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ARTICLE

Association Between Maternal Autoantibody Levels and Neurodevelopmental Outcomes in Infants Born to Mothers With Rheumatic Disease

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Abstract

Aims/Background Maternal autoimmune conditions have been associated with adverse pregnancy outcomes and neonatal complications, with potential impacts on fetal neurodevelopment. However, the specific associations between maternal autoantibody levels and neurodevelopmental outcomes in the context of rheumatic diseases remain incompletely understood. Therefore, this study aimed to investigate the relationship between maternal autoantibody profiles and infant neurodevelopmental outcomes in a cohort of mothers with rheumatic diseases, and to evaluate their diagnostic value in predicting neurodevelopmental disorders.

Methods This retrospective case-control study included patients admitted for antenatal care with rheumatic conditions from January 2017 to June 2022. Participants were categorised into the normal neurodevelopment group (n = 404) and the neurodevelopmental disorder group (n = 111) based on infant neurodevelopmental outcomes. Maternal cytokines and hormone levels, as well as autoantibody levels, were measured and analysed. Statistical analyses, including correlation and multivariable logistic regression, were employed to evaluate associations between maternal biomarkers and infant neurodevelopmental outcomes.

Results Statistically significant differences were observed between the two groups in terms of birth length, maternal cytokine levels (interleukin-6 [IL-6], interleukin-10 [IL-10], interleukin-4 [IL-4]), hormone levels (progesterone, thyroxine), and maternal autoantibody levels (anti-Sjögren's-syndrome-related antigen A [anti-SSA], anti-Sjögren's-syndrome-related antigen B [anti-SSB], anti-double-stranded DNA [anti-dsDNA], anti-ribonucleoprotein [anti-RNP], and anti-Smith [anti-Sm] antibodies) ($p < 0.05$). Correlation analysis revealed significant associations between specific maternal autoantibodies and neurodevelopmental parameters, as well as a positive correlation between birth length and neurodevelopmental parameters ($p < 0.001$). The multiple regression model showed that maternal autoantibody levels had a strong diagnostic value for predicting infant neurodevelopment.

Conclusion This study provides compelling evidence supporting the relationship between maternal autoantibodies, cytokines, and hormone levels and neurodevelopmental outcomes in infants born to mothers with rheumatic disease.

Key words: rheumatic diseases; autoantibodies; neurodevelopmental disorders; pregnancy outcome; risk factors; infant

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Introduction

Rheumatic diseases encompass a diverse group of autoimmune disorders characterised by immune dysregulation and systemic inflammation, presenting unique

challenges for pregnant women and their offspring (Chighizola et al, 2023; Mo et al, 2022; Motta et al, 2020). Maternal autoimmune conditions have been associated with an increased risk of adverse pregnancy outcomes and neonatal complications (El Miedany and Palmer, 2021; Sangah et al, 2023). Of particular interest is the potential impact of maternal autoantibody levels on fetal neurodevelopment and the subsequent neurobehavioral outcomes in offspring (Dale and Brenton, 2016; He et al, 2022; Mohebalizadeh et al, 2024). Increasing evidence suggests that maternal autoantibodies and associated immune dysregulation may impact fetal brain development and contribute to neurodevelopmental abnormalities in infants born to mothers with autoimmune conditions (Han et al, 2021; Klein and Molad, 2021; McLellan et al, 2022). Within the spectrum of rheumatic diseases, maternal autoantibodies, cytokines, and hormonal imbalances may play a critical role in shaping the neurodevelopmental trajectories of offspring. However, the precise relationships between maternal autoantibody levels and neurodevelopmental outcomes in rheumatic disease remain incompletely understood.

The prevalence of rheumatic diseases during pregnancy varies, with estimates ranging from 0.2% to 1% of all pregnancies. Although rheumatic diseases encompass a broad range of conditions, including systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis, they share common features of immune system dysregulation and autoantibody production that may have implications for fetal and neonatal health (Barbhaiya and Bermas, 2013). Several studies have documented an elevated risk of adverse pregnancy outcomes, including preterm birth, intrauterine growth restriction, and neonatal complications, in pregnancies complicated by maternal rheumatic diseases (Jara et al, 2019; Singh et al, 2023). Additionally, emerging evidence suggests a potential association between maternal autoantibodies and adverse neurodevelopmental outcomes in offspring, highlighting the need for a comprehensive understanding of the complex interactions between maternal autoimmunity and fetal neurodevelopment (Han et al, 2021; Kwon et al, 2022; Merz et al, 2022).

In this context, the present study aimed to investigate the relationship between maternal autoantibody levels and neurodevelopmental outcomes in infants born to mothers with rheumatic disease. Understanding the complex interplay among maternal autoantibodies, cytokines, and hormonal profiles and their potential impact on fetal neurodevelopment is essential for informing the development of targeted interventions to optimise neurodevelopmental outcomes in this at-risk population. By elucidating these associations, this study contributes to the growing body of maternal-fetal medicine research and highlights the need for personalised approaches to mitigate the potential impact of maternal autoimmunity on fetal neurodevelopment.

Methods

Study Design

This study was approved by the Institutional Review Board and the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (Approval number:

2024ZSLYEC-249). Informed consent was waived for this retrospective study, as only de-identified patient data were utilised, posing no potential harm or impact on patient care. This exemption was granted in accordance with ethical and regulatory guidelines related to retrospective studies, and formal approval was received from the Institutional Review Board and the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University. This research was conducted as a retrospective case-control study. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and with the Declaration of Helsinki in 2013 and its later amendments or comparable ethical standards. Patients were selected from rheumatic disease antenatal admissions at our institution between January 2017 and June 2022. Based on the neurodevelopmental outcomes of their infants, participants were categorised into the normal neurodevelopment group (n = 404) and the neurodevelopmental disorder group (n = 111).

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Patients who met the diagnostic criteria for rheumatic disease (Haffejee, 1992); (2) Singleton pregnancies reaching full term with live births; (3) Maternal age between 20–40 years; (4) Normal mental and cognitive function; (5) Complete and accessible medical records.

Exclusion criteria: (1) Patients with multiple systemic comorbidities; (2) Patients with severe dysfunction of vital organs, such as the heart, liver, or lungs; (3) Patients with severe coagulation disorders; (4) Patients with twin or multiple pregnancies; (5) Patients with full-term infants with low birth weight or macrosomia; (6) Patients with conception via artificial insemination or *in vitro* fertilization; (7) Patients with history of neonatal resuscitation following birth asphyxia.

Grouping Method

Neurodevelopmental status of infants was assessed using a customised neurobehavioral development screening questionnaire, adapted from the five developmental domains outlined in the "Developmental Survey Questionnaire" and selected items from the "Bayley Scales of Infant Development". The questionnaire evaluated the following domains: Language development (e.g., ability to produce repetitive sounds like "dada" and "mama"), gross motor skills (e.g., standing with support), fine motor skills (e.g., pincer grasp of small objects), problem-solving abilities (e.g., releasing a toy voluntarily), and personal-social interactions (e.g., participation in ball-throwing games). Each domain included representative questions selected for their relevance to early infant neurodevelopment.

Three independent researchers conducted telephone follow-ups with the parents at 12 months postpartum to administer the questionnaire. Responses were scored as follows: "No" = 0 points, "Possibly" = 10 points, and "Yes" = 20 points, yielding a maximum score of 100. A cutoff score of <50 was used to indicate potential neurodevelopmental abnormalities, as suggested by McHenry et al (2021). Infants scoring ≥ 50 were categorised into the normal neurodevelopment group, while those scoring <50 were categorised into the neurodevelopmental disorder

group. This approach allowed for a focused assessment of neurodevelopmental outcomes relevant to maternal rheumatic disease.

Laboratory Tests

Patients' general clinical data were collected through a systematic review of medical records and included maternal age, gestational age at delivery, history of smoking and alcohol consumption, presence of hypertension, diabetes, or hyperlipidemia, rheumatic disease type, and infant birth length and weight.

Following an 8-hour overnight fast, 5 mL of venous blood was drawn from the antecubital vein of each patient the following morning. Blood samples were centrifuged at 3000 rpm for 5 minutes at room temperature. Levels of interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-10 (IL-10), tumour necrosis factor-α (TNF-α), interferon-gamma (IFN-γ), and plasma insulin were measured using Quantikine ELISA Kits (R&D Systems, Minneapolis, MN, USA; Catalog numbers: D4050, D6050, D1000B, DTA00D, DIF50, and DINS00, respectively). Anti-double-stranded DNA (anti-dsDNA) antibody levels were quantified using the EUROIMMUN Anti-dsDNA-NcX ELISA Kit (Euroimmun, Lübeck, Germany; Catalog number: EQ 6841-9601). Hormonal biomarkers, including estradiol (E2), progesterone (P), cortisol (COR), and thyroxine (T4) were quantified using chemiluminescent immunoassay with the ADVIA Centaur XP Immunoassay System (Siemens Healthcare Diagnostics, Erlangen, Germany; Reagent codes: 10647093, 10647095, 10647091, and 10647089). Levels of anti-Sjögren's-syndrome-related antigen A (anti-SSA), anti-Sjögren's-syndrome-related antigen B (anti-SSB), anti-ribonucleoprotein (anti-RNP), and anti-Smith (anti-Sm) antibodies were determined using the BioPlex 2200 ANA Screen Assay (Beckman Coulter, Brea, CA, USA; Kit code: B36652).

Statistical Methods

Statistical analyses were conducted using SPSS version 29.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages (n [%]). For categorical variables, chi-square tests were performed using the standard formula when the sample size was $\geq$40 and the theoretical frequency (T) was $\geq$5. When T was between 1 and 5, the chi-square test with continuity correction was used. For sample sizes $<$40 or T $<$1, Fisher's exact test was employed. The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed data were expressed as mean $\pm$ standard deviation and analysed using independent-sample *t*-tests with variance correction when necessary. Non-normally distributed data were presented as medians (25th percentile, 75th percentile) and analysed using the Wilcoxon rank-sum test. A two-sided *p*-value $<$ 0.05 was considered statistically significant.

Pearson correlation analysis was used to examine the relationships between maternal laboratory biomarkers, including cytokines, hormone levels, autoantibodies, and neurobehavioral development screening questionnaire scores, treated as continuous variables. The normality of questionnaire scores was confirmed using the Shapiro-Wilk test, validating the assumptions for Pearson correlation analysis. Variables that indicated statistically significant differences in both group compar-

Table 1. General and demographic characteristics of study participants.

Parameter	Normal neurodevelopment group (n = 404)	Neurodevelopmental disorder group (n = 111)	t/χ^2	*p*-value
Maternal age (years)	31.32 ± 3.14	30.89 ± 4.13	1.020	0.309
Gestational age (weeks)	38.54 ± 1.23	38.47 ± 1.58	0.456	0.649
Smoking history, n (%)	39 (9.65%)	13 (11.71%)	0.406	0.524
Drinking history, n (%)	35 (8.66%)	13 (11.71%)	0.957	0.328
Hypertension, n (%)	43 (10.64%)	9 (8.11%)	0.617	0.432
Diabetes, n (%)	38 (9.41%)	13 (11.71%)	0.519	0.471
Hyperlipidemia, n (%)	23 (5.69%)	9 (8.11%)	0.871	0.351
Rheumatology classification			0.410	0.938
Type I, n (%)	81 (20.05%)	22 (19.82%)		
Type II, n (%)	120 (29.70%)	32 (28.83%)		
Type III, n (%)	164 (40.59%)	44 (39.64%)		
Type IV, n (%)	39 (9.65%)	13 (11.71%)		
Birth length (cm)	50.03 ± 3.17	48.96 ± 3.16	3.166	0.002
Birth weight (kg)	3.21 ± 0.58	3.14 ± 0.65	0.992	0.322
Neurobehavioral development screening scores	95.67 ± 3.68	46.67 ± 2.11	131.722	<0.001

isons (difference analysis) and correlation analyses were included as covariates in a multivariate logistic regression model. This regression analysis was conducted to examine the independent contributions of maternal biomarkers to neurodevelopmental outcomes, defined by a questionnaire cutoff score (<50 indicating disorders; ≥50 indicating normal development). Covariates were selected based on their statistical significance ($p < 0.05$) and biological relevance to neurodevelopment.

Results

General Information and Demographic Characteristics

In our study investigating the association between maternal autoantibody levels and neurodevelopmental outcomes in infants born to mothers with rheumatic disease, no statistically significant differences were observed between the normal neurodevelopment group (n = 404) and the neurodevelopmental disorder group (n = 111) in terms of maternal age ($p = 0.309$), gestational age at delivery ($p = 0.649$), smoking history ($p = 0.524$), drinking history ($p = 0.328$), hypertension ($p = 0.432$), diabetes ($p = 0.471$), hyperlipidemia ($p = 0.351$), or rheumatic disease classification ($p = 0.938$). However, a statistically significant difference was observed in infant length ($p = 0.002$), while birth weight did not differ significantly between groups ($p = 0.322$). Infants in the neurodevelopmental disorder group exhibited significantly lower scores on the neurobehavioral development screening questionnaire compared to those in the normal neurodevelopment group ($p < 0.001$) (Table 1). These findings suggest a potential association between maternal autoantibody levels and infant birth length, highlighting the need for further research into the effects of maternal autoantibodies on fetal growth and neurodevelopment.

Table 2. Maternal cytokine levels in the normal neurodevelopment and neurodevelopmental disorder groups (pg/mL).

Parameter	Normal neurodevelopment group (n = 404)	Neurodevelopmental disorder group (n = 111)	*t*-value	*p*-value
IL-4	3.44 ± 0.84	3.66 ± 0.98	2.226	0.027
IL-6	8.53 ± 1.15	8.85 ± 1.35	2.267	0.025
IL-10	6.48 ± 0.63	6.68 ± 0.84	2.389	0.018
TNF-α	7.92 ± 1.85	8.22 ± 2.03	1.445	0.149
IFN-γ	5.96 ± 1.42	6.12 ± 1.65	0.939	0.349

Note: IL, interleukin; TNF, tumour necrosis factor; IFN, Interferon.

Table 3. Maternal hormone levels in the normal neurodevelopment and neurodevelopmental disorder groups (ng/mL).

Parameter	Normal neurodevelopment group (n = 404)	Neurodevelopmental disorder group (n = 111)	*t*-value	*p*-value
Progesterone	80.75 ± 10.26	84.34 ± 10.36	3.258	0.001
Thyroxine	10.13 ± 1.57	10.58 ± 1.24	3.196	0.002
Estradiol	120.13 ± 15.26	122.47 ± 18.25	1.233	0.219
Cortisol	160.36 ± 20.48	163.23 ± 22.37	1.281	0.201
Insulin	15.67 ± 3.68	16.18 ± 3.58	1.301	0.194

Maternal Cytokine Levels

In examining the relationship between maternal cytokine profiles and neurodevelopmental outcomes in infants born to mothers with rheumatic disease, we observed statistically significant differences in the levels of IL-6 ($p = 0.025$), IL-10 ($p = 0.018$), and IL-4 ($p = 0.027$) between the normal neurodevelopment group and the neurodevelopmental disorder group (Table 2). However, no statistically significant differences were found in TNF-α ($p = 0.149$) or IFN-γ ($p = 0.349$) levels. These findings suggest that specific cytokines may be associated with neurodevelopmental outcomes and underscore the need for further investigation into their role in the pathophysiology of neurodevelopmental disorders in this population.

Maternal Hormone Levels

Statistically significant differences were identified in progesterone ($p = 0.001$) and thyroxine ($p = 0.002$) levels between the normal neurodevelopment group and the neurodevelopmental disorder group (Table 3). However, no significant differences were observed in estradiol ($p = 0.219$), cortisol ($p = 0.201$), or insulin ($p = 0.194$) levels between the two groups. These findings underscore the potential influence of specific hormones, particularly progesterone and thyroxine, on neurodevelopmental outcomes in this population. The findings suggest the need for further investigation into the role of these hormones in fetal brain development and subsequent neurobehavioral performance.

Table 4. Maternal autoantibody levels in the normal neurodevelopment and neurodevelopmental disorder groups (U/mL).

Parameter	Normal neurodevelopment group (n = 404)	Neurodevelopmental disorder group (n = 111)	*t*-value	*p*-value
Anti-SSA	24.56 ± 7.21	27.32 ± 8.94	3.002	0.003
Anti-SSB	18.45 ± 5.67	20.17 ± 5.78	2.821	0.005
Anti-dsDNA	10.23 ± 3.45	11.35 ± 4.56	2.406	0.017
Anti-RNP	14.78 ± 4.56	15.95 ± 4.23	2.437	0.015
Anti-Sm	9.85 ± 2.98	10.67 ± 2.68	2.646	0.008

Note: SSA, Sjögren's-syndrome-related antigen A; SSB, Sjögren's-syndrome-related antigen B; dsDNA, double-stranded DNA; RNP, ribonucleoprotein; Sm, Smith.

Maternal Autoantibody Levels

In our investigation into the relationship between maternal autoantibody profiles and neurodevelopmental outcomes in infants born to mothers with rheumatic disease, statistically significant differences were observed between the normal neurodevelopment group and the neurodevelopmental disorder group in the levels of anti-SSA ($p = 0.003$), anti-SSB ($p = 0.005$), anti-dsDNA ($p = 0.017$), anti-RNP ($p = 0.015$), and anti-Sm ($p = 0.008$) (Table 4). These findings highlight the potential contribution of specific maternal autoantibodies to adverse neurodevelopmental outcomes, indicating a possible immunological mechanism affecting fetal neural development.

Correlation Analysis

In our investigation into the association between maternal autoantibody levels and neurodevelopmental outcomes in infants born to mothers with rheumatic disease, correlation analysis revealed significant associations between specific maternal biomarkers and neurodevelopmental scores, which reflect neurodevelopmental status (Fig. 1). Specifically, birth length demonstrated a significant positive correlation with neurodevelopmental scores, with a correlation coefficient of 0.524 ($p < 0.001$), indicating that shorter birth length is associated with lower neurodevelopmental scores and increased risks of neurodevelopmental disorders. Additionally, several maternal biomarkers exhibited significant negative correlations with neurodevelopmental scores, suggesting that elevated levels of these biomarkers are associated with poorer neurodevelopmental outcomes. These biomarkers include IL-6 ($r = –0.577$, $p < 0.001$), IL-10 ($r = –0.719$, $p < 0.001$), IL-4 ($r = –0.417$, $p < 0.001$), progesterone ($r = –0.687$, $p < 0.001$), and thyroxine ($r = –0.386$, $p < 0.001$). Similarly, multiple maternal autoantibodies were significantly negatively correlated with neurodevelopmental scores: anti-SSA ($r = –0.626$, $p < 0.001$), anti-SSB ($r = –0.619$, $p < 0.001$), anti-dsDNA ($r = –0.375$, $p < 0.001$), anti-RNP ($r = –0.504$, $p < 0.001$), and anti-Sm ($r = –0.420$, $p < 0.001$). All correlations reported were statistically significant, highlighting the potential influence of maternal immune and endocrine factors on early neurodevelopmental trajectories in offspring.

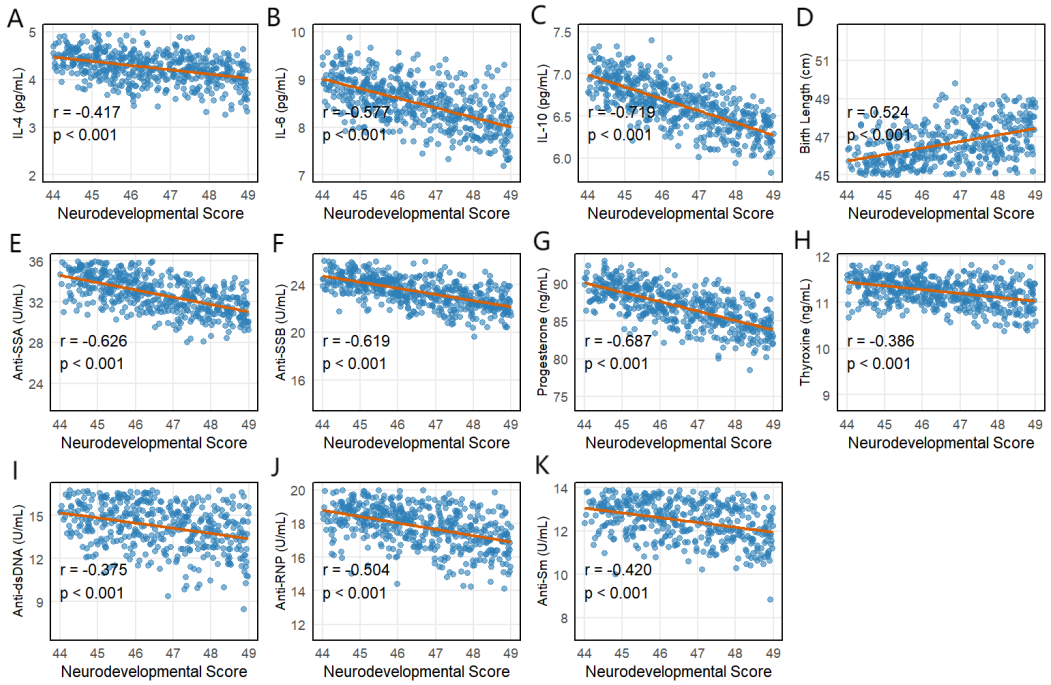

Fig. 1. Correlation analysis of maternal autoantibody levels with neurodevelopmental scores in offspring of rheumatic mothers. Scatter plots show the correlation between maternal biomarker levels and neurodevelopmental scores in infants. (A) IL-4. (B) IL-6. (C) IL-10. (D) Birth Length. (E) Anti-SSA. (F) Anti-SSB. (G) Progesterone. (H) Thyroxine. (I) Anti-dsDNA. (J) Anti-RNP. (K) Anti-Sm.

Multifactor Logistic Regression Analysis

In further analysis of the relationship between maternal autoantibody levels and neurodevelopmental outcomes in infants born to mothers with rheumatic disease, multivariate logistic regression revealed a notable finding (Table 5). The model demonstrated that maternal autoantibody levels had a significant diagnostic value for predicting infant neurodevelopmental status. These results suggest that specific maternal immunological markers (including autoantibodies, cytokines, and hormones) may serve as independent predictors of neurodevelopmental risk, contributing valuable insights into early identification and potential intervention strategies for high-risk infants.

Discussion

The relationship between maternal autoantibody levels and neurodevelopmental outcomes in infants born to mothers with rheumatic disease remains a significant area of interest in maternal-fetal medicine (Andreoli et al, 2023; Götestam Skorpen et al, 2016; Lubrano et al, 2024). Our retrospective case-control study aimed to investigate potential associations between maternal cytokines, hormones, and autoantibody levels and neurodevelopmental outcomes in infants born to mothers with rheumatic disease. By analysing a comprehensive range of maternal and neonatal parameters, we elucidated the impact of maternal autoantibodies on fetal neurodevelopment.

Table 5. Multivariate logistic regression analysis of risk factors associated with neurodevelopmental disorders.

Parameter	Coefficient (β)	Standard error	Wald statistic	*p*-value	Odds ratio (OR)	95% CI lower	95% CI upper
Birth length (cm)	–0.133	0.038	–3.522	<0.001	0.875	0.813	0.943
IL-6	0.239	0.100	2.381	0.017	1.270	1.043	1.545
IL-10	0.423	0.172	2.460	0.014	1.526	1.090	2.138
IL-4	0.314	0.140	2.247	0.025	1.369	1.041	1.800
Progesterone	0.040	0.012	3.469	<0.001	1.041	1.018	1.065
Thyroxine	0.211	0.083	2.526	0.012	1.235	1.048	1.454
Anti-SSA	0.049	0.015	3.191	0.001	1.050	1.019	1.082
Anti-SSB	0.059	0.021	2.809	0.005	1.061	1.018	1.105
Anti-dsDNA	0.081	0.032	2.570	0.010	1.084	1.019	1.154
Anti-RNP	0.055	0.027	2.015	0.044	1.057	1.002	1.115
Anti-Sm	0.108	0.041	2.664	0.008	1.114	1.029	1.206

A key finding of our study was the observed association between maternal autoantibody levels and fetal growth parameters, particularly birth length. This finding suggests a potential influence of maternal autoantibodies on fetal growth, which may, in turn, affect neurodevelopmental outcomes in this population. Notably, we identified statistically significant differences in the levels of anti-SSA, anti-SSB, anti-dsDNA, anti-RNP, and anti-Sm autoantibodies between the normal neurodevelopment group and the neurodevelopmental disorder group. These results suggest a potential link between elevated maternal autoantibody levels and adverse neurodevelopmental outcomes in offspring. This observation aligns with previous studies (Romanowska-Próchnicka et al, 2021; Soh and Nelson-Piercy, 2017), which have proposed that maternal autoantibodies, especially anti-SSA and anti-SSB antibodies, may contribute to the pathogenesis of neurodevelopmental disorders in infants born to mothers with autoimmune diseases.

Maternal autoantibodies and pro-inflammatory cytokines may promote neuroinflammation in the developing fetal brain (Andreoli et al, 2019a; Reis et al, 2024). The presence of specific maternal autoantibodies, such as anti-SSA and anti-SSB, has been associated with an increased risk of neurodevelopmental disorders in offspring, potentially mediated by autoantibody-induced neuroinflammation. Similarly, elevated levels of pro-inflammatory cytokines, including IL-6, have been linked to adverse neurodevelopmental outcomes, highlighting the role of neuroinflammation in fetal brain development and subsequent neurobehavioral outcomes (Marder and Johnson, 2020).

Furthermore, the observed correlations between maternal autoantibody levels and neurodevelopmental outcomes support a potential relationship between these immunological factors and fetal brain development. Notably, birth length demonstrated a positive correlation with neurodevelopmental scores, suggesting that better neurodevelopmental outcomes are associated with longer birth length, possibly reflecting more favourable intrauterine growth in the context of maternal autoim-

munity. Importantly, elevated maternal autoantibody levels, including anti-SSA (r = –0.42), anti-SSB (r = –0.57), anti-dsDNA (r = –0.56), anti-RNP (r = –0.42), and anti-Sm (r = –0.52), were significantly associated with lower neurodevelopmental scores, highlighting their potential adverse impact on infant neurodevelopment. These findings underscore the need for further investigation into the mechanistic pathways by which maternal autoantibodies and immunological factors influence fetal neurodevelopment. Future research should aim to identify the biological mechanisms involved and explore potential preventative or therapeutic interventions to mitigate adverse outcomes.

Moreover, the correlation coefficients (r values) observed in our study, while statistically significant, are relatively low, indicating a weak yet consistent association between maternal autoantibody levels and neurodevelopmental outcomes. In the context of complex biological systems such as fetal neurodevelopment, it is essential to recognise that multiple interacting factors may contribute to the observed outcomes. Even modest correlations can be meaningful when interpreted within this broader physiological framework. For instance, studies by Havdahl et al (2022) and Ellul et al (2022) have also reported modest correlations between maternal factors and offspring neurodevelopment, yet these findings have been pivotal in advancing our understanding of potential early risk markers.

In addition to maternal autoantibody levels, our study evaluated maternal cytokine and hormone profiles in relation to neurodevelopmental outcomes in infants born to mothers with rheumatic disease. We observed significant differences in the levels of IL-6, IL-10, and IL-4 between the normal neurodevelopment group and the neurodevelopmental disorder group, suggesting potential associations between these cytokines and adverse neurodevelopmental outcomes. These findings align with existing literature (Castro-Gutierrez et al, 2021; Märker-Hermann and Fischer-Betz, 2010), highlighting the role of pro-inflammatory cytokines in mediating neurodevelopmental abnormalities in offspring of mothers with autoimmune conditions. Maternal autoantibodies and altered cytokine profiles can impair placental function and fetal nutrient transport, thereby impacting fetal neurodevelopment. Placental dysfunction may lead to intrauterine growth restriction, altered nutrient availability, and compromised oxygen delivery to the developing fetal brain, all of which can have long-term effects on neurodevelopmental trajectories (Ganhão et al, 2021). Similarly, our study identified significant differences in progesterone and thyroxine levels between the two study groups, implicating these hormones in the modulation of fetal neurodevelopment.

Notably, the observed correlations between maternal hormone levels and neurodevelopmental outcomes further support the potential role of the maternal hormonal milieu in shaping fetal brain development and subsequent neurobehavioral outcomes. Hormones such as progesterone and thyroxine play critical roles in fetal brain maturation and function (Andreoli et al, 2019b). Dysregulation of these hormone levels within the maternal-fetal environment may disrupt normal neurodevelopmental processes, potentially influencing neuronal migration, differentiation, and synaptic connectivity in the developing fetal brain (Tian et al, 2023).

The complex interplay between maternal autoantibodies, cytokines, and hormones in the context of fetal neurodevelopment underscores the multifactorial nature of this relationship. It is increasingly recognised that maternal immune dysregulation, characterised by autoantibody production and cytokine imbalance, may influence fetal neurodevelopment through various mechanisms, including neuroinflammation, oxidative stress, and altered placental function (Østensen et al, 2012; Shao and Chen, 2024; Soh and Nelson-Piercy, 2015). Moreover, the potential role of hormones such as progesterone and thyroxine in modulating neurodevelopmental processes warrants further investigation to clarify their specific contributions to fetal brain maturation and function.

Notably, our study has several implications for clinical practice and future research in maternal-fetal medicine. The identification of specific maternal biomarkers, including autoantibodies, cytokines, and hormones, as potential predictors of adverse neurodevelopmental outcomes in infants born to mothers with rheumatic disease highlights the need for early risk stratification and targeted interventions to optimise neurodevelopmental trajectories in this vulnerable population.

While our study links maternal autoantibodies, cytokines, and hormone levels with neurodevelopmental outcomes in infants of mothers with rheumatic disease, it is not without limitations. First, we did not evaluate paternal immune and endocrine factors, which may also influence fetal neurodevelopment. Future studies should incorporate both maternal and paternal contributions. Second, the absence of a healthy control group limits the interpretation of the specific effects of maternal rheumatic disease on fetal neurodevelopment, including such a group would enhance the clarity of these associations. Third, although we did not directly measure cytokine and hormone levels in infants, the differences observed in maternal profiles suggest potential fetal effects. Future studies should include direct assessments of infant biomarkers to confirm these associations. Lastly, we did not examine maternal mental and cognitive status, which might indirectly influence fetal neurodevelopment. Future research should investigate these indirect influences. In summary, while our findings provide valuable insights, additional studies are needed to address these gaps and achieve a more comprehensive understanding of the mechanisms underlying fetal neurodevelopment.

Conclusion

In conclusion, our study provides compelling evidence of an association between maternal autoantibodies, cytokines, and hormone levels and neurodevelopmental outcomes in infants born to mothers with rheumatic disease. The observed associations between maternal biomarkers and fetal neurodevelopment underscore the complex interplay of maternal immune and endocrine factors in shaping the neurodevelopmental trajectories of offspring. These findings hold significant implications for identifying at-risk pregnancies and developing targeted interventions to optimise neurodevelopmental outcomes in this high-risk population. Future research efforts should aim to elucidate the underlying pathophysiological mechanisms of these associations and to design personalised strategies for managing preg-

nant women with rheumatic disease, thereby mitigating the potential impact of maternal autoimmunity on fetal neurodevelopment.

Key Points

- Elevated levels of IL-4, IL-6, and IL-10 were significantly associated with neurodevelopmental disorders in infants born to mothers with rheumatic disease.
- Higher levels of progesterone and thyroxine showed significant correlations with neurodevelopmental disorders in infants.
- Increased levels of anti-SSA, anti-SSB, anti-dsDNA, anti-RNP, and anti-Sm were significantly linked to adverse neurodevelopmental outcomes in infants.
- Infants with neurodevelopmental disorders had significantly lower birth lengths compared to those with normal neurodevelopment.
- Infants diagnosed with neurodevelopmental disorders scored significantly lower on the neurobehavioral development screening questionnaire.
- No significant differences were observed between groups in terms of maternal age, gestational age, smoking history, drinking history, hypertension, diabetes, hyperlipidemia, or rheumatologic classification.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

BQL and PJX designed the study. BQL, JX, MXL, XG, and PJX performed the analyses. BQL analysed the data and drafted the manuscript. PJX revised the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study has been approved by the Institutional Review Board and the Ethics Committee of the the Sixth Affiliated Hospital of Sun Yat-sen University (Approval number: 2024ZSLYEC-249). Informed consent was waived for this retrospective study, as only deidentified patient data were utilised, posing no potential harm or impact on patient care. This exemption was granted in accordance with ethical and regulatory guidelines related to retrospective studies, and formal approval was received from the Institutional Review Board and the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University, and the study complies with the Declaration of Helsinki (2013).

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Conflict of Interest

The authors declare no conflict of interest.

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