

TERATOGENIC EFFECTS OF MATERNAL MEDICATION USE DURING PREGNANCY: A COMPREHENSIVE REVIEW

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ABSTRACT

The use of medications during pregnancy is a complex issue, as the health of the mother and fetus must be carefully balanced. While medications are often necessary to manage chronic conditions, they can also pose risks to fetal development. Teratogenic effects, which result in birth defects or developmental abnormalities, are a significant concern. Many medications have been identified as potential teratogens, including certain anticonvulsants, antidepressants, and antihypertensives. The risk of teratogenic effects depends on various factors, including the type of medication, dosage, and timing of exposure during pregnancy. Understanding the teratogenic potential of maternal medication use is crucial for informed decision-making and optimal pregnancy outcomes. This comprehensive review aimed at providing an in-depth analysis of the current evidence on the teratogenic effects of maternal medication use during pregnancy. The risks associated with various classes of medications, including anticonvulsants, antidepressants, antihypertensives, and others, highlighting the specific teratogenic effects and the factors that influence these risks, such as dosage and timing of exposure were also discussed in this review. Challenges of balancing maternal health with fetal safety and provide guidance on informed decision-making and risk assessment were addressed. Furthermore, strategies for minimizing harm to the developing fetus, including medication optimization, dose adjustment, and close monitoring were elucidated. By

synthesizing the existing literature, this review aimed at informing clinical practice and guide research directions, ultimately contributing to improved pregnancy outcomes and reduced risk of birth defects. Our analysis in this review highlighted the need for careful consideration of the potential teratogenic effects of maternal medication use and underscores the importance of collaborative decision-making between healthcare providers and pregnant women. This review provides a valuable resource for healthcare professionals, researchers, and expectant mothers seeking to navigate the complex issues surrounding medication use during pregnancy.

Keywords: Teratogens, Maternal Medication, Pregnancy, Birth Defects, Fetal Development, Medication Safety

INTRODUCTION

Teratogenicity refers to the capacity of a substance to cause structural or functional abnormalities in a developing embryo or fetus. Teratogens can include medications, environmental toxins, infections, and even maternal health conditions. The significance of teratogenic effects lies in their potential to result in lifelong disabilities, increased healthcare burdens, and profound emotional and psychological impacts on families. Medications such as thalidomide, isotretinoin, and certain antiepileptics have historically demonstrated severe teratogenic outcomes, prompting rigorous regulatory oversight and the development of pregnancy risk classification systems (Mitchell *et al.*, 2011). Understanding teratogenic mechanisms whether through disruption of cell signaling, interference with nutrient supply, or induction of oxidative stress is vital for developing safer therapeutic strategies and guiding informed clinical decisions. In humans, a substance is considered teratogenic if consistent evidence shows an increased risk of malformations, with biological plausibility and reproducible findings across studies (Shepard, 2001). The effects of a teratogen depend on the timing of exposure (first trimester, especially weeks 3–8 of gestation, being the most vulnerable), the drug's dose and duration, maternal and fetal genetic susceptibility, and maternal metabolic factors.

Teratogenicity manifests itself in a variety of ways, ranging from major congenital malformations (e.g., neural tube defects, cardiac anomalies, limb deformities) to growth restriction, neurodevelopmental disorders, and functional impairments that continue into postnatal life). Thalidomide, isotretinoin, and several antiepileptic medications are classic instances that have brought attention to the significance of cautious prescribing and drug safety review during pregnancy (Briggs *et al.*, 2017; Andrade *et al.*, 2016). A complicated and important part of maternal healthcare is the use of medication during pregnancy, which is generally described as the administration of pharmacological substances to treat, manage, or prevent sickness in pregnant women. Pharmacological management becomes particularly difficult during pregnancy due to physiological changes that can modify drug metabolism, distribution, and excretion. Both acute ailments like infections or pain and chronic problems like diabetes, epilepsy, or hypertension may be treated with medication. Withholding therapy can often be more dangerous for the mother and fetus than the drug itself. Therefore, it is crucial to comprehend the pharmacodynamics and pharmacokinetics of medications during pregnancy in order to protect fetal development and maintain mother health (Andrade *et al.*, 2004). Even while taking medication may be necessary in some situations, there are risks involved. Pharmacotherapy's advantages must be balanced against

any potential drawbacks, especially those that could impact fetal development. While certain drugs involve a considerable risk of congenital defects, miscarriage, or developmental delays, others are thought to be reasonably safe. Exposure timing is important because organogenesis takes place and the fetus is most susceptible to teratogenic insults during the embryonic stage, particularly between weeks three and eight of pregnancy (Brent, 2004). Due to ethical restrictions on clinical trials in pregnant patients, clinicians must strike this delicate balance and frequently rely on scant data. As a result, post-marketing surveillance, registries, and observational studies are commonly used to inform prescribing decisions.

The current study is aimed at presenting a thorough investigation into the teratogenic consequences associated with maternal medication use during pregnancy. It will explore the mechanisms by which certain pharmaceuticals exert harmful effects on fetal development, highlighting well-documented teratogens and examining the pharmacological profiles of commonly prescribed drugs. Special attention will be given to how timing, dosage, and duration of exposure influence fetal outcomes, recognizing that the gestational stage plays a critical role in vulnerability to teratogenic effects. In addition to clinical pharmacology, the review will address the ethical and methodological challenges inherent in studying drug safety in pregnant populations. These include the exclusion of pregnant women from randomized controlled trials, reliance on observational data, and the limitations of existing registries and reporting systems. The role of pharmacovigilance and post-marketing surveillance will be emphasized as essential tools in identifying and managing risks. Furthermore, the review will analyze current regulatory frameworks such as the FDA's Pregnancy and Lactation Labeling Rule (PLLR), alongside international guidelines and risk assessment models used by healthcare professionals to guide prescribing decisions. By synthesizing evidence from clinical trials, case reports, cohort studies, and regulatory databases, this review aims to support safer prescribing practices and promote maternal-fetal health. Ultimately, the objective is to bridge the gap between therapeutic necessity and fetal protection, offering a nuanced understanding of pharmaceutical use during pregnancy. This comprehensive approach seeks to empower clinicians with evidence-based strategies that prioritize both maternal well-being and fetal safety.

Teratogenic Mechanisms and Risk Factors

Teratogenesis, the process by which congenital anomalies arise due to exposure to harmful agents during pregnancy, is governed by a complex interplay of genetic, environmental, and molecular factors. At its core, teratogenicity reflects the disruption of normal embryonic development, often through interference with cellular signaling, gene expression, or metabolic pathways. Genetic predisposition plays a pivotal role in determining susceptibility to teratogens. Variations in maternal and fetal genes, particularly those involved in drug metabolism such as cytochrome P450 enzymes, can significantly influence the degree of fetal exposure and the resultant risk of malformation (Finnell *et al.*, 2004). For instance, polymorphisms in genes encoding detoxifying enzymes may render certain fetuses more vulnerable to oxidative stress induced by teratogenic compounds. Environmental influences further modulate teratogenic outcomes. Factors such as maternal nutrition, exposure to pollutants, and concurrent illnesses can amplify or mitigate the effects of teratogens. Nutritional deficiencies particularly folate have been linked to neural tube defects, while maternal infections like rubella or Zika virus can cause severe structural anomalies. Moreover, molecular mechanisms underpinning teratogenesis often involve disruption of critical

developmental pathways. Teratogens may interfere with morphogen gradients, induce apoptosis in proliferating cells, or alter epigenetic regulation, leading to aberrant organogenesis. For example, isotretinoin, a known teratogen, affects retinoic acid signaling, which is essential for craniofacial and neural development (Lammer *et al.*, 1985).

This epigenetic dimension of teratogenesis is vividly illustrated in Figure 1, which depicts how prenatal alcohol exposure can reprogram the fetal epigenome and trigger a cascade of developmental consequences. Alcohol, acting as a teratogen, does not directly mutate DNA but alters gene expression through modifications to histones and dysregulation of non-coding RNAs such as miRNAs and lncRNAs. These epigenetic shifts compromise the integrity of developmental signaling, resulting in immune system dysfunction, congenital anomalies like microcephaly and heart defects, and disruption of the hypothalamic-pituitary-adrenal (HPA) axis. The latter leads to a hyperresponsive stress system, predisposing the individual to neuroendocrine disorders later in life. Figure 1 thus reinforces the concept that teratogens exert their effects not only through direct cellular damage but also by subtly reshaping the molecular architecture that governs embryonic development. These insights underscore the precision required in fetal programming and the profound consequences of even transient exposures during critical windows of gestation.

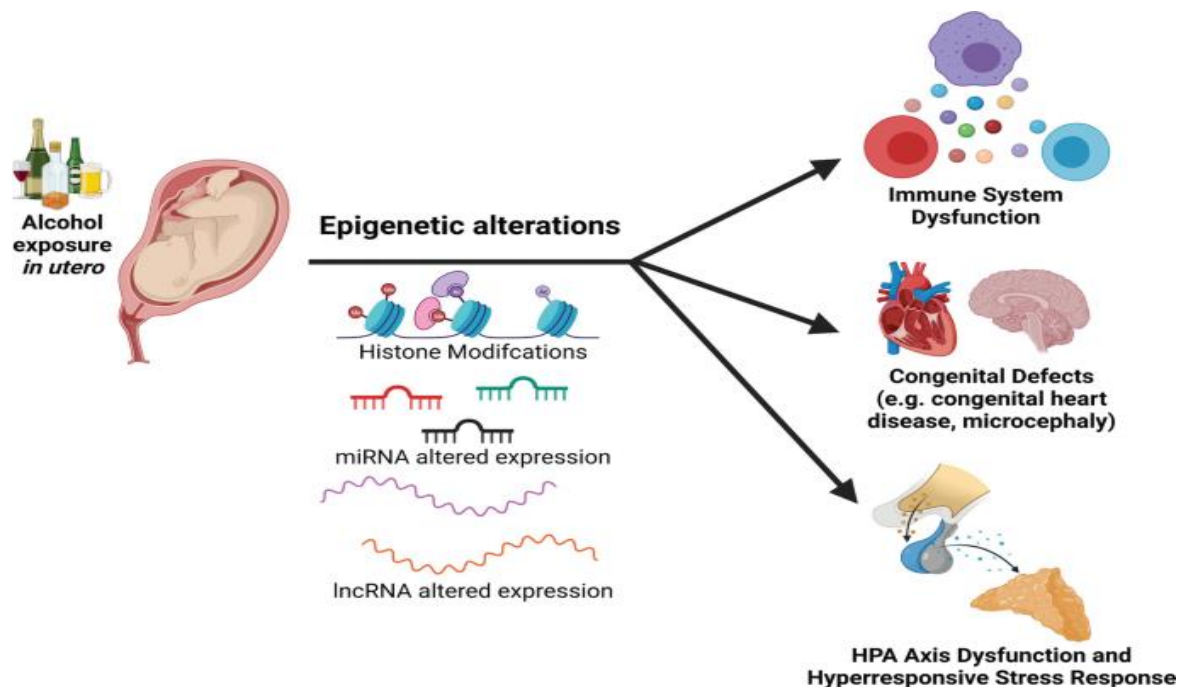


Figure 1. Epigenetic pathways linking prenatal alcohol exposure to teratogenic outcomes

Source: Lammer *et al.* (1985)

The risk of teratogenic effects is not uniform across all pregnancies but is shaped by several key factors, including medication dosage, timing of exposure, and individual susceptibility. Dosage is a critical determinant; higher concentrations of a teratogen are more likely to overwhelm protective mechanisms and cause damage. However, even low doses can be harmful if the exposure occurs during a vulnerable developmental window. Timing is perhaps the most decisive factor in

teratogenesis. The embryonic period, spanning weeks 3 to 8 of gestation, is characterized by rapid cell differentiation and organ formation. Exposure to teratogens during this phase can result in major structural anomalies, whereas exposure during the fetal period (weeks 9 to birth) may lead to functional deficits or growth retardation (Sadler, 2012). For instance, thalidomide exposure between days 20 and 36 post-conception is associated with limb malformations, highlighting the narrow window of vulnerability.

Individual susceptibility further complicates risk assessment. Genetic variability in drug metabolism, placental transport, and DNA repair mechanisms can influence how a fetus responds to teratogenic insults. Additionally, maternal factors such as age, health status, and concurrent medication use can alter pharmacokinetics and enhance teratogenic potential. The placenta, while serving as a selective barrier, is not impervious; lipophilic drugs and those with low molecular weight can readily cross into fetal circulation. Moreover, the immature fetal liver lacks the enzymatic capacity to detoxify many compounds, increasing the risk of accumulation and toxicity (Koren *et al.*, 2006). These nuances underscore the importance of individualized risk evaluation in prenatal pharmacotherapy.

Figure 2 illustrates this vulnerability with a developmental timeline that maps organogenesis across gestational weeks. It highlights how the neural tube closes around week 4, the heart forms between weeks 3–6, and limb buds emerge shortly thereafter. These windows represent peak sensitivity, where even brief exposure to teratogens such as antiepileptic drugs or environmental toxins can result in major structural abnormalities. As development progresses into the second and third trimesters, the risk of gross malformations declines, but the fetus remains vulnerable to functional impairments. These later stages are critical for neurodevelopment, endocrine regulation, and immune system maturation. Teratogenic exposure during this period may not visibly alter anatomy but can disrupt long-term cognitive and physiological outcomes. For example, exposure to valproic acid later in pregnancy has been associated with cognitive deficits and autism spectrum disorders, even in the absence of overt malformations (Christensen *et al.*, 2013). The diagram also underscores that teratogenic risk is not uniform across gestation. Early exposure may result in pregnancy loss or major malformations, while later exposure may lead to subtler but still significant developmental challenges. These findings highlight the need for vigilance throughout gestation, not just during early development.

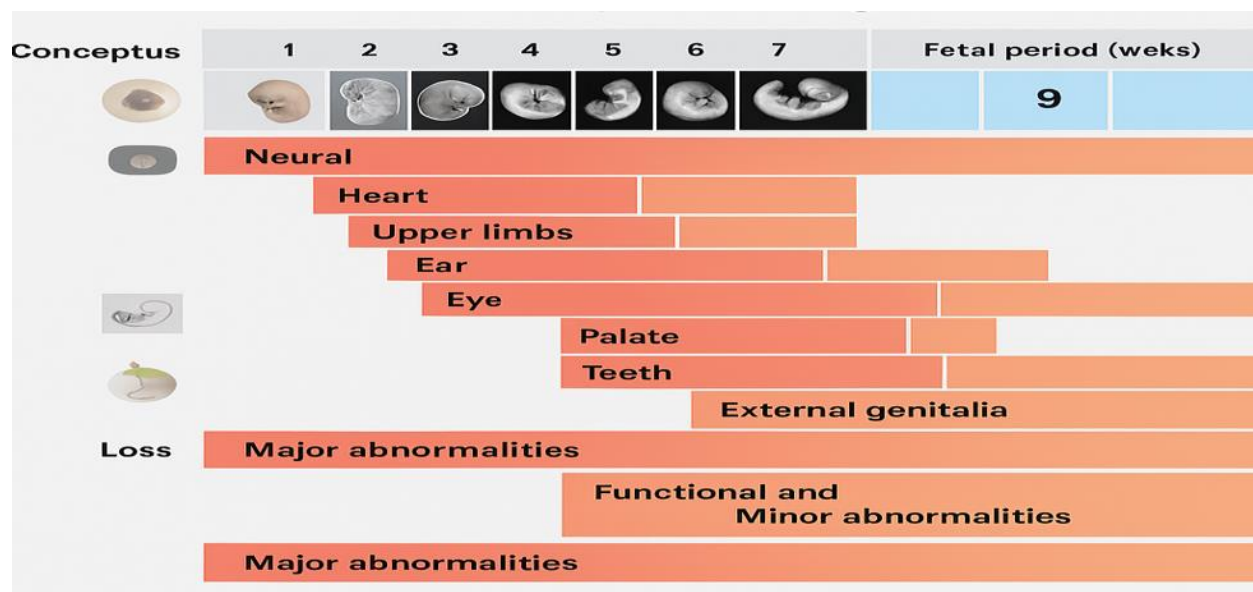


Figure 2. Critical periods of fetal development and vulnerability to teratogens

Source: Rengasamy (2016)

Anticonvulsants: Specific Teratogenic Effects and Risks

Anticonvulsants are among the most extensively studied teratogenic medications due to their widespread use in epilepsy and bipolar disorder. Several agents within this class have been implicated in a spectrum of congenital anomalies. Valproic acid, in particular, is associated with a high risk of neural tube defects (NTDs), including spina bifida, with an estimated incidence of 1–2% in exposed pregnancies (Meador *et al.*, 2009). The teratogenicity of valproate is dose-dependent and linked to its interference with folate metabolism and histone deacetylase inhibition, which disrupts gene expression during neural development.

Figure 3 illustrates these mechanisms in detail, showing how valproic acid impairs two critical epigenetic pathways. First, it disrupts the folate-dependent one-carbon cycle, reducing the availability of S-adenosylmethionine (SAME), a key methyl donor required for DNA and histone methylation. This leads to hypomethylation, compromising the regulation of genes essential for neural tube closure. Second, valproate inhibits histone deacetylase (HDAC), resulting in excessive histone acetylation and a relaxed chromatin structure (Christensen *et al.*, 2013). This hyperacetylation alters transcriptional timing and fidelity, potentially activating or silencing genes inappropriately during early neural development. Together, these epigenetic disturbances affect the expression of key developmental regulators such as *Pax3*, *Shh*, and *Bmp4*, increasing the risk of structural anomalies like spina bifida and anencephaly. The diagram titled “Prenatal VPA Teratogenicity” underscores the importance of maintaining epigenetic homeostasis during gestation and highlights the molecular basis for valproate’s teratogenic potential.

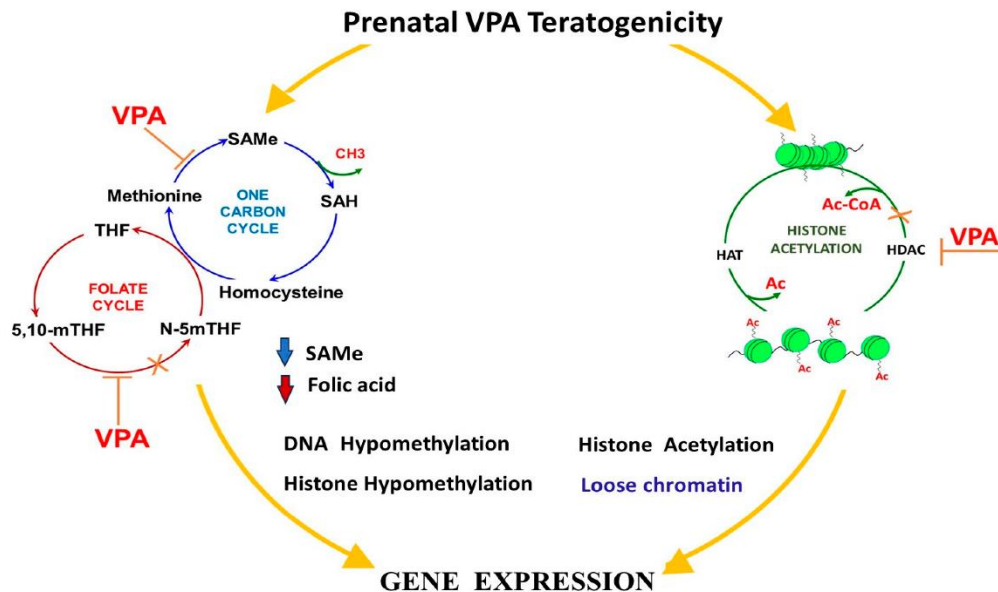


Figure 3. Mechanism of prenatal VPA teratogenicity

Source: Meador *et al.* (2009)

Carbamazepine, another commonly used anticonvulsant, also carries a risk of NTDs, though lower than valproate. It has been associated with craniofacial anomalies, cardiac defects, and developmental delays. Phenytoin exposure can result in fetal hydantoin syndrome, characterized by growth deficiency, microcephaly, and dysmorphic facial features. Lamotrigine, while considered safer, is not entirely risk-free; some studies suggest a modest increase in the risk of cleft lip and palate, although findings remain inconclusive (Hernández-Díaz *et al.*, 2012).

Antidepressants: Specific Teratogenic Effects and Risks

Depression during pregnancy is a significant public health concern, and antidepressants particularly selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed to manage maternal mental health. While SSRIs are generally considered low-risk, emerging data suggest potential associations with specific congenital anomalies. Paroxetine, for instance, has been linked to an increased risk of cardiac defects, especially atrial and ventricular septal defects, when used during the first trimester (Wurst *et al.*, 2010). The mechanism may involve serotonin's role in embryonic cell signaling and heart development.

SSRIs function by blocking the serotonin transporter (SERT), thereby increasing serotonin (5-HT) levels in the synaptic cleft. As illustrated in the diagram, this elevated serotonin activates postsynaptic receptors, triggering a cascade involving adenylyl cyclase (AC), cyclic AMP (cAMP), and protein kinase A (PKA). PKA then phosphorylates the transcription factor CREB, which promotes the transcription of brain-derived neurotrophic factor (BDNF) mRNA. BDNF protein, translated from this mRNA, plays a critical role in neuronal survival, synaptic plasticity, and mood regulation key therapeutic outcomes in adults (Christensen *et al.*, 2013). However, during fetal development, this same pathway can have unintended consequences. Serotonin acts not only as a neurotransmitter but also as a morphogen a signaling molecule that regulates cell proliferation, migration, and differentiation, particularly in neural crest cells. These cells contribute

to the formation of craniofacial structures, cardiac tissue, and the central nervous system. Disruption of serotonin homeostasis during early gestation, as caused by SSRIs, may interfere with the tightly regulated timing of these developmental processes (Wurst *et al.*, 2010). The downstream activation of CREB and BDNF, while beneficial in mature neurons, may alter gene expression patterns in progenitor cells, increasing the risk of structural anomalies such as craniosynostosis, cleft palate, and septal heart defects.

Other SSRIs such as fluoxetine and sertraline have shown mixed results in teratogenic studies. Some reports suggest a slight increase in the risk of persistent pulmonary hypertension of the newborn (PPHN) and neonatal adaptation syndrome, characterized by irritability, tremors, and feeding difficulties (Wurst *et al.*, 2010). These effects are thought to result from serotonergic overstimulation in utero and withdrawal after birth, further underscoring the delicate balance required in fetal serotonin signaling.

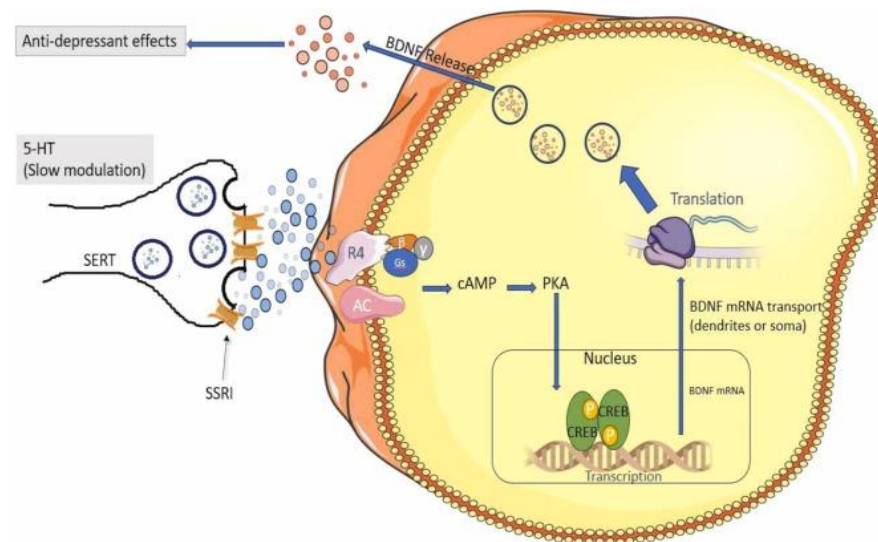


Figure 4. Molecular mechanism by which selective serotonin reuptake inhibitors (SSRIs) exert their antidepressant effects.

Source: Sánchez *et al.* (2021)

Tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have not demonstrated consistent teratogenic effects, though data are limited. Bupropion, used for depression and smoking cessation, has been associated with a possible increase in cardiac malformations, though findings are not definitive. Importantly, untreated maternal depression itself poses risks, including poor prenatal care, preterm birth, and developmental delays, underscoring the need for careful risk-benefit analysis.

Antihypertensives: Specific Teratogenic Effects and Risks

Hypertension in pregnancy, whether chronic or gestational, necessitates pharmacologic intervention to prevent complications such as preeclampsia and intrauterine growth restriction. However, not all antihypertensives are safe for use during pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated due to their well-documented teratogenic effects. Exposure during the second and third trimesters has

been associated with fetal renal dysgenesis, oligohydramnios, pulmonary hypoplasia, limb contractures, hypocalvaria, and even neonatal death (Barr *et al.*, 1994; August *et al.*, 2024). These adverse outcomes stem from the disruption of the renin-angiotensin-aldosterone system (RAAS), a hormonal cascade essential for fetal renal perfusion and development. As illustrated in the RAAS diagram, the liver produces angiotensinogen, which is converted to angiotensin I by renin released from the kidney in response to reduced perfusion. Angiotensin I is then converted to angiotensin II by ACE, primarily in the lungs. Angiotensin II plays a pivotal role in stimulating aldosterone release, vasoconstriction, and water retention mechanisms that maintain blood pressure and fluid balance. In the fetus, angiotensin II is crucial for nephrogenesis and vascular development. ACE inhibitors block the conversion of angiotensin I to angiotensin II, while ARBs prevent angiotensin II from binding to its AT1 receptors, leading to fetal hypotension, impaired renal blood flow, and reduced urine output. This cascade results in oligohydramnios, which in turn contributes to pulmonary hypoplasia and other structural anomalies. The teratogenic potential of these drugs has been substantiated in both clinical and epidemiological studies, prompting strong recommendations against their use during pregnancy (Lovegrove *et al.*, 2020).

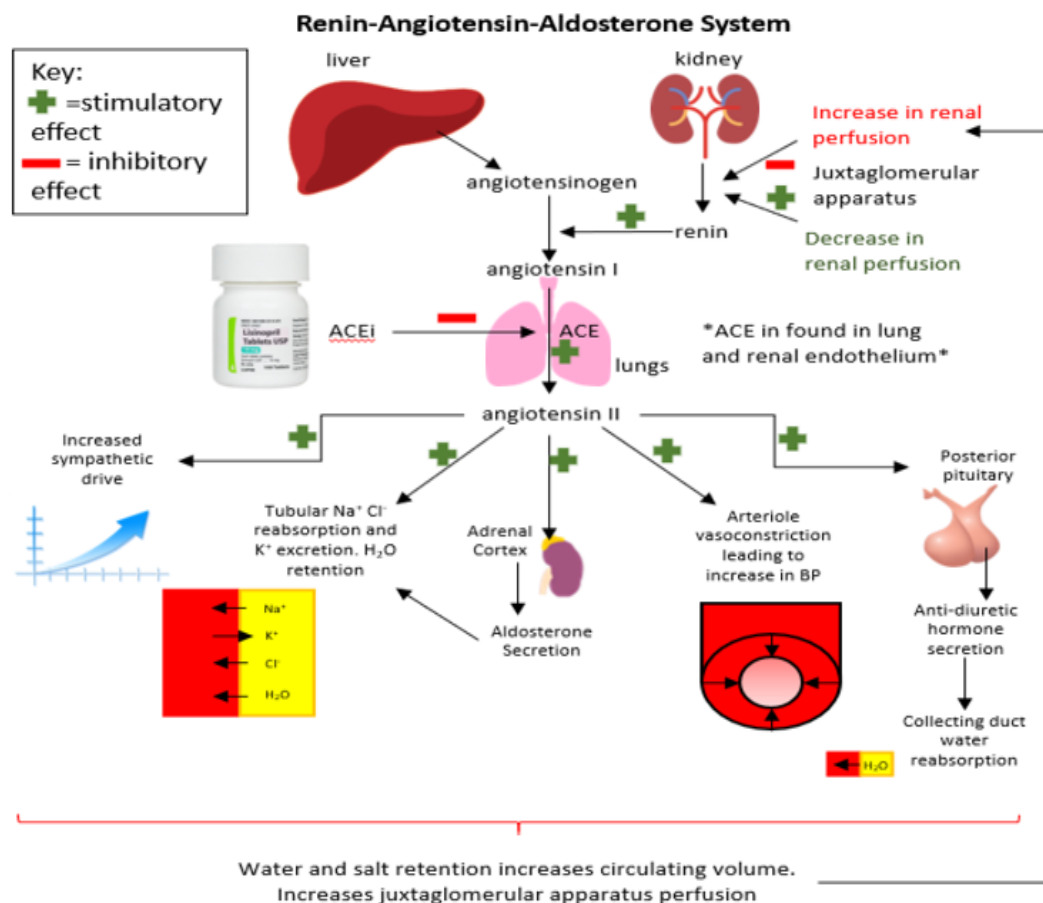


Figure 5. Renin-Angiotensin-Aldosterone System (RAAS)

Source: Lovegrove *et al.* (2020)

Safer alternatives include labetalol, methyldopa, and nifedipine. Methyldopa, a centrally acting alpha-agonist, has a long history of use in pregnancy and is generally considered safe, though it may cause maternal fatigue and depression. Labetalol, a mixed alpha/beta-blocker, is effective and well-tolerated, with no significant teratogenic effects reported. Calcium channel blockers like nifedipine are also widely used, particularly in managing preterm labor, and have not been associated with major congenital anomalies. Diuretics are typically avoided unless absolutely necessary, as they may reduce plasma volume and impair placental perfusion. Beta-blockers, while generally safe, have been linked to fetal growth restriction and neonatal bradycardia in some studies, necessitating close monitoring.

Other Medication Classes: Specific Teratogenic Effects and Risks

Beyond the major classes discussed, several other medications warrant attention for their teratogenic potential. Retinoids, particularly isotretinoin used for severe acne, are among the most potent teratogens known. Exposure during early pregnancy can result in craniofacial anomalies, cardiac defects, and central nervous system malformations. Due to its high risk, isotretinoin is subject to strict pregnancy prevention programs (Wurst *et al.*, 2010).

Warfarin, an anticoagulant, crosses the placenta and can cause fetal warfarin syndrome, characterized by nasal hypoplasia, stippled epiphyses, and neurodevelopmental deficits. Low molecular weight heparin is preferred during pregnancy due to its safety profile. Antibiotics also vary in teratogenic risk. Tetracyclines can impair bone growth and cause tooth discoloration, while aminoglycosides may lead to ototoxicity. Safer options include penicillins, cephalosporins, and erythromycin (Lovegrove *et al.*, 2020). Fluoroquinolones are generally avoided due to concerns about cartilage toxicity, although human data are limited. Antidiabetic medications present another area of concern. While insulin is the gold standard for managing gestational diabetes, some oral agents like metformin and glyburide are increasingly used. Metformin has not shown significant teratogenic effects and may even reduce the risk of miscarriage in women with polycystic ovary syndrome (PCOS). However, long-term data on neurodevelopmental outcomes remain sparse. Finally, antipsychotics and mood stabilizers used in psychiatric disorders pose complex risks. Lithium, for example, has been associated with Ebstein's anomaly a rare cardiac defect though the absolute risk is low (August *et al.*, 2024). Atypical antipsychotics such as olanzapine and risperidone have not demonstrated consistent teratogenic effects but may contribute to gestational diabetes and neonatal adaptation issues.

Clinical Considerations and Risk Assessment

Managing medication use during pregnancy demands a delicate equilibrium between safeguarding maternal health and minimizing fetal risk. Pregnancy is not a contraindication to treatment, but rather a condition that necessitates heightened vigilance and individualized care. Untreated maternal illnesses whether chronic conditions like epilepsy, hypertension, or depression, or acute infections can pose serious threats to both mother and fetus. For instance, uncontrolled seizures may lead to trauma, hypoxia, or miscarriage, while untreated depression can impair maternal bonding and prenatal care adherence (Yonkers *et al.*, 2009). Thus, the clinical imperative is not to avoid medication altogether, but to ensure that therapeutic decisions are grounded in evidence, tailored to the patient's condition, and sensitive to gestational timing.

Balancing maternal health with fetal safety requires a nuanced understanding of pharmacokinetics during pregnancy. Physiological changes such as increased plasma volume, altered hepatic enzyme activity, and enhanced renal clearance can affect drug absorption and efficacy. These changes may necessitate dose adjustments to maintain therapeutic levels without exceeding thresholds that could harm the fetus. Moreover, the placenta, while selective, does not fully protect the fetus from xenobiotics (Brown *et al.*, 2023). Lipophilic drugs, low molecular weight compounds, and those not bound to plasma proteins can cross into fetal circulation, potentially exerting teratogenic effects. Clinicians must therefore consider both maternal pharmacodynamics and fetal vulnerability when prescribing medications. The pathways and consequences of infections further illustrate this complexity during pregnancy, as shown in Diagram 6 (Brown *et al.*, 2023). Infections may reach the fetus via transplacental transmission, ascending infection from the genital tract, disruption of fetal membranes, or sexual transmission. Once pathogens breach these barriers, they can trigger systemic maternal responses such as sepsis, respiratory distress, and obstetric hemorrhage, which may culminate in maternal death. The fetal repercussions are equally severe, ranging from growth restriction and birth defects to neurodevelopmental disorders, sensory impairments, and fetal demise. These outcomes underscore the importance of early screening, vaccination, and infection control as part of a comprehensive risk assessment strategy.

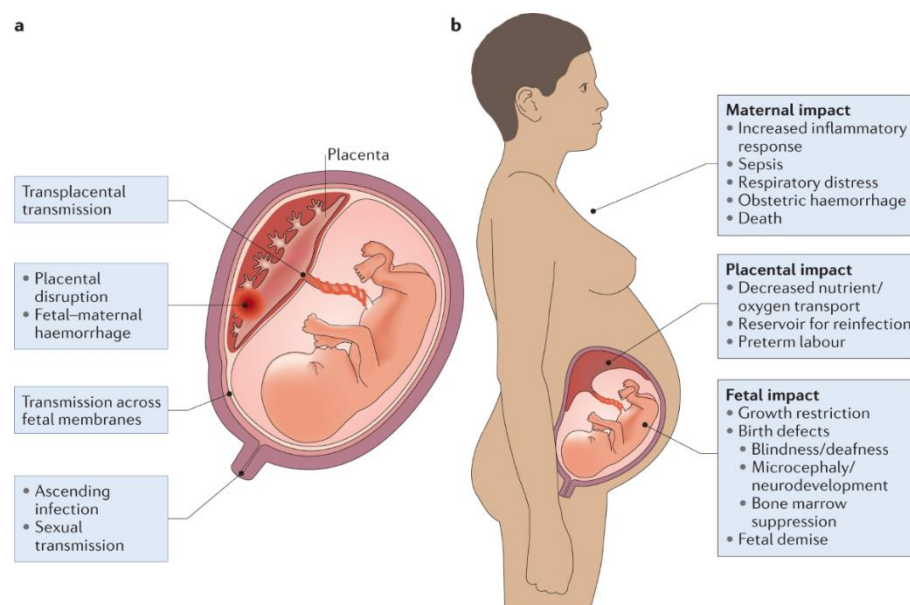


Figure 6. Maternal and fetal Impact of infection during pregnancy

Source: Brown *et al.* (2023).

Risk assessment and counseling are central to responsible prenatal pharmacotherapy. Women often face anxiety and uncertainty regarding medication use during pregnancy, especially when confronted with conflicting information or limited data. Effective counseling begins with a thorough evaluation of the patient's medical history, current medications, and pregnancy stage. Tools such as the FDA's Pregnancy and Lactation Labeling Rule (PLLR) provide structured guidance, replacing the former letter-based system with narrative summaries that detail risks, benefits, and clinical considerations (Food and Drug Administration, 2015). These resources

empower clinicians to communicate transparently, enabling shared decision-making that respects both medical necessity and patient autonomy. Counseling should also address the limitations of available data. Due to ethical constraints, randomized controlled trials in pregnant populations are rare, and most safety data derive from observational studies, registries, and post-marketing surveillance (Brown *et al.*, 2023). Clinicians must interpret these findings cautiously, acknowledging potential biases and gaps. For example, while some antidepressants have been linked to neonatal adaptation syndrome, the absolute risk remains low, and the consequences of untreated maternal depression may be more severe. Presenting such information in context helps patients make informed choices without undue fear or guilt.

Medication optimization and dose adjustment are critical strategies for minimizing teratogenic risk while maintaining therapeutic efficacy. Whenever possible, monotherapy is preferred over polytherapy, particularly in conditions like epilepsy or hypertension, where multiple agents may compound fetal risk. Selecting drugs with favorable safety profiles those with extensive human data and low teratogenic potential is essential. For instance, switching from valproic acid to lamotrigine in women with epilepsy may reduce the risk of neural tube defects, though seizure control must remain the priority (Tomson *et al.*, 2011). Dose adjustment is not merely a matter of reducing exposure; it involves recalibrating treatment to account for physiological changes and disease progression. In some cases, therapeutic drug monitoring (TDM) can guide dosing, especially for medications with narrow therapeutic windows. Adjustments should be dynamic, reflecting changes in maternal weight, renal function, and gestational age. Moreover, clinicians must remain vigilant for signs of subtherapeutic response or toxicity, adjusting regimens as needed to preserve maternal stability and fetal safety (Joseph and Abah, 2023).

Strategies for Minimizing Teratogenic Risks

One of the foundational principles in medication management during pregnancy is the preference for monotherapy over polytherapy. Monotherapy the use of a single drug to manage a condition is generally associated with a lower teratogenic risk compared to polytherapy, which involves multiple medications. This distinction is particularly relevant in the treatment of epilepsy, where studies have shown that the risk of congenital malformations increases significantly with the number of antiepileptic drugs (AEDs) used. For instance, valproic acid, when used alone, already poses a high risk for neural tube defects, but when combined with other anticonvulsants, the teratogenic burden escalates (Tomson *et al.*, 2011). The rationale behind favoring monotherapy lies in reducing cumulative exposure to teratogens and simplifying pharmacokinetic interactions, which can become unpredictable with multiple agents.

This principle is visually reinforced in Figure 7, which depicts seizure relapse rates over time in patients treated with monotherapy versus polytherapy. The chart shows that polytherapy consistently contributes a larger proportion of relapse rates across all follow-up intervals, with the highest relapse occurring in the first six months. In contrast, monotherapy demonstrates a more favorable trajectory, with lower relapse rates and a steadier decline over time. These findings underscore the dual advantage of monotherapy: enhanced seizure control and reduced fetal exposure to multiple teratogens. In clinical practice, especially during pregnancy, the goal is not merely to suppress symptoms but to do so with the least pharmacologic burden. When polytherapy is unavoidable such as in treatment-resistant psychiatric disorders or complex autoimmune

conditions clinicians must carefully select agents with the lowest known teratogenic profiles, use the minimum effective doses, and monitor maternal and fetal outcomes closely. This strategy aligns with broader efforts to minimize teratogenic risks while maintaining therapeutic efficacy (Schneiderman, 1999).

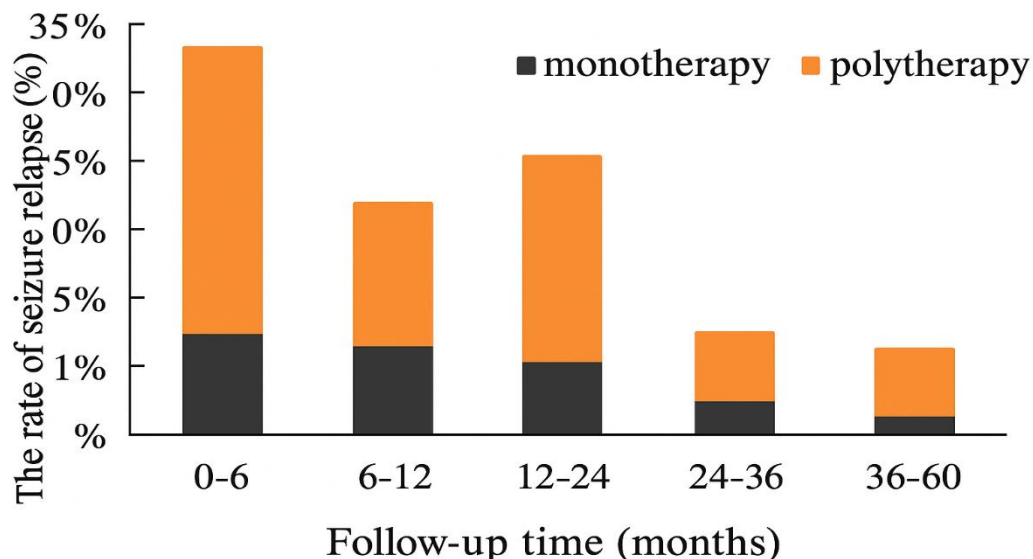


Figure 7. Seizure relapse rates over time: monotherapy vs. polytherapy in pregnancy-associated epilepsy management

Source: Schneiderman (1999)

Dose adjustment and therapeutic monitoring are equally vital in minimizing teratogenic effects. Pregnancy induces profound physiological changes that alter drug absorption, distribution, metabolism, and excretion. Increased plasma volume, enhanced renal clearance, and changes in hepatic enzyme activity can all influence drug levels, potentially rendering standard doses ineffective or toxic. For example, lamotrigine clearance increases significantly during pregnancy, necessitating dose escalation to maintain seizure control (Pennell *et al.*, 2008). Without appropriate adjustments, subtherapeutic levels may lead to breakthrough seizures, posing risks to both mother and fetus. Conversely, failure to reduce doses postpartum can result in toxicity. Therapeutic drug monitoring (TDM) offers a solution by enabling clinicians to track serum drug concentrations and tailor dosing accordingly. Cognitive behavioral therapy (CBT), for instance, has demonstrated efficacy in treating depression and anxiety during pregnancy, offering a drug-free option that avoids fetal exposure to psychotropic agents (O'Connor *et al.*, 2016). Similarly, physical therapy, acupuncture, and relaxation techniques may alleviate chronic pain or hypertension, reducing the need for analgesics or antihypertensives with known teratogenic potential. These alternatives are particularly valuable when pharmacologic options carry high fetal risks or when patients express a preference for non-medication-based approaches.

Lifestyle modifications further enhance maternal and fetal outcomes by addressing underlying risk factors. Nutritional interventions, such as folic acid supplementation, are well established in

preventing neural tube defects and should be initiated preconceptionally whenever possible. Regular physical activity, adequate sleep, and stress reduction techniques contribute to overall maternal health and may reduce the severity of conditions like gestational diabetes or hypertension, thereby lowering the need for pharmacologic intervention. Avoidance of known teratogens such as alcohol, tobacco, and illicit drugs is also paramount, as these substances can compound the effects of prescribed medications and independently contribute to adverse fetal outcomes. This emphasis on lifestyle is further illustrated in diagram 8 below, which depicts how maternal behaviors ranging from poor diet and alcohol use to sedentary habits can influence fetal development and long-term health. These exposures, shaped by genetic predisposition and pre-pregnancy metabolic status, contribute to in utero programming that predisposes the child to cardiometabolic diseases (Brown *et al.*, 2023). The mechanisms underlying this phenomenon include epigenetic modifications such as DNA methylation and histone changes, as well as disruptions in the gut microbiome, all of which can alter gene expression and metabolic regulation. Postnatally, these effects are compounded by environmental factors like diet and screen time, increasing the risk of

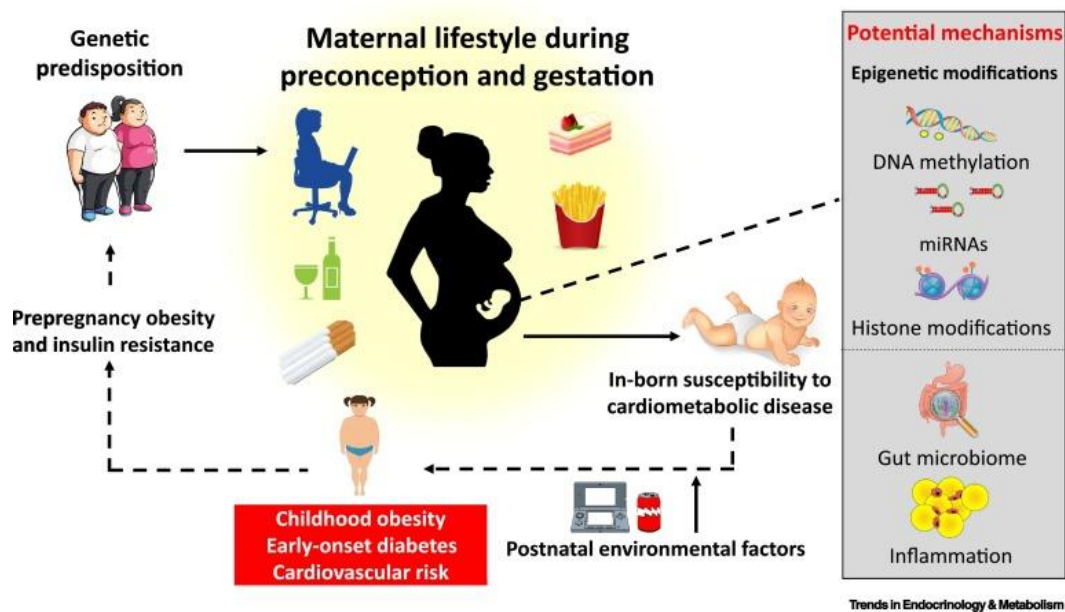


Figure 8. Lifestyle modifications in enhancing both maternal and fetal well-being

Source: Muglia *et al.* (2022)

Ultimately, the strategies for minimizing teratogenic risks during pregnancy must be individualized, evidence-based, and responsive to the dynamic physiological changes of gestation. Clinicians must engage in shared decision-making with patients, providing clear, contextualized information about the risks and benefits of treatment options. By prioritizing monotherapy when feasible, adjusting doses based on pharmacokinetic changes, and incorporating alternative therapies and lifestyle modifications, healthcare providers can optimize maternal health while safeguarding fetal development. This integrative approach not only reduces the incidence of congenital anomalies but also fosters a more holistic and patient-centered model of prenatal care.

Special Populations and Considerations

Managing medication use during pregnancy becomes particularly complex when addressing the needs of special populations. These include women with chronic medical conditions, those with mental health disorders, and other vulnerable groups such as adolescents, women with substance use disorders, or those with limited access to healthcare. Each subgroup presents unique challenges that require individualized, evidence-based approaches to ensure both maternal health and fetal safety.

Pregnant women with chronic conditions often rely on long-term pharmacotherapy to maintain physiological stability. Conditions such as diabetes, hypertension, epilepsy, and autoimmune diseases demand continuous management, as uncontrolled disease activity can pose significant risks to both mother and fetus. For example, poorly controlled diabetes increases the likelihood of congenital anomalies, macrosomia, and preterm birth, while untreated hypertension can lead to preeclampsia and placental abruption (American College of Obstetricians and Gynecologists, 2020). In these cases, medication cannot be withheld; instead, clinicians must carefully select agents with favorable safety profiles and adjust dosages to accommodate the altered pharmacokinetics of pregnancy. Insulin remains the gold standard for gestational diabetes, while methyldopa and labetalol are preferred for hypertension due to their established safety records. Regular monitoring, including blood pressure checks, glucose levels, and fetal growth assessments, is essential to ensure therapeutic efficacy and minimize adverse outcomes.

Other special populations also require tailored strategies for medication management during pregnancy. Adolescents, for instance, may face unique psychosocial pressures and are often less likely to receive consistent prenatal care, increasing the risk of medication nonadherence or misuse. Women with substance use disorders may be prescribed medications such as methadone or buprenorphine to manage opioid dependence, both of which have been shown to improve maternal and neonatal outcomes when used appropriately (Jones *et al.*, 2010). Additionally, women with limited access to healthcare due to socioeconomic barriers, geographic isolation, or systemic inequities may struggle to obtain necessary medications or monitoring. In such cases, public health interventions, community outreach, and telemedicine can play vital roles in bridging gaps and ensuring continuity of care.

Ultimately, managing medication use in special populations during pregnancy demands a holistic, patient-centered approach. It requires clinicians to weigh the risks and benefits of treatment within the context of each woman's medical history, psychosocial environment, and access to resources. Through interdisciplinary collaboration, ongoing monitoring, and compassionate counseling, healthcare providers can support optimal outcomes for both mother and child, even in the face of complex and multifaceted challenges.

Future Directions and Research Gaps

The comprehensive review on teratogenic effects of maternal medication use during pregnancy underscores a critical need for deeper scientific inquiry and systemic reform in how pharmacotherapy is approached during gestation. Despite the growing body of literature, significant research gaps persist, particularly in the realm of clinical trials, long-term fetal outcomes, and pharmacokinetic variability. One of the most pressing limitations is the historical exclusion of pregnant individuals from randomized controlled trials due to ethical and legal

concerns, which has resulted in a reliance on retrospective data, animal models, and post-marketing surveillance. These sources, while informative, often lack the granularity and reliability needed to guide nuanced clinical decisions (Andrade *et al.*, 2004). Furthermore, the teratogenic potential of many drugs remains poorly understood, especially beyond the first trimester, leaving clinicians to navigate a landscape of uncertainty when prescribing medications for chronic or acute conditions during pregnancy. Another major limitation lies in the scarcity of longitudinal studies that assess the developmental, cognitive, and behavioral outcomes of children exposed to medications in utero (Arowora *et al.*, 2024). Most teratogenic assessments focus on structural anomalies detectable at birth, while subtle neurodevelopmental effects may only emerge years later. Additionally, the pharmacokinetics of pregnancy marked by changes in plasma volume, renal clearance, and hepatic metabolism can significantly alter drug efficacy and toxicity, yet these physiological shifts are rarely accounted for in dosing guidelines (Mitchell *et al.*, 2011). The lack of stratified data across diverse populations, including adolescents, individuals with comorbidities, and those from low-resource settings, further compounds the issue, limiting the generalizability of existing findings and perpetuating health disparities.

Looking forward, future research must prioritize the development of ethically sound frameworks that allow for the inclusion of pregnant individuals in clinical trials. This includes adaptive trial designs, enhanced informed consent protocols, and robust safety monitoring systems. Investigating the molecular mechanisms of teratogenicity through genomics, proteomics, and metabolomics could yield predictive biomarkers that help stratify risk and personalize treatment plans (Arowora *et al.*, 2023). Moreover, the expansion of pregnancy-specific drug registries and international collaborative databases would facilitate real-time surveillance and data sharing, improving the evidence base for medication safety. Advanced pharmacokinetic modeling, such as physiologically based pharmacokinetic (PBPK) simulations, offers promising avenues for optimizing dosing regimens tailored to the dynamic physiology of pregnancy (Zhao *et al.*, 2012). Integrating artificial intelligence and machine learning to analyze large-scale health records could also accelerate the identification of teratogenic signals and inform clinical guidelines. Ultimately, bridging these research gaps requires a multidisciplinary approach that combines clinical expertise, technological innovation, and patient-centered ethics. By investing in rigorous, inclusive, and forward-thinking research, the medical community can move closer to ensuring that medication use during pregnancy is both safe and effective not only for the mother, but for the lifelong health of the child.

CONCLUSION

The teratogenic effects of maternal medication use during pregnancy represent a complex intersection of pharmacology, developmental biology, and clinical ethics. This comprehensive review has underscored the critical importance of gestational timing, drug selection, and maternal-fetal physiology in shaping outcomes. Evidence consistently shows that certain medications such as valproic acid, ACE inhibitors, and SSRIs carry heightened risks for congenital anomalies when exposure occurs during key developmental windows. Neural tube defects, cardiac malformations, and neurodevelopmental disorders have been linked to these agents, particularly when used in the first trimester or in combination with other drugs. The preference for monotherapy over polytherapy emerges as a cornerstone of safer prescribing, especially in epilepsy and psychiatric

care, where minimizing pharmacologic load can significantly reduce teratogenic risk without compromising maternal stability.

Clinical practice must evolve to reflect these findings through proactive risk assessment, individualized treatment plans, and multidisciplinary collaboration. The integration of pharmacokinetic knowledge recognizing how pregnancy alters drug absorption, metabolism, and clearance is essential for dose optimization. Moreover, lifestyle modifications such as nutritional support, physical activity, and avoidance of known teratogens amplify the protective effect of careful medication management. Infections, too, pose a dual threat to maternal and fetal health, and their transmission pathways and inflammatory consequences demand vigilant screening and timely intervention. For researchers, the implications are equally profound. There is a pressing need for longitudinal studies that track neurodevelopmental outcomes beyond birth, as well as molecular investigations into epigenetic mechanisms and fetal programming. The role of the placenta as both a barrier and a conduit for xenobiotics remains a fertile area for exploration, particularly in understanding differential drug transfer and fetal susceptibility.

Ultimately, informed decision-making is the linchpin of optimal pregnancy outcomes. Clinicians must balance maternal health needs with fetal safety, engaging patients in transparent discussions about risks, benefits, and alternatives. This review affirms that pregnancy is not a contraindication to treatment, but a call for precision, compassion, and evidence-based care. By aligning pharmacologic strategy with developmental insight and patient-centered values, we move closer to safeguarding two lives with every prescription.

CONFLICT OF INTEREST

The authors declared that there is no conflict of interest

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