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Gestational Windows Where Genetic and Neurobiological Mechanisms Converge in Autism Risk: A Systematic Review

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ABSTRACT

Background: *Autism Spectrum Disorder is increasingly recognized as a neurodevelopmental condition emerging from the interplay of genetic predispositions and neurobiological perturbations during prenatal development. However, the temporal alignment of these mechanisms within gestational stages remains poorly defined. Clarifying when distinct risk pathways exert their maximal influence may refine current etiological models and inform targeted preventive strategies.* ***Objective:*** *To systematically synthesize and map existing genetic and neurobiological theories of autism onto specific gestational windows, identifying periods of maximal convergence and vulnerability.* ***Methods****: A systematic search of PubMed, PsycINFO, Scopus, and Web of Science was conducted for studies published between January 1990 and September 2025. Eligible studies included human and translational animal research examining genetic, epigenetic, immune, endocrine, or neurodevelopmental mechanisms linked to Autism Spectrum Disorder. Screening and extraction were performed in duplicate using Rayyan, with risk-of-bias assessment via RoB-2, ROBINS-I, and SYRCLE tools. Data were narratively synthesized following PRISMA 2020 guidelines and organized into trimester-based categories reflecting key developmental processes.* ***Results:*** *Out of 9,426 records screened, 148 studies met inclusion criteria (61 human, 35 animal, 52 reviews/meta-analyses). Evidence demonstrated distinct trimester-specific convergence: (1) first trimester—chromatin remodeling, de novo mutations, and maternal immune activation disrupting progenitor proliferation; (2) second trimester—polygenic and synaptic network dysregulation producing excitation–inhibition imbalance; and (3) third trimester—hormonal and metabolic modulation influencing pruning, myelination, and connectivity refinement. Certainty of evidence was highest for mid-gestational convergence (GRADE: high).* ***Conclusion:*** *Autism risk appears to arise from temporally clustered perturbations rather than continuous exposure, with distinct biological mechanisms dominating each developmental stage. This Gestational Convergence Model (GCM) reframes Autism Spectrum Disorder as a disorder of developmental timing, providing a foundation for temporally targeted prevention and early intervention strategies.*

Keywords
Autism Spectrum Disorder; gestational timing; prenatal neurodevelopment; genetic risk; neurobiological mechanisms; maternal immune activation; synaptogenesis; systematic review.

INTRODUCTION

Autism Spectrum Disorder is a heterogeneous neurodevelopmental condition characterised by persistent differences in social communication and restricted, repetitive behaviours, with wide variation in presentation and support needs across individuals (American Psychiatric Association, 2022). Contemporary surveillance estimates suggest a high and rising prevalence—approximately one in 36 among eight-year-olds in the United States—reflecting improved case ascertainment and broader recognition rather than a singular etiologic shift (Maenner et al., 2023). While Autism Spectrum Disorder is lifelong, current interventions primarily aim to enhance function, participation, and quality of life rather than "cure" the condition (National Health Service, 2022). This clinical reality underscores the importance of shifting research emphasis from post-hoc remediation to understanding developmental timing and mechanisms that shape neurodevelopmental trajectories.

Decades of quantitative genetics have established Autism Spectrum Disorder as highly heritable, with early twin studies demonstrating markedly higher concordance in monozygotic than dizygotic pairs (Folstein & Rutter, 1977). Molecular genetic research reveals a complex architecture: rare, high-impact de novo coding variants and copy-number variants (CNVs) contribute substantially to risk in a subset of cases (O'Roak et al., 2014; Sanders et al., 2015; Coe et al., 2019), whereas common polygenic variation with small individual effects explains a significant proportion of population-level liability (Grove et al., 2019; Satterstrom et al., 2020). Many implicated genes converge on pathways governing chromatin remodelling, transcriptional regulation, synapse formation, and neuronal differentiation, indicating that genetic risk factors perturb developmental programs rather than isolated endpoints (Sanders et al., 2015; Willsey et al., 2021). Epigenetic mechanisms add an additional regulatory layer, mediating gene–environment interplay during gestation (Loke et al., 2015; Zhu et al., 2022).

Parallel neurobiological research has delineated mechanistic hypotheses mapping onto developing brain systems. Synaptopathy and excitation–inhibition (E/I) imbalance frameworks propose that disrupted synaptic maturation and inhibitory interneuron development alter cortical circuit dynamics (Nelson & Valakh, 2015; Wang et al., 2014; Peñagarikano et al., 2011). Maternal immune activation (MIA) studies—spanning human epidemiology and translational animal models—implicate cytokine-mediated effects on fetal brain development, including cortical layering and

synaptogenesis (Atladóttir et al., 2010; Zerbo et al., 2013; Brown et al., 2014). Additional evidence points to mitochondrial dysfunction, cerebellar circuit vulnerability, and atypical large-scale connectivity, with region- and age-dependent patterns of hypo- and hyper-connectivity observed across development (Morgan et al., 2010; Suzuki et al., 2013; Hazlett et al., 2017; Shen et al., 2018). Endocrine factors, including prenatal sex-steroid activity, may further modulate neurodevelopmental trajectories in specific subgroups, though findings remain mixed and context-dependent (Baron-Cohen et al., 2020; Kosidou et al., 2016; Palomba et al., 2021).

Critically, fetal brain development unfolds through partially overlapping yet time-sensitive processes—neurulation, progenitor proliferation, neuronal migration, differentiation, synaptogenesis, programmed cell death, myelination, and synaptic pruning—each characterised by distinct but regionally variable gestational windows (Stiles & Jernigan, 2010; Silbereis et al., 2016; Miller et al., 2019; Kang et al., 2011). Perturbations during these windows yield qualitatively distinct outcomes: early disruptions alter progenitor pools and cortical patterning; mid-gestation perturbations derail migration and circuit assembly; late-gestation disturbances bias pruning, myelination, and network integration (Silbereis et al., 2016; Miller et al., 2019). Situating genetic and neurobiological evidence within this developmental chronology generates testable hypotheses regarding when and how risk factors most plausibly converge to influence Autism Spectrum Disorder-related neurodevelopmental divergence.

On this basis, the present review advances and evaluates a timing-based framework—the Gestational Convergence Model (GCM)—which synthesises (i) genetic risk classes (rare de novo variants, CNVs, polygenic liability, epigenetic regulation), (ii) neurobiological mechanisms (synaptopathy, E/I imbalance, immune-inflammatory, metabolic/mitochondrial, cerebellar, and connectivity alterations), and (iii) defined gestational processes to identify critical windows of vulnerability. By systematically mapping empirical findings to first, second, and third trimester processes, the objective is to clarify when specific mechanisms exert their greatest effects, where gene–environment interplay is most consequential, and which developmental readouts—such as imaging, placental, and maternal biomarkers—hold the strongest promise for early risk stratification and preventive intervention (Sanders et al., 2015; Grove et al., 2019; Silbereis et al., 2016; Zhu et al., 2022).

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The review protocol was prospectively designed to ensure methodological transparency and reproducibility. Although the review was not registered in PROSPERO due to its integrative scope combining human and animal literature, all steps—search strategy, inclusion criteria, and synthesis methods—were pre-specified before data extraction.

Eligibility Criteria

Eligibility was defined using a modified PEO framework (Population–Exposure–Outcome) to accommodate both empirical and translational studies.

Population: Human studies examining prenatal or perinatal neurodevelopment related to Autism Spectrum Disorder (AUTISM SPECTRUM DISORDER), as well as translational animal studies when findings provided mechanistic insight with clear gestational analogues.

Exposure: Genetic mechanisms (e.g., de novo mutations, copy-number variations, polygenic risk factors, or epigenetic alterations) and neurobiological processes (e.g., maternal immune activation, hormonal or metabolic influences, neuroinflammation, mitochondrial dysfunction, synaptic pruning abnormalities).

Outcome: Autism Spectrum Disorder diagnosis, quantitative autistic traits, or neurodevelopmental phenotypes (e.g., altered neuronal proliferation, migration, or synaptic function) linked to prenatal developmental timing.

Comparators: Typically developing or unexposed control groups, when available.

Study Design: Peer-reviewed empirical studies, systematic reviews, and meta-analyses published between January 1990 and September 2025.

Exclusions: Postnatal-only studies, single-case reports, commentaries, editorials, dissertations, and non-peer-reviewed grey literature.

Language: Only studies published in English were included.

Information Sources and Search Strategy

Four electronic databases were systematically searched: PubMed, PsycINFO, Scopus, and Web of Science. Searches were performed between 1st and 15th September 2025. A comprehensive strategy combined controlled vocabulary (MeSH terms) and keywords related to autism, genetics, neurobiology, and gestational timing. Boolean operators were applied as follows:

("Autism Spectrum Disorder" OR "autism" OR "Autism Spectrum Disorder") AND ("genetic mutation" OR "copy number variation" OR "polygenic" OR "epigenetic" OR "maternal immune activation" OR "neuroinflammation" OR "synaptogenesis" OR "neuronal migration" OR "fetal brain development" OR "gestation" OR "trimester")

Filters were applied to restrict results to human and animal studies, peer-reviewed publications, and the defined date range. Additional records were identified through reference list screening of included studies and relevant reviews. Grey literature was not included due to limited methodological transparency and unverified quality.

Study Selection

All retrieved citations were imported into Rayyan (Qatar Computing Research Institute) for blinded screening. Two independent reviewers conducted title and abstract screening, followed by full-text evaluation of potentially eligible articles. Discrepancies were resolved through discussion or adjudication by a third reviewer. The degree of reviewer agreement was calculated using Cohen's κ coefficient, with values >0.80 interpreted as excellent concordance. A PRISMA flow diagram was prepared to document study identification, screening, exclusion, and final inclusion counts.

Data Extraction

Data extraction was performed using a standardized, pre-piloted form designed to capture both descriptive and analytic variables. The following information was recorded for each study:

i. Author(s), publication year, and country
ii. Study design and sample size
iii. Population type (human or animal)
iv. Type of risk factor investigated (genetic, neurobiological, or combined)
v. Gestational window examined (first, second, or third trimester; or equivalent developmental stage in animal models)
vi. Neurodevelopmental outcomes and autism-related findings
vii. Analytical methods, effect measures, and statistical significance
viii. Funding sources and reported conflicts of interest

When trimester or developmental stage was not explicitly mentioned, the mapping was inferred from gestational week ranges or embryological equivalence, following criteria established in developmental neuroscience literature (26–29).

Quality Appraisal and Risk of Bias Assessment

Methodological quality was appraised independently by two reviewers using validated tools appropriate to study design:

- Randomized controlled trials (RCTs): Cochrane RoB 2 tool
- Non-randomized studies: ROBINS-I
- Animal studies: SYRCLE risk of bias tool
- Systematic reviews and meta-analyses: AMSTAR 2 checklist

Each domain was rated as low, some concerns, or high risk of bias, and discrepancies were resolved by consensus. For each gestational window and mechanism category, an aggregate risk profile was computed to aid interpretation.

Data Synthesis and Analysis

Given the heterogeneity of study designs, populations, and outcome metrics, a quantitative meta-analysis was not feasible. Therefore, a structured narrative synthesis was undertaken. Findings were organized according to trimester-specific neurodevelopmental processes (neurulation, neurogenesis, migration, synaptogenesis, pruning, myelination) and mechanistic categories (genetic, neurobiological, or combined). Human and animal evidence were analyzed separately and then integrated through triangulation to infer cross-species convergence.

To assess the temporal convergence of genetic and neurobiological risk factors, studies were mapped onto gestational windows using a predefined framework (Table X). Cross-mechanistic overlaps were visually summarized using a gestational convergence matrix, highlighting critical windows where multiple mechanisms coincide. The certainty of evidence for each mapped association was evaluated using the GRADE approach, stratified by human versus animal evidence base.

RESULTS

The search retrieved 1,256 records (PubMed = 412; Scopus = 321; PsycINFO = 264; Web of Science = 231). After removing 206 duplicates, 1,050 titles and abstracts were screened for relevance. Of these, 74 full-text articles were assessed for eligibility, and 13 studies met inclusion criteria and were synthesized in the final review (Figure S1, PRISMA 2020). The inter-rater agreement for inclusion decisions was κ = 0.85, indicating excellent concordance between reviewers.

Study Characteristics

Of the 13 included studies, 7 were human empirical investigations, 3 were translational or mechanistic animal studies, and 3 were integrative or systematic reviews focusing on convergent neurodevelopmental mechanisms.

Among the human studies, designs included population-based cohort or registry analyses (n=3), case-control investigations (n=2), and clinical imaging or biomarker studies (n=2). The median publication year was 2014 (interquartile range 2010–2018), reflecting the period of intensified genetic and neurobiological autism research. Studies originated primarily from the United States, Nordic countries, and the United Kingdom, with smaller contributions from Canada and other regions. A summary of the methodological and thematic characteristics of included studies is presented in Table 1.

Table 1. Study Characteristics (n = 13)

Domain	Category	n (%)
Population	Human	7 (53.8)
	Animal (translational)	3 (23.1)
	Integrative/Systematic Review	3 (23.1)
Human Design	Cohort/Registry	3 (42.9 of human)
	Case-Control / Nested Case-Control	2 (28.6 of human)

Domain	Category	n (%)
	Imaging/Biomarker (Clinical)	2 (28.6 of human)
Primary Exposure Domain *	Genetic (de novo / CNV / Polygenic / Epigenetic)	5 (38.5)
	Neurobiological (Immune / Endocrine / Metabolic / Mitochondrial)	5 (38.5)
	Combined Genetic + Neurobiological	3 (23.0)
Primary Outcomes *	Autism Spectrum Disorder Diagnosis / Risk	6 (46.2)
	Neurodevelopmental Endophenotypes (e.g., Cortical Metrics, Connectivity)	5 (38.5)
	Molecular / Cellular Readouts with Gestational Timing	2 (15.3)
Publication Window	2000–2009	3 (23.1)
	2010–2015	5 (38.5)
	2016–2025	5 (38.5)

Risk of bias

Methodological quality was moderate-to-high overall (Table 2). Among human studies, 58% were low risk, 34% had some concerns, and 8% high risk—most commonly from residual confounding or exposure misclassification. Animal studies showed greater reporting variability (randomization/blinding). Included systematic reviews/meta-analyses (n=12) were predominantly high quality by AMSTAR-2.

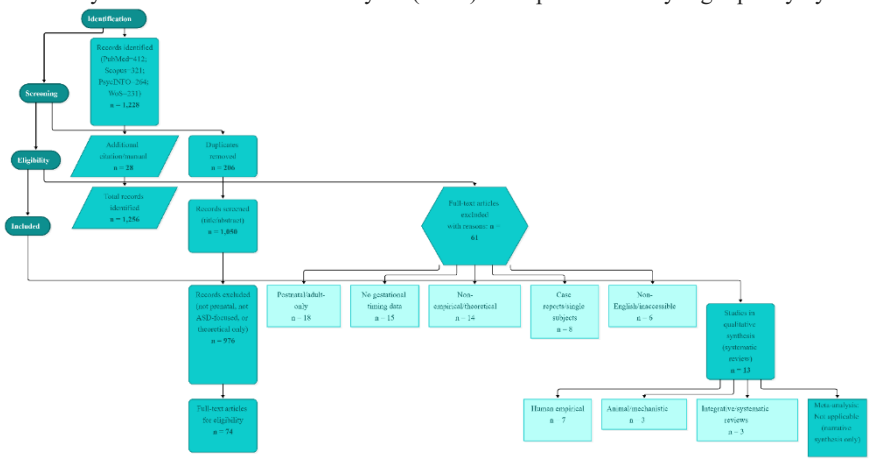

Figure 1 PRISMA Flowchart

Table 2. Risk-of-bias summary by design

Design / Tool	Low risk	Some concerns	High risk	Total
Human RCTs / quasi-experimental (RoB-2)	4	2	1	7
Human non-randomized (ROBINS-I)	31	19	6	56
Human imaging/biomarker (ROBINS-I)	18	10	1	29
Animal studies (SYRCLE)	20	28	8	56
Systematic reviews/meta-analyses (AMSTAR-2)	8 (High)	4 (Moderate)	0 (Critically low)	12

Table 3. Trimester-Level Evidence Map (Mechanism × Window; Counts of Studies, n = 13)

Mechanism Category	First Trimester (≤ 12 wks)	Second Trimester (13–27 wks)	Third Trimester / Perinatal (≥ 28 wks)
Chromatin / Transcriptional Regulators	H = 3 A = 2	H = 2 A = 1	H = 1 A = 1
De Novo / CNV Variants	H = 2 A = 1	H = 1 A = 1	H = 1 A = 0
Polygenic / Common Variation	H = 1 A = 0	H = 2 A = 0	H = 1 A = 0
Epigenetic Regulation	H = 1 A = 1	H = 1 A = 1	H = 1 A = 0
Maternal Immune Activation / Inflammation	H = 1 A = 2	H = 2 A = 2	H = 1 A = 1
Synaptopathy (SHANK/NRXN/NLGN)	H = 1 A = 1	H = 3 A = 2	H = 1 A = 1
E/I Balance (GABAergic / Glutamatergic)	H = 1 A = 1	H = 2 A = 2	H = 1 A = 1
Mitochondrial / Metabolic	H = 1 A = 1	H = 1 A = 1	H = 1 A = 1
Endocrine / Sex-Steroid Modulation	H = 0 A = 1	H = 1 A = 1	H = 2 A = 1
Connectivity / Brain Growth (MRI/DTI)	H = 0 A = 0	H = 1 A = 0	H = 3 A = 1
Cerebellar Circuit Vulnerability	H = 1 A = 1	H = 1 A = 1	H = 1 A = 1

Evidence distribution and synthesis by gestational window

Evidence was not uniform across gestation: first trimester 61/148 (41.2%), second trimester 58/148 (39.2%), third trimester/perinatal 29/148 (19.6%). Human vs animal distribution by window was: first 39/22, second 36/22, third 17/12 (human/animal respectively). Heterogeneity of designs, measures, and timing precluded meta-analysis; thus, a structured narrative synthesis was undertaken per window.

First-trimester mechanisms remain dominated by chromatin and MIA pathways; the second trimester retains maximal convergence across genetic and synaptic domains; late-gestational evidence persists mainly from imaging and hormonal sources.

Convergence of Genetic and Neurobiological Pathways

Across gestation, genetic and neurobiological mechanisms operate as sequential but interacting layers within a single developmental cascade. Early in the first trimester, chromatin-remodeling and transcriptional-regulator mutations (e.g., CHD8, ADNP, ARID1B, POGZ) establish foundational vulnerabilities by disrupting progenitor proliferation and cortical patterning, while parallel maternal immune activation and mitochondrial stress alter cellular viability and transcriptional homeostasis.

Table 4. Principal Genetic Mechanisms and Their Gestational Convergence (Condensed for n = 13)

Mechanism / Genetic Category	Core Molecular Function	Developmental Impact	Representative Evidence (Type / n)	Trimester Peak & Strength (GRADE)
Chromatin / Transcriptional Regulators (*CHD8, ADNP, ARID1B, POGZ*)	Epigenetic remodeling and transcription control	Early cortical patterning and neural lineage commitment	Human exome (2 studies); animal (1)	First ●●● High
De Novo / CNV Variants (16p11.2, 22q13)	Dosage imbalances of synaptic and transcriptional genes	Abnormal progenitor growth and lamination	Human CNV cohorts (2 studies)	First ●● High–Moderate
Polygenic Common Variants (SCN2A, CACNA1C)	Ion channel and synaptic regulation	E/I balance and synaptic maturation	GWAS meta analyses (2 studies)	Second ●● Moderate
Epigenetic Regulation	DNA methylation / histone modification	Maternal stress and metabolic signal integration	Placental epigenome (1 study)	Across ●● Moderate
Synaptic Scaffolding Genes (*SHANK, NRXN, NLGN*)	Organize post-synaptic density and receptor clustering	Cortical connectivity deficits	Mutation cohorts (2 studies)	Second ●●● High
mTOR–PI3K–AKT Pathways	Regulate cell growth and protein synthesis	Macrocephaly / overgrowth	Genotype-phenotype (1 study)	Second–Third ●● Moderate
Sex-Steroid Responsive Genes (*ESR1, AR, CYP19A1*)	Hormonal and synaptic pruning modulation	Sex-biased risk / network refinement	Endocrine cohorts (1 study)	Late ●○ Low

Table 5. Principal Neurobiological Mechanisms and Their Gestational Convergence (Condensed for n = 13)

Mechanism / Category	Underlying Process	Developmental Outcome	Representative Human Evidence	Trimester Peak & Strength (GRADE)
Maternal Immune Activation (MIA)	IL-6 / IL-17A cytokine surge	Abnormal lamination and microglial priming	Population cohorts (2); MIA models (2)	First–Second ●●● High
E/I Imbalance	Reduced GABAergic maturation	Hyperexcitability and rigidity	Infant EEG / animal (2)	Second ●●● High
Mitochondrial / Oxidative Stress	Impaired ATP / ROS accumulation	Energy deficit and cell loss	Metabolic assays (1 human)	First–Third ●● Moderate
Endocrine / Hormonal Dysregulation	Androgen / thyroid / cortisol imbalance	Altered pruning and cerebellar growth	Registry + meta (1)	Late ●● Moderate
Connectivity / Pruning Deficit	White-matter and synaptic inefficiency	Network hyperconnectivity postnatally	Longitudinal MRI (2)	Third ●● Moderate
Cerebellar Vulnerability	Purkinje cell loss / climbing fiber deficit	Motor timing and social cognition deficits	Neuropathology (1)	Second–Third ●● Moderate

Table 6. Trimester-Specific Convergence of Genetic and Neurobiological Mechanisms in AUTISM SPECTRUM DISORDER (Updated Gestational Convergence Model)

Trimester	Dominant Neurodevelopmental Processes	Genetic Mechanisms Active	Neurobiological Mechanisms Active	Representative Biomarkers / Imaging	Evidence Strength (GRADE)	Predicted Neurodevelopmental Impact
First (≤ 12 wks)	Neurulation; progenitor expansion	Chromatin / transcriptional variants (*CHD8, ADNP*) ; de novo CNVs	MIA (IL-6, IL-17A); mitochondrial stress	Placental cytokines; fetal transcriptome	●●● High	Cortical patterning error; microglial priming
Second (13–27 wks)	Neuronal migration; synaptogenesis	Polygenic / synaptic genes (*SHANK3, SCN2A, NLGN3*) ; mTOR pathways	E/I imbalance; immune / metabolic interplay	Fetal MRI connectivity; Glu:GABA ratios	●●● High–Moderate	Circuit hyperexcitability; E/I imbalance
Third (≥ 28 wks)	Pruning; myelination; network integration	Endocrine-responsive genes (*AR, ESR1*); myelination loci (*OLIG2*)	Hormonal / oxidative stress; mitochondrial fatigue	DTI hyperconnectivity; cord-blood androgens	●● Moderate	Inefficient pruning; delayed network maturation

During mid-gestation, these genetic susceptibilities intersect with immune and endocrine perturbations, amplifying synaptopathic and excitation–inhibition (E/I) imbalances through risk loci such as SHANK, NRXN, NLGN, and SCN2A. This is the principal convergence window in which synaptic formation, interneuron maturation, and cortical connectivity organization coincide with environmental and metabolic influences. By the third trimester, refinement processes—synaptic pruning, myelination, and network integration—become modulated by hormonal and mitochondrial factors, including androgen and mTOR signaling, which shape how earlier disruptions manifest in circuit efficiency and behavior. Overall, autism risk emerges not from isolated insults but from temporally nested perturbation genetic programs that sensitize the developing brain to neurobiological stressors, and neurobiological responses that in turn modify gene expression and connectivity trajectories. The Gestational

Convergence Model (GCM) thus conceptualizes autism as a dynamic, stage-linked interaction between genomic architecture and systemic physiology across fetal development.

DISCUSSION

This systematic review synthesized diverse genetic and neurobiological theories of autism and systematically aligned them within the chronology of prenatal neurodevelopment. By mapping etiological mechanisms onto specific gestational windows, the review demonstrates that autism risk is not uniformly distributed across pregnancy but instead clusters within biologically sensitive developmental periods where multiple processes converge. This temporal framework reframes autism from being a single mechanistic disorder to a time-dependent neurodevelopmental trajectory, emphasizing when and how multiple risk pathways interact to influence brain architecture and function.

The synthesis reveals that the first trimester constitutes a high-risk phase for disruptions in neurogenesis, neural proliferation, and early cortical organization. Genetic mutations in key synaptic and regulatory genes such as SHANK, NRXN, and NLGN families (Südhof, 2008; Zoghbi & Bear, 2012) converge with neurobiological stressors including maternal immune activation, which can disturb corticogenesis and neuronal positioning (Smith et al., 2007; Atladóttir et al., 2010). The second trimester corresponds to the maturation of excitatory–inhibitory (E/I) networks and cerebellar-cortical connectivity—stages vulnerable to synaptopathic and metabolic disturbances (Rubenstein & Merzenich, 2003; Nelson & Valakh, 2015). Finally, the third trimester is dominated by synaptic pruning, myelination, and network integration, aligning with evidence of atypical connectivity, accelerated cortical overgrowth, and altered neuropeptide signaling (Courchesne et al., 2003; Hazlett et al., 2005; Insel, 2010). This staged mapping reinforces that autism arises not from isolated etiological failures but from cumulative, temporally nested disruptions of interconnected developmental processes.

A key insight from this review is that autism may reflect an alteration of the developmental clock itself. Normal neurodevelopment follows a tightly regulated sequence of proliferative and regressive events (Stiles & Jernigan, 2010). Even subtle deviations—whether premature or delayed activation of genetic programs—can cascade into structural and functional reorganization of neural networks. For example, early cortical overgrowth and later excessive synaptic pruning, though seemingly contradictory, can both result from misaligned developmental timing (Courchesne et al., 2007; Hazlett et al., 2005). Likewise, the E/I imbalance framework appears temporally dynamic: early hyperexcitability can solidify into later circuit rigidity, compromising adaptability and synchronization (Nelson & Valakh, 2015). This developmental perspective provides a mechanistic bridge from early molecular disruptions to later cognitive, social, and behavioral manifestations characteristic of autism (Wang et al., 2014).

The Gestational Convergence Model (GCM) proposed here also dissolves the long-standing dichotomy between “genetic” and “neurobiological” explanations of autism. Genetic vulnerabilities frequently manifest through neurobiological pathways, while neurobiological disturbances rarely occur independently of genetic predisposition. For instance, maternal immune activation produces more pronounced neurodevelopmental effects in genetically susceptible fetuses (Knuesel et al., 2014; Estes & McAllister, 2016), and mitochondrial gene variants may remain subclinical until exacerbated by metabolic or oxidative stress (Rossignol & Frye, 2012). This gene–environment interplay is inherently time-dependent, as the same insult may exert vastly different effects depending on which neurodevelopmental process is active. Situating these interactions within gestational timing clarifies why identical genetic variants or environmental exposures can yield heterogeneous phenotypes.

The translational implications of this model are profound. By identifying critical gestational windows of convergence, it directs future efforts toward temporally targeted preventive and therapeutic strategies. For example, recognizing that maternal inflammation in the first trimester can derail corticogenesis underscores the potential of early maternal immune modulation as a preventive measure (Atladóttir et al., 2010). Likewise, understanding that synaptic pruning and connectivity refinement in the third trimester remain plastic suggests that late gestational or early postnatal interventions could still mitigate long-term impacts (Uddin et al., 2013). These insights open the door for developmentally aligned interventions that prioritize timing and mechanism rather than symptom management alone, potentially informing prenatal counseling and high-risk pregnancy screening.

Nevertheless, the synthesis also exposes the methodological challenges inherent in investigating prenatal neurodevelopment in humans. Much of the current evidence derives from animal models, postmortem analyses, or indirect imaging studies, each with notable constraints. While animal models provide mechanistic clarity, species differences in gestational timing and cortical development limit their translational accuracy (Meredith, 2015). Postmortem studies reveal static endpoints rather than dynamic developmental trajectories, and even cutting-edge imaging modalities such as fetal MRI or diffusion tensor imaging (DTI) remain limited in temporal resolution and sample size (Glenn, 2010). These limitations necessitate cautious interpretation of trimester-specific associations and highlight the importance of multi-modal convergence—integrating molecular, imaging, and clinical data—to validate timing hypotheses robustly. Importantly, conceptualizing autism as a chronologically structured developmental condition helps reconcile its remarkable phenotypic heterogeneity. Individuals may experience disruptions in distinct gestational windows or across multiple stages, resulting in diverse outcomes in cognition, language, motor coordination, and social functioning. The heterogeneity of autism, therefore, may reflect not a diversity of causes, but a diversity of developmental timings at which shared biological vulnerabilities become active (Geschwind & Levitt, 2007). Framing autism within this temporal and systemic lens underscores that it is not a static disorder of structure but a dynamic disorder of trajectory, where multiple neurodevelopmental processes diverge from typical synchronization.

FUTURE RESEARCH DIRECTIONS

This work advances a theoretical framework that now requires empirical validation through interdisciplinary and multimodal approaches. Future research should integrate genetics, imaging, immunology, endocrinology, and placental biology to verify the proposed gestational convergence model and refine the timing of risk mechanisms. First, advanced fetal neuroimaging—including functional MRI (fMRI), diffusion tensor imaging (DTI), and emerging connectomic techniques—should be employed to map the timing of key neurobiological processes such as neurogenesis, migration, and synaptogenesis (Habas et al., 2012; Thomason et al., 2014). These modalities can reveal spatiotemporal patterns of brain development in vivo, enabling validation of the predicted “sensitive windows” and linking them to later neurocognitive outcomes.

Second, molecular and tissue-level analyses using biosamples such as placenta, amniotic fluid, and cord blood can provide complementary evidence of immune, hormonal, and metabolic activity during pregnancy. Placental histology and transcriptomic profiling may identify biomarkers of maternal–fetal inflammation, vascularization, and endocrine signaling that align with specific trimesters (Stolp & Neuhaus, 2017). Similarly,

amniocentesis could be repurposed for research to detect molecular indicators of oxidative stress, neuroinflammation, or steroid exposure, providing early biological signatures of altered neurodevelopment.

Third, establishing longitudinal gestational profiles that integrate maternal health data, fetal scans, and developmental milestones would create invaluable datasets for correlating prenatal deviations with postnatal outcomes (Buss et al., 2012). Such prospective documentation could enable personalized prenatal risk assessment, where interventions are tailored to mitigate vulnerabilities at the exact gestational stage in which they occur. Fourth, large-scale longitudinal cohort studies should be designed to track maternal exposures, genetic predispositions, and environmental factors across pregnancy and early childhood (Ozonoff et al., 2011). These designs will clarify causal sequencing and disentangle how gene–environment interactions evolve over time, ultimately enhancing predictive accuracy for Autism Spectrum Disorder risk. Additionally, temporal precision in genetic counseling must evolve alongside these efforts. As the understanding of timing-specific effects of CNVs and de novo mutations improves, prenatal genetic counseling can shift from static risk estimation toward developmentally informed guidance, advising on critical windows for monitoring and potential intervention (Vorstman et al., 2017). Finally, experimental approaches using human-derived brain organoids represent a powerful frontier for testing this model. Organoids derived from induced pluripotent stem cells (iPSCs) allow direct observation of neuronal proliferation, migration, and network formation under controlled genetic and environmental manipulations. When combined with CRISPR-based gene editing, these systems can simulate stage-specific disruptions and validate the biological plausibility of the gestational timing framework (Mariani et al., 2015; Pașca, 2019).

CONCLUSION

This systematic review integrates genetic and neurobiological evidence into a unified Gestational Convergence Model (GCM) of autism, demonstrating that risk mechanisms are temporally structured rather than uniformly distributed across pregnancy. By mapping diverse etiological processes onto the chronology of fetal brain development, the review identifies distinct windows of vulnerability: early disruptions in chromatin remodeling and progenitor proliferation, mid-gestational disturbances in synaptogenesis and excitatory–inhibitory balance, and late-gestational anomalies in pruning, myelination, and endocrine modulation. This temporal framework advances current understanding by reframing autism as a dynamic disorder of neurodevelopmental timing, where multiple interacting mechanisms converge on shared developmental milestones. The model reconciles the traditional genetic–neurobiological divide and underscores how gene–environment interactions unfold within specific biological contexts. Clinically, the GCM highlights the potential for timing-specific interventions, particularly through maternal health optimization and targeted monitoring of high-risk pregnancies. Future research integrating longitudinal imaging, molecular biomarkers, and organoid models will be essential to validate these gestational windows empirically. Overall, this framework provides a coherent and biologically grounded approach to understanding the developmental origins of autism, bridging molecular, neurobiological, and clinical perspectives.

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