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REVIEW

The dual face of human chorionic gonadotropin in the CNS: neuroprotection, signaling, and possible pathological effects

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Abstract

Background Human chorionic gonadotropin (hCG) is a glycoprotein hormone critical for reproduction, particularly in pregnancy maintenance and fertility treatments. Beyond reproduction, hCG may influence immune regulation, cancer biology, and neurological processes.

Objective This review critically examines the current evidence regarding the potential neurological effects of hCG, synthesizing findings from experimental and clinical studies to assess its proposed roles in neuroinflammation, oxidative stress, and blood–brain barrier modulation.

Result Dysregulated hCG levels—arising from pregnancy complications, assisted reproductive technologies (ART), or hCG-secreting tumors—have been associated with markers of neurotoxicity, including neuroinflammation, oxidative stress, and altered blood–brain barrier integrity. Evidence remains largely associative, and causal mechanisms linking hCG to neurobiological vulnerability are not yet established. Proposed pathways include modulation of immune cell activity, neurotransmitter signaling, and endothelial function.

Conclusion hCG exhibits a dual nature: essential for reproduction and immune adaptation, yet potentially neurotoxic under dysregulated conditions. This review synthesizes mechanistic hypotheses, highlights knowledge gaps, and underscores the need for rigorous longitudinal and experimental studies to clarify hCG's impact on the nervous system.

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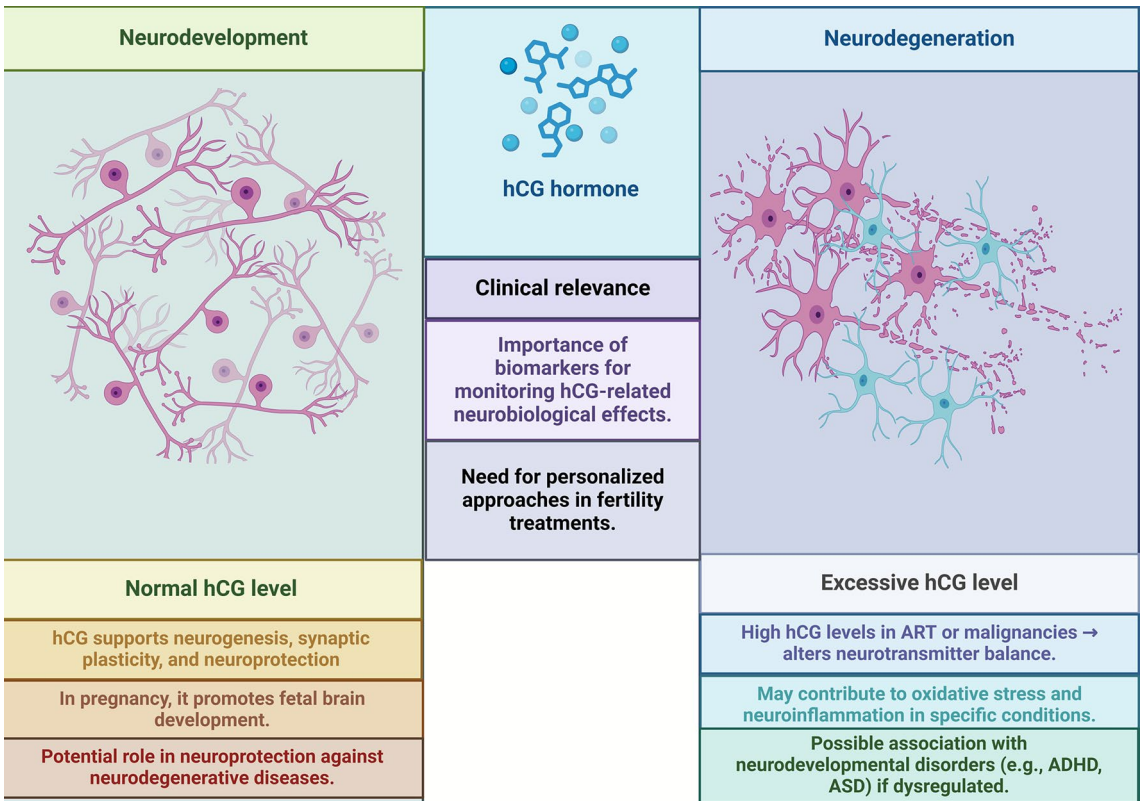
Graphical abstract



Highlights

1. Human chorionic gonadotropin (hCG) plays a critical role in reproduction, but emerging evidence suggests its involvement in neurotoxic processes.
2. Dysregulated hCG levels are linked to neuroinflammation, oxidative stress, and disruption of the blood–brain barrier, contributing to neurological dysfunction.
3. Elevated hCG levels in pregnancy, assisted reproductive technologies (ART), and hCG-secreting tumors may exacerbate cognitive impairments and neurological disorders.
4. The review synthesizes emerging evidence on pathways through which hCG may be associated with neurotoxic outcomes, including neuroinflammation, oxidative imbalance, and alterations in neurotransmitter signaling.
5. Clinical implications of hCG exposure in reproductive settings are discussed, highlighting the need for better risk management strategies in neurological health.
6. The dual role of hCG—essential for reproduction yet potentially harmful to neurobiology—underscores the need for targeted therapeutic interventions.
7. Future research should aim to define neurological biomarkers and investigate therapeutic strategies within the context of the hypothesized neurobiological effects associated with hCG exposure.

Keywords Assisted reproductive technologies · Blood–brain barrier · Cognitive impairments · Human chorionic gonadotropin · Neurodegenerative diseases · Neuroinflammation · Oxidative stress

Introduction

Human chorionic gonadotropin (hCG) is a glycoprotein hormone primarily known for its pivotal role in reproduction, particularly in pregnancy and fertility treatments [1, 2]. Produced by the placenta during pregnancy, hCG is essential for maintaining the corpus luteum and stimulating the secretion of progesterone, a hormone crucial for sustaining the early stages of pregnancy [3, 4]. Beyond its reproductive significance, hCG has garnered increasing attention for its involvement in immune modulation, cancer biology, and more recently, its potential implications in neurological health [5, 6]. The versatility of hCG's actions, driven by its interaction with luteinizing hormone/choriogonadotropin receptors (LHCGR), highlights its broader physiological functions, extending beyond the reproductive system.

While hCG's roles in reproduction and immune regulation are well-established, emerging research has begun to explore its potential effects on the nervous system [7]. In some clinical settings such as pre-eclampsia, elevated β-hCG levels have been correlated with increased systemic inflammation, oxidative-stress markers, and in a subset of cases with evidence of blood–brain barrier injury and CNS inflammation in mothers [8, 9]. However, these observations remain associative, and direct causal links between hCG and neuroinflammation, oxidative stress, or blood–brain barrier (BBB) disruption, particularly in ART or tumor-related hCG exposure, have not yet been demonstrated.

Some epidemiological studies have observed associations between maternal serum hCG or hCG-related pregnancy conditions (e.g., hyperemesis gravidarum) and increased risk of ASD in offspring [10]. However, these findings remain observational, and direct causal mechanisms remain unproven. Thus, while the hypothesis that altered hCG exposure may influence neurodevelopment remains intriguing, it is currently unproven and requires rigorous longitudinal and mechanistic follow-up. These observations remain highly speculative, as they are based primarily on associative data subject to numerous confounders, including maternal health, genetic background, environmental exposures, and ART protocols. Consequently, any proposed connection between hCG exposure and neurodevelopmental disorders should be considered as an intriguing hypothesis rather than an established causal relationship. Rigorous longitudinal and mechanistic studies are required to clarify whether and how maternal or pharmacological hCG influences neurodevelopment.

This review aims to provide a comprehensive analysis of the potential neurobiological effects of hCG, with a focus on its signaling pathways and how they may intersect with processes such as neuroinflammation, oxidative stress, and neurotransmitter regulation. We will examine both physiological and pathological contexts of hCG exposure, including pregnancy, ART, and hCG-secreting tumors, highlighting where evidence is robust and where hypotheses remain untested. By integrating current experimental and clinical data, this review seeks to present a balanced perspective on the dual nature of hCG, its neuroprotective roles in some contexts, and its potential for contributing to neurological dysfunction in others—while clearly delineating speculative associations from established findings.

hCG: functions and systemic effects

Structure and secretion of hCG

hCG is a glycoprotein hormone primarily secreted by the syncytiotrophoblast cells of the placenta during pregnancy [11]. Structurally, hCG belongs to the glycoprotein hormone family, sharing a common α-subunit with luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), while its β-subunit is unique and confers its biological specificity [12–14]. This β-subunit contains critical glycosylation sites, which influence its stability, receptor binding affinity, and bioactivity [1].

hCG secretion follows a dynamic pattern during pregnancy, with levels rising exponentially in the first trimester, peaking around 8–12 weeks of gestation, and gradually declining thereafter [15]. Beyond pregnancy, low levels of hCG are also detectable in non-pregnant individuals, as it is produced in small amounts by the pituitary gland [16]. In addition, hCG isoforms, including hyperglycosylated hCG (hCG-H) and free β-hCG, play distinct roles in trophoblast invasion and tumor progression, highlighting its diverse physiological and pathological significance [17, 18].

hCG receptors and signal transduction pathways

The biological effects of hCG are primarily mediated through its interaction with the LHCGR, a G protein-coupled receptor (GPCR) belonging to the rhodopsin-like GPCR family [19]. LHCGR is predominantly expressed in reproductive tissues, including the ovaries, testes, and placenta, where it plays a crucial role in steroidogenesis and gametogenesis [20]. However, its expression extends beyond classical reproductive sites, being detected in immune cells, endothelial cells, and various tumors, suggesting a broader systemic role for hCG [21].

Upon ligand binding, hCG initiates a signaling cascade primarily through the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway [22]. This pathway

activates cAMP response element-binding protein (CREB), which regulates the transcription of genes involved in cell proliferation, differentiation, and survival [23]. In reproductive tissues, this mechanism supports progesterone synthesis in the corpus luteum, sustains early pregnancy, and regulates ovarian follicular maturation and spermatogenesis [24, 25].

Beyond the classical cAMP-PKA pathway, hCG engages alternative signaling cascades, enabling diverse biological responses. The phosphatidylinositol-3-kinase (PI3K)/Akt pathway is a key mediator of cell survival and angiogenesis, particularly in trophoblast cells, where it facilitates placental vascular remodeling [26]. Similarly, the mitogen-activated protein kinase (MAPK) pathway is implicated in cell proliferation, differentiation, and migration, contributing to trophoblast invasion and tumor progression [27]. In addition, the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway plays a role in immune modulation, influencing inflammatory cytokine production and immune cell differentiation [28].

The widespread distribution of LHCGR in the brain, immune system, and certain malignancies suggests that hCG signaling extends beyond reproduction. The receptor's presence in neurons and glial cells raises the possibility of hCG-driven neuroendocrine regulation, while its expression in immune cells implies a role in immunosuppression and inflammation control [29, 30]. Furthermore, aberrant hCG signaling has been implicated in tumorigenesis, cancer metastasis, and immune evasion, highlighting the need for further exploration of its systemic effects [31]. Understanding the multi-faceted signaling mechanisms of hCG is essential for elucidating its physiological roles and potential contributions to neurological and immune-related disorders.

Role of hCG in reproduction, immune modulation, and cancer

Reproductive functions

hCG plays a pivotal role in pregnancy maintenance by stimulating progesterone production from the corpus luteum, essential for endometrial receptivity and fetal development. In addition, it supports placental angiogenesis, trophoblast differentiation, and maternal immune tolerance [32]. Emerging evidence suggests that hCG may also regulate ovarian follicular dynamics and influence spermatogenesis in males, emphasizing its broader impact on reproductive endocrinology.

Immune modulation

Beyond reproduction, hCG exerts profound immunomodulatory effects, contributing to maternal–fetal immune tolerance. It promotes a Th2-dominant immune response, suppresses Th1-mediated inflammation, and enhances regulatory T cell (Treg) activity, thereby preventing fetal rejection [33]. hCG also modulates macrophage polarization, shifting them towards an anti-inflammatory M2 phenotype, which may have implications in both pregnancy and immune-related disorders [34, 35].

Oncogenic potential of hCG

Aberrant hCG expression is observed in various malignancies, including choriocarcinoma, testicular cancer, ovarian cancer, and certain gastrointestinal tumors [31, 36]. Cancer cells exploit hCG signaling to promote angiogenesis, immune evasion, and metastatic progression [37]. Notably, hCG-H, a highly glycosylated isoform, is implicated in tumor aggressiveness by inhibiting apoptosis and facilitating immune escape mechanisms [38]. The presence of hCG receptors in the nervous system raises concerns about its potential neurotoxic effects in oncological settings, warranting further investigation.

Distinct biological contexts of hCG exposure: physiological, pathological, and pharmacological differences

hCG exists in multiple biological contexts, defined by distinct isoforms, glycosylation patterns, concentrations, and likely different receptor engagement and downstream signaling consequences [39]. These differences are essential when interpreting potential effects of hCG on the CNS and for avoiding inappropriate extrapolation across experimental systems.

Physiological hCG (pregnancy)

In normal pregnancy, hCG is produced by the syncytiotrophoblast of the placenta and is secreted in a regulated pattern with changing isoform composition over gestation [40]. One important variant is hyperglycosylated hCG (hCG-H), produced by extravillous cytotrophoblasts, which predominates early in pregnancy, but declines later in gestation [41]. The controlled levels and specific glycoform profile of physiological hCG ensure that receptor activation likely remains within physiological limits. Regular pregnancy-derived hCG supports maternal–fetal endocrine regulation, immune adaptation, and placental function [42]. Because of this regulated context, findings based on pregnancy-level hCG should not be assumed to represent effects of supraphysiologic exposure or pathological isoforms.

Pathological hCG (trophoblastic and non-trophoblastic tumors)

In contrast, in certain malignancies such as trophoblastic disease or germ-cell tumors, aberrant forms of hCG

are produced, including hCG-H and free β-subunits, with altered glycosylation and structural features compared to physiological hCG [43]. These tumor-derived variants often reach concentrations substantially higher than those observed during normal pregnancy [43]. Functional studies indicate that hyperglycosylated hCG in these pathological settings exhibits distinct biological activities, including enhanced invasiveness, proliferation, and immunomodulatory capacity, which diverge from the classical endocrine role of hCG [17]. Given these structural and functional differences, the pathophysiological consequences of tumor-derived hCG cannot be assumed equivalent to those of physiological pregnancy hCG.

Pharmacological hCG (clinical or ART use)

Exogenous administration of hCG, for example in ART or other clinical applications, introduces hCG in bolus doses that produce supraphysiologic peaks. Depending on the preparation, the hCG may include a mixture of isoforms, including hyperglycosylated variants or free subunits [44]. The pharmacokinetics (dose, timing, half-life) and receptor occupancy in pharmacological scenarios differ substantially from physiological pregnancy, and thus downstream signaling and tissue effects may diverge accordingly. As a result, observations derived from pharmacologic hCG exposure should not be directly equated to effects of endogenous placenta-derived hCG or tumor-derived hCG.

Implications for interpreting CNS-related hCG effects

These distinctions underscore that hCG's influence on the CNS is highly context-dependent. When interpreting neurobiological outcomes, such as receptor activation, signaling pathways, inflammation or neurotoxicity, one must carefully consider the source, isoform, glycosylation status, dosage, and exposure pattern of hCG. Extrapolations across these biologically distinct categories must be made with caution, and only when appropriate controls and context-specific data are available.

hCG and the nervous system

Emerging evidence suggests that hCG plays a role in neurodevelopment, neuroprotection, and neuroimmune interactions [45]. The presence of hCG receptors in the central nervous system (CNS) supports the hypothesis that this hormone has direct regulatory functions in brain physiology [46]. However, dysregulated hCG levels—whether excessive or deficient—have been implicated in neurological disorders, neuroinflammation, and cognitive dysfunction, necessitating further exploration of its neurobiological significance [7].

Expression of hCG receptors in neural and glial cells

The potential expression of LHCGR in the CNS provides a putative molecular basis for hCG's neurological effects. Studies in animal models and in vitro systems have reported LHCGR expression in neurons, astrocytes, microglia, and oligodendrocytes, suggesting that hCG may influence multiple neural processes [47, 48]. In rodent models, LHCGR has been detected in regions such as the hypothalamus, hippocampus, and cerebral cortex, which are critical for neuroendocrine regulation, cognition, and synaptic plasticity [49].

Neurons expressing LHCGR in these models respond to hCG stimulation by activating intracellular signaling pathways, including cAMP/PKA, PI3K/Akt, and MAPK, which are involved in neuronal survival, differentiation, and synaptic remodeling [50]. Similarly, glial cells, particularly astrocytes and microglia, have been shown to express LHCGR in preclinical studies, implicating hCG in potential neuroinflammatory modulation [51]. Some preclinical data, notably in inflammatory or injury models, suggest that hCG may modulate microglial activation toward a less reactive phenotype and attenuate neuroinflammation, and that under specific conditions, it might influence glial-mediated neurotrophic support [52]. However, to date, there is no robust evidence from adult human CNS tissue showing hCG-induced neurotrophic factor release from astrocytes or sustained anti-inflammatory polarization of microglia. The presence of LHCGR in oligodendrocytes suggests a possible role in myelination and neural repair, though this remains largely unexplored.

Importantly, it must be emphasized that the expression and functional significance of LHCGR in the adult human CNS remain a subject of ongoing debate. Direct evidence from adult human brain tissue is limited, and many findings are extrapolated from rodent models, neonatal tissue, or in vitro systems [53, 54]. Therefore, while these data provide a conceptual framework for hCG-mediated neuroendocrine and neuroimmune effects, the relevance to adult human physiology and pathology remains hypothetical. Future studies using human CNS tissue and physiologically relevant models are required to clarify whether LHCGR is expressed functionally in neurons and glial cells, and to determine the true impact of hCG signaling in the human brain.

Physiological functions of hCG in brain development and neuroprotection

During early brain development, hCG is believed to contribute to neurogenesis, neuronal differentiation, and synaptic maturation. Studies have demonstrated that hCG can enhance neuronal survival by activating pro-survival pathways such as PI3K/Akt, while also stimulating the release of brain-derived neurotrophic factor (BDNF), a key regulator of neuroplasticity [55, 56]. In addition, hCG has been implicated in angiogenesis within the CNS, ensuring adequate blood supply to developing neuronal networks [57].

Beyond its role in development, hCG exhibits neuroprotective properties in the adult brain. Experimental studies, including those in neonatal mouse models, suggest that hCG can mitigate neurodegenerative processes by reducing inflammatory-mediated neuronal loss and apoptosis. For instance, in a neonatal hypoxia–ischemia model, hCG administration significantly reduced cortical and hippocampal tissue loss, preserved parvalbumin-positive interneurons, and attenuated microglial activation, indicating its potential in neuroprotection [7, 58]. For instance, hCG has been found to reduce β-amyloid accumulation and tau phosphorylation, two hallmarks of Alzheimer's disease (AD) [59]. In addition, hCG may modulate dopaminergic and serotonergic neurotransmission, influencing mood regulation and cognitive function [60]. These findings raise the possibility of hCG-based therapeutic strategies for neurodegenerative and neuropsychiatric disorders.

Pathological consequences of dysregulated hCG levels

While physiological levels of hCG appear to support neural health, dysregulated hCG expression—either excessive or deficient—has been associated with neurological dysfunction and disease states. Elevated hCG levels, often observed in gestational trophoblastic diseases and certain cancers, have been linked to neuroinflammation and cognitive impairment, possibly due to aberrant activation of glial cells and disruption of neuroimmune homeostasis [61]. Conversely, insufficient hCG levels during pregnancy have been correlated with an increased risk of neurodevelopmental disorders, including autism spectrum disorder (ASD) and schizophrenia, suggesting a critical role for hCG in fetal brain maturation [62–64].

In addition, abnormal hCG signaling has been implicated in neuro-oncology, particularly in tumors such as glioblastoma and medulloblastoma, where it may promote tumor growth, angiogenesis, and immune evasion [65]. The ability of certain brain tumors to produce hCG autonomously further complicates its role in neuropathology, raising concerns about its potential as a biomarker for tumor progression.

Mechanistic pathways potentially associated with hCG-related neurotoxicity

Growing evidence suggests that hCG may influence neuroimmune pathways relevant to neuroinflammatory states. In murine microglial cultures, hCG under pro-inflammatory conditions enhances nitric oxide and TNF-α production, consistent with a shift toward a pro-inflammatory phenotype [66]. Conversely, in a neonatal mouse model of systemic inflammation plus hypoxia-ischemia, hCG administration reduced microglial immunoreactivity and mitigated neurodegeneration [7]. These findings indicate that hCG exposure can modulate microglial activation and neuroimmune tone, but direct mechanistic evidence in the human CNS remains lacking. Rather than representing a confirmed neurotoxic cascade, current data support a conceptual framework in which dysregulated or excessive hCG exposure could contribute to oxidative stress, altered neuronal homeostasis, and susceptibility to cognitive or neuropsychiatric disturbances in specific physiological or pathological contexts (Table 1).

hCG-mediated modulation of pro-inflammatory cytokines

Aberrant hCG signaling in microglia can upregulate the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), IL-6, and IL-1β, leading to a sustained inflammatory environment in the CNS [67]. These cytokines can disrupt the BBB, promoting the infiltration of peripheral immune cells and further exacerbating neuroinflammation [68]. In addition, activated microglia can release ROS and nitric oxide (NO), inducing oxidative stress and neuronal apoptosis (see Fig. 1) [69].

Moreover, chronic hCG exposure has been linked to enhanced NF-κB signaling, a key transcription factor that regulates inflammatory gene expression [70, 71]. Persistent NF-κB activation sustains microglial priming, making the CNS more vulnerable to secondary inflammatory insults, such as infections, trauma, or neurodegenerative triggers. This mechanism may be particularly relevant in AD, Parkinson's disease (PD), and multiple sclerosis (MS), where neuroinflammation is a key pathological feature [72, 73].

Impact of chronic inflammation on neuronal function and survival

Chronic neuroinflammation driven by hCG can have profound effects on neuronal function and survival. Pro-inflammatory cytokines and oxidative stress can disrupt synaptic integrity, impairing neurotransmission and contributing to cognitive decline [74]. In addition, excessive inflammation can interfere with adult neurogenesis, particularly in

Table 1 Hypothetical mechanisms and potential neurobiological effects of altered hCG levels

Category	Proposed mechanism/effect	Potential clinical relevance	Speculative outcomes
hCG and neuroinflammation	Altered hCG levels may influence microglial activation and pro-inflammatory cytokine release (e.g., TNF-α, IL-6, IL-1β)	Could contribute to neuroinflammatory processes observed in neurodegenerative or neurocognitive disorders	Hypothetical: chronic neuroinflammation, cognitive impairments, exacerbation of neurodegenerative processes
hCG and oxidative stress	Dysregulated hCG may promote reactive oxygen species (ROS) generation, potentially leading to oxidative stress in neuronal and glial cells	Could be associated with oxidative stress-related neuropathologies	Hypothetical: mitochondrial dysfunction, neuronal or glial cell damage, exacerbation of neurodegeneration
Blood–brain barrier disruption	Altered hCG levels might affect brain endothelial cells and BBB permeability	Could influence susceptibility to neurotoxicants and CNS inflammation	Hypothetical: increased vulnerability to neurotoxic substances, neuroinflammation, neuronal injury
Neurotransmitter dysregulation	hCG exposure may modulate neurotransmitter systems (dopamine, serotonin, GABA)	Potential relevance to psychiatric conditions, such as anxiety, depression, or schizophrenia	Hypothetical: cognitive and mood disturbances, exacerbation of psychiatric symptoms
Pregnancy-related hCG effects	Abnormal maternal hCG levels might contribute to altered neurodevelopment in offspring	Could be relevant for neurodevelopmental conditions like ASD, ADHD, or schizophrenia	Hypothetical: potential neurodevelopmental impairments, cognitive or behavioral issues in offspring
ART and pharmacological hCG	Exogenous hCG administration may result in supraphysiologic exposure with unknown CNS consequences	Could influence neurodevelopment in offspring conceived via ART	Hypothetical: long-term cognitive or neurobehavioral outcomes, requiring further study
hCG-secreting tumors	Tumor-derived hCG could affect neurological function through paraneoplastic or neuroimmune mechanisms	Potential relevance in patients with hCG-secreting malignancies, e.g., choriocarcinoma or testicular cancer	Hypothetical: cognitive decline, motor dysfunction, or neuroimmune alterations; evidence primarily preclinical or associative

This table summarizes hypothetical and proposed mechanisms based on preclinical and associative clinical evidence. None of the pathways should be interpreted as established causal relationships. Further experimental and longitudinal studies are required to validate these potential effects of hCG on the CNS

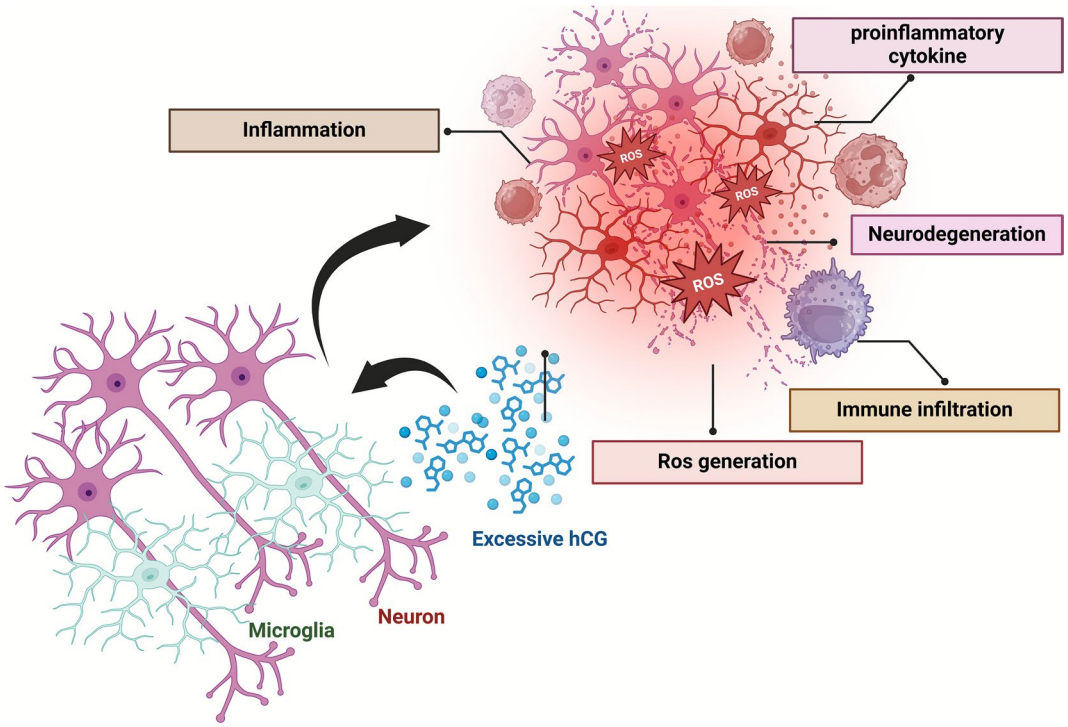


Fig. 1 Hypothetical mechanisms of hCG-associated neurobiological effects. This figure presents a conceptual model of how altered hCG levels may influence neurobiological processes. Based on preclinical and associative clinical studies, elevated or dysregulated hCG could potentially modulate immune cell activity and microglial responses, contribute to oxidative stress and mitochondrial dysfunction, and influence neuronal survival. These interactions are presented as proposed pathways rather than established causal relationships. The figure is intended to summarize current hypotheses and guide future research into the neurobiological effects of hCG. ROS, reactive oxygen species; hCG, human chorionic gonadotropin

the hippocampus, a brain region critical for learning and memory [75].

Prolonged exposure to elevated hCG levels has been associated with neuroinflammatory states that may, in theory, contribute to glial reactivity and altered synaptic pruning, processes that resemble those described in neurodevelopmental conditions such as ASD and schizophrenia, although direct mechanistic links remain unproven [76]. Furthermore, neuroinflammation has been implicated in dopaminergic neurodegeneration, raising concerns about the potential role of hCG dysregulation in Parkinsonian syndromes.

Overall, these findings suggest that while hCG can exert beneficial effects on the CNS under physiological conditions, chronic or dysregulated hCG exposure may trigger harmful neuroinflammatory cascades, contributing to neurotoxicity and neurodegeneration. Further research is needed to delineate the precise conditions under which hCG transitions from a neuroprotective to a neurotoxic agent, which could have significant implications for neurodegenerative disease pathogenesis and therapeutic interventions.

Oxidative stress and mitochondrial dysfunction

Excessive or dysregulated hCG signaling has been associated with mitochondrial dysfunction and increased oxidative stress in placental models of fetal growth restriction and pre-eclampsia [77]. While these findings highlight a potential mechanism by which hCG may influence cellular homeostasis, direct mechanistic evidence linking hCG to mitochondrial dysfunction in neurons or the human CNS remains speculative. This raises the hypothesis that similar pathways could, under specific pathological conditions, affect neurodevelopment or contribute to neurological disorders, but further studies are needed to test this connection. This oxidative burden can compromise mitochondrial function, resulting in cellular damage, energy deficits, and accelerated neurodegeneration [7]. As discussed, the interplay between hCG, oxidative stress, and mitochondrial disturbances has been proposed to influence neurobiological pathways relevant to conditions such as AD and PD. Current evidence supports potential associations, but further studies are needed to determine whether these interactions contribute to neuronal vulnerability or disease progression.

Disruption of antioxidant defense and redox imbalance in neurodegeneration

The disruption of redox homeostasis due to excessive ROS production not only inflicts direct oxidative damage, but also undermines the brain's intrinsic antioxidant defense mechanisms. Key enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx), which play crucial roles in neutralizing ROS, become overwhelmed, leading to sustained oxidative injury [78]. This persistent oxidative stress accelerates neuronal dysfunction and is a hallmark feature in the pathogenesis of chronic neurodegenerative disorders, including Alzheimer's and Parkinson's disease [79, 80].

Mitochondrial bioenergetics and neurodegeneration

Mitochondria, as the powerhouses of the cell, are essential for maintaining cellular energy metabolism [81]. In neurons, mitochondria play an integral role in maintaining synaptic function, neurotransmission, and overall cellular homeostasis [82]. However, excessive hCG signaling can impair mitochondrial bioenergetics, leading to decreased ATP production, mitochondrial membrane depolarization, and alterations in mitochondrial dynamics, including impaired fusion and fission processes [77, 83]. These mitochondrial dysfunctions contribute to energy deficits and increased vulnerability to neurodegeneration.

Mitochondria are both sources and targets of ROS, and in neurodegenerative conditions, the cumulative oxidative damage can compromise mitochondrial integrity [84]. Findings from indirect and in vitro models indicate that hCG has been associated with alterations in mitochondrial homeostasis [85]. These changes may create a milieu that favors mitochondrial permeability transition (MPT), which in turn could allow release of cytochrome c and activation of caspase-dependent apoptotic pathways [85]. In addition, evidence from experimental models and patient studies links neuronal mitochondrial dysfunction to synaptic deficits and features of neurodegenerative progression in disorders such as AD, PD, and HD [86].

Emerging evidence suggests that mitochondrial dysfunction induced by hCG may also contribute to neuroinflammation, as damaged mitochondria release damage-associated molecular patterns (DAMPs), which activate microglial cells and promote further oxidative stress [87]. This results in a self-perpetuating cycle of mitochondrial damage, ROS production, and neuroinflammation, driving the pathogenesis of neurodegenerative diseases.

BBB disruption

The BBB plays a critical role in maintaining the homeostasis of the CNS by selectively regulating the entry of ions, nutrients, and other molecules into the brain [88]. Disruption of the BBB is a common feature of many neurological disorders and has been implicated in neuroinflammation, neurodegeneration, and neurovascular dysfunction [89]. Increasing evidence suggests that hCG, a hormone typically associated with reproductive processes, may also influence BBB integrity, contributing to BBB permeability changes and increased susceptibility to neurotoxicant entry [90]. Dysregulated or excessive hCG signaling may have significant implications for the pathogenesis of neurodegenerative diseases by facilitating the entry of neurotoxic substances, immune cells, and inflammatory mediators into the brain.

hCG receptors in brain endothelium and permeability alterations

The LHCGR, which mediates the biological effects of hCG, is expressed not only in reproductive tissues but also in the brain vasculature, particularly in brain endothelial cells [91]. Studies have shown that LHCGR is present in endothelial cells forming the BBB, suggesting that hCG may directly interact with the vascular endothelium, influencing barrier function [92]. The activation of LHCGR on these endothelial cells may trigger intracellular signaling pathways that affect tight junction proteins such as claudins, occludins, and zonula occludens, which are critical for maintaining the structural integrity of the BBB.

Upon hCG binding to LHCGR, signaling pathways—including cAMP/PKA, PI3K/Akt, and MAPK—may lead to the disruption of endothelial tight junctions and increased paracellular permeability [93]. As described in the previous section, LHCGR enhances these signaling pathways, which, in endothelial cells, may contribute to BBB permeability changes. This enhanced permeability allows the passage of macromolecules, inflammatory cytokines, and potentially neurotoxic agents from the bloodstream into the brain, which can contribute to neuroinflammation and neurodegeneration [94].

Recent studies suggest that excessive hCG levels, as seen in gestational trophoblastic diseases or hCG-secreting tumors, may further exacerbate BBB dysfunction, increasing its permeability and potentially enabling neurotoxicant entry that could accelerate neurodegenerative processes [95]. In contrast, insufficient hCG signaling during pregnancy has been associated with the development of neurodevelopmental disorders, indicating that optimal levels of hCG are crucial for maintaining BBB integrity during fetal brain development [96].

Neurotransmitter dysregulation

Neurotransmitter systems play a critical role in regulating brain function, mood, and behavior [97]. Dysregulation of

neurotransmitter pathways is a hallmark feature of several psychiatric and neurodegenerative disorders [98]. Emerging evidence suggests that hCG may influence neurotransmitter systems, contributing to both dopaminergic and serotonergic/GABAergic dysfunction [1]. These disruptions are implicated in various neuropsychiatric conditions, including schizophrenia, anxiety, depression, and Parkinson's disease [99]. Understanding how hCG impacts neurotransmitter regulation is essential for elucidating its potential role in neurotoxic processes and the development of psychiatric disorders.

hCG, dopaminergic dysfunction, and psychiatric disorders

The dopaminergic system, which regulates mood, reward, and motor control, is highly sensitive to hormonal fluctuations, including those induced by hCG [100]. In particular, dopamine receptors and dopamine transporter expression have been found to be modulated by hCG signaling in both the CNS and peripheral tissues [101]. Dysregulated hCG signaling has been linked to alterations in dopamine metabolism, leading to dopaminergic dysfunction that may contribute to the pathophysiology of psychiatric disorders such as schizophrenia, bipolar disorder, and drug addiction [102].

Studies have shown that excessive hCG levels, as seen in gestational trophoblastic diseases, hCG-secreting tumors, or hCG-induced medication protocols, can lead to increased dopaminergic activity, potentially disrupting normal dopaminergic balance [103]. This disruption may contribute to symptoms of mania, psychosis, and impulsivity, which are common in psychiatric conditions such as schizophrenia and bipolar disorder [104]. Furthermore, hCG-induced dopaminergic alterations may be involved in PD, where dopamine depletion leads to motor and cognitive deficits. In PD, elevated hCG levels may accelerate dopaminergic neurodegeneration by altering the delicate balance of dopamine release and reuptake in the brain [105].

Research also suggests that hCG-induced stimulation of the dopamine D2 receptor can lead to dopaminergic overactivation, which is associated with the development of psychotic symptoms [106]. This overactivation is particularly concerning in patients undergoing fertility treatments involving hCG, where dopamine receptor dysregulation may increase the risk of developing psychiatric disturbances [107]. Furthermore, dopaminergic dysregulation in the prefrontal cortex and striatum, regions critical for cognitive and emotional regulation, may contribute to impulsivity, aggression, and irritability in affected individuals [108, 109].

Serotonin and GABAergic alterations: links to anxiety and depression

In addition to its impact on dopamine signaling, hCG has been implicated in the modulation of other critical neurotransmitter systems, including [110]. The serotonergic system regulates mood, anxiety, and emotional stability, while the GABAergic system is central to inhibitory neurotransmission and anxiolytic effects [111]. Dysregulation in either of these systems can lead to anxiety, depression, and other mood disorders, conditions that are increasingly being linked to altered hCG levels.

Serotonin is a key neurotransmitter in the regulation of mood and anxiety. Recent studies have highlighted that elevated hCG levels, often observed in pregnancy or hCG-producing tumors, can modulate the serotonin receptor system, particularly 5-HT1A and 5-HT2A receptors [112, 113]. These receptors are involved in regulating serotonin release and receptor sensitivity in the brain, with alterations leading to anxiety-like behaviors and depressive symptoms. Specifically, excess hCG may interfere with serotoninergic tone, contributing to dysphoria, irritability, and increased susceptibility to depression [114]. This link is particularly relevant in gestational depression, where altered hCG fluctuations correlate with mood disturbances and emotional regulation.

Similarly, GABA, the primary inhibitory neurotransmitter in the brain, plays a crucial role in maintaining anxiety regulation and emotional stability [115]. GABAergic dysfunction has been implicated in various anxiety disorders and depression, with GABA receptor alterations contributing to the pathogenesis of these conditions [115]. Evidence suggests that hCG-induced changes in GABAergic signaling may contribute to the development of anxiety disorders by modulating the expression of GABA receptors in the CNS [116]. Disruptions in GABA receptor functionality can lead to heightened neural excitability and increased anxiety, as seen in clinical studies involving individuals with elevated hCG levels during pregnancy or fertility treatments [117].

Clinical and translational relevance of hCG-induced neurotoxicity

While hCG is classically recognized for its role in pregnancy, emerging research has begun to explore its potential impact on the nervous system. Some studies have observed associations between altered maternal hCG levels, whether elevated, reduced, or aberrantly glycosylated, and markers of neurodevelopment in offspring [118]. These observations have led to hypotheses suggesting that dysregulated hCG exposure could influence neurodevelopmental trajectories, potentially contributing to conditions such as ASD, ADHD, or schizophrenia [119].

However, it is important to emphasize that these links remain highly speculative. A large population-based study using discordant sibling and paternal negative controls failed to establish a clear causal link between maternal prenatal diagnoses and offspring autism, underscoring the influence

of familial and sociodemographic confounders [120]. Direct causal mechanisms connecting maternal or pharmacological hCG exposure to neurodevelopmental disorders in humans have not been established.

Consequently, any proposed association between hCG exposure and neurodevelopmental outcomes should be considered an intriguing hypothesis rather than an established effect. Future research, particularly rigorous longitudinal and mechanistic studies, is required to clarify whether and how maternal or pharmacological hCG may influence fetal brain development. Understanding these potential effects could provide a framework for identifying interventions, but current clinical relevance remains uncertain.

Neurological consequences of hCG in pregnancy and fetal development

During pregnancy, hCG levels rise significantly and exert a range of physiological effects, primarily related to maintaining pregnancy and supporting fetal development [121]. However, an increasing body of research suggests that alterations in hCG secretion, especially maternal dysregulation, can have profound effects on neurodevelopment [122]. As previously discussed, excessive maternal hCG levels, such as those observed in gestational trophoblastic diseases or hCG-secreting tumors, may increase the risk of neurological disorders in offspring, including autism, ADHD, and schizophrenia.

Maternal hCG dysregulation can influence fetal brain development via multiple mechanisms, including altered neurotransmitter systems, disrupted placental function, and increased neuroinflammatory processes [63]. These alterations may disrupt the normal formation of brain regions involved in cognitive function, social behavior, and emotional regulation, potentially leading to long-term neurodevelopmental deficits [123]. For instance, disrupted serotoninergic, dopaminergic, and GABAergic signaling systems due to abnormal hCG exposure can impair synaptic pruning and neurogenesis, contributing to the development of autistic traits and behavioral issues in children [124, 125].

Moreover, increased hCG levels in early pregnancy have been correlated with a higher risk of preterm birth, which is another known risk factor for neurodevelopmental disorders [126, 127]. Preterm infants often experience neurological complications, including cerebral palsy, cognitive delays, and learning disabilities, which may be linked to early disruptions in brain development associated with maternal hCG abnormalities [128].

hCG in ART and neurological risks

ART, particularly IVF, have revolutionized the management of infertility and have become standard treatments for couples struggling to conceive [129, 130]. However, the hormonal protocols employed during ART, including the use of high-dose hCG, have raised concerns about potential neurological risks for both mothers and offspring [131]. While hCG is essential for the success of IVF by supporting ovarian function and inducing ovulation, its potential neurotoxic effects and long-term impact on cognitive and neurobehavioral development in offspring remain an area of significant scientific inquiry [132]. Emerging studies suggest that elevated levels of hCG, often employed in ART regimens, may interfere with normal neurological function and development [133].

Impact of high-dose hCG in IVF on cognitive function

High-dose hCG is widely used in ART to induce ovulation and support implantation, but emerging evidence suggests potential neurological risks for both mothers and offspring [134]. In mothers, elevated hCG levels may disrupt dopamine and serotonin signaling, contributing to mood disorders, memory deficits, and anxiety, while also being linked to gestational hypertension and pre-eclampsia, which can impair cerebral perfusion and promote neuroinflammation [135]. In offspring, excessive hCG exposure during critical neurodevelopmental stages may disrupt synaptic plasticity, impair neurogenesis, and alter cognitive function, increasing the risk of learning disabilities, attention deficits, and delayed language development [136, 137]. In addition, hCG-induced neuroendocrine dysregulation may affect the hypothalamic–pituitary–gonadal axis, further influencing long-term neurological outcomes in ART-conceived children.

Long-term neurobehavioral effects in offspring conceived via ART

The long-term neurobehavioral effects of high-dose hCG and other ART-related factors on offspring are increasingly recognized [138]. While ART has enabled successful pregnancies, concerns are growing about its impact on neurodevelopment, influenced by maternal hormonal treatments, embryo culture conditions, and procedural interventions [139, 140]. Children conceived through ART, particularly those exposed to high-dose hCG, may face an elevated risk of neurodevelopmental disorders such as ASD, ADHD, language delays, and cognitive deficits [141, 142]. Contributing factors include elevated hCG levels, higher rates of preterm birth, and multiple pregnancies, all of which may disrupt fetal brain development [77, 143]. Preterm birth, a common ART outcome, further exacerbates the risk of motor, learning, and behavioral impairments [144]. However, the full extent of these effects remains unclear, necessitating further longitudinal studies to assess ART's neurological impact and inform safer clinical practices.

hCG-secreting tumors and paraneoplastic neurological syndromes

The presence of hCG is not only a marker of pregnancy but also of several tumor types, particularly hCG-secreting tumors. These malignancies, including choriocarcinoma, testicular cancer, and other hCG-producing tumors, can lead to a variety of neurological symptoms [145, 146]. These symptoms are often associated with paraneoplastic neurological syndromes (PNS), in which the immune response to the tumor leads to widespread neurological dysfunction [147]. The production of hCG by these tumors may contribute to neuroimmune dysregulation, influencing both the CNS and peripheral nervous system (PNS).

Choriocarcinoma and hCG-driven neurological symptoms

Choriocarcinoma, a rare and aggressive gestational trophoblastic disease, is a potent hCG-secreting tumor with significant neurological implications [148]. Excessive hCG levels drive neuroinflammation, oxidative stress, and neurotransmitter dysregulation, manifesting as headaches, visual disturbances, seizures, and, in severe cases, coma [149]. Beyond direct neurotoxicity, hCG can induce paraneoplastic immune responses, leading to neural tissue damage and worsening neurological dysfunction [150, 151]. Moreover, high hCG concentrations are strongly associated with tumor metastasis, particularly to the brain, liver, and lungs, complicating disease management [152, 153]. Cerebral metastases exacerbate neurological deficits, highlighting the urgency of early recognition and intervention. Understanding the neurotoxic and metastatic roles of hCG in choriocarcinoma is crucial for improving patient outcomes.

Future directions and therapeutic strategies

The ongoing research into hCG-induced neurotoxicity has highlighted the complexity of its impact on the nervous system. Future studies should focus on refining experimental models and clinical studies to better understand the underlying pathophysiological mechanisms. Moreover, targeted therapeutic strategies are critical to mitigate the neurotoxic effects of hCG, particularly in populations at risk, such as pregnant women, those undergoing ART, and individuals with hCG-secreting tumors.

Targeting hCG pathways for neuroprotection

Targeting the molecular pathways affected by hCG provides a promising strategy for neuroprotection. By inhibiting the LHCGR signaling pathway, it may be possible to reduce the neuroinflammatory and oxidative stress responses triggered by hCG.

Anti-hCG antibodies and hormonal modulation

One potential therapeutic approach involves the use of anti-hCG antibodies to neutralize the toxic effects of hCG. These antibodies could be designed to block the binding of hCG to its receptor, preventing the activation of harmful signaling pathways. Hormonal modulation may also provide a therapeutic avenue by reducing excessive hCG levels in individuals with hCG-secreting tumors or those undergoing fertility treatments.

Potential use of anti-inflammatory and antioxidant therapies

Given the central role of neuroinflammation and oxidative stress in hCG-induced neurotoxicity, anti-inflammatory and antioxidant therapies could serve as potential treatments. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and natural antioxidants may help alleviate the inflammatory and oxidative damage induced by hCG. In addition, neuroprotective agents that target mitochondrial dysfunction could be explored for their potential in protecting the nervous system from hCG-related damage.

Clinical implications for neurological disease prevention

As the research into hCG-induced neurotoxicity progresses, it is crucial to identify early biomarkers of neurotoxicity and develop risk stratification models to prevent neurological diseases in populations with high hCG exposure.

Risk stratification in fertility treatments and pregnancy

Risk stratification in individuals undergoing fertility treatments or pregnancy could be pivotal in identifying those at high risk of neurotoxic effects from hCG. Monitoring hCG levels and using biomarkers of neuroinflammation and oxidative stress could help identify individuals who may be susceptible to cognitive or behavioral disorders later in life.

Biomarkers for early detection of hCG-associated neurotoxicity

The identification of reliable biomarkers for early detection of hCG-induced neurotoxicity is essential. These biomarkers could include neuroinflammatory cytokines, oxidative stress markers, and altered gene/protein expression profiles, enabling clinicians to diagnose neurotoxicity early and take appropriate action.

Conclusion

The exploration of hCG-induced neurotoxicity presents an exciting and rapidly evolving field. Understanding the dual role of hCG in neurobiology is critical, as its neuroprotective effects in some contexts may be overshadowed by its potential for neurotoxicity in others. Bridging experimental insights with clinical applications will require multidisciplinary research and collaboration among experts in neurotoxicology, endocrinology, reproductive health, and neurology (Fig. 2).

Revisiting the dual role of hCG in neurobiology

It is important to recognize that hCG has a dual role in neurobiology—while it may support neuroprotection under certain conditions, dysregulated hCG levels can lead to neurotoxic effects. A deeper understanding of this balance is essential for developing targeted therapeutic strategies.

Bridging experimental insights to clinical applications

The integration of experimental models and clinical research will help bridge the gap between basic science and real-world applications. By developing biomarkers for early detection and therapeutic strategies, clinicians can more effectively manage hCG-related neurotoxicity in vulnerable populations.

Need for rigorous investigation and multidisciplinary research

Given the complex nature of hCG-induced neurotoxicity, it is crucial to conduct rigorous research that spans multiple

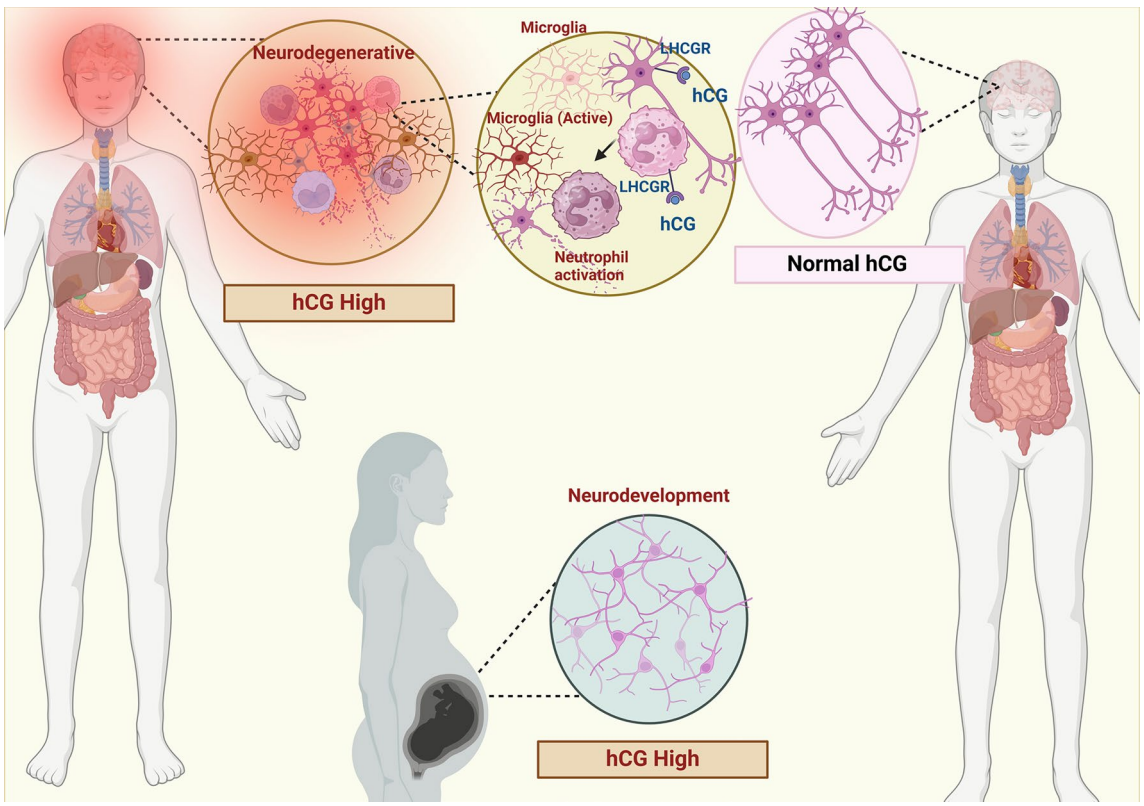


Fig. 2 The dual role of hCG in neurobiology: protective vs. pathological effects. This figure illustrates the contrasting effects of hCG on brain health, emphasizing its potential neurotoxic effects when excessively elevated versus its physiological role in maintaining neurological function. On the left, an individual with an inflamed brain is depicted, with a zoomed-in section highlighting immune cell infiltration and neuroinflammation. Excessive hCG levels are shown as a contributing factor to neurodegeneration, potentially through increased microglial activation, cytokine release (e.g., TNF-α, IL-6, IL-1β), and oxidative stress. In the middle, the figure illustrates how dysregulated, high hCG levels facilitate neurodegeneration by disrupting neuronal homeostasis, impairing blood–brain barrier integrity, and altering neurotransmitter balance. On the right, a healthy individual with normal hCG levels is shown, representing a balanced neurobiological state where cognitive function and neuronal integrity are maintained hCG, human chorionic gonadotrophin; TNF, tumor necrosis factor

disciplines. Only through multidisciplinary collaboration will we fully understand the neurological implications of hCG and develop effective therapeutic interventions for individuals affected by hCG-associated neurotoxicity.

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Declarations

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent form This study does not use animal or human samples.

Consent for publication Not applicable.

References

1. Nwabuobi C, Arlier S, Schatz F, Guzeloglu-Kayisli O, Lockwood CJ, Kayisli UA (2017) hCG: biological functions and clinical applications. Int J Mol Sci. https://doi.org/10.3390/ijms18102037
2. Eftekhar M, Mojtahedi MF, Miraj S, Omid M (2017) Final follicular maturation by administration of GnRH agonist plus HCG versus HCG in normal responders in ART cycles: an RCT. Int J Reprod Biomed 15(7):429
3. Cole LA (2010) Biological functions of hCG and hCG-related molecules. Reprod Biol Endocrinol 8(1):102
4. Miraj S, Forood AMK, Azimi S, Panahinia P, Ebadi E, Moradpanah S et al (2025) The cardiovascular burden of gonadotropin-releasing hormone (GnRH) therapy: mechanisms, risks, and interventions. Cardiovasc Toxicol 25(9):1411–1428
5. Schumacher A, Zenclussen AC (2019) Human chorionic gonadotropin-mediated immune responses that facilitate embryo implantation and placentation. Front Immunol. https://doi.org/10.3389/fimmu.2019.02896
6. Abdolrazaghnejad A, Miraj S (2022) Can coronavirus disease 2019 effect on human reproduction? Adv Biomed Res 11(1):55
7. Miller B, Crider A, Aravamuthan B, Galindo R. Human chorionic gonadotropin decreases cerebral cystic encephalomalacia and parvalbumin interneuron degeneration in a pro-inflammatory model of mouse neonatal hypoxia-ischemia. bioRxiv. 2024.
8. Wang R, Chen L, Wang X, Liu Y (2021) Association between serum beta-human chorionic gonadotropin and inflammation, oxidative stress in pregnancy-induced hypertension. Microvasc Res 135:104130
9. Cheng X, Huang J, Li H, Zhao D, Liu Z, Zhu L et al (2024) Quercetin: a promising therapy for diabetic encephalopathy through inhibition of hippocampal ferroptosis. Phytomedicine 126:154887
10. Windham GC, Lyall K, Anderson M, Kharrazi M (2016) Autism spectrum disorder risk in relation to maternal mid-pregnancy serum hormone and protein markers from prenatal screening in California. J Autism Dev Disord 46(2):478–488
11. Heidegger H, Jeschke U (2018) Human Chorionic Gonadotropin (hCG)-an endocrine, regulator of gestation and cancer. Int J Mol Sci. https://doi.org/10.3390/ijms19051502
12. Boime I, Ben-Menahem D (1999) Glycoprotein hormone structure-function and analog design. Recent Prog Horm Res 54:271–288 (**discussion 88-9**)
13. Abbasi S, Rezaei J, Bazi F, Mousavi MA, Rassouli S, Zamanpour Z et al (2024) Association between metabolic syndrome and risk of endometrial cancer; a systematic review and meta-analysis. Immunopathologia Persa. 11(2):e41724
14. Xu Z, Li E-H, Liu J, Zhang Y-J, Xiao R, Chen X-Z et al (2025) Postpartum hemorrhage emerges as a key outcome of maternal SARS-CoV-2 omicron variant infection surge across pregnancy trimesters. J Infect Public Health 18(6):102733
15. Larraín D, Caradeux J (2024) β-human chorionic gonadotropin dynamics in early gestational events: a practical and updated reappraisal. Obstet Gynecol Int 2024:8351132
16. Ogino MH, Tadi P. Physiology, Chorionic Gonadotropin. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.; 2025.
17. Herghelegiu CG, Veduta A, Stefan MF, Magda SL, Ionascu I, Radoi VE et al (2023) Hyperglycosylated-hCG: its role in trophoblast invasion and intrauterine growth restriction. Cells. https://doi.org/10.3390/cells12121647
18. Lee CL, Chiu PC, Hautala L, Salo T, Yeung WS, Stenman UH et al (2013) Human chorionic gonadotropin and its free β-subunit stimulate trophoblast invasion independent of LH/hCG receptor. Mol Cell Endocrinol 375(1–2):43–52
19. Casarini L, Santi D, Brigante G, Simoni M (2018) Two hormones for one receptor: evolution, biochemistry, actions, and pathophysiology of LH and hCG. Endocr Rev 39(5):549–592
20. Chambers AE, Stanley PF, Randeva H, Banerjee S (2011) Microvesicle-mediated release of soluble LH/hCG receptor (LHCGR) from transfected cells and placenta explants. Reprod Biol Endocrinol 9:64
21. Luo M, Yang X, Zhou M, Zhang J, Yu B, Lian H et al (2024) Integrated single-cell and spatial transcriptomics reveal microenvironment disruptions by androgen in mouse ovary. iScience 27(10):111028
22. Weedon-Fekjær MS, Taskén K (2012) Review: spatiotemporal dynamics of hCG/cAMP signaling and regulation of placental function. Placenta 33:S87–S91
23. Lonze BE, Ginty DD (2002) Function and regulation of CREB family transcription factors in the nervous system. Neuron 35(4):605–623

24. Stocco C, Telleria C, Gibori G (2007) The molecular control of corpus luteum formation, function, and regression. Endocr Rev 28(1):117–149
25. Zhao Y, Wu J, Jia H, Wang X, Zheng R, Jiang F et al (2019) PROKR2 mutations in idiopathic hypogonadotropic hypogonadism: selective disruption of the binding to a Gα-protein leads to biased signaling. FASEB J 33(3):4538–4546
26. Zhou H, Zhao C, Wang P, Yang W, Zhu H, Zhang S (2023) Regulators involved in trophoblast syncytialization in the placenta of intrauterine growth restriction. Front Endocrinol (Lausanne) 14:1107182
27. Lawless L, Qin Y, Xie L, Zhang K (2023) Trophoblast differentiation: mechanisms and implications for pregnancy complications. Nutrients. https://doi.org/10.3390/nu15163564
28. Leduc K, Bourassa V, Asselin E, Leclerc P, Lafond J, Reyes-Moreno C (2012) Leukemia inhibitory factor regulates differentiation of trophoblastlike BeWo cells through the activation of JAK/STAT and MAPK3/1 MAP kinase-signaling pathways. Biol Reprod 86(2):54
29. Furcron AE, Romero R, Mial TN, Balancio A, Panaitescu B, Hassan SS et al (2016) Human chorionic gonadotropin has anti-inflammatory effects at the maternal-fetal interface and prevents endotoxin-induced preterm birth, but causes dystocia and fetal compromise in mice. Biol Reprod 94(6):136
30. Ahmadi MH, Maleknia M, Khoshbakht R, Rezaeeyan H (2024) Evaluation of the hematological inflammatory parameters in the patients with immune thrombocytopenic purpura: a case–control study. Health Sci Rep 7(2):e1900
31. Chang C, Chen YL, Wang YW, Chen HW, Hsu CW, Lin KC et al (2024) Aberrant trophoblastic differentiation in human cancer: an emerging novel therapeutic target (Review). Oncol Rep. https://doi.org/10.3892/or.2024.8701
32. Schumacher A, Zenclussen AC (2019) Human chorionic gonadotropin-mediated immune responses that facilitate embryo implantation and placentation. Front Immunol 10:2896
33. Lentz LS, Stutz AJ, Meyer N, Schubert K, Karkossa I, von Bergen M et al (2022) Human chorionic gonadotropin promotes murine Treg cells and restricts pregnancy-harmful proinflammatory Th17 responses. Front Immunol 13:989247
34. Zhang YH, He M, Wang Y, Liao AH (2017) Modulators of the balance between M1 and M2 macrophages during pregnancy. Front Immunol 8:120
35. Hou Q, Wu J, Zhao Y, Wang X, Jiang F, Chen D-N et al (2020) Genotypic and phenotypic spectrum of CCDC141 variants in a Chinese cohort with congenital hypogonadotropic hypogonadism. Eur J Endocrinol 183(3):245–254
36. Ataei Azimi S, Siyasari A, Abutalebi Nasrabad S, Saboori A, Biglarifar R, Shamsghahfarokhi S, et al. Socioeconomic disparities in uterine cervical cancer burden; an ecological assessment of global incidence and mortality patterns by human development index in 2022. Immunopathol Persa
37. Iles RK, Delves PJ, Butler SA (2010) Does hCG or hCGβ play a role in cancer cell biology? Mol Cell Endocrinol 329(1–2):62–70
38. Hryniewicki AT, LaFree A (2022) An immaculate deception: persistently elevated serum β-hcg in metastatic signet ring cell gastric adenocarcinoma. J Emerg Med 62(4):475–479
39. Gridelet V, Perrier d'Hauterive S, Polese B, Foidart JM, Nisolle M, Geenen V (2020) Human chorionic gonadotrophin: new pleiotropic functions for an "old" hormone during pregnancy. Front Immunol 11:343
40. Guibourdenche J, Handschuh K, Tsatsaris V, Gerbaud P, Leguy MC, Muller F et al (2010) Hyperglycosylated hCG is a marker of early human trophoblast invasion. J Clin Endocrinol Metab 95(10):E240–E244
41. Gridelet V, Perrier d'Hauterive S, Polese B, Foidart J-M, Nisolle M, Geenen V. Human Chorionic Gonadotrophin: New Pleiotropic Functions for an "Old" Hormone During Pregnancy. Frontiers in Immunology. 2020;Volume 11 - 2020.
42. Cole LA (2011) Human chorionic gonadotropin (hCG) and hyperglycosylated hCG: the mediators that control human pregnancy. Expert Rev Obstet Gynecol 6(3):273–283
43. Cole LA, Butler SA (2008) Hyperglycosylated human chorionic gonadotropin and human chorionic gonadotropin free beta-subunit: tumor markers and tumor promoters. J Reprod Med 53(7):499–512
44. Riccetti L, Pignatti E, Simoni M. Heterogeneity of human chorionic gonadotropin (hCG) in commercial preparations of hCG and human menopausal gonadotropin. Endocrine Abstracts. 2015.
45. Wang SM, Wang Q, Ye LY, Chen SX, Tao L, Yang ZS (2022) Effects of hCG on DA neuronal death of Parkinson's disease. Biochem Biophys Res Commun 617(Pt 2):41–47
46. Lei ZM, Rao CV (2001) Neural actions of luteinizing hormone and human chorionic gonadotropin. Semin Reprod Med 19(1):103–109
47. Leng D, Zeng B, Wang T, Chen BL, Li DY, Li ZJ (2024) Single nucleus/cell RNA-seq of the chicken hypothalamic-pituitary-ovarian axis offers new insights into the molecular regulatory mechanisms of ovarian development. Zool Res 45(5):1088–1107
48. Luo F, Liu L, Guo M, Liang J, Chen L, Shi X et al (2024) Deciphering and targeting the ESR2–miR-10a-5p–BDNF axis in the prefrontal cortex: advancing postpartum depression understanding and therapeutics. Research 7:0537
49. Ryu V, Gumerova A, Korkmaz F, Kang SS, Katsel P, Miyashita S et al (2022) Brain atlas for glycoprotein hormone receptors at single-transcript level. Elife. https://doi.org/10.7554/eLife.79612
50. Mey M, Bhatta S, Casadesus G (2021) Luteinizing hormone and the aging brain. Vitam Horm 115:89–104
51. Geng T, Sun Y, Cheng L, Cao Y, Zhang M, Hong Z et al (2022) Downregulation of LHCGR attenuates COX-2 expression and induces luteinized unruptured follicle syndrome in endometriosis. Front Endocrinol (Lausanne) 13:853563
52. Furcron A-E, Romero R, Mial TN, Balancio A, Panaitescu B, Hassan SS et al (2016) Human chorionic gonadotropin has anti-inflammatory effects at the maternal-fetal interface and prevents endotoxin-induced preterm birth, but causes dystocia and fetal compromise in Mice1. Biol Reprod 94(6):1–13
53. Lei ZM, Rao CV, Kornyei JL, Licht P, Hiatt ES (1993) Novel expression of human chorionic gonadotropin/luteinizing hormone receptor gene in brain. Endocrinology 132(5):2262–2270
54. Mann ON, Kong CS, Lucas ES, Brosens JJ, Hanyaloglu AC, Brighton PJ (2022) Expression and function of the luteinizing hormone choriogonadotropin receptor in human endometrial stromal cells. Sci Rep 12(1):8624
55. Singh M, Krishnamoorthy VR, Kim S, Khurana S, LaPorte HM (2024) Brain-derived neuerotrophic factor and related mechanisms that mediate and influence progesterone-induced neuroprotection. Front Endocrinol (Lausanne) 15:1286066
56. Bathina S, Das UN (2015) Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci 11(6):1164–1178
57. Brouillet S, Hoffmann P, Chauvet S, Salomon A, Chamboredon S, Sergent F et al (2012) Revisiting the role of hCG: new regulation of the angiogenic factor EG-VEGF and its receptors. Cell Mol Life Sci 69(9):1537–1550
58. Zhou Y, Zhu L, Li H, Xie W, Liu J, Zhang Y et al (2022) In vivo and in vitro neuroprotective effects of maca polysaccharide. Front Biosci-Landmark 27(1):8
59. Nikmahzar E, Jahanshahi M, Elyasi L, Saeidi M, Babakordi F, Bahlakeh G (2019) Human chorionic gonadotropin attenuates amyloid-β plaques induced by streptozotocin in the rat brain by affecting cytochrome c-ir neuron density. Iran J Basic Med Sci 22(2):166–172

60. Barth C, Villringer A, Sacher J (2015) Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. Front Neurosci 9:37
61. Gonzalez J, Popp M, Ocejo S, Abreu A, Bahmad HF, Poppiti R (2024) Gestational trophoblastic disease: complete versus partial hydatidiform moles. Diseases. https://doi.org/10.3390/diseases12070159
62. Jash S, Sharma S (2021) In utero immune programming of autism spectrum disorder (ASD). Hum Immunol 82(5):379–384
63. Miranda A, Sousa N (2018) Maternal hormonal milieu influence on fetal brain development. Brain Behav 8(2):e00920
64. Yu P, Shen L, Tang L (2025) Multimodal DTI-ALPS and hippocampal microstructural signatures unveil stage-specific pathways in Alzheimer's disease progression. Front Aging Neurosci 17:1609793
65. Pollack IF (2008) Diagnostic and therapeutic stratification of childhood brain tumors: implications for translational research. J Child Neurol 23(10):1179–1185
66. Kim HM, Rim HK, Shin T, Kim JJ, Park ST, Oh JM et al (2000) Human chorionic gonadotropin induces nitric oxide synthesis by murine microglia. Int J Immunopharmacol 22(6):453–461
67. Clark IA, Atwood CS (2011) Is TNF a link between aging-related reproductive endocrine dyscrasia and Alzheimer's disease? J Alzheimers Dis 27(4):691–699
68. Sulhan S, Lyon KA, Shapiro LA, Huang JH (2020) Neuroinflammation and blood-brain barrier disruption following traumatic brain injury: pathophysiology and potential therapeutic targets. J Neurosci Res 98(1):19–28
69. Masuda K, Tsutsuki H, Kasamatsu S, Ida T, Takata T, Sugiura K et al (2018) Involvement of nitric oxide/reactive oxygen species signaling via 8-nitro-cGMP formation in 1-methyl-4-phenylpyridinium ion-induced neurotoxicity in PC12 cells and rat cerebellar granule neurons. Biochem Biophys Res Commun 495(3):2165–2170
70. Qiao L, Hu S, Liu S, Zhang H, Ma H, Huang K et al (2019) MicroRNA-21-5p dysregulation in exosomes derived from heart failure patients impairs regenerative potential. J Clin Invest 129(6):2237–2250
71. Naghinezhad J (2019) PI3K/AKT/mTOR pathway in ATLL: from basic biology to preclinical study. J Cell Mol Pharmacol 3(104):62–64
72. Cantero-Fortiz Y, Boada M (2024) The role of inflammation in neurological disorders: a brief overview of multiple sclerosis, Alzheimer's, and Parkinson's disease'. Front Neurol 15:1439125
73. Chen Y, Yin P, Chen Q, Zhang Y, Tang Y, Jin W et al (2025) Neurodegenerative diseases and immune system: From pathogenic mechanism to therapy. Neural Regen Res 10:4103
74. MohanKumar SMJ, Murugan A, Palaniyappan A, MohanKumar PS (2023) Role of cytokines and reactive oxygen species in brain aging. Mech Ageing Dev 214:111855
75. Chesnokova V, Pechnick RN, Wawrowsky K (2016) Chronic peripheral inflammation, hippocampal neurogenesis, and behavior. Brain Behav Immun 58:1–8
76. Geloso MC, D'Ambrosi N (2021) Microglial pruning: relevance for synaptic dysfunction in multiple sclerosis and related experimental models. Cells 10(3):686
77. Kiyokoba R, Uchiumi T, Yagi M, Toshima T, Tsukahara S, Fujita Y et al (2022) Mitochondrial dysfunction-induced high hCG associated with development of fetal growth restriction and pre-eclampsia with fetal growth restriction. Sci Rep 12(1):4056
78. Olufunmilayo EO, Gerke-Duncan MB, Holsinger RMD (2023) Oxidative stress and antioxidants in neurodegenerative disorders. Antioxidants. https://doi.org/10.3390/antiox12020517
79. Pimentel C, Batista-Nascimento L, Rodrigues-Pousada C, Menezes RA (2012) Oxidative stress in Alzheimer's and Parkinson's diseases: insights from the yeast *Saccharomyces cerevisiae*. Oxid Med Cell Longev 2012:132146
80. Tang L, Liu L, Li G, Jiang P, Wang Y, Li J (2019) Expression profiles of long noncoding RNAs in intranasal LPS-mediated Alzheimer's disease model in mice. Biomed Res Int 2019(1):9642589
81. Casanova A, Wevers A, Navarro-Ledesma S, Pruimboom L (2023) Mitochondria: it is all about energy. Front Physiol 14:1114231
82. Tripathi K, Ben-Shachar D (2024) Mitochondria in the central nervous system in health and disease: the puzzle of the therapeutic potential of mitochondrial transplantation. Cells. https://doi.org/10.3390/cells13050410
83. Chen W, Zhao H, Li Y (2023) Mitochondrial dynamics in health and disease: mechanisms and potential targets. Signal Transduct Target Ther 8(1):333
84. Zorov DB, Juhaszova M, Sollott SJ (2014) Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev 94(3):909–950
85. Bernardi P, Gerle C, Halestrap AP, Jonas EA, Karch J, Mnatsakanyan N et al (2023) Identity, structure, and function of the mitochondrial permeability transition pore: controversies, consensus, recent advances, and future directions. Cell Death Differ 30(8):1869–1885
86. Wang W, Zhao F, Lu Y, Siedlak SL, Fujioka H, Feng H et al (2023) Damaged mitochondria coincide with presynaptic vesicle loss and abnormalities in Alzheimer's disease brain. Acta Neuropathol Commun 11(1):54
87. Yu H, Ren K, Jin Y, Zhang L, Liu H, Huang Z et al (2025) Mitochondrial DAMPs: key mediators in neuroinflammation and neurodegenerative disease pathogenesis. Neuropharmacology 264:110217
88. Kadry H, Noorani B, Cucullo L (2020) A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. Fluids Barriers CNS 17(1):69
89. Wu YC, Sonninen TM, Peltonen S, Koistinaho J, Lehtonen Š (2021) Blood-brain barrier and neurodegenerative diseases-modeling with iPSC-derived brain cells. Int J Mol Sci. https://doi.org/10.3390/ijms22147710
90. Wilson AC, Clemente L, Liu T, Bowen RL, Meethal SV, Atwood CS (2008) Reproductive hormones regulate the selective permeability of the blood-brain barrier. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1782(6):401–407
91. Lund M, Pearson AC, Sage MAG, Duffy DM (2023) Luteinizing hormone receptor promotes angiogenesis in ovarian endothelial cells of *Macaca fascicularis* and *Homo sapiens*†. Biol Reprod 108(2):258–268
92. Atwood CS, Bowen RL (2015) The endocrine dyscrasia that accompanies menopause and andropause induces aberrant cell cycle signaling that triggers re-entry of post-mitotic neurons into the cell cycle, neurodysfunction, neurodegeneration and cognitive disease. Horm Behav 76:63–80
93. Gündüz D, Troidl C, Tanislav C, Rohrbach S, Hamm C, Aslam M (2019) Role of PI3K/Akt and MEK/ERK signalling in cAMP/Epac-mediated endothelial barrier stabilisation. Front Physiol 10:1387
94. Takata F, Nakagawa S, Matsumoto J, Dohgu S (2021) Blood-brain barrier dysfunction amplifies the development of neuroinflammation: understanding of cellular events in brain microvascular endothelial cells for prevention and treatment of BBB dysfunction. Front Cell Neurosci. https://doi.org/10.3389/fncel.2021.661838

95. Ngan HYS, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK et al (2021) Diagnosis and management of gestational trophoblastic disease: 2021 update. Int J Gynaecol Obstet 155(Suppl 1):86–93
96. Miller B, Crider A, Aravamuthan B, Galindo R. Human chorionic gonadotropin decreases cerebral cystic encephalomalacia and parvalbumin interneuron degeneration in a pro-inflammatory model of mouse neonatal hypoxia-ischemia. bioRxiv. 2024:2024.03.27.587006.
97. Jiang Y, Zou D, Li Y, Gu S, Dong J, Ma X et al (2022) Monoamine neurotransmitters control basic emotions and affect major depressive disorders. Pharmaceuticals (Basel). https://doi.org/10.3390/ph15101203
98. Davis SE, Cirincione AB, Jimenez-Torres AC, Zhu J (2023) The impact of neurotransmitters on the neurobiology of neurodegenerative diseases. Int J Mol Sci. https://doi.org/10.3390/ijms242015340
99. Kano O, Ikeda K, Cridebring D, Takazawa T, Yoshii Y, Iwasaki Y (2011) Neurobiology of depression and anxiety in Parkinson's disease. Parkinsons Dis 2011:143547
100. Radwan B, Liu H, Chaudhury D (2019) The role of dopamine in mood disorders and the associated changes in circadian rhythms and sleep-wake cycle. Brain Res 1713:42–51
101. Puri NM, Romano GR, Lin TY, Mai QN, Irannejad R (2022) The organic cation transporter 2 regulates dopamine D1 receptor signaling at the Golgi apparatus. Elife. https://doi.org/10.7554/eLife.75468
102. Song J, Kim J (2016) Degeneration of dopaminergic neurons due to metabolic alterations and Parkinson's disease. Front Aging Neurosci 8:65
103. Rosenfeld CS (2024) Placenta extracellular vesicles: messengers connecting maternal and fetal systems. Biomolecules 14(8):995
104. Kerr-Gaffney J, Nuerzati Y, Kopra EI, Young AH (2024) Impulsivity in first-degree relatives at risk of psychosis and mania: a systematic review and meta-analysis. Psychol Med 54(13):1–9
105. Wang S, Wang Q, Ye L, Chen S, Tao L, Yang Z (2022) Effects of hCG on DA neuronal death of Parkinson's disease. Biochem Biophys Res Commun 617:41–47
106. Zheng P, Su QP, Jin D, Yu Y, Huang X-F (2020) Prevention of neurite spine loss induced by dopamine D2 receptor overactivation in striatal neurons. Front Neurosci 14:642
107. Speranza L, Miniaci MC, Volpicelli F (2025) The role of dopamine in neurological, psychiatric, and metabolic disorders and cancer: a complex web of interactions. Biomedicines 13(2):492
108. Di Domenico D, Mapelli L (2023) Dopaminergic modulation of prefrontal cortex inhibition. Biomedicines. 11(5):1276
109. Zhou Z, Yan Y, Gu H, Sun R, Liao Z, Xue K et al (2024) Dopamine in the prefrontal cortex plays multiple roles in the executive function of patients with Parkinson's disease. Neural Regen Res 19(8):1759–1767
110. Alhajeri MM, Alkhanjari RR, Hodeify R, Khraibi A, Hamdan H (2022) Neurotransmitters, neuropeptides and calcium in oocyte maturation and early development. Front Cell Dev Biol 10:980219
111. Ellerbrock I, Sandström A, Tour J, Fanton S, Kadetoff D, Schalling M et al (2021) Serotonergic gene-to-gene interaction is associated with mood and GABA concentrations but not with pain-related cerebral processing in fibromyalgia subjects and healthy controls. Mol Brain 14(1):81
112. Sonier B, Lavigne C, Arseneault M, Ouellette R, Vaillancourt C (2005) Expression of the 5-HT2A serotoninergic receptor in human placenta and choriocarcinoma cells: mitogenic implications of serotonin. Placenta 26(6):484–490
113. Pawluski JL, Li M, Lonstein JS (2019) Serotonin and motherhood: from molecules to mood. Front Neuroendocrinol 53:100742
114. Daut RA, Fonken LK (2019) Circadian regulation of depression: a role for serotonin. Front Neuroendocrinol 54:100746
115. Nuss P (2015) Anxiety disorders and GABA neurotransmission: a disturbance of modulation. Neuropsychiatr Dis Treat 11:165–175
116. Licht P, Harbarth P, Merz WE (1992) Evidence for a modulation of human chorionic gonadotropin (hCG) subunit messenger ribonucleic acid levels and hCG secretion by gamma-aminobutyric acid in human first trimester placenta in vitro. Endocrinology 130(1):490–496
117. Deems NP, Leuner B (2020) Pregnancy, postpartum and parity: resilience and vulnerability in brain health and disease. Front Neuroendocrinol 57:100820
118. Cainelli E, Vedovelli L, Bisiacchi P (2024) The mother–child interface: a neurobiological metamorphosis. Neuroscience 561:92–106
119. Balachandar V, Mahalaxmi I, Raj N, Narayanasamy A, Gopalakrishnan A. New insights into Epigenetics as an Influencer: An associative study between maternal prenatal factors in Autism Spectrum Disorder (ASD). Neurology Perspectives. 2022;2.
120. Khachadourian V, Arildskov ES, Grove J, O'Reilly PF, Buxbaum JD, Reichenberg A et al (2025) Familial confounding in the associations between maternal health and autism. Nat Med 31(3):996–1007
121. Barjaktarovic M, Korevaar TI, Jaddoe VW, de Rijke YB, Visser TJ, Peeters RP et al (2017) Human chorionic gonadotropin (hCG) concentrations during the late first trimester are associated with fetal growth in a fetal sex-specific manner. Eur J Epidemiol 32(2):135–144
122. Movsas TZ, Weiner RL, Greenberg MB, Holtzman DM, Galindo R (2017) Pretreatment with human chorionic gonadotropin protects the neonatal brain against the effects of hypoxic-ischemic injury. Front Pediatr 5:232
123. Nayan NM, Husin A, Siran R (2024) The risk of prenatal bisphenol A exposure in early life neurodevelopment: insights from epigenetic regulation. Early Hum Dev 198:106120
124. Zhao H, Mao X, Zhu C, Zou X, Peng F, Yang W et al (2021) GABAergic system dysfunction in autism spectrum disorders. Front Cell Dev Biol 9:781327
125. Martin H, Choi JE, Rodrigues AR, Eshel N (2025) Review: dopamine, serotonin, and the translational neuroscience of aggression in autism spectrum disorder. JAACAP Open 3(1):29–41
126. Skogler J, Moberg T, Tancredi L, Styrmisdóttir L, Hedayati E, Alarcon-Ruiz CA et al (2023) Association between human chorionic gonadotropin (hCG) levels and adverse pregnancy outcomes: a systematic review and meta-analysis. Pregnancy Hypertens 34:124–137
127. Alharbi H, Saeed Alshehry A, Alsadoun A, Ahmad M, Sawsan Aloshd M (2024) Exploring the prognostic significance of β-HCG levels in cervicovaginal secretions and maternal risk factors for early birth. Cell Mol Biol Noisy-le-grand. 70(2):38–43
128. Eskild A, Monkerud L, Jukic AM, Åsvold BO, Lie KK (2018) Maternal concentrations of human chorionic gonadotropin (hCG) and risk for cerebral palsy (CP) in the child. A case control study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 228:203–208
129. Graham ME, Jelin A, Hoon AH Jr., Wilms Floet AM, Levey E, Graham EM (2023) Assisted reproductive technology: short- and long-term outcomes. Dev Med Child Neurol 65(1):38–49
130. Yang J, Yao Y-L, Lv X-Y, Geng L-H, Wang Y, Adu-Gyamfi EA et al (2025) The safety and efficacy of inactivated COVID-19 vaccination in couples undergoing assisted reproductive technology: a prospective cohort study. Vaccine 45:126635
131. La Rovere M, Franzago M, Stuppia L (2019) Epigenetics and neurological disorders in ART. Int J Mol Sci 20(17):4169

132. Li J, Zhu X, Zhu W, Li L, Wei H, Zhang S (2024) Research progress on the impact of human chorionic gonadotropin on reproductive performance in sows. Animals. https://doi.org/10.3390/ani14223266
133. Braga A, Biscaro A, do Amaral Giordani JM, Viggiano M, Elias KM, Berkowitz RS et al (2018) Does a human chorionic gonadotropin level of over 20,000 IU/L four weeks after uterine evacuation for complete hydatidiform mole constitute an indication for chemotherapy for gestational trophoblastic neoplasia? Eur J Obstet Gynecol Reprod Biol 223:50–55
134. Ahmadi H, Aghebati-Maleki L, Rashidiani S, Csabai T, Nnaemeka OB, Szekeres-Bartho J (2023) Long-term effects of ART on the health of the offspring. Int J Mol Sci. https://doi.org/10.3390/ijms241713564
135. Haim A, Albin-Brooks C, Brothers H, Breach M, Leuner B (2025) Gestational stress disrupts dopamine and oxytocin signaling in the postpartum reward system of rats: implications for mood, motivation and mothering. Sci Rep 15(1):1450
136. Holme JA, Myhre O, Øvrevik J (2024) Adverse neurodevelopment in children associated with prenatal exposure to fine particulate matter (PM2.5) – possible roles of polycyclic aromatic hydrocarbons (PAHs) and mechanisms involved. Reprod Toxicol 130:108718
137. Gogne A. Antenatal Factors Influencing Fetal Neurodevelopment. In: Gogne A, editor. Neurodevelopmental Disorders in Adult Women: Special Considerations in the Perinatal Period. Cham: Springer Nature Switzerland; 2025. p. 163–90.
138. Wei ZT, Lu XL, Zhang G, Yu J, Li H, Jia GH et al (2014) The long-term effects of superovulation on fertility and sexual behavior of male offspring in mice. J Assist Reprod Genet 31(5):555–560
139. Hart RJ, Wijs LA (2022) The longer-term effects of IVF on offspring from childhood to adolescence. Front Reprod Health 4:1045762
140. Utsunomiya T, Yao T, Itoh H, Kai Y, Kumasako Y, Setoguchi M et al (2022) Creation, effects on embryo quality, and clinical outcomes of a new embryo culture medium with 31 optimized components derived from human oviduct fluid: A prospective multicenter randomized trial. Reprod Med Biol 21(1):e12459
141. Bergh C, Wennerholm UB (2020) Long-term health of children conceived after assisted reproductive technology. Ups J Med Sci 125(2):152–157
142. Lo H, Weng SF, Tsai EM (2022) Neurodevelopmental disorders in offspring conceived via in vitro fertilization vs intracytoplasmic sperm injection. JAMA Netw Open 5(12):e2248141
143. Möllers LS, Yousuf EI, Hamatschek C, Morrison KM, Hermanussen M, Fusch C et al (2022) Metabolic-endocrine disruption due to preterm birth impacts growth, body composition, and neonatal outcome. Pediatr Res 91(6):1350–1360
144. Fitzallen GC, Taylor HG, Bora S (2020) What do we know about the preterm behavioral phenotype? A narrative review. Front Psychiatry 11:154
145. Lei N, Lei LL, Wang CH, Mei CR (2024) Pure testicular choriocarcinoma, a rare and highly malignant subtype with challenging treatment: a case report and review of the literature. Mol Clin Oncol 20(1):1
146. Devos B, Willemse C, Sterckx M, Debruyne J, Stappaerts I, Van den Mooter T et al (2024) Beta-HCG secretion by a pulmonary choriocarcinoma in a male patient. Case Rep Oncol Med 2024:8731806
147. Binks S, Uy C, Honnorat J, Irani SR (2022) Paraneoplastic neurological syndromes: a practical approach to diagnosis and management. Pract Neurol 22(1):19–31
148. Mangla M, Singla D, Kaur H, Sharma S (2017) Unusual clinical presentations of choriocarcinoma: a systematic review of case reports. Taiwan J Obstet Gynecol 56(1):1–8
149. Wei H, Zhang T, Liu B, Xue X, Wang G (2016) Choriocarcinoma of unknown origin with multiple organ metastasis and cerebral hemorrhage: a case report and literature review. Oncol Lett 11(6):3749–3752
150. Jaz K, Miedziarek C, Piasek E, Florek A, Nowak-Markwitz E, Zaborowski MP (2023) Choriocarcinoma complicated with intra-abdominal and intrapleural hemorrhage in pregnancy - case report. Front Oncol 13:1198553
151. Sharma N, Kundal R, Kaushal V (2022) Immunobiology and immunotherapy of gestational trophoblastic disease. Gynecol Obstetrics Clin Med 2(2):76–81
152. Li XM, Liu XY, Liu ZX (2015) Choriocarcinoma with multiple lung, skull and skin metastases in a postmenopausal female: a case report. Oncol Lett 10(6):3837–3839
153. Kang S, Zaidi AJ, Shokouh-Amiri M, Wiley E, Venepalli NK (2019) A case report of paraneoplastic syndrome in β-hCG-secreting duodenal adenocarcinoma. J Gastrointest Oncol 10(6):1151–1156