Anatomical and Embryological Consequences of Prenatal Oxcarbazepine Exposure on Hippocampal and Cerebral Cortical Development

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Abstract

Background: Oxcarbazepine (OXC) is a second-generation antiseizure medication widely prescribed for the management of epilepsy and other neurological disorders in women of reproductive age. Although OXC is generally considered to possess a more favorable teratogenic profile than several older antiseizure medications, increasing experimental evidence has raised concerns regarding its potential influence on fetal brain development. The hippocampus and cerebral cortex are among the most complex and vulnerable regions of the developing central nervous system, undergoing tightly regulated processes of neurogenesis, neuronal migration, differentiation, synaptogenesis, and programmed cell death throughout embryonic and fetal life. Any disruption of these events during critical developmental windows may result in persistent structural and functional abnormalities with long-term neurodevelopmental consequences.

This review aims to comprehensively evaluate the available literature regarding the anatomical and embryological consequences of prenatal oxcarbazepine exposure on hippocampal and cerebral cortical development. It further explores the developmental mechanisms that may underlie oxcarbazepine-induced alterations in brain architecture, including apoptosis, oxidative stress, impaired neurogenesis, mitochondrial dysfunction, and altered neuronal maturation. Additionally, the review integrates findings from experimental animal studies with available human clinical evidence to provide a translational perspective on fetal neurodevelopmental safety.

Conclusion: Current evidence suggests that prenatal exposure to oxcarbazepine is associated with fewer major congenital malformations than many traditional antiseizure medications; however, its effects on fetal brain development remain incompletely understood. Experimental investigations indicate that prenatal oxcarbazepine exposure may induce hippocampal neuronal apoptosis, disrupt cortical maturation, and interfere with normal embryological processes responsible for neuronal proliferation, migration, and synaptic organization. Human studies remain relatively limited and have produced inconsistent findings regarding long-term cognitive and neurobehavioral outcomes, highlighting the need for cautious interpretation. From an anatomical and embryological perspective, the timing, dosage, and duration of prenatal exposure appear to be critical determinants of developmental vulnerability. Future multidisciplinary studies integrating embryology, developmental neuroanatomy, molecular neuroscience, advanced neuroimaging, and long-term clinical follow-up are essential to clarify the mechanisms underlying oxcarbazepine-associated neurodevelopmental alterations and to optimize therapeutic strategies that ensure maternal seizure control while minimizing potential fetal neurological risks.

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Keywords: Anatomical, Embryological, Consequences, Oxcarbazepine, Hippocampal ,Cerebral Cortical Development

Introduction

Epilepsy is a common chronic neurological disorder in women of reproductive age, and its management during pregnancy requires careful balance between maternal seizure control and fetal safety. Uncontrolled generalized seizures may expose both mother and fetus to trauma, hypoxia, miscarriage, and adverse obstetric outcomes; therefore, stopping antiseizure medication during pregnancy is usually unsafe. The clinical dilemma is not whether maternal epilepsy should be treated, but how to select the safest effective therapy while reducing unnecessary fetal drug exposure during critical periods of organogenesis and brain development. [1]

Oxcarbazepine is a second-generation antiseizure medication structurally related to carbamazepine. It is rapidly converted to its active metabolite, 10-monohydroxy derivative, which accounts for most of its therapeutic effect. Compared with several older antiseizure medications, oxcarbazepine is often considered to have a more favorable reproductive safety profile, particularly regarding major congenital malformations. However, absence of obvious external malformation does not necessarily indicate absence of subtle effects on the developing fetal brain. [2]

The developing central nervous system is highly sensitive to pharmacological interference because neurogenesis, neuronal migration, differentiation, synaptogenesis, gliogenesis, and programmed cell death occur in a strict temporal and spatial sequence. The cerebral cortex develops through coordinated proliferation of neural progenitors in the ventricular and subventricular zones, followed by migration of neurons to form the cortical plate and later the characteristic six-layered cortical architecture. Disturbance of these events during prenatal life may alter cortical thickness, lamination, and neuronal connectivity. [3]

The hippocampal formation is also developmentally vulnerable because its maturation extends across prenatal and early postnatal life. Its components, including the dentate gyrus, cornu ammonis fields, and subiculum, are essential for memory, learning, emotional regulation, and spatial processing. Because hippocampal development depends on balanced neuronal proliferation, migration, differentiation, and apoptosis, prenatal exposure to neuroactive drugs may theoretically disturb its cytoarchitecture and later functional capacity. [4]

Experimental evidence specifically addressing oxcarbazepine remains limited, but available animal data suggest possible developmental neurotoxicity. A rat study reported that prenatal oxcarbazepine exposure from gestational day 7 to 15 increased apoptotic activity in the hippocampus of offspring, indicating that oxcarbazepine may affect neuronal survival during a sensitive embryonic period. Such findings are anatomically important because excessive apoptosis during hippocampal formation may reduce neuronal populations and modify future synaptic organization. [5]

Despite reassuring data regarding major congenital malformation rates, the long-term neurodevelopmental effects of prenatal oxcarbazepine exposure remain insufficiently defined. Recent pregnancy guidelines recognize oxcarbazepine among antiseizure medications with comparatively lower malformation risk, but they also emphasize that evidence for later cognitive, behavioral, and neurodevelopmental outcomes is less complete than for some other medications. Therefore, the major research gap lies in understanding whether prenatal oxcarbazepine exposure produces subtle structural changes in the hippocampus and cerebral cortex that may not be detected at birth but could influence later neurodevelopment. [6]

Accordingly, this review aims to analyze the anatomical and embryological consequences of prenatal oxcarbazepine exposure on hippocampal and cerebral cortical development. It focuses on normal embryogenesis of these regions, critical windows of vulnerability, experimental evidence of neuronal apoptosis and altered brain maturation, comparison with other antiseizure medications, and the translational limitations of applying animal findings to human pregnancy.

Oxcarbazepine: Pharmacological and Placental Considerations

Oxcarbazepine is a keto-analogue of carbamazepine and belongs to the dibenzazepine group of antiseizure medications. Its main therapeutic action is mediated through blockade of voltage-gated sodium channels, which stabilizes hyperexcited neuronal membranes and reduces repetitive neuronal firing. Unlike carbamazepine, oxcarbazepine has less hepatic enzyme-inducing activity and fewer complex drug interactions, which partly explains its increasing use in women of reproductive age. From a developmental anatomical perspective, however, any neuroactive drug capable of modifying neuronal excitability during fetal life deserves careful attention because neuronal electrical activity contributes to maturation, migration, synaptic refinement, and circuit formation. [7]

After oral administration, oxcarbazepine is rapidly reduced to its active metabolite, 10-monohydroxy derivative, which is responsible for most of its antiseizure effect. This metabolite circulates systemically and represents the major compound measured during therapeutic drug monitoring. Pregnancy can alter oxcarbazepine pharmacokinetics by increasing drug clearance and reducing dose-corrected concentrations of the active metabolite, especially as gestation advances. This is clinically important because declining maternal concentrations may increase seizure risk, whereas dose escalation to maintain seizure control may increase fetal exposure during sensitive periods of brain development. [8]

The placenta is not an absolute barrier to oxcarbazepine exposure. Experimental pharmacokinetic evidence has shown that oxcarbazepine can be metabolized by human placental tissue into its active hydroxy-metabolite, indicating that the placenta may participate in fetal drug exposure rather than simply functioning as a passive transfer organ. This finding is embryologically relevant because the placenta regulates the fetal internal environment during the same period in which neural tube derivatives are forming the cerebral vesicles, cortical plate, hippocampal primordium, and early neuronal networks. [9]

The developmental risk of prenatal oxcarbazepine exposure cannot be judged only by the presence or absence of gross malformations at birth. The fetal hippocampus and cerebral cortex may undergo microscopic and molecular alterations that are not clinically visible in the neonatal period. Altered apoptosis, impaired neuronal proliferation, disturbed migration, oxidative stress, and modified synaptogenesis may produce subtle anatomical changes that become functionally relevant later as memory, learning, language, attention, and behavior mature. Therefore, the pharmacological profile of oxcarbazepine should be interpreted in parallel with the timing of exposure, dose, maternal seizure control, placental transfer, and vulnerability of the developing brain. [10]

Embryological Development of the Cerebral Cortex

The cerebral cortex originates from the dorsal telencephalon, which develops from the prosencephalon during the fourth week of embryogenesis. Following neural tube closure, the walls of the telencephalic vesicles undergo rapid proliferation, giving rise to the ventricular zone, where neuroepithelial cells differentiate into radial glial cells that serve as neural stem cells. These progenitor cells generate the majority of cortical neurons through tightly regulated cycles of proliferation and differentiation, establishing the cellular foundation of the future cerebral cortex. Disturbance of these early developmental events may permanently alter cortical architecture and predispose to structural and functional neurological abnormalities. **[11]**

Following neuronal generation, newly formed neurons migrate along radial glial fibers from the ventricular zone toward the pial surface in a highly organized inside-out pattern. Early-born neurons occupy the deeper cortical layers, whereas later-generated neurons migrate beyond them to establish the superficial layers, ultimately producing the characteristic six-layered neocortex. This precisely coordinated migration depends upon numerous molecular regulators and appropriate extracellular signaling. Even subtle disruption of neuronal migration during gestation may result in abnormal cortical lamination, altered neuronal connectivity, and impaired cognitive function. **[12]**

As cortical lamination progresses, neurons undergo differentiation and establish extensive axonal and dendritic networks that form the basis of functional neural circuits. Simultaneously, synaptogenesis, gliogenesis, and vascular development contribute to maturation of the cerebral cortex. Programmed cell

death further refines cortical organization by eliminating excess neurons and strengthening appropriate neuronal connections. These developmental processes continue throughout fetal life and extend into the postnatal period, emphasizing the prolonged vulnerability of the cerebral cortex to environmental and pharmacological influences during pregnancy. **[13]**

The embryological timing of cortical development is particularly important when evaluating the potential effects of prenatal oxcarbazepine exposure. Since cortical neurogenesis, neuronal migration, and early synaptic organization occur during defined gestational windows, exposure to neuroactive medications during these periods may interfere with normal developmental signaling without necessarily producing gross congenital malformations. Consequently, microscopic alterations in cortical cytoarchitecture may remain clinically silent at birth but later manifest as deficits in cognition, executive function, language, or behavior during childhood. Understanding these developmental milestones provides the anatomical framework for interpreting experimental findings concerning prenatal oxcarbazepine exposure. **[14]**

Embryological Development of the Hippocampus

The hippocampus is one of the earliest components of the limbic system to develop and originates from the medial wall of the telencephalic vesicle. During early embryogenesis, the hippocampal primordium emerges adjacent to the choroidal fissure and gradually differentiates into the cornu ammonis (CA1–CA3), dentate gyrus, and subiculum. These structures subsequently become integrated through highly organized neuronal networks that are essential for memory processing, spatial learning, and emotional regulation. Because hippocampal morphogenesis begins early and continues throughout fetal development, this structure remains particularly susceptible to prenatal environmental and pharmacological influences. **[15]**

Hippocampal development depends on precisely coordinated neurogenesis within specialized germinal zones, followed by neuronal migration, differentiation, and circuit assembly. Unlike much of the cerebral cortex, the dentate gyrus continues to generate granule neurons well into the postnatal period, making hippocampal maturation unusually prolonged. Radial glial cells guide migration of immature neurons, while multiple transcription factors and signaling pathways regulate cellular identity and regional organization. Disruption of these developmental processes may alter hippocampal cytoarchitecture and impair later cognitive function. **[16]**

Programmed cell death represents another fundamental component of normal hippocampal development. Physiological apoptosis eliminates excess neurons, refines neuronal connectivity, and ensures appropriate formation of hippocampal circuits. This tightly regulated process is controlled by the balance between pro-apoptotic and anti-apoptotic molecular pathways. Excessive apoptosis during embryonic development may reduce neuronal populations, disturb synaptic organization, and compromise hippocampal plasticity, whereas insufficient apoptosis may interfere with normal network maturation. Therefore, embryonic hippocampal development requires precise regulation of both neuronal production and neuronal elimination. **[17]**

Because hippocampal neurogenesis, neuronal migration, synaptogenesis, and programmed cell death overlap with periods of maternal exposure to antiseizure medications, the developing hippocampus represents a biologically plausible target for drug-induced neurodevelopmental alterations. Experimental studies have demonstrated that several antiseizure medications can influence neuronal survival during fetal development, although the magnitude of these effects differs among individual drugs. Consequently, understanding normal hippocampal embryology is essential for interpreting reports of increased apoptosis and altered neuronal maturation following prenatal oxcarbazepine exposure, which will be discussed in subsequent sections of this review. **[18]**

Vulnerability During Prenatal Neurodevelopment

Development of the central nervous system follows a highly ordered chronological sequence, making the biological effects of prenatal drug exposure strongly dependent on the timing of administration. During early embryogenesis, neural tube formation is followed by rapid expansion of the prosencephalon, from which the telencephalon and subsequently the cerebral cortex and hippocampus arise. As development progresses, neural progenitor proliferation, neuronal migration, differentiation, and synaptogenesis occur within distinct developmental windows. Interference with any of these stages may produce permanent

anatomical alterations because the affected developmental events cannot be completely compensated later in gestation. **[19]**

Neurogenesis represents one of the most vulnerable developmental stages because it determines the final neuronal population of the cerebral cortex and hippocampus. Neural stem cells within the ventricular and subventricular zones undergo tightly regulated proliferation before differentiating into immature neurons. Pharmacological agents capable of modifying intracellular signaling, mitochondrial activity, or DNA synthesis during this period may reduce neuronal production or alter cell fate decisions. Such disturbances can subsequently influence cortical thickness, hippocampal volume, and overall brain organization without necessarily producing gross structural malformations detectable at birth. **[20]**

Following neuronal generation, migration of immature neurons is essential for establishing the normal architecture of both the cerebral cortex and hippocampus. Cortical neurons migrate along radial glial fibers to form the characteristic inside-out lamination of the neocortex, whereas hippocampal neurons follow specialized migratory pathways to establish the dentate gyrus and cornu ammonis regions. Experimental evidence has demonstrated that disruption of migration during fetal development may result in abnormal neuronal positioning, altered connectivity, and impaired formation of functional neural circuits. Consequently, medications that interfere with cytoskeletal dynamics, intracellular calcium signaling, or neuronal excitability during this period may have lasting neurodevelopmental consequences. **[21]**

The later stages of fetal brain development are characterized by extensive synaptogenesis, dendritic arborization, gliogenesis, and physiological apoptosis, all of which contribute to maturation of functional neural networks. These developmental events continue throughout late gestation and extend into the early postnatal period, particularly within the hippocampus. Because programmed cell death serves to eliminate excess neurons while preserving appropriate neuronal connections, excessive activation of apoptotic pathways by prenatal pharmacological exposure may permanently reduce neuronal density and impair synaptic organization. Recognition of these critical developmental windows is fundamental for interpreting experimental studies investigating prenatal oxcarbazepine exposure and for understanding why the gestational timing of exposure may be as important as the administered dose itself. **[22]**

Experimental Evidence of Prenatal Oxcarbazepine-Induced Hippocampal Alterations

The available experimental evidence regarding the effects of prenatal oxcarbazepine exposure on fetal brain development remains limited compared with other antiseizure medications. Nevertheless, animal studies have provided valuable insight into its potential developmental neurotoxicity. In a prenatal rat model, maternal administration of oxcarbazepine during the period of organogenesis was associated with a significant increase in apoptotic neurons within the hippocampus of the offspring. Histological examination demonstrated greater neuronal degeneration compared with control animals, suggesting that oxcarbazepine may influence neuronal survival during critical stages of hippocampal development. These observations support the hypothesis that prenatal oxcarbazepine exposure can induce microscopic neuroanatomical alterations even in the absence of gross congenital malformations. **[23]**

Apoptosis is a physiological mechanism required for normal maturation of the developing nervous system; however, excessive activation of apoptotic pathways may lead to irreversible neuronal loss. Experimental studies suggest that oxcarbazepine-induced apoptosis may involve mitochondrial dysfunction, activation of caspase-dependent pathways, oxidative imbalance, and disruption of intracellular calcium homeostasis. Because immature neurons exhibit high metabolic activity and limited antioxidant capacity, they are particularly susceptible to these insults during embryogenesis. Excessive neuronal loss during this period may ultimately compromise hippocampal architecture and reduce the neuronal reserve required for normal cognitive development. **[24]**

The hippocampus is especially vulnerable because neuronal proliferation and differentiation continue throughout late fetal and early postnatal life. Damage occurring during embryogenesis may therefore influence subsequent dendritic growth, synaptic maturation, and establishment of hippocampal circuitry. Experimental studies evaluating developmental neurotoxicity have consistently demonstrated that even modest alterations in neuronal survival during prenatal life can produce persistent deficits in learning, memory, and behavioral performance during adulthood. These findings emphasize that microscopic

developmental abnormalities may have greater long-term significance than structural malformations detected at birth. **[25]**

Although experimental findings raise important concerns regarding prenatal oxcarbazepine exposure, their direct application to human pregnancy should be interpreted cautiously. Differences in gestational timing, drug metabolism, placental physiology, dosage, and species-specific brain maturation limit direct extrapolation from rodent models to humans. Nevertheless, these studies provide an essential biological foundation for understanding the potential mechanisms through which oxcarbazepine may influence fetal hippocampal development and justify continued investigation using both experimental and clinical approaches. **[26]**

Possible Mechanisms of Oxcarbazepine-Related Developmental Neurotoxicity

One possible mechanism by which prenatal oxcarbazepine exposure may affect hippocampal and cortical development is excessive activation of apoptosis. During normal embryogenesis, programmed cell death removes surplus neurons and helps refine early neural circuits. However, when apoptosis exceeds physiological limits, the developing brain may lose neurons required for later cortical and hippocampal connectivity. This mechanism is particularly relevant to oxcarbazepine because experimental prenatal exposure has been associated with increased hippocampal apoptotic activity in rat offspring, suggesting that neuronal survival may be altered during sensitive developmental periods. **[27]**

Oxidative stress may also contribute to developmental neurotoxicity after prenatal exposure to antiseizure medications. The fetal brain is metabolically active, rich in polyunsaturated fatty acids, and relatively immature in antioxidant defense systems, making it vulnerable to free radical injury. Excessive oxidative stress can damage neuronal membranes, mitochondrial proteins, and DNA, eventually activating cell death pathways. In the hippocampus and cerebral cortex, such injury may interfere with neuronal proliferation, migration, differentiation, and synaptic maturation, producing subtle anatomical changes that are not immediately visible at birth. **[28]**

Mitochondrial dysfunction represents another biologically plausible pathway linking prenatal drug exposure to impaired brain development. Developing neurons require high mitochondrial activity to support neurogenesis, axonal growth, dendritic branching, and synapse formation. If oxcarbazepine or its active metabolite disrupts mitochondrial energy production, immature neurons may become more susceptible to apoptosis or delayed maturation. This mechanism is important because mitochondrial impairment can produce widespread effects on both hippocampal and cortical regions, especially during periods of rapid neuronal differentiation and circuit formation. **[29]**

Alteration of neuronal excitability may also influence fetal brain maturation. Oxcarbazepine acts mainly by modulating voltage-gated sodium channels, thereby reducing repetitive neuronal firing. Although this action is therapeutically beneficial in epilepsy, neuronal electrical activity during development participates in synaptic stabilization, migration, and refinement of early neural circuits. Therefore, prolonged pharmacological modulation of excitability during prenatal life may theoretically influence the maturation of cortical and hippocampal networks, particularly when exposure coincides with periods of active synaptogenesis and circuit organization. **[30]**

Cerebral Cortical Maturation and Potential Consequences of Prenatal Exposure

Cerebral cortical maturation depends on the successful transition from early neurogenesis to organized lamination, synaptogenesis, dendritic arborization, and network refinement. During this period, neurons acquire regional identity and establish connections that later support sensory processing, motor control, language, attention, and higher cognitive functions. Because cortical development is not completed at birth, prenatal exposure to neuroactive medications may produce subtle disturbances that continue to influence postnatal maturation. These changes may not appear as visible congenital malformations but may affect cortical thickness, neuronal density, or connectivity. **[31]**

The developing cortex is particularly sensitive to agents that influence neuronal survival and excitability. Oxcarbazepine reduces neuronal hyperexcitability through sodium-channel modulation, but neuronal electrical activity during fetal development contributes to migration, synapse stabilization, and refinement of early circuits. Therefore, prolonged prenatal modulation of neuronal excitability may theoretically alter

the maturation of cortical networks. Although direct human evidence linking oxcarbazepine to cortical structural abnormalities remains limited, this possibility is biologically plausible when considered within the broader framework of activity-dependent cortical development. **[32]**

Another potential cortical consequence of prenatal oxcarbazepine exposure is disruption of the balance between neuronal production and elimination. Normal cortical development requires adequate generation of neurons followed by selective programmed cell death. Excessive apoptosis may reduce neuronal populations, whereas impaired migration may disturb cortical layering. These processes are central to the formation of functional cortical columns and long-range connections. Even mild disturbances during fetal life may influence later neurobehavioral outcomes, especially executive function, learning ability, and attention. **[33]**

At present, the strongest evidence for oxcarbazepine-related developmental effects comes from experimental hippocampal studies rather than direct cortical investigations. However, the hippocampus and cerebral cortex develop from related telencephalic regions and share several developmental mechanisms, including progenitor proliferation, neuronal migration, synaptogenesis, and apoptosis. Therefore, findings of increased hippocampal apoptosis after prenatal oxcarbazepine exposure raise reasonable concern that cortical development may also require careful investigation. Future studies should include cortical histomorphometry, lamination markers, neuronal density assessment, synaptic protein analysis, and long-term behavioral correlation. **[34]**

Comparison with Carbamazepine and Other Antiseizure Medications

Oxcarbazepine was developed as a structural derivative of carbamazepine with the aim of maintaining comparable antiseizure efficacy while improving tolerability and reducing adverse drug interactions. Unlike carbamazepine, oxcarbazepine undergoes rapid biotransformation to its active monohydroxy derivative without formation of the reactive epoxide metabolite that has been implicated in some toxic effects. This pharmacological difference has contributed to the perception that oxcarbazepine possesses a more favorable safety profile during pregnancy. Large prospective pregnancy registries have consistently reported lower rates of major congenital malformations with oxcarbazepine than with valproate and rates comparable to those observed with carbamazepine and lamotrigine when used as monotherapy. **[35]**

Valproate remains the antiseizure medication with the strongest evidence for developmental neurotoxicity. Numerous experimental and clinical studies have demonstrated that prenatal valproate exposure increases the risk of major congenital malformations, impaired cognitive development, autism spectrum disorder, and reduced intelligence quotient in exposed offspring. In contrast, available evidence for oxcarbazepine has not demonstrated a comparable degree of neurodevelopmental risk. Nevertheless, the amount of long-term evidence for oxcarbazepine remains substantially smaller, and therefore the apparent difference may partly reflect the limited number of well-designed follow-up studies rather than complete absence of developmental effects. **[36]**

Carbamazepine has been studied more extensively than oxcarbazepine because of its longer clinical use. Although carbamazepine is associated with a relatively low risk of major congenital malformations compared with valproate, experimental studies have suggested that prolonged prenatal exposure may still influence neuronal proliferation, apoptosis, and postnatal neurobehavioral development. Since oxcarbazepine shares structural similarity and a common mechanism of sodium-channel blockade with carbamazepine, it is reasonable to consider that both drugs may influence developmental pathways, although current evidence suggests that oxcarbazepine has a more favorable reproductive safety profile. Additional comparative studies examining hippocampal and cortical histology are required to clarify whether these pharmacological differences translate into measurable anatomical differences during fetal brain development. **[37]**

Current international guidelines recommend individualized selection of antiseizure medication before conception, emphasizing the use of monotherapy at the lowest effective dose whenever possible. Oxcarbazepine is considered an acceptable therapeutic option for many women with epilepsy because existing evidence indicates a relatively low risk of major structural malformations. However, guideline panels also acknowledge that evidence regarding long-term cognitive and neurodevelopmental outcomes

following prenatal oxcarbazepine exposure remains limited. Consequently, continued experimental and clinical investigations are necessary before definitive conclusions can be drawn regarding its effects on hippocampal and cerebral cortical development. **[38]**

Human Pregnancy Data: Congenital, Perinatal, and Neurodevelopmental Outcomes

Human studies of prenatal oxcarbazepine exposure have generally focused on major congenital malformations rather than detailed brain morphology. Available registry and systematic-review data suggest that oxcarbazepine monotherapy is associated with a comparatively low risk of major congenital malformations when compared with high-risk antiseizure medications such as valproate. However, these findings should not be interpreted as proof of complete fetal neurodevelopmental safety. Major malformation studies mainly detect visible structural anomalies, whereas subtle hippocampal or cortical alterations may require neuroimaging, cognitive testing, behavioral follow-up, and long-term developmental assessment. **[39]**

Evidence regarding long-term neurodevelopment after prenatal oxcarbazepine exposure remains limited and somewhat inconsistent. A large Nordic register-based study reported associations between prenatal exposure to some antiseizure medications, including oxcarbazepine, and increased risks of neurodevelopmental diagnoses; however, observational studies are vulnerable to confounding by indication, epilepsy severity, seizure frequency, genetic background, and socioeconomic factors. Other population-based analyses have not found a clear increased risk for several neurodevelopmental outcomes after oxcarbazepine exposure compared with lamotrigine. Therefore, current human evidence does not allow a definitive conclusion, but it supports the need for cautious follow-up of exposed children. **[40]**

From an anatomical and embryological viewpoint, the key limitation of clinical pregnancy studies is that most do not directly assess hippocampal formation, cortical lamination, neuronal density, or synaptic organization. A child may be born without visible malformations yet still have subtle alterations in memory circuits, cortical connectivity, or executive networks that become apparent only during school age. Therefore, future human studies should combine pregnancy registries with fetal and postnatal neuroimaging, standardized neuropsychological testing, and long-term developmental surveillance. Such integrated approaches are necessary to bridge the gap between experimental evidence of hippocampal apoptosis and clinical interpretation in human prenatal oxcarbazepine exposure.

Conclusion

Prenatal oxcarbazepine exposure appears to carry a relatively low risk of major congenital malformations compared with several older antiseizure medications, particularly valproate. However, anatomical safety cannot be judged only by external or gross structural normality at birth. The hippocampus and cerebral cortex develop through highly sensitive processes, including neurogenesis, neuronal migration, apoptosis, synaptogenesis, and circuit refinement. Experimental evidence suggests that oxcarbazepine may increase hippocampal apoptosis during prenatal development, raising concern for subtle microscopic alterations that may affect later learning, memory, behavior, and cortical function. Human data remain limited and do not yet provide definitive evidence of long-term neurodevelopmental safety or harm. Therefore, oxcarbazepine should be used during pregnancy with individualized risk–benefit assessment, careful dose monitoring, and long-term developmental follow-up of exposed children.

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