is a critical determinant of treatment outcomes. Untreated maternal depression itself poses significant risks, including dysregulation of HPA axis, reduced BDNF levels, and impaired placental function, all of which adversely affect fetal development (Lommatzsch et al. 2006; Christian et al. 2016). Addressing maternal depression can stabilize these physiological systems, thereby reducing risks to the fetus. However, individual variations in maternal response to treatment, influenced by factors such as the severity of depression and comorbid conditions, must be considered.

The pharmacological properties of antidepressants, including their receptor affinities and systemic effects, also significantly influence outcomes. For instance, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been associated with both positive and negative neurobehavioral effects in offspring, depending on the dosage and timing of exposure (Dhaliwal et al. 2020). By contrast, venlafaxine, a serotonin-noradrenaline reuptake inhibitor (SNRI), has demonstrated anxiety-reducing effects in animal models (Bogi et al. 2018). Additionally, atypical antidepressants such as mirtazapine and bupropion have shown promise in reversing stress-induced anxiogenic effects, likely through their impact on serotonergic and catecholaminergic systems (Grinchii et al. 2024).

Thus, by integrating these factors – timing, maternal state, and pharmacodynamics – clinicians can better assess the risks and benefits of antidepressant use during pregnancy. Such a personalized approach allows for more precise interventions that not only address maternal mental health but also mitigate potential risks to offspring development. Continued research is essential to refine these strategies and provide clearer guidelines for clinical practice.

Funding. The work of the authors was supported by the grants APVV-20-0202, APVV-22-0061, VEGA-2/0057/22 and VEGA-2/0045/24.

Acknowledgements. The authors thank Dr. Marta Gaburjaková for the critical proof-reading of this manuscript, as well as for excellent assistance with the preparations of the figures.

Conflict of interest. The authors declare no conflicts of interest.

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Received: January 16, 2026

Final version accepted: March 23, 2026