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AN ANALYSIS OF PSYCHOPHYSIOLOGICAL DEVELOPMENT IN CHILDREN BORN THROUGH IN VITRO FERTILIZATION HIGHLIGHTING COGNITIVE AND BEHAVIORAL CHARACTERISTICS

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SUMMARY

More than ten million infants have been conceived through in vitro fertilization (IVF), but uncertainties remain about whether methods used in assisted conception leave any trace of their influence on psychophysiological development in later life. This review presents findings from empirical and meta-analytic studies published between 2010 and 2025 about cognitive and behavioral features of children born through IVF and other assisted reproductive technologies. A narrative-synthesis method was used to examine peer-reviewed cohort studies, registry-based studies, systematic reviews, and meta-analyses about neuromotor, cognitive, behavioral, psychosocial, and epigenetic features of development from infancy to adolescence. The findings suggest that after adjusting for multiple pregnancies, prematurity, and low birthweight, cognitive trajectories of children conceived through IVF do not differ much from those of naturally conceived children, with only better performance of IVF children in language and inconsistent school achievements. Behavioral features, such as attention control and emotional-social functioning, are similar in both groups of children; however, several registry-based cohorts revealed slightly higher risks of attention deficit-hyperactivity disorders, and children conceived

via intracytoplasmic sperm injection show higher relative risks of intellectual disabilities and autism spectrum disorders than children conceived via conventional IVF. Epigenetic and imprinting mechanisms are considered plausible biological mediators for these differential risks, but at a low-risk level regardless of procedure type. The concept of determiner–mediator–outcome structure is put forth to provide an explanatory framework for biomedical, perinatal, and familial determiners. Pooled evidence (2010-2025) revealed equal cognitive and psychological performance in children born using assisted reproductive technology compared to children born naturally, with relative risks around 1 for intellectual disabilities (RR=1.01), autism spectrum disorders (RR=0.98), and behavioral disorders (RR=1.04), but greater risks of neurodevelopmental complications existed in children born via I. The integration of findings also highlights procedure-specificity, that is, fresh vs frozen embryo transfer and IVF vs ICSI, as the key analytic variable, which was overshadowed by previous undifferentiated comparisons. Implications include procedure-specific postnatal monitoring, parental counseling, and longitudinal follow-ups into the teenage years in order to understand better the academic and psychosocial development of these offspring.

Key words: *in vitro fertilization, assisted reproductive technology, cognitive development, behavioral development, child neurodevelopment, psychophysiological outcomes.*

INTRODUCTION

A sizeable number of couples who are of reproductive age suffer from infertility, and assisted reproduction technologies, mainly IVF and ICSI, have emerged as the main remedy in such cases. In fact, since the delivery of the first child conceived through IVF back in 1978, there have been more than ten million ART babies born around the world, and the issue of epigenetic programming has been a constant worry since the early days of ART [15]. There have been many studies on the physiological effects that these procedures exert on the babies in terms of neuromotor, cognitive and behavioral performance [2][4].

Although early cohort studies, including the first cross-sectional study of young adults born through IVF in the US, showed encouraging results concerning their physical and psychological well-being, allaying some initial fears about the technique [19], systematic reviews have shown a rather mixed picture: whereas cognitive performance among children conceived through conventional IVF was similar to that of naturally conceived children in the higher quality studies, there was inconsistency in the results concerning children conceived through ICSI; they varied between no differences and modestly reduced intelligence scores [1]. At the same time, another series of register studies has explored the association of fertility treatments with childhood diagnoses of mental disorders, finding that while the association existed, it could not be fully attributed to the treatment procedure, since parental infertility and perinatal complications were confounding factors [3][25][26].

One of the major methodological problems that has been consistent throughout all the articles analyzed in this review is that of the aggregation of different procedures into a single ART category, including conventional IVF, ICSI, fresh embryo transfer, and frozen embryo transfer. This makes a lot of sense clinically because the aggregated evidence shows that the risk of neurodevelopmental problems is not the same for each ART procedure. In fact, ICSI-conceived children have a higher risk of intellectual disability and autism than do conventional IVF-conceived children [5][6]. Narrative reviews also highlight the need for monitoring the health status in terms of neurodevelopment, heart disease, and metabolic disorders when new techniques become available [20].

Under these conditions, the current paper will attempt to examine the issue from a psychophysiological perspective by looking at the relationship between the two areas of literature, which should be treated not separately but rather interdependently and reflecting the common developmental architecture of the organism, which is influenced by the biomedicine, perinatal, and familial factors. Another example that illustrates the necessity to distinguish the impact of the subfertility condition from the fertility treatment itself on the outcomes of children can be found in the register-based research on the risk of autism-spectrum disorder after infertility and fertility treatment [12]. The rest of the paper will discuss the above-mentioned architecture in more detail.

Novel Contribution and Objectives

The central goal of this study is the identification, through systematic review of literature published from 2010 to 2025, of cognitive and behavioral traits related to IVF conception, and construction of an explanatory framework for these factors, in terms of biomedical, perinatal, and familial determinants, that can be used to inform tailored clinical monitoring. In comparison with earlier domain-specific literature reviews, this effort makes the following innovative contributions:

- Development of an integrated cognitive and behavioral framework for determination of the mediation process, as opposed to separate consideration of the two domains within independent literatures.
- Distinction, in the analysis, between procedural subtypes of IVF, namely traditional IVF compared to ICSI and fresh compared to frozen embryo transfer.
- Birth of a qualitative comparability index to allow cross-domain benchmarking of indicators related to cognition, motor skill, attention, social-emotional development, and autism spectrum disorder against a common metric.
- Extending the systematic review to include epigenetic and genomic imprinting mechanisms as candidates for biological mediators of procedural factors and downstream behavioral traits.
- Synthesis of risk gradient into a protocol for neonatal and psychoeducational monitoring that is applicable in regions that have growing assisted reproductive services.

Organization of the Paper

The rest of this report is organized as follows. Section II contextualizes the analysis in relation to existing literature in the fields of cognitive psychology, behavior, psychosocial science, and epigenetics and critically examines the methodologies used in two highly relevant previous meta-analyses. Section III lays out the framework on which this synthesis rests. Section IV describes the search and synthesis methodology, while Section V compares results among the various procedural and developmental categories. Section VI elaborates on the implications of the results for practice and further research. Section VII identifies the limitations of the synthesis, and Section VIII concludes the paper.

RELATED WORK

Cognitive Outcomes

Cognition has been studied more extensively than other developmental processes in assisted reproduction research. A review limited to investigations of cognitive outcomes measured from four years of age and onwards revealed no difference in cognitive composite scores between children conceived through conventional IVF and control subjects conceived naturally in higher-quality studies, while the findings on children conceived through ICSI procedures have been conflicting, ranging from no significant difference to a decrease of three points in the composite intelligence quotient [1]. A more recent analysis including twenty studies and more than twenty-three thousand IVF-conceived children suggested similar cognitive functioning, with early evidence that different aspects of cognitive function (language and motor abilities, specifically) might vary by procedure [24]. Restricting reviews to effects on neurodevelopmental outcomes after assisted reproduction indicates that psychomotor development, language development, and social functioning are similar in children born through assisted reproduction compared with children spontaneously conceived when perinatal factors are accounted for [20]. A large recent meta-analysis of the psychological effects including eighty-nine studies indicated similar intelligence and psychomotor development in ART and naturally conceived children with improved language abilities but poorer academic performance in ART-conceived children [18].

Behavioral, Attentional, and Autism-Spectrum Outcomes

Behavioral and psychiatric outcomes show a relatively heterogeneous pattern of evidence than do cognitive outcomes. In a meta-analysis of ten high-quality studies, the ART-conceived children as a homogeneous category were found to be at increased risk of cerebral palsy compared to naturally

conceived children, whereas no elevated risk of intellectual disability, autism-spectrum disorder or behavioral problems was detected [5]. Within the same analysis, when procedure type was separated into subgroups, the ICSI-conceived children were at a significantly higher risk of both intellectual disability and autism-spectrum disorder, but not of cerebral palsy, than those conceived by the conventional IVF method [5]. Also register-based cohort evidence corroborates the procedure-specificity finding: national case-control analysis from Finland found an elevated risk of autism-spectrum disorder among the IVF-conceived children [8]; similarly, a large US-based registry study found an association between the risk of autism-spectrum disorder in the ART-conceived children and treatment with ART as well as parental infertility, which was partially mitigated by adjusting for multiple gestations and birth factors [9]. In addition, a cohort of Swedish nationals indicated an increased risk of autism and intellectual disability in children who were conceived via ICSI using surgically aspirated sperm [7]. In respect of ADHD, the epidemiological evidence displays a similar pattern of partial attenuation when the effect of maternal infertility alone is considered: a population-based cohort study showed that ADHD risk was increased in children conceived by infertile women in general terms rather than through IVF or ICSI specifically [21]. Danish register-based studies similarly linked the fertility treatments, especially ovulation induction, with increased risk of childhood and adolescent mental disorders [3], while another register-based Danish study showed that the risk of mental disorders was increased in children conceived by infertile women irrespective of treatment received [4]. Register-based evidence on intellectual disability shows that ART conception is a small but significant risk factor even when the potential confounding effects have been controlled. Population-based follow-up information indicates a modest increase in the risk of autism spectrum disorder in children conceived through assisted reproduction techniques [10]. Modern cohort data from Australia, however, failed to detect any link between maternal ART use and mental disorder diagnosis among offspring when controlling for appropriate covariates, implying that results may be sensitive to differences in cohort composition, follow-up period, and method of adjustment [23]. On the other hand, a review on the association between ART use and increased autism risk showed that, while many individual studies have found increased risk of autism due to certain ART procedures, overall evidence is inconsistent and very study-specific [22].

Psychosocial and Family-Contextual Outcomes

On the whole, psychosocial adjustment of children born via medically assisted reproduction has turned out to be either as good or, more often, better when compared with their naturally conceived counterparts. As evidenced by one study conducted on a sample in the UK, children born via medically assisted reproduction demonstrated consistently better psychosocial adjustment than naturally conceived children at the ages ranging from three to fourteen years old; the reason behind this trend was largely attributed to the advantageous socioeconomic and demographic profile of couples undergoing fertility treatment [17]. The behavioral, social and emotional profiles of children conceived through IVF also revealed the presence of characteristic patterns of psychosocial adjustment that correlated well with various physical development markers, indicating the joint effect of conception method and overall family environment on the psychosocial adjustment of children conceived through medically assisted reproduction. These findings were supported by recent meta-analytical research demonstrating better psychosocial development of ART-conceived children based on maternal assessments, although other mental health-related indices remained comparable or slightly inferior to those of naturally conceived children [18].

Epigenetic and Genomic-Imprinting Mechanisms

There is, however, a separate body of literature that examines changes in the biological pathways of epigenetics and genomic imprinting as potential mechanisms linking ART procedures to resultant phenotypes. Studies investigating the occurrence of imprinting disorders in children born through ART have noted the higher rate of ART conception in such children, which has been associated with ART procedure exposure during sensitive windows for epigenetic reprogramming [11][13]. Mechanistic studies using animal models and induced pluripotent stem cells have additionally identified likely pathways through which ART procedures might lead to an epigenetic effect on imprinting, while stressing that the clinical risks of such effects remain very low compared to the relative risks that have

been noted in registry comparisons [14]. In broader studies on changes in genomic imprinting following ART, the presence of alterations in the methylation status of imprinted genes without the presence of alterations in the entire genome has been reported [15]. Molecular studies examining the mechanisms of the regulation of imprinted genes during gametogenesis and early embryonic development have suggested that it is the controlled ovarian stimulation and prolonged in vitro embryo culture that is the major concern from a mechanistic perspective [16].

Positioning of the Present Analysis Relative to Prior Reviews

Two particular methodologically important reviews need to be considered in detail since they provided the basis for the approach used in the current meta-analysis. The meta-analysis that pooled ten cohort and case-control studies performed the Newcastle-Ottawa quality assessment before combining, limited its scope to only seventeen full-texts selected out of more than fifteen hundred abstracts and distinguished between ICSI and conventional IVF and between frozen and fresh embryo transfer; such methodology provided the most obvious indication that neurodevelopmental risk is specifically associated with ICSI, rather than with ART treatment as a whole [5]. On the other hand, eighty-nine studies included in the meta-analysis of parents' and children's psychological well-being covered all three aspects simultaneously, namely cognitive, psychosocial, and functioning in families; it allowed establishing of a consistent positive psychosocial pattern that was not found in specific reviews of procedures focused on neurodevelopmental disorder diagnosis [18]. Combining the two approaches in terms of disaggregation and cross-domain integration, the current synthesis uses them both in a single determinant-mediator-outcome architecture while extending the scope to include genomic-imprinting mechanisms that were not accounted for in either of the two reviews.

CONCEPTUAL FRAMEWORK AND ANALYTICAL ARCHITECTURE

Outcomes for cognition and behavior linked to IVF conception are not due to one single exposure, but rather to a series of biomedical, perinatal and familial factors that operate on the same underlying neurodevelopmental substrate. Figure 1 represents this series as a five-step conceptual framework process, which starts with pre-conception and procedure-related variables, such as stimulation protocol, embryo culture conditions, and choice between IVF and ICSI, and ends up with the cognitive and behavioral/psychosocial domains of outcomes.

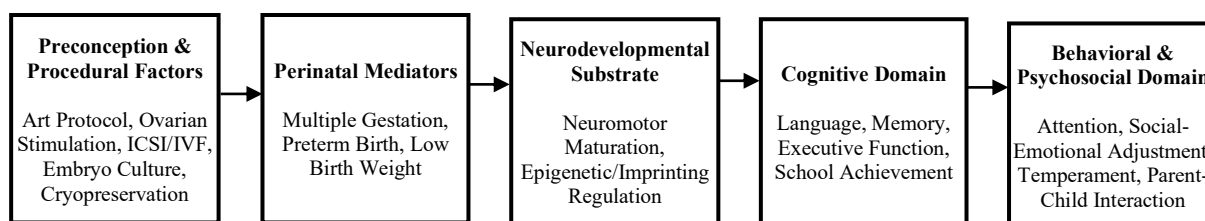


Figure 1. Conceptual flow of psychophysiological development in IVF-conceived children

This chain is presented in figure 2 by means of determinant-mediator-outcome framework, where determinants that include biomedical, perinatal, familial, and epigenetics are arranged within a mediating layer of neurodevelopmental process to produce cognitive, behavioral, and psychosocial outcomes.

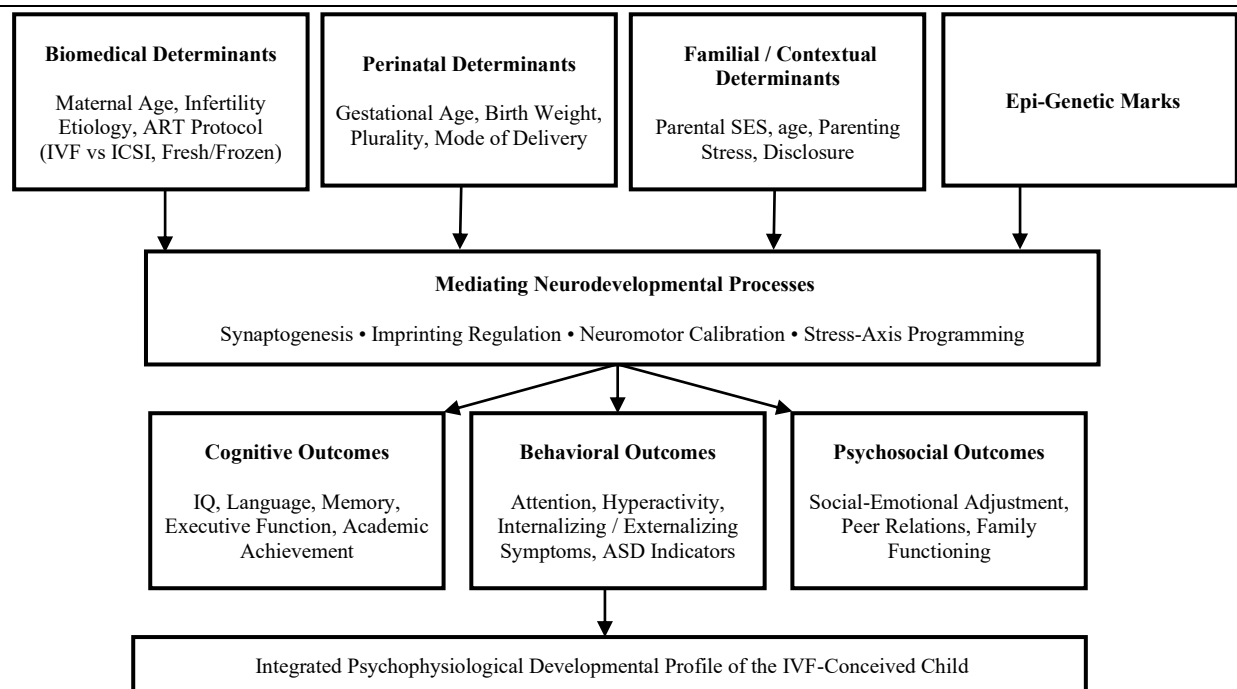


Figure 2. Determinant-mediator-outcome architecture applied in the present analysis

MATERIALS AND METHODS

This paper utilizes a design for narrative synthesis involving both qualitative thematic analysis and presentation of previously published pooled risk estimates. Such a design was chosen due to the fact that the primary studies used in this review have very heterogeneous outcomes, follow-ups, and definitions of control groups, which makes it impossible to conduct a new meta-analysis of quantitative nature.

Search and Identification Strategy

The literature was sourced via systematic searching in PubMed, Scopus, Web of Science, and Google Scholar within the period January 2010-2025. The search was done using keywords related to assisted reproductive techniques ("in vitro fertilization", "intracytoplasmic sperm injection", "assisted reproductive technique") and outcomes of development ("cognitive development", "neurodevelopment", "behavioral outcome", "autism spectrum disorder", "attention-deficit/hyperactivity disorder", "psychosocial adjustment", "genomic imprinting"). Additional articles from reference lists of systematic reviews and meta-analyses identified were also reviewed for relevant primary research.

Eligibility Criteria

Eligible studies included original cohort studies, register-based studies, case-control studies, or meta-analyses of studies that compared the IVF- or ICSI-conceived children to naturally conceived or other ART-conceived comparison groups in relation to at least one measure of cognitive functioning, behavior problems, psychosocial adaptation, or epigenetics after the neonatal period. Excluded from the literature search were studies limited to obstetrical and/or perinatal outcomes that lacked any developmental follow-up assessment. Non-English language and pre-2010 publications were also excluded, except for several seminal publications that were considered highly cited.

Domains of Assessment

Data acquisition was guided by four developmental constructs: general cognitive development and school performance; behavioral and attentional control, including autism spectrum and attention deficit hyperactivity disorder measures; psychosocial adjustment and family context; and epigenetics/genomic

imprinting status. Table 1 provides an overview of the tests and outcome measures used most often in each of the four areas reviewed.

Table 1. Developmental domains, representative indicators, and typical assessment approaches synthesized across the reviewed literature

Domain	Representative Indicators	Typical Assessment Approach
Cognitive	Composite IQ, language, memory, executive function, academic achievement	Standardized developmental and intelligence scales; national school-achievement records
Behavioral / Attentional	ADHD diagnosis, autism-spectrum diagnosis, hyperactivity, internalizing/externalizing symptoms	Register-based clinical diagnosis; parent- and teacher-report behavioral checklists
Psychosocial / Family	Peer relations, emotional adjustment, parent-child relationship quality	Parent- and self-report psychosocial questionnaires; family-functioning inventories
Epigenetic / Imprinting	Imprinting-syndrome diagnosis, locus-specific methylation status	Clinical genetic diagnosis; targeted and genome-wide methylation assays

Synthesis and Comparability Indexing

The pooled risk ratios as provided by the eligible meta-analyses were retrieved as being directly separated by the type of procedure. Simultaneously, a comparability index based on qualitative measures was created for six developmental domains, evaluating the overall trend described by the literature reviewed according to a five-point scale, where five is indicative of comparability between children born after IVF/ART procedures and those born naturally and one is indicative of the disadvantage of children born after IVF/ART procedures. This index is shown in figure 5.

COMPARATIVE ANALYSIS AND FINDINGS

Figure 3 shows risk ratios for ART-born versus naturally born children in relation to four different developmental endpoints. The risk ratio of cerebral palsy is increased in ART-born children, but ratios for intellectual disability, autism spectrum disorder, and behavior problems fall within the vicinity of one, suggesting overall comparability of the two populations, when the ART population is not categorized by procedure.

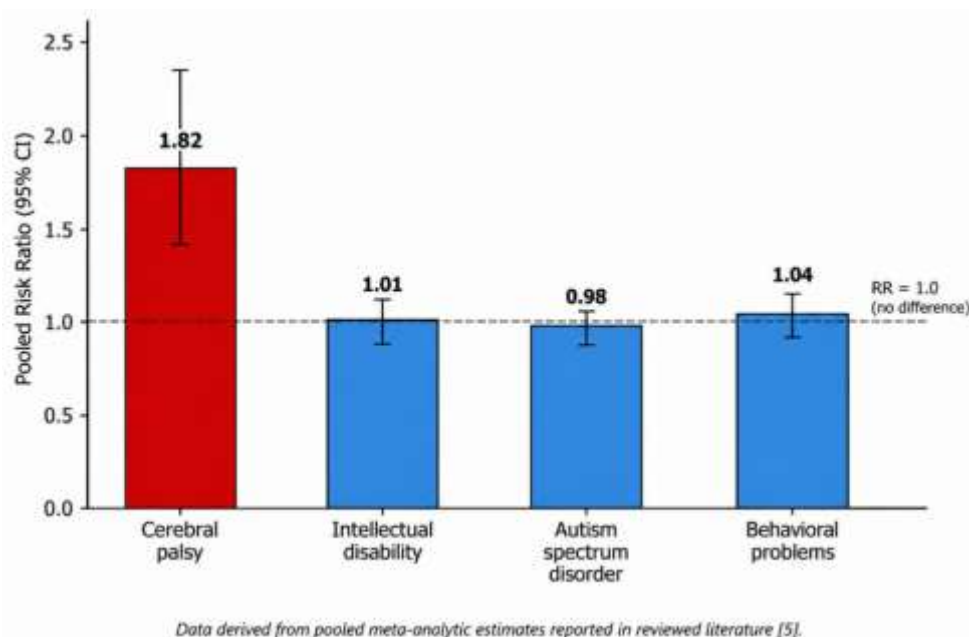


Figure 3. Pooled risk ratios for neurodevelopmental outcomes: ART-Conceived versus naturally conceived children

In figure 4, the same evidence base is disaggregated into procedural subtypes, showing the comparison between children conceived through ICSI and those conceived using conventional IVF. In contrast to figure 3, figure 4 shows a completely different pattern because the risk of cerebral palsy between the two groups does not show any difference; however, the risk ratio of intellectual disability and autism spectrum disorder climbs above one in the ICSI group.

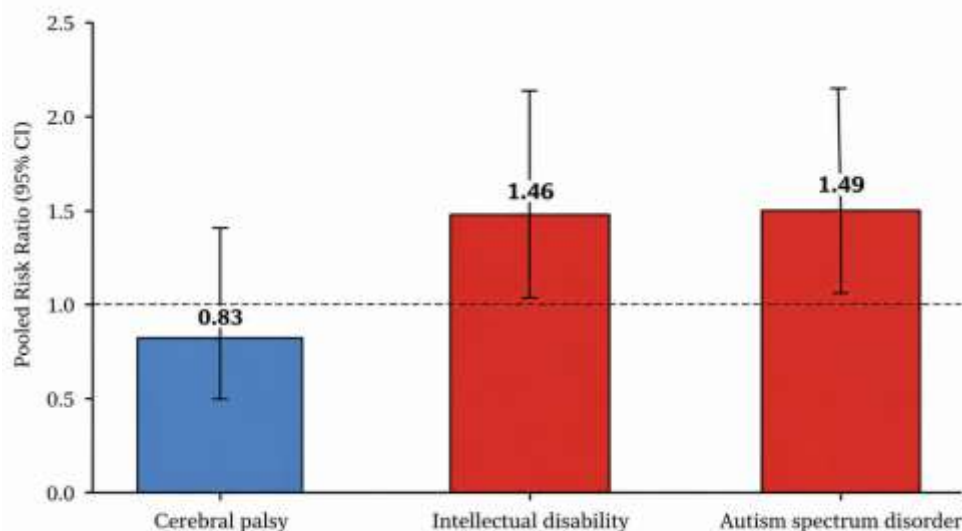


Figure 4. Neurodevelopmental risk ratios: ICSI-Conceived versus Conventional IVF-Conceived children

Figure 5 represents the qualitative comparability index for the narrative synthesis in Section 5 in relation to six domains. Cognition, language, and social-emotional development are all located in the upper part of the index, which reflects the general comparability found in most studies reviewed. The bottom part of the index represents attention and autism spectrum disorders (Table 2).

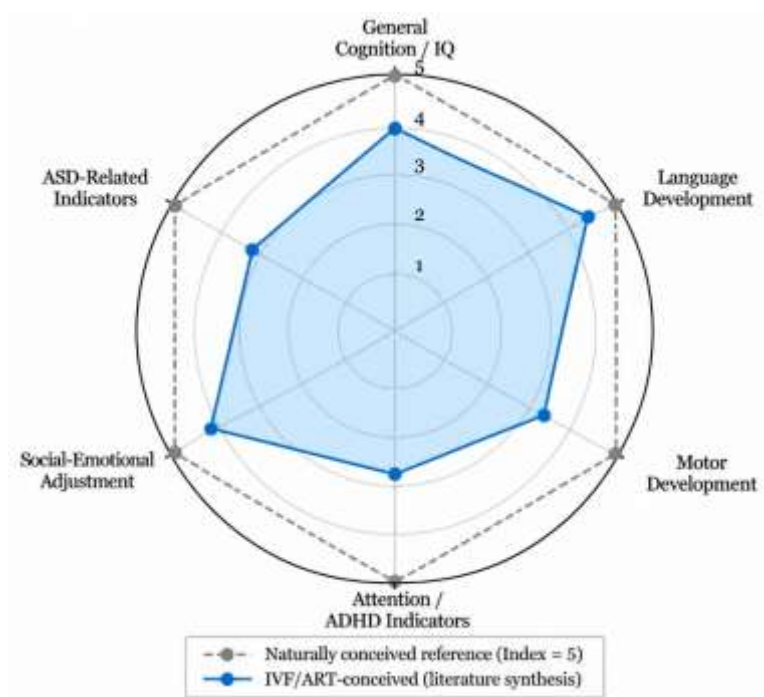


Figure 5. Literature-synthesis comparability index across psychophysiological domains

Summary of Comparative Patterns

Table 2. Summary of comparative patterns across developmental domains and their sensitivity to procedural subtype

Outcome Domain	Pattern Observed	Procedural Sensitivity
General cognition / IQ	Broadly comparable across groups	Low
Language development	Comparable to modestly favorable for ART-conceived children	Low
Motor development	Comparable, contingent on gestational-age adjustment	Moderate
Attention / ADHD	Modestly elevated in several register cohorts	Moderate
Autism-spectrum indicators	Elevated specifically within ICSI subgroup	High
Social-emotional adjustment	Comparable to favorable, explained by family advantage	Low

DISCUSSION

These implications of the comparison pattern found are very clear in terms of clinical counseling and subsequent planning. Aggregate comparisons between ART and natural conception, such as those described in figure 3, underestimate the developmental risks in the ICSI group while overestimating risks in the larger population of children conceived via conventional IVF. The findings replicate the arguments put forth in previous systematic reviews of particular fertility interventions, and meta-analysis stratified by procedures, as detailed in Section 4.5 [1] [5]. The results further support the argument in favor of procedure-specific counseling in relation to ART, especially considering the worldwide increase in ICSI use.

The relatively positive psychological and social profile of these offspring seems to be due more to their socio-economic and demographic status as patients of fertility treatment rather than a beneficial impact of the treatment per se, a difference which has particular significance for areas in which access to fertility treatment technology is increasing outside the traditionally narrow socio-economic range of earlier adopters. In light of increasing availability of assisted reproductive services within Central Asia's health care system, it is likely that there will be an increase in the socio-demographic diversity of the patient pool, possibly eliminating the very advantage that had balanced the risks in previous studies.

Attention and autism-spectrum disorders comprise the most uncertain element of the evidence base, with the Australian longitudinal cohort disagreeing with several European register-based cohorts owing to factors other than simple contradiction, namely varying periods of follow-up, covariates adjusted for, and the underlying population autism-spectrum disorder base rate [3] [4] [9] [10]. This would mean that attentional and autism-spectrum risk estimates need to be considered in a cohort-specific manner and not universally generalizable until longer follow-up period, procedure-stratified cohorts are obtained beyond the small group of evidence dominated by national registry data.

From a biological mechanism perspective, the evidence provided on epigenetic and genomic imprinting serves as a plausible connection between controlled ovarian stimulation and prolonged embryo culture and the increased relative risk found only within the ICSI subgroup without meaning that any absolute clinical risk for each child is large. The determinant-mediator-outcome framework proposed herein explicitly takes into account this aspect by including epigenetics as just one of several mediators and not a sole causal pathway, as done with the comprehensive long-term outcome literature [20].

LIMITATIONS

This synthesis depends upon pre-existing pooled estimates and narrative information instead of analyzing participant-level data, which limits the ability to model procedural, perinatal, and family risk factors precisely. Heterogeneity with respect to outcome measures, follow-up period, and comparison groups makes direct comparisons between the studies difficult, and the qualitative comparability scale

shown in figure 5 should therefore be seen as an illustrative tool rather than a new pooled statistic. Geographical diversity in the underlying evidence base is largely limited to Western European, North American, and East Asian registries, making the generalization to Central Asia difficult until regional longitudinal data becomes available.

CONCLUSION

Analysis was done on studies in cognition, behavior, psychosocial factors, and epigenetics published from 2010 to 2025 for children conceived using in vitro fertilization and other assisted reproductive technologies, categorizing the information according to a model of determinant-mediator-outcome structure, including biomedical, perinatal, and family determinates as well as subsequent outcomes of development. Pooled evidence (2010-2025) revealed equal cognitive and psychological performance in children born using assisted reproductive technology compared to children born naturally, with relative risks around 1 for intellectual disabilities (RR=1.01), autism spectrum disorders (RR=0.98), and behavioral disorders (RR=1.04), but greater risks of neurodevelopmental complications existed in children born via I. There is general equality between cognitive performance, language acquisition, and social-emotional development among those children conceived through in vitro fertilization and naturally conceived children when perinatal factors such as multiple gestation, preterm births, and low birth weights have been adequately controlled for, with the former being largely a result of the better social and economic status of those seeking treatment. However, there is a differential risk of neurobehavioral problems with the assisted reproductive technology methods, in that intracytoplasmic sperm injection but not in vitro fertilization carries an increased risk of intellectual disabilities and autism-spectrum disorders. The genomic imprinting and epigenetic processes provide a biologically sensible, although not yet entirely known, process that explains this risk gradient according to the particular procedure employed, and deserves further investigation, alongside the clinical follow-ups of course. The attention and autism-spectrum data are the least well-defined part of the evidence base, showing cohort-specific variability which implies that longitudinal and stratified by type of procedure follow-up research is necessary to make generalizations. In practice, this means that there should be different surveillance and parents' counseling practices, depending on the type of procedure used, and that it would be valuable to set up longitudinal procedure-stratified developmental cohorts in regions that see increased development of assisted reproduction services capabilities, such as Central Asian health care systems, in order to characterize the cognitive and behavioral outcomes of locally conceived children directly without making assumptions based on data collected in different geographical locations.

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