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Understanding the potential impact of trimester-specific maternal immune activation due to SARS-CoV-2 on early human neurodevelopment and the role of cytokine balance

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ABSTRACT

Purpose: The COVID-19 pandemic presents significant future health challenges. Its impact on pregnant women and their newborn is a particular area of concern. This study aims to examine the potential role of maternal immune activation (MIA), due to SARS-CoV-2 infection, on early neurodevelopment.

Methods: We analysed 107 mother-infant dyads from the COGESTCOV-19 study in Cantabria, Spain, which included 59 SARS-CoV-2 exposed (cases) and 48 unexposed (controls) mothers, recruited between December 2020 and February 2022. Cytokine levels (IL-6 and IL-10) were obtained from maternal blood and cord blood. Neurodevelopment was assessed using the Neonatal Behavioral Assessment Scale (NBAS) at six weeks of age. Trimester of infection was considered in the main analyses.

Results: Results showed no significant overall delays in early neurodevelopment due to maternal SARS-CoV-2 infection. Control infants performed better in some NBAS items. However, cases infants showed trimester-specific differences. First-trimester exposure was related to motor and reflex delays, second-trimester to poorer performances in motor tasks and autonomic stability, and third-trimester to weaker state organization, regulation, and reflexes. Some correlations between cytokine levels and NBAS performance showed moderate associations.

Conclusions: These findings highlight the need for ongoing neurodevelopmental monitoring of infants born during the COVID-19 pandemic. The study enhances our understanding of MIA's impact on early development, emphasizing the importance of addressing homeostatic mechanisms in mothers and newborns.

1. Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has presented significant global health challenges, particularly impacting vulnerable populations such as pregnant women and their newborn children (Ayesa-Arriola et al., 2021). Maternal infections during pregnancy have been linked to adverse long-term mental health outcomes, as suggested by historical data indicating increased schizophrenia rates following the

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1918 Spanish influenza pandemic (Kępińska et al., 2020). Despite modern socioeconomic and sanitary conditions have improved, concerns persist, underscored by the recent pandemic context (Woods et al., 2023). While vertical transmission of the virus from mother to fetus is rare, the maternal immune response to infection can still have substantial consequences in the offspring (Otero and Antonson, 2022). Research on maternal immune activation (MIA) has demonstrated that the inflammatory response triggered by infections can interfere with normal brain development, resulting in various neurodevelopmental difficulties (Han et al., 2021; Ellul et al., 2023). However, much of this evidence comes from animal models (Velloso et al., 2022; Lins et al., 2019; Smith et al., 2007; Estes and McAllister, 2016; Munarriz-Cuezva and Meana, 2025), which, although capable of replicating specific symptoms, struggle to fully encompass the complexities of human pregnancy and development (Ryan and Bauman, 2022; Ruiz et al., 2013; Solek et al., 2018). Therefore, understanding the potential impact of MIA due to SARS-CoV-2 in human neurodevelopment is crucial for addressing any potential risks.

Cytokines play a critical role in the inflammatory response, balancing pro-inflammatory factors such as interleukin-6 (IL-6) with anti-inflammatory factors like interleukin-10 (IL-10) (Azaiz et al., 2022; Dhar et al., 2021; Shuffrey et al., 2022). Research has indicated that SARS-CoV-2 infection can alter these levels of cytokines (Azaiz et al., 2022; Dhar et al., 2021; Shuffrey et al., 2022). Elevated IL-6 levels have been linked to adverse neurodevelopmental outcomes, including increased risk for conditions like autism and schizophrenia spectrum disorders (Smith et al., 2007; Solek et al., 2018; Shuffrey et al., 2022; Allswede et al., 2020; Goines and Ashwood, 2013). In contrast, IL-10's anti-inflammatory properties may help mitigate excessive inflammation (Azaiz et al., 2022). Remarkable, the IL-6/IL-10 ratio serves as a homeostatic index of the body's inflammatory response, and has proven to be a reliable prognosis indicator in various medical conditions, including SARS-CoV-2 (Azaiz et al., 2022; Biswas et al., 2023; Tampoia et al., 2017)). Timing during exposure to MIA has also been proposed as a critical factor, as neurogenesis is highly dynamic throughout gestation (Ryan and Bauman, 2022; Goines and Ashwood, 2013; Firestein et al., 2023; Bilbo and Schwarz, 2012). However, studies on the impact of infection across trimesters show mixed results, with some linking greater risks to first-trimester exposure and others to third-trimester infection (Ayesa-Arriola et al., 2023; Spann et al., 2018; Jiang et al., 2016). Rodent models further illustrate stage-specific effects, where early gestational exposure (day 9.5) tends to result in schizophrenia-like symptoms, while later exposure (day 17) is associated with autism spectrum disorder-like behaviors (Munarriz-Cuezva and Meana, 2025).

This study is timely given the extensive reach of the COVID-19 pandemic (datadot [Internet]), offering a unique opportunity to examine the effects of MIA on fetal and infant development on a larger scale. It aims to assess the neurodevelopmental outcomes of infants born to pregnant women infected with SARS-CoV-2 at different trimesters compared to paired control infants using the Neonatal Behavioral Assessment Scale (NBAS) (Brazelton, 1973) at six weeks of age, exploring correlations with cytokines (IL-6, IL-10 and IL-6/IL-10 ratio) levels. To our knowledge, it is the first comprehensive evaluation of early neurodevelopmental outcomes using this extensive assessment in neonates exposed to MIA due to SARS-CoV-2. We hypothesize that exposure to SARS-CoV-2 during pregnancy will result in specific inflammation that impacts the newborn's neurobehavioral development in affected cases, with paired controls expected to demonstrate better outcomes than some of these groups.

2. Methods

2.1. Sample

The investigation encompassed 107 mother-infant dyads recruited within the COGESTCOV-19 (Cohort of COVID-19 Pregnant Women and Newborns: Examination of Biological and Psychological Factors Associated with Neurodevelopment) study (Ayesa-Arriola et al., 2023). These included 59 exposed cases: 10 infected during the first gestational term, 27 during the second, and 22 during the third (hereinafter referred to as 1TI, 2TI, and 3TI respectively), alongside 48 unexposed controls (Fig. 1). Recruitment took place between December first, 2020, and February 28th, 2022, in Cantabria, Spain. The study relied on voluntary cooperation from midwives and obstetricians who informed pregnant women about the research, which was additionally publicized on social media platforms. Each exposed woman was matched with an unexposed pair based on maternal age, parity, and estimated delivery date. The research adhered to guidelines set by the Marqués de Valdecilla University Hospital Review Board (internal code 2020.190) and followed ethical standards, including those of the Declaration of Helsinki. Before participation, all subjects provided informed consent. Further details can be found in Barrio-Martínez et al. (2024).

2.2. Interviews with pregnant women

At the initial visit, preceding blood tests and interviews, participants were assured that their data and that of their infants would remain confidential, with all identifiers removed to ensure anonymity. Data collection involved semi-structured interviews to enable a thorough exploration of participants' circumstances and experiences. During the prenatal interview, mothers provided sociodemographic information as well as details on their medical and psychological status. Anxiety was assessed using the STAI (Spielberger, 2012), stress during pregnancy with the PDQ (Caparros-Gonzalez et al., 2019), social readjustment with the SRSS (Holmes and Rahe, 1967), quality of couple relationship with the CRP (Arteta-Sandoval et al., 2022), quality of sleep with the COS (Bobes et al., 1998), and fear of COVID-19 with the Fear of COVID-19 Scale (Ahorsu et al., 2022). All interviews were conducted by expert psychologists.

Postnatally, information was gathered concerning delivery (natural birth vs induced birth and vaginal delivery vs caesarean section) and neonatal outcomes (gestational age, full term status). APGAR scores at 1st and 5th minute after birth were retrieved from medical records. The interview framework was developed through a critical review of existing literature, utilizing open-ended questions to facilitate unrestricted discussion and avoid biasing responses towards predetermined categories or the researcher's assumptions. Postnatal depression was assessed using EPDS (Cox et al., 1987).

All women in the exposed group confirmed positive for SARS-CoV-2 via polymerase chain reaction tests (Barrio-Martínez et al., 2024). Infection severity was categorized according to previously established criteria, where patients with mild disease typically convalesce at home, whereas those with moderate or severe SARS-CoV-2 infection require hospitalization for observation and supportive care (Gandhi et al., 2020).

2.3. Neurodevelopmental assessment in infants

Neurobehavioral functioning was evaluated using the Neonatal Behavioral Assessment Scale (NBAS) (Brazelton, 1973). The NBAS includes 27 behavioral items scored from 1 to 9, grouped into six subdomains.

- Habituation (Items 1–4): Assesses the newborn's ability to reduce responses to repetitive, non-threatening stimuli. indicating neurological integrity and sensory processing capabilities.
- Social Interactive Responses and Capabilities/Orientation (Items 5–11): Evaluates the newborn's responsiveness to social stimuli: such as voice, faces, and touch, reflecting their emerging communication skills and readiness to bond with caregivers.

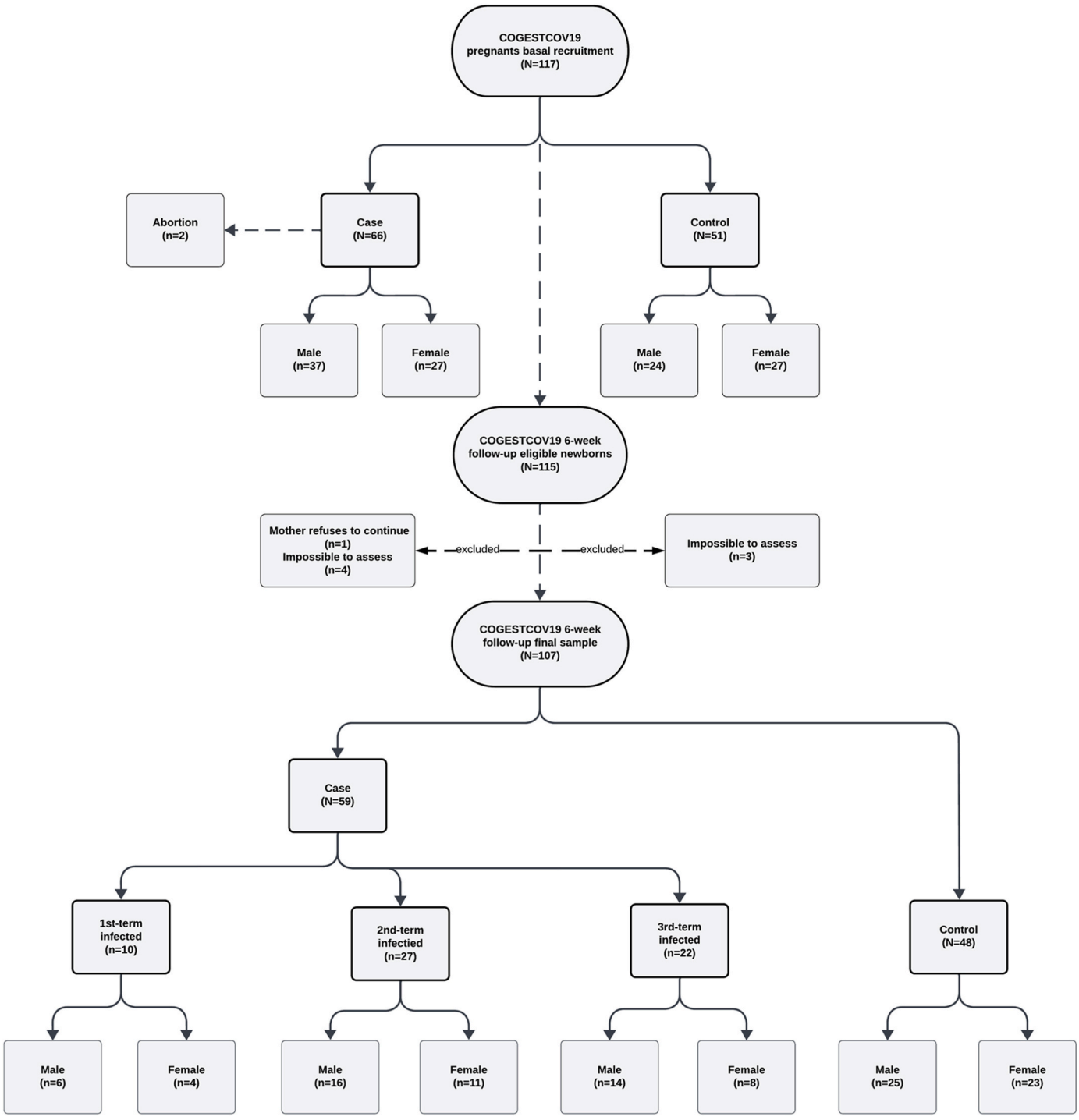

Fig. 1. COGESTCOV19 6-week follow-up sample flowchat.

- Motor System (Items 12–16): Focuses on muscle tone, movement quality, and coordination, providing insights into neurological maturity and physical development.
- State Organization (Items 17–20): Assesses the newborn's ability to manage and structure physiological and behavioral states: essential for social interactions, feeding, and self-soothing.
- State Regulation (Items 21–24): Measures the newborn's capacity to transition smoothly between different states and maintain balanced arousal levels, indicating emotional and physiological stability.
- Autonomic Stability (Items 25–27): Examines physiological stability, including heart rate, respiration, and colour changes, reflecting autonomic nervous system regulation and resilience to environmental stress.

The scale includes item 28 (smiles) and supplementary items (items 29 to 35). Additionally, the NBAS assesses 18 primitive reflexes to provide information about central nervous system integrity and potential neurological issues. Composite scores for each NBAS subdomain were calculated using two methods.

- Selective Composite Scores: Averaged items excluding subjects with incomplete data (ensures equal item weighting but reduces sample size)
- Comprehensive Composite Scores: Averaged items including all available data, regardless of completeness (includes all available data but overemphasizes certain items).

The assessments took place at the Instituto de Investigation Marqués de Valdecilla research laboratory in Santander-Cantabria, Spain. The environment was controlled, with assessments occurring midway between feedings in a tranquil, semi-darkened room maintained at 22–27 °C. The NBAS was administered and scored by two independent certified examiners. Items requiring specific infant states (e.g. habituation during deep or light sleep, orientation during alert state) were anticipated to have variable completion rates.

2.4. Cytokines

Maternal blood samples collected during the first prenatal visit and cord blood samples drawn into EDTA-coated tubes at birth were immediately stored at −80 °C in the Valdecilla Biobank (Ayesa-Arriola et al., 2023). Plasma was extracted by centrifugation at 3000 rpm during 10 min at room temperature. IL-6 and IL-10 concentrations were measured by Enzyme-Linked Immunosorbent Assay (ELISA) using Enzo Life Sciences' high sensitivity ELISA Kit (Catalog #: ENZ-KIT178-0001) for IL-6 and ELISA Kit (Catalog #: ADI-900-036) for IL-10, following manufacturer's instructions. The IL-6/IL-10 ratio was calculated following previous methodology (Dhar et al., 2021). This ratio provides a measure of the pro-inflammatory to anti-inflammatory balance, with a higher ratio indicating a greater proportion of IL-6 relative to IL-10. A logarithmic transformation (log10) was applied to the cytokine values to manage data dispersion and biases, facilitating more robust statistical analysis. The normalized values were calculated as follows:

IL-6_log10: IL-6_log10 = log10(IL-6)

IL-10_log10: IL-10_log10 = log10(IL-10)

IL-6_IL-10_ratio_log10: IL-6_IL-10_ratio_log10 = log10(IL-6/IL-10)

2.5. Statistical analysis

Statistical analyses employed chi-square and Fisher's tests for categorical variables. Numerical variables were compared using t-tests and Mann-Whitney U tests for case-control comparisons, while ANOVAs, F-Wells tests, Kruskal-Wallis tests, and ANCOVAs were used for term infection comparisons. Covariation strategy prioritized key neurodevelopmental factors (gestational age, infant sex, NBAS age, maternal age, education) and controlled for group differences (salary, anxiety). Post-hoc analyses were conducted with significance set at a Bonferroni-corrected p-value of < 0.05. Pearson correlation analysis was conducted to examine the relationships between cytokine levels and NBAS items and composite scores. All tests were two-tailed and performed using R version 4.3.2 (2024-05-27).

3. Results

Despite high maternal homogeneity, newborn neurobehavioral outcomes varied significantly with the trimester of maternal COVID-19 infection, as shown by three analytical approaches with varying levels of adjustment. First trimester infection (1TI) resulted in weaker motor and reflex performance, second trimester infection (2TI) delays in motor tasks and autonomic stability, and third trimester infection (3TI) poorer state organization, regulation, and reflexes. Control (C) infants generally performed better but exhibited some deficits in state organization and autonomic stability. Cytokines showed significant correlations with various NBAS items and composite scores, predominantly weak but with moderate to strong associations observed in some instances. All comparisons were statistically significant at $p < .05$.

A detailed breakdown of the case-control comparisons is provided in the supplementary material (Tables S1 and S2).

3.1. Sociodemographic and physiological findings

3TI- mothers had lower educational attainment and were more likely to earn less than €20.000 annually compared to C. 1TI-mothers had higher STAIE scores than 2TI-mothers. Normalized maternal IL6 and IL10 levels did not show significant differences (Fig. 2). All sociodemographic results are presented in Table 1.

3.2. Neurodevelopment findings

The 1TI children exhibited significantly poorer passive arm movements compared to 3TI, 2TI, and C, and a weaker ankle clonus reflex compared to C. The 2TI children demonstrated significantly poorer pull-to-sit performance compared to 1TI and poorer crawling performance compared to C. The 3TI children showed significantly poorer rapidity of build-up, lability of states, state organization comprehensive composite score, and lability of skin compared to 1TI. They also had significantly poorer lability of states, state organization comprehensive composite score, Babinski reflex, lability of skin, rapidity of build-up, and state organization selective composite score compared to 2TI, and poorer Babinski reflex compared to C. The C children showed significantly poorer lability of states and state organization comprehensive composite score compared to 2TI, with a trend toward a poorer response to decrement to bell compared to 3TI ($p = .051$). All NBAS results are presented in Table 2.

3.3. NBAS and cytokines correlations

Maternal IL-6 levels showed a moderate positive correlation with habituation selective CS ($r = 0.560$. $p \leq .05$). Maternal IL-10 levels exhibited a strong positive correlation with habituation selective CS ($r = 0.792$. $p \leq .01$) and a moderate positive correlation with response decrement to tactile stimulation of the foot ($r = 0.646$. $p \leq .05$). The maternal IL-6/IL-10 ratio showed a moderate negative correlation with response decrement to tactile stimuli of the foot ($r = -0.682$. $p \leq .05$) and habituation selective CS ($r = -0.594$. $p \leq .05$). Detailed correlations between cytokine levels and NBAS items and CS are respectively provided in Table 3, Table S3, and illustrated in Fig. 3.

4. Discussion

Our study explores the potential impact of maternal inflammation due to SARS-CoV-2, attending trimester of infection, on infant outcomes at six weeks of age. The rigorous case-control pairing strategy ensured homogeneity among maternal groups, thereby minimizing confounding factors that could affect neonatal outcomes. Adjustments for remaining maternal differences highlighted the significant implications of maternal health during pregnancy on developmental scores. Additionally, varying correlations between gestational cytokine (IL-6, IL-10 and IL-6/IL-10 ratio) levels, and NBAS items and composite scores highlighted potential connections with specific developmental domains, emphasizing the complex relationship between MIA and infant health.

4.1. Absence of differences between groups

Our study yielded mixed evidence regarding neurodevelopmental outcomes among groups. Controls exhibited fewer significant differences, with only notable variations in the liability of states and comprehensive state organization compared to 2TI. Significant

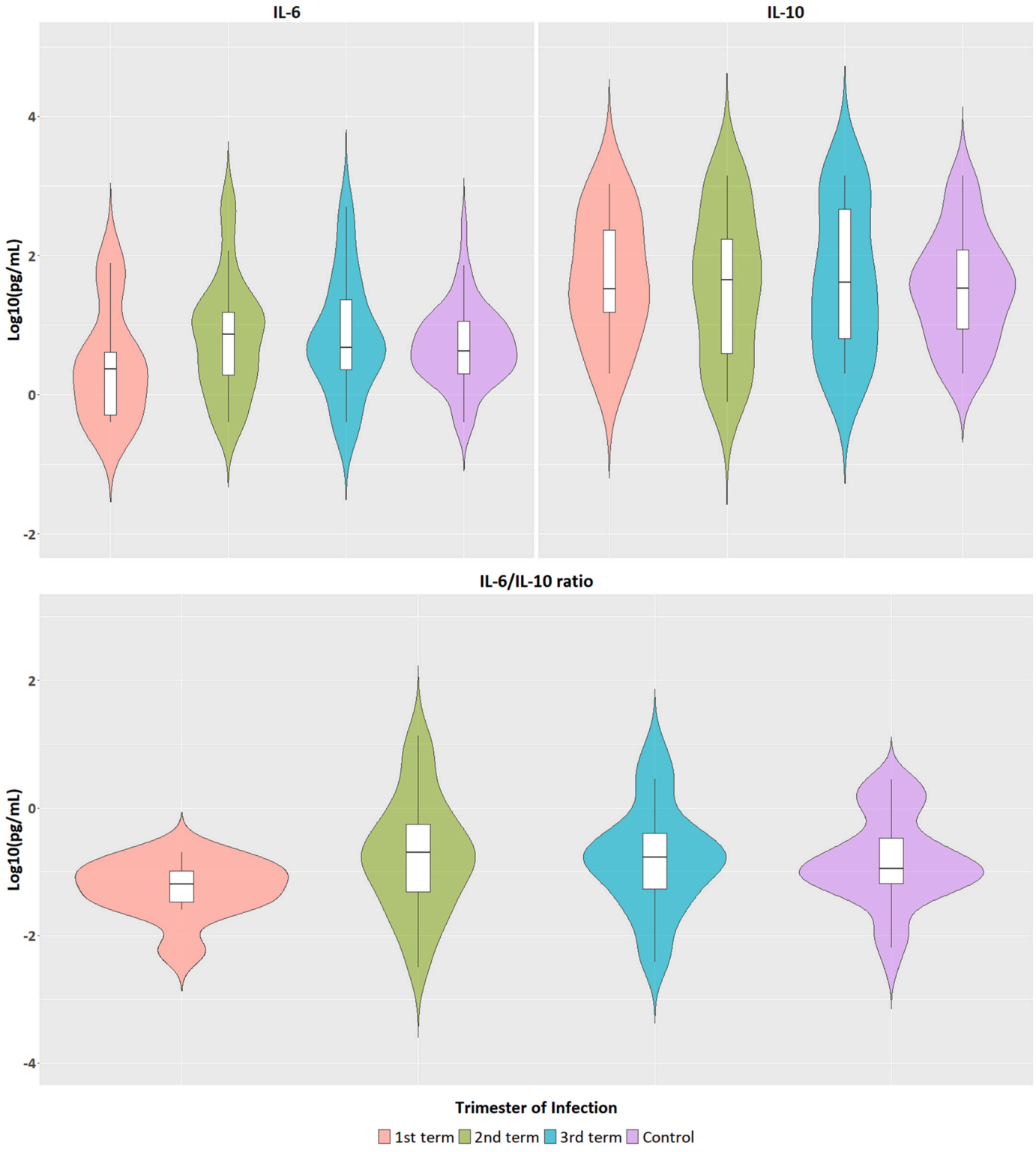

Fig. 2. Violin plots show no statistically significant differences in Log10-normalized IL-6, IL-10, and IL-6/IL-10 ratio levels among mothers across different infection trimesters and controls. An IL-6/IL-10 ratio above 0 indicates a disruption in the balance between pro-inflammatory and anti-inflammatory responses.

distinctions were primarily observed among the case groups.

The 3TI children showed poorer outcomes compared to other groups, differing notably from 1TI and 2TI groups, and from controls only in the Babinsky reflex. Some variations also appeared between other case groups and controls, albeit less frequently. Remarkably, 3TI subjects exhibited the most adverse outcomes, with significant differences in 11 comparisons and outperforming another group only once, in passive arm movements compared to 1TI.

Although IL levels did not differ statistically between case and control groups, IL-6 levels were consistently higher in 2TI and 3TI groups compared to 1TI and controls. Even after excluding 1TI children due to a small sample size, secondary analysis showed no statistical difference between the addressed cytokines levels. These results contrast with those in previous research that suggest poorer developmental outcomes

Table 1
Sociodemographic, clinical and physiological information of COGESTCOV19 mother-newborn dyads at 6-week follow-up.

	1st term			2nd term			3rd term			Control						
	N = 10			N = 27			N = 22			N = 48						
Sociodemographic	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**Statistic**	**Value**	**P-value**	**Post-Hoc**
Mother																
Age (years)	10	35.40	3.63	27	33.44	3.88	22	33.32	3.60	48	34.42	3.69	F	1.118	0.345	
Years of education	10	15.50	6.20	27	15.96	4.67	22	14.82	4.03	48	17.94	4.26	X^2	7.823	0.050	3 < 4*
	N	**n**	**(%)**	**N**	**n**	**(%)**	**N**	**N**	**(%)**	**N**	**n**	**(%)**				
Married or with parther	10	10	100.00	27	25	92.59	22	20	90.91	48	45	93.75	X^2	6.741	0.664	
Annual salary (≤€20k)	9	7	77.8	24	15	62.5	22	17	77.30	46	17	37	Fisher	12.909	0.005	3 > 4*
Primiparous (Yes)	10	5	50.00	27	15	55.56	22	14	63.64	48	28	58.33	X^2	0.618	0.892	
Alcohol (Yes)	10	2	20.00	27	1	3.70	22	0	0.00	47	3	6.38	Fisher	5.410	0.179	
Tabaco (Yes)	10	1	10.00	27	2	7.41	22	1	4.55	48	3	6.25	Fisher	0.379	0.889	
Newborn	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**				
Gestational age (weeks)	10	39.80	1.30	27	40.01	1.02	22	40.27	1.35	48	39.86	1.05	X^2	5.098	0.165	
Age (days)	10	42.70	2.50	27	44.93	3.35	22	44.46	10.45	48	43.71	2.63	X^2	7.478	0.058	NS
1st minute APGAR score	9	8.8	0.7	26	8.5	1.6	22	8.6	1.0	47	8.5	1.0	X^2	0.743	0.863	
5th minute APGAR score	9	10.0	0.0	26	9.5	0.9	22	9.3	1.0	47	9.6	0.7	X^2	5.969	0.113	
	N	**n**	**(%)**	**N**	**n**	**(%)**	**N**	**N**	**(%)**	**N**	**n**	**(%)**				
Sex (Male)	10	6	60.00	27	16	59.26	22	14	63.64	48	25	52.08	X^2	0.962	0.811	
Full term (Yes)	10	10	100.00	27	27	100.00	22	21	95.45	48	48	100.00	Fisher	3.900	0.299	
Natural birth (Yes)	10	4	40.00	27	20	74.07	22	13	59.09	47	23	48.94	X^2	5.657	0.130	
Vaginal delivery (Yes)	10	7	70.00	27	25	92,59	22	21	95.46	48	39	81.25	X^2	5.627	0.131	
Clinical	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**				
PDQ	10	22.2	7.79	27	21.63	8.04	22	20.86	8.35	48	24.08	8.00	F	1.019	0.388	
SRRS	10	167.8	90.90	27	155.78	79.29	22	147.09	79.97	48	141.23	66.52	F	0.458	0.712	
CRP Anxiety	10	47.4	12.73	27	51.30	16.58	22	49.00	15.34	48	52.46	13.71	F	0.494	0.687	
STAI-E	10	16.8	7.02	27	9.52	4.74	22	10.05	6.72	48	12.10	8.02	X^2	8.860	0.031	1 > 2*
COS	10	36	8.81	27	29.70	5.55	22	33.00	8.55	48	33.88	9.03	X^2	5.737	0.125	
PSS	10	23.1	4.70	27	21.89	5.22	22	18.77	7.30	48	19.98	7.56	F	1.445	0.234	
Fear to COVID-19 scale	10	14.4	4.62	27	13.41	4.31	22	13.32	4.24	48	14.17	5.20	X^2	0.658	0.883	
EPDS	10	5.2	1.75	27	5.22	2.55	22	5.18	3.90	48	5.56	3.56	F-w	0.109	0.955	
	N	**n**	**(%)**	**N**	**n**	**(%)**	**N**	**N**	**(%)**	**N**	**n**	**(%)**				
Hospitalization (yes)	10	0	0.00	27	1	0.04	22	0	0.00				X^2	1.206	0.547	
Symptoms during COVID-19 (yes)	10	8	80.00	27	26	96.30	21	21	100.00				Fisher	5.747	0.074	NS
Fever (yes)	10	7	70.00	25	15	60.00	20	10	50.00				X^2	1.158	0.560	
Cough (yes)	10	4	40.00	25	18	72.00	20	10	50.00				X^2	3.871	0.144	
Fatigue (yes)	10	6	60.00	25	11	44.00	20	8	40.00				X^2	1.115	0.573	
Muscle pain (yes)	10	5	50.00	25	12	48.00	20	11	55.00				X^2	0.222	0.895	
Diarrhea (yes)	10	3	30.00	25	4	16.00	20	3	15.00				Fisher	1.155	0.588	
Headache (yes)	10	5	50.00	25	16	64.00	19	7	36.84				X^2	3.206	0.201	
Others (yes)	10	9	90.00	25	21	84.00	20	19	95.00				Fisher	1.394	0.552	
Physiological	10	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**				
Mother																
Weight (kg)	10	68.72	14.62	26	72.53	12.05	22	73.73	11.94	48	72.10	12.37	X^2	1.061	0.786	
Length (cm)	10	163.20	4.69	27	164.22	6.59	22	163.09	6.90	48	164.13	6.71	F	0.187	0.905	
BMI	10	25.88	6.00	26	26.94	4.40	22	27.77	4.59	48	26.76	4.23	X^2	1.438	0.697	
Pospartum systolic blood pressure	10	111.40	15.39	22	115.00	10.66	20	107.40	9.15	36	113.69	10.51	X^2	7.153	0.067	NS
Postpartum diastolic blood pressure	10	68.40	10.85	22	67.82	8.68	20	68.40	5.83	36	67.83	7.80	X^2	0.251	0.969	
Mother IL6 (log10(pg/mL))	10	0.42	0.81	27	0.82	0.84	20	0.83	0.85	48	0.69	0.56	F	0.919	0.435	
Mother IL10 (log10(pg/mL))	10	1.69	0.91	27	1.58	1.06	20	1.64	1.06	48	1.53	0.80	X^2	0.278	0.964	
Mother IL-6/IL-10 ratio (log10(pg/mL))	10	−1.26	0.45	27	−0.75	0.90	20	−0.81	0.83	48	−0.85	0.69	F	1.141	0.336	
Newborn																
Weight (g)	10	3338.00	591.92	27	3379.74	406.67	22	3302.05	499.45	48	3374.48	433.13	F	0.157	0.925	
Lenght (cm)	10	50.10	1.35	26	50.27	1.89	22	50.09	2.09	48	50.14	2.03	F	0.042	0.989	
Newborn IL6 (log10(pg/mL))	7	1.28	0.44	24	1.59	0.65	19	1.64	0.60	33	1.42	0.57	F	1.111	0.350	
Newborn IL10 (log10(pg/mL))	7	1.72	0.83	24	1.43	1.01	19	1.45	1.01	33	1.48	0.75	X^2	0.760	0.859	
Newborn IL-6/IL-10 ratio (log10(pg/mL))	7	−0.44	0.88	24	0.17	1.05	19	0.19	0.95	33	−0.06	0.80	F	1.096	0.356	

PDQ: Prenatal Distress Questionnaire; SRRS: Social Readjustment Rating Scale; CRP: Couple Relationship Quality Scale; STAI: State-Trait Anxiety Inventory; COS: Oviedo Sleep Questionnaire; PSS: Percieved Stress Scale; EDPS: Edinburgh Postnatal Depression Scale; BMI: Body Mass Index; *p < .05; NS: not significant.

Table 2
NBAS scores of COGESTCOV19 newborns at 6-week follow-up.

	1st term			2nd term			3rd term			Control			Adjusted for maternal education, maternal salary, STAI, maternal age, gestational age, infant age at NBAS assessment, and infant sex.			
	N = 10			N = 27			N = 22			N = 48						
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	Statistic	Value	P-value	Post-Hoc
Habituation																
1-Response decrement to light	5	6.3	3.5	12	5.2	3.4	12	6.8	3.1	24	5.4	2.9	F	0.524	0.668	
2-Response decrement to rattle	5	4.8	4.4	11	6.0	3.0	13	3.8	3.8	20	4.4	2.9	F	1.431	0.249	
3-Response decrement to bell	2	5.0	3.5	11	5.3	3.9	6	7.5	3.1	17	4.5	2.5	F	2.757	0.063	3 > 4 (p = .051)
4-Response decrement to tactile stimulation of the foot	0	0.0	0.0	2	9.4	0.9	6	4.8	3.2	5	5.3	3.7	F	0.325	0.745	
Habituation selective composite score	0	0.0	0.0	2	8.1	1.3	5	7.4	2.2	5	5.6	2.1	F	0.587	0.630	
Habituation comprehensive composite score	5	5.1	1.3	15	5.0	0.7	14	4.8	0.8	24	4.3	0.6	F	0.362	0.781	
Orientation																
5-Animate visual orientation	9	4.9	2.3	24	5.5	2.6	21	4.1	2.4	44	5.5	2.5	F	0.975	0.409	
6-Animate visual and auditory orientation	9	4.6	2.7	24	6.3	2.4	21	5.2	2.6	41	6.5	2.6	F	2.443	0.070	NS
7-Inanimate visual orientation	9	4.2	2.3	24	4.0	2.4	20	2.2	2.3	39	3.9	3.0	F	1.938	0.131	
8-Inanimate visual and auditory orientation	8	5.2	2.2	24	5.6	2.4	20	4.5	2.2	39	5.6	3.0	F	0.604	0.614	
9-Animate auditory orientation	7	4.6	2.4	24	5.9	2.3	17	5.7	2.5	40	5.7	2.5	F	0.199	0.896	
10-Inanimate auditory orientation	9	6.5	2.1	24	6.1	2.1	20	5.8	1.8	40	5.8	2.1	F	0.900	0.445	
11-Alertness	9	5.3	2.7	23	6.1	2.4	21	5.0	2.7	42	5.7	2.4	F	0.602	0.616	
Orientation selective composite score	7	5.3	1.8	23	5.6	1.8	17	4.5	2.0	36	5.6	2.0	F	0.678	0.569	
Orientation comprehensive composite score	9	5.1	2.0	24	5.7	1.7	21	4.7	2.0	44	5.5	2.0	F	0.668	0.574	
Motor system																
12-General tone	10	8.5	1.7	26	8.7	1.8	22	8.8	1.9	48	9.1	1.6	F	0.540	0.656	
13-Motor maturity	10	6.3	1.8	26	5.9	2.1	22	7.2	2.6	48	6.7	2.7	F	0.757	0.521	
14-Pull-to-sit	10	6.5	1.9	26	4.7	1.6	22	5.6	2.0	46	5.4	1.9	F	3.163	0.029	1 > 2 *
15-Defensive movement	9	7.5	1.1	25	6.6	1.5	19	7.0	1.8	45	6.7	1.9	F	0.462	0.710	
16-Activity	10	7.8	1.4	26	7.6	2.3	22	7.2	3.3	47	7.6	2.7	F	0.182	0.908	
Motor system selective composite score	9	7.3	1.0	25	6.7	1.0	19	7.2	1.4	44	7.2	1.1	F	1.498	0.221	
Motor system comprehensive composite score	10	7.3	1.0	26	6.7	1.0	22	7.2	1.4	48	7.0	1.3	F	1.066	0.368	
State organization																
17-Peak of excitement	10	6.8	2.1	26	6.6	2.3	22	4.5	2.6	47	5.4	3.0	F	3.043	0.033	NS
18-Rapidity of build-up	10	8.4	2.1	26	7.4	1.9	22	5.2	3.6	47	6.8	2.3	F	4.340	0.007	1 > 3 2 > 3 *
19-Irritability	10	5.8	1.9	26	5.7	2.1	20	5.1	3.2	46	5.2	2.4	F	0.479	0.698	
20-Lability of states	10	7.5	2.0	26	7.6	1.7	22	5.1	3.0	47	5.7	2.5	F	7.303	0.000	2 > 3 2 > 4 **; 1 > 3 *
State organization selective composite score	10	7.1	1.4	26	6.8	1.3	20	5.2	2.7	45	5.9	1.8	F	4.505	0.006	2 > 3 *
State organization comprehensive composite score	10	7.1	0.6	26	6.8	0.4	22	4.9	0.4	48	5.7	0.3	F	5.963	0.001	2 > 3 **; 1 > 3 2 > 4 *
State regulation																
21-Cuddliness	10	5.6	1.7	25	4.8	1.9	21	4.4	1.7	47	4.5	1.9	F	1.372	0.257	
22-Consolability	5	5.8	1.4	19	4.6	2.3	19	5.5	2.6	41	5.1	2.9	F	0.251	0.860	
23-Self-quieting	8	5.6	2.8	23	4.9	3.1	20	3.7	3.2	43	4.0	2.7	F	1.909	0.135	
24-Hand-to-mouth	10	2.6	3.1	27	3.1	3.0	22	3.1	3.0	48	3.0	2.6	F	0.141	0.935	
State regulation selective composite score	5	4.6	1.1	17	4.4	1.6	18	4.0	2.2	40	4.2	1.7	F	1.545	0.211	
State regulation comprehensive composite score	10	4.7	1.2	27	4.2	1.8	22	4.2	2.1	48	4.1	1.9	F	0.468	0.706	
Autonomic stability																
25-Tremolousness	10	8.1	2.5	27	7.7	2.7	21	8.5	2.5	48	8.5	2.4	F	1.010	0.392	
26-Startles	10	8.1	1.4	27	7.3	2.4	22	7.0	2.8	45	7.4	2.1	F	0.785	0.506	
27-Lability of skin	10	8.8	1.8	27	8.2	2.1	22	6.0	3.1	48	7.7	2.2	F	5.128	0.003	2 > 3 **; 1 > 3 *
Autonomic stability selective composite score	10	6.8	1.2	24	6.7	1.2	21	6.0	1.7	48	6.5	1.1	F	1.222	0.307	
Autonomic stability comprehensive composite score	10	8.3	1.3	27	7.8	1.7	22	7.1	2.6	48	7.8	1.5	F	1.598	0.196	
Smiles																
28-Smiles	10	2.0	1.6	24	2.6	2.2	21	2.0	2.0	48	1.9	1.9	F	0.147	0.931	
Supplementary items																
29-Quality of alertness	10	5.6	1.9	27	5.9	2.3	22	5.4	2.3	48	5.9	2.2	F	0.202	0.895	
30-Cost of attention	10	6.6	2.1	26	6.3	1.9	22	5.9	2.3	48	5.5	2.4	F	1.663	0.181	
31-Examiner facilitation	10	5.6	1.8	27	6.0	1.8	22	5.4	2.8	48	5.1	2.3	F	1.278	0.287	

(*continued on next page*)

Table 2 (*continued*)

	1st term N = 10			2nd term N = 27			3rd term N = 22			Control N = 48			Adjusted for maternal education, maternal salary, STAI, maternal age, gestational age, infant age at NBAS assessment, and infant sex.			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	Statistic	Value	P-value	Post-Hoc
32-General irritability	10	7.0	1.8	27	6.3	1.8	22	4.9	3.0	48	5.7	2.1	F	2.179	0.096	NS
33-Robustness and endurance	10	6.6	2.2	26	7.0	1.6	22	6.1	2.8	48	5.7	2.7	F	2.052	0.112	
34-State regulation	10	7.4	1.7	27	7.3	2.0	22	7.0	2.3	48	7.3	2.0	F	0.101	0.959	
35-Examiner's emotional response	10	7.9	2.1	27	7.7	2.0	22	7.4	2.3	48	8.3	2.0	F	1.199	0.315	
Reflexes																
1-Plantar grasp	10	2.0	0.0	26	2.0	0.2	1.91	0.3	0.3	48	2.0	0.0	F	1.267	0.291	
2-Babinski	10	2.0	0.0	26	2.0	0.0	1.86	0.4	0.4	48	2.0	0.0	F	4.165	0.008	3<4 **; 2>3 *
3-Ankle clonus	10	1.2	0.4	26	1.5	0.5	1.63	0.5	0.6	45	1.7	0.5	F	3.152	0.029	1 < 4 *
4-Rooting	10	1.8	0.4	26	1.6	0.5	1.73	0.5	0.5	48	1.8	0.4	F	1.623	0.190	
5-Sucking	10	1.9	0.3	26	1.9	0.3	1.95	0.2	0.2	48	2.0	0.2	F	0.253	0.859	
6-Glabella	8	1.9	0.4	24	1.8	0.4	1.82	0.4	0.4	47	1.9	0.3	F	0.423	0.737	
7-Passive movements - legs	10	1.7	0.5	26	1.8	0.4	1.95	0.2	0.2	47	1.9	0.3	F	2.224	0.091	NS
8-Passive movements - arms	10	1.6	0.5	25	1.9	0.3	2	0.0	0.0	48	1.9	0.3	F	3.861	0.012	1 < 3 **; 1 < 2 1 < 4 *
9-Palmar grasp	10	2.0	0.0	26	2.0	0.2	2	0.0	0.0	47	2.0	0.2	F	0.369	0.776	
10-Placing	10	1.9	0.3	26	2.0	0.2	1.9	0.3	0.3	47	1.9	0.2	F	0.952	0.419	
11-Standing	10	1.9	0.3	26	1.9	0.3	1.86	0.4	0.4	47	2.0	0.2	F	0.813	0.490	
12-Walking	10	1.9	0.3	26	1.5	0.5	1.82	0.4	0.4	46	1.8	0.4	F	2.417	0.072	NS
13-Crawling	9	1.9	0.3	25	1.7	0.5	1.86	0.4	0.4	46	1.9	0.2	F	3.318	0.024	2 < 4 *
14-Incurvation (galiant response)	9	1.8	0.4	26	1.6	0.5	1.86	0.4	0.4	45	1.8	0.4	F	2.627	0.056	2 < 3 (p = .098)
15-Tonic deviation of head and eyes	9	2.0	0.0	22	1.7	0.5	1.68	0.5	0.5	41	1.7	0.5	F	0.843	0.475	
16-Nystagmus	9	1.4	0.5	21	1.5	0.5	1.39	0.5	0.6	38	1.5	1.6	F	0.086	0.967	
17-Tonic neck reflex	9	1.9	0.3	25	1.6	0.5	1.74	0.5	0.5	42	1.5	0.5	F	2.260	0.088	1 > 4 (p = .092)
18-Moro reflex	9	1.9	0.3	25	1.8	0.4	1.85	0.4	0.4	41	1.9	0.4	F	0.134	0.940	

**p < .01; *p < .05; NS: not significant.

Table 3
Pearson correlations between normalized IL leves and NBAS selective and comprehensive composite scores (CS).

	Maternal IL-6 levels			Maternal IL-10 levels			Maternal IL-6/IL-10 ratio levels		
	Pearson Correlation	Sig. (bilateral)	N	Pearson Correlation	Sig. (bilateral)	N	Pearson Correlation	Sig. (bilateral)	N
Habituation Selective CS	0.560	0.058	12	0.792**	0.002	12	−0.594*	0.042	12
Habituation Comprehensive CS	0.068	0.616	56	0.051	0.710	56	0.006	0.964	56
Orientation Selective CS	0.279*	0.012	81	0.294**	0.008	81	−0.089	0.428	81
Orientation Comprehensive CS	0.253*	0.013	96	0.275**	0.007	96	−0.086	0.406	96
Motor System Selective CS	0.192	0.062	95	0.101	0.332	95	0.058	0.574	95
Motor System Comprehensive CS	0.088	0.374	104	0.052	0.602	104	0.022	0.827	104
State Organization Selective CS	−0.023	0.823	99	0.009	0.926	99	−0.033	0.749	99
State Organization Comprehensive CS	−0.041	0.680	104	0.029	0.768	104	−0.074	0.458	104
State Regulation Selective CS	0.046	0.691	78	0.142	0.214	78	−0.141	0.217	78
State Regulation Comprehensive CS	0.067	0.495	105	0.070	0.481	105	−0.020	0.839	105
Autonomic Stability Selective CS	0.016	0.877	98	0.021	0.840	98	−0.010	0.921	98
Autonomic Stability Comprehensive CS	0.017	0.867	105	0.025	0.800	105	−0.014	0.884	105

** and * indicate correlations significant at the 0.01 and 0.05 levels. respectively.

in subjects exposed to MIA(9,14,17–19). Many MIA studies in animal models involve artificially elevated immune levels rarely seen in typical human infections (Munarriz-Cuezva and Meana, 2025; Warner, 2021; Comparative Animal Models of Human Viral Infections, 2022). During the COVID-19 pandemic, most infected pregnant women were asymptomatic or suffered mild symptoms (Shuffrey et al., 2022; Sutton et al., 2020); in our sample, only one out of 59 women required hospitalization. This may explain why cytokine levels in our sample, though elevated in subjects infected in the second and third trimesters, did not reach statistical significance, potentially not attaining neurodevelopmentally disruptive levels, notable on an observational scale at 6 weeks of age (Smith et al., 2007; Solek et al., 2018; Shuffrey et al., 2022; Firestein et al., 2023).

4.2. Associations between cytokine levels and neurodevelopmental outcomes

Research on the relationship between gestational maternal cytokines and offspring development has yielded mixed results (Yu et al., 2020). In our study, maternal IL-6 positively correlated with newborn IL-10 and IL-6, while maternal IL-10 was strongly correlated with newborn IL-10. These correlations suggest that maternal cytokines may influence neonatal development through mechanisms such as placental permeability or stimulation of placental cytokines production, indicating their complementary roles in homeostasis and neurodevelopment (Wu et al., 2017; Mardini et al., 2016; Zaretsky et al., 2004; Hsiao and Patterson, 2011).

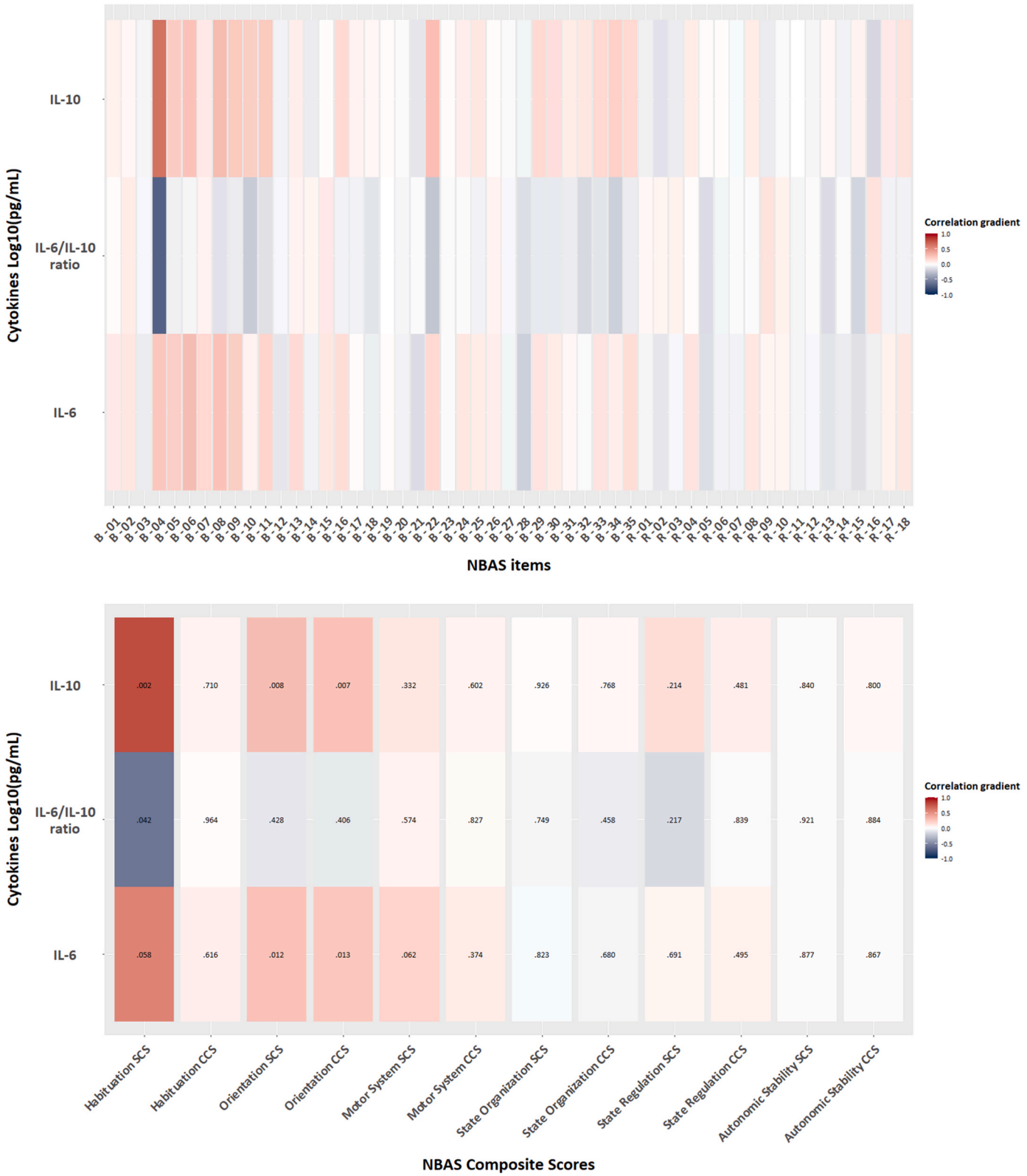

Fig. 3. The top heat map displays Pearson correlations between individual NBAS items and Log10-normalized IL-6, IL-10, and IL-6/IL-10 ratio, including items used for composite scores, as well as additional items 28 (smiles), supplementary items 29–35, and reflex items (R). The bottom heat map illustrates correlations and p-values for NBAS selective and comprehensive composite scores (CS). The colorimetric gradient indicates: red represents a direct correlation and blue an inverse correlation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4.2.1. The role of maternal IL-6

Literature on gestational pro-inflammatory IL-6 and neurodevelopment often reports adverse outcomes (Jones et al., 2017; Buka et al., 2001; Goldstein et al., 2014; Gilman et al., 2016; Rasmussen et al., 2019). Nevertheless, some studies observe no association (Yu et al., 2020; Dozmorov et al., 2018), or even positive effects (Spann et al., 2018). Our study identified weak positive correlations between maternal IL-6 and various aspects of neonatal sensory responsiveness, picturing a potential role in visual and auditory orientation. In line with our findings, Spann et al. (2018) noted that higher maternal CRP and IL-6 levels correlated positively with toddler cognitive scores assessed with Bayley Scales of Infant and Toddler Development-III (Bayley, 2012) at 14 months of age, indicating MIA might sometimes promote adaptive neurodevelopmental responses (Spann et al., 2018).

4.2.2. The role of maternal IL-10

Findings in gestational anti-inflammatory IL-10 and neurodevelopment is also inconsistent (Yu et al., 2020). Though generally linked to better pregnancy and mental health outcomes (Azizieh and Raghupathy, 2017; Robertson et al., 2006; Harden et al., 2013), our study found stronger positive correlations between maternal IL-10 and neurodevelopmental outcomes compared to IL-6. Significant correlations were observed for responses to tactile stimulation, visual and auditory orientation, and approaching moderate correlations with consolability. The strongest association observed was with the habituation selective composite score. However, sample size discrepancies due to the deep-sleep assessment requirements for this domain—unlike the wakeful state assessments used for other domains—likely influenced this score's result. The social/orientation domain showed more consistent results across methodological approaches, moving towards moderate levels for IL-6 and stronger for IL-10. These findings suggest that maternal IL-10 may influence neonatal social engagement and responsiveness, underscoring its role in modulating MIA (Bilbo and Schwarz, 2012; Azizieh and Raghupathy, 2017; Robertson et al., 2006; Harden et al., 2013)). Given that impaired social responsiveness is linked to neurodevelopmental disorders like autism, these results highlight the need for more research into how maternal inflammation affects social neurodevelopment and strategies to mitigate risks (Estes and McAllister, 2016; Jiang et al., 2018; Ronström et al., 2023).

4.2.3. Maternal inflammation homeostasis

Inflammation initially aims to contain or remove threats, followed by a slower anti-inflammatory response to prevent tissue damage, and restore normal function. Balancing inflammation is complex, especially during pregnancy, which involves significant maternal and fetal changes (Abu-Raya et al., 2020). IL-6 is a key pro-inflammatory cytokine in pathogen response, while IL-10 balances these responses (Azaiz et al., 2022; Gilman et al., 2016; O'Connor et al., 2000). Our analysis of the IL-6/IL-10 ratio revealed mostly negative correlations with neonatal neurodevelopmental outcomes. The strongest correlation was observed with response decrement to tactile stimulation, with weaker associations for consolability, auditory orientation, and state regulation. This supports similar previous findings on the impact of maternal inflammatory dysregulation on early neurodevelopmental milestones highlighting that imbalances in maternal homeostasis may adversely affect neonatal self-regulation (Yu et al., 2020). A moderately significant association with the habituation composite score suggests that elevated MIA may impair neonatal sensory adaptation. These results imply that MIA dysregulation could have detrimental effects on offspring neurodevelopment, potentially indicating increased vulnerability to future developmental challenges. Further research is needed to identify effective inflammation/homeostatic markers for monitoring and preventive interventions.

4.3. Strengths and limitations

A major strength of this study is its focus on a human cohort, which provides direct insights into how maternal cytokine levels during SARS-CoV-2 infection influence early neonatal neurodevelopment. By meticulously matching participants based on sociodemographic and clinical characteristics, we ensured a methodologically robust sample that accurately reflects a specific population segment. This careful selection minimizes potential confounding factors, thereby enhancing the validity of our findings. Furthermore, this study is among the first to comprehensively evaluate early neurodevelopmental outcomes in neonates exposed to MIA due to SARS-CoV-2, using the extensive tool. The rigorous administration of the NBAS, combined with the careful normalization of biological data, ensured consistent and reliable assessments, allowing us to explore the nuanced relationship between maternal cytokine levels and infant neurobehavior. Finally, the study's design allows for a detailed examination of the effects of MIA across different trimesters of pregnancy, offering valuable insights into the timing and nature of potential neurodevelopmental risks. This approach underscores the importance of ongoing monitoring and support for infants born during the COVID-19 pandemic, contributing to our understanding of MIA's impact on child development.

However, several limitations should be noted. The relatively small sample size of 107 mother-infant dyads may limit the statistical power to detect subtle associations and may not represent the broader population. The specificity of our sample, while provides valuable insights into a particular population stratum, may limit generalizability of the findings to a broader general population. Individual variability in maternal immune responses and environmental factors could also influence the results. The classification of SARS-CoV-2 infection severity was based primarily on the symptoms severity and the need for hospitalization, with most women experiencing mild or asymptomatic infections. This may not fully capture the impact of more severe infections on infant neurobehavioral development. Furthermore, the sample size constraints limited the ability to conduct sex-stratified analyses, potentially obscuring interactions with the trimester of infection, despite the covariation precautions applied. Even with the measures considered in the study, the potential influence of additional unmeasured obstetric or perinatal variables on neurodevelopmental outcomes remains uncertain. Additionally, the study focused on measuring IL-6 and IL-10 levels as pro and anti-inflammatory markers, excluding other relevant cytokines. The assessment of infant neurobehavioral development using the NBAS at six weeks of age, while robust, may not capture all potential developmental changes that could manifest later. Another consideration is the observational nature of the study, which means that associations identified cannot be interpreted as causal. Although statistical adjustments were made for various covariates, the possibility of residual confounding cannot be entirely discarded.

4.4. Future directions

Future research should focus on longitudinal studies to track developmental trajectories in infants exposed to varying maternal cytokine levels and explore additional immune markers. Enhancing sample sizes and diversifying populations would improve the generalizability of the findings. Sex should be addressed as a key factor as well as its potential interactions with the trimester of infection prioritized to uncover sex-specific effects, addressing current limitations. Investigating factors such as maternal nutrition, exercise habits and additional access to healthcare during pregnancy, is crucial as these variables could act as confounding factors, including a broader range of immune markers, such as TNF-α or IL-1β, would provide a more comprehensive understanding of the maternal inflammatory response. Studies tracking developmental trajectories over an extended period would be valuable in comprehending the enduring impact of maternal immune activation. Additionally, incorporating methods that explore underlying neural

mechanisms alongside observational assessments would provide deeper insights beyond task performance. Future studies could also benefit from employing more sophisticated analytical techniques to further address potential confounding issues.

5. Conclusions

Our study suggests that dysregulations in maternal inflammation homeostasis may affect early human development increasing vulnerability. This underscores a multifaceted relationship between MIA and neurodevelopment that appears to be dose dependent. Given that most infections are mild or asymptomatic, particularly in countries with advanced public health systems or privileged populations, ongoing research into maternal immune influences during pregnancy is essential for developing preventive measures. However, social differences and vulnerabilities could affect outcomes in less advantaged conditions. Monitoring cytokine levels and other inflammatory markers can help identify at-risk populations early. These findings provide a basis for targeted interventions aimed at improving maternal health and reducing the risk of adverse neurodevelopmental outcomes in offspring, thereby informing clinical practices and public health policies to support maternal and child well-being.

CRediT authorship contribution statement

Alexandre Díaz-Pons: Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis, Data curation, Conceptualization. **Sergio Castaño-Castaño:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Formal analysis. **Víctor Ortiz-García de la Foz:** Visualization, Software, Formal analysis, Data curation. **Ángel Yorca-Ruiz:** Software, Formal analysis. **Carlos Martínez-Asensi:** Software, Formal analysis, Data curation. **Eva Munarriz-Cuezva:** Writing – review & editing, Writing – original draft, Validation. **Rosa Ayesa-Arriola:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.100956.

Data availability

The data supporting the findings of this article is available upon request from the corresponding author, RAA.

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