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STORCH Brazil: multicenter cohort study protocol to investigate neurodevelopmental paths and functioning in infants exposed to STORCH in Brazil

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Abstract

Background The acronym STORCH encompasses gestational infections that can lead to congenital syndromes or adverse neurological outcomes in children. In Brazil and worldwide, there has been an alarming increase in confirmed cases of STORCH in recent years. However, no study has examined the impact of STORCH on infants' neurodevelopmental outcomes in a large, multi-center cohort, recruiting a substantial number of participants, with analysis across a broad set of variables and ages and based on the International Classification of Functioning, Disability and Health (ICF) model.

Objective To examine the association between the exposure to classic STORCH (syphilis, toxoplasmosis, rubella, cytomegalovirus infection, and herpes simplex) on components of functioning in infants from 3 to 24 months old in Brazil.

Methods We propose a multi-center prospective cohort study that includes data collection in at least one city from each geographical region of Brazil. A proposed total sample size of 296 infants will be included at 3 months (12–15 weeks post term). They will be equitably divided into: (a) an exposed group ($n = 148$), consisting of those diagnosed with any congenital STORCH infection or whose mothers experienced prenatal STORCH infection; (b) an unexposed group ($n = 148$). Assessments are carried out longitudinally at 3, 6, 9, 12, 18, and 24 months of age. Assessment tools include Prechtl's General Movements Assessment, Hammersmith Infant Neurological Examination, Alberta Infant Motor Scale; Bayley Scales of Infant and Toddler Development; Survey of Well-being of Young Children; Autism Observational Scale for Infants; Modified Checklist for Autism in Toddlers; Child Behavior Checklist; and Young Children's Participation and Environment Measure. Descriptive analyses, including the calculation of relative risk, and logistic regressions will be conducted to examine the association between gestational exposure to STORCH agents and infants' responses/outcomes.

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Discussion The STORCH Brazil study will investigate the impact of STORCH exposure on functioning, including neurodevelopmental trajectories, in infants during their first two years, aligning with the ICF framework. This will enhance understanding of the characteristics and needs of STORCH-exposed infants, aiding therapists in making informed clinical decisions. The results might support public policies tailored to this population. Findings will be disseminated to ensure knowledge translation.

Clinical trial number Not applicable.

Keywords Cerebral palsy, Autism spectrum disorders, Prenatal care, Infant follow-up, Infant development, Congenital infection

Background

The acronym TORCH is universally used to denote the main group of gestational infections or diseases that can lead to congenital syndromes or adverse outcomes in children. They can be transmitted to the fetus or newborn during pregnancy, childbirth, or shortly after birth. Classically, TORCH includes Toxoplasmosis, Other (syphilis), Rubella, Cytomegalovirus, and Herpes simplex [1–4]. As additional infections causing similar problems have been identified, the "O" that stands for "other" has encompassed infections like human immunodeficiency virus, hepatitis, varicella-zoster, and Zika virus, among others [5–7]. In Brazil, the alarming incidence of gestational and congenital syphilis in recent years [8] has led to the widespread adoption of the STORCH acronym, with "S" representing syphilis, as endorsed by the Ministry of Health [9].

Although some STORCH infections are treatable in the prenatal period, transmission to the fetus is not always prevented [7, 10]. In low- and middle-income countries, these infections are major causes of permanent disability in children [11]. Pathogens of the STORCH group present a strong central nervous system tropism [12]; therefore, the affected newborn may present various outcomes identified at birth or during prenatal care, such as brain calcifications, hydrocephaly, and congenital malformations caused by brain damage [7, 12, 13]. When pathogens access the fetal brain, they disrupt its maturation and trigger an inflammatory environment, resulting in secondary neurodevelopmental impairments, including cerebral palsy [13].

However, brain lesions may represent only the most severe end of a wide range of damage caused by STORCH. Growing evidence suggests that prenatal exposure to some infectious pathogens can affect fetal brain development subtly, leading to neurodevelopmental issues that are often hard to detect early, such as cognitive delay and autism spectrum disorders ASD [14–16]. Hence, some neurological issues and long-term neurodevelopmental problems may not be apparent at birth or in early life, often being recognized years later [10].

Findings of a systematic review showed that while the risk of cerebral palsy in infants with congenital cytomegalovirus infection or congenital herpes ranged from 24.3 to 29.9%, the risk of developing a mild sequela across at least one neurodevelopmental domain (e.g., cognitive, motor, or learning impairments) varied between 4.1% and 37.5% for infants with congenital toxoplasmosis, rubella, cytomegalovirus infection, or herpes. Among those with impairments, 6.0–94.0% were identified with cognitive delays, general developmental delays, or learning difficulties at 6 months or more after birth [17]. In congenital syphilis, motor delay has been reported in 17.6% of infants at 12 and 24 months of age [16]. This data shows that mild neurodevelopmental problems, which can be challenging to detect timely, may be present in a substantial proportion of the STORCH-exposed population.

Despite the challenges in the early detection of neurodevelopmental problems, advancements in assessment tools offer promising pathways for identifying at-risk infants. Recent studies have indicated that brain function, assessed through spontaneous movements before 5 months of age [18, 19] along with neurological examinations conducted between 9 and 12 months [20, 21], serves as a highly predictive method for later neurodevelopmental impairment [22]. Some research has investigated the impact of prenatal infections on neurodevelopment as measured by these tools. In infants exposed prenatally to the Zika virus [23, 24] and SARS-CoV-2 [25–27], findings suggest limitations in spontaneous movements and neurological responses observed at least 3 months post-term. Additionally, studies on prenatal exposure to syphilis and toxoplasmosis have reported a significant number of infants exhibiting reduced motor repertoire and abnormal spontaneous movements by 3 to 4 months [28]. However, the absence of control groups and follow-up assessments in many of these studies underscores the need for robust cohort studies to understand better the impact of STORCH infections on early behaviors and future outcomes. An Italian cohort study demonstrated that infants exposed to maternal syphilis, toxoplasmosis, and cytomegalovirus scored lower in cognitive and motor development at 12 months compared to unexposed infants [16]. Nevertheless, considerable knowledge gaps remain in this field.

The literature review highlights a gap in the thorough assessment of infants exposed to STORCH infections particularly within the framework of the International Classification of Functioning, Disability and Health (ICF). The ICF model emphasizes the interaction between a person's health condition and overall functioning within their environment [29]. While the teratogenic effects of STORCH infections on infants' body structures and functions, including brain function assessed by spontaneous movements [23, 28], and activities such as cognitive and motor skills [16] have been studied, factors related to their participation—such as engagement with toys and involvement in routine care—remain underexplored. Moreover, barriers to their participation, including contextual factors like the home environment, have yet to be fully investigated. Assessments based on the ICF model could facilitate early identification of functioning issues and enable timely, targeted therapeutic approaches to improve functional outcomes [22, 30] in STORCH-exposed infants. Additionally, while these infants are at risk for various neurodevelopmental problems, further research tracking their specific outcomes is lacking [31].

To the best of our knowledge, no study has examined the impact of classic STORCH on infants' outcomes in a large, geographically distributed cohort, with analysis across a broad set of variables based on the ICF framework, and throughout several months after birth.

Objectives

This paper outlines a study protocol aimed at examining the influence of the exposure to classic STORCH (syphilis, toxoplasmosis, rubella, cytomegalovirus infection, and herpes simplex) on the components of functioning in infants from 3 to 24 months old in Brazil. We raise the following primary question: Do infants with prenatal STORCH exposure demonstrate more impairments in functioning, including body structures and function, activities, participation, and contextual factors, compared to unexposed infants during the first two years of life in Brazil? The following specific objectives will be studied:

a) to compare the global and detailed spontaneous movements between exposed and unexposed infants at 3 months of age;
b) to verify the association between STORCH-exposure and neurological responses and gross motor performance in infants at 3, 6, 9, 12, 15, and 24 months of age;
c) to verify the association between STORCH-exposure and global (cognitive, language, and motor) development in infants at 6, 12, and 24 months of age;
d) to verify the association between STORCH-exposure and risk of neurodevelopmental disorders (e.g.: ASD, attention-deficit/hyperactivity disorder ADHD) in infants at 6, 9, 12, 15, and 24 months of age;
e) to verify the association between STORCH-exposure and level of participation and quality of environment in infants at 3, 12, and 24 months of age;
f) to examine associations between the global and detailed spontaneous movements at 3 months with neurological responses, gross motor development, and global development in exposed and unexposed infants at 3, 6, 9, 12, 15, and 24 months of age;
g) to examine associations between level of participation and quality of environment with neurological responses, gross motor development, and global development in exposed infants and unexposed infants at 3, 6, 9, 12, 15, and 24 months of age;
h) to examine associations between the global and detailed spontaneous movements and neurological responses with the diagnosis of cerebral palsy and neurodevelopmental disorders in exposed and unexposed infants over the months.

Methods

Study design and ethics

This protocol describes a multicenter prospective cohort study that will have at least five participant recruitment centers, with at least one center in each of the five geographical regions of Brazil (Fig. 1). Ethical approval was obtained before the start of the project by the Ethical Committee on Human Research of the Federal University of Mato Grosso do Sul (CAAE: 81691424.8.0000.0320). Infants' enrolment started in July 2024 and is expected to be completed by December 2026. As of October 2024, we have enrolled 57 infants. A written, informed legal consent form is signed by the parents before the infant is included in the study.

Study setting

The project is coordinated at the Federal University of Mato Grosso do Sul, in Campo Grande. Co-participating centers include the Federal University of Amazonas, in Manaus; the Federal University of Rio Grande do Norte, in Natal; the Federal University of Pampa, in Uruguaiana; and the University of São Paulo, in São Paulo. Participants are recruited from hospitals, state medical laboratories, and ambulatory healthcare services at each center. Participants are also recruited via social media through the divulgation of the study by the involved researchers.

Data collection occurs in the involved research laboratories or ambulatory healthcare services, or at the infant's home environment when parents prefer.

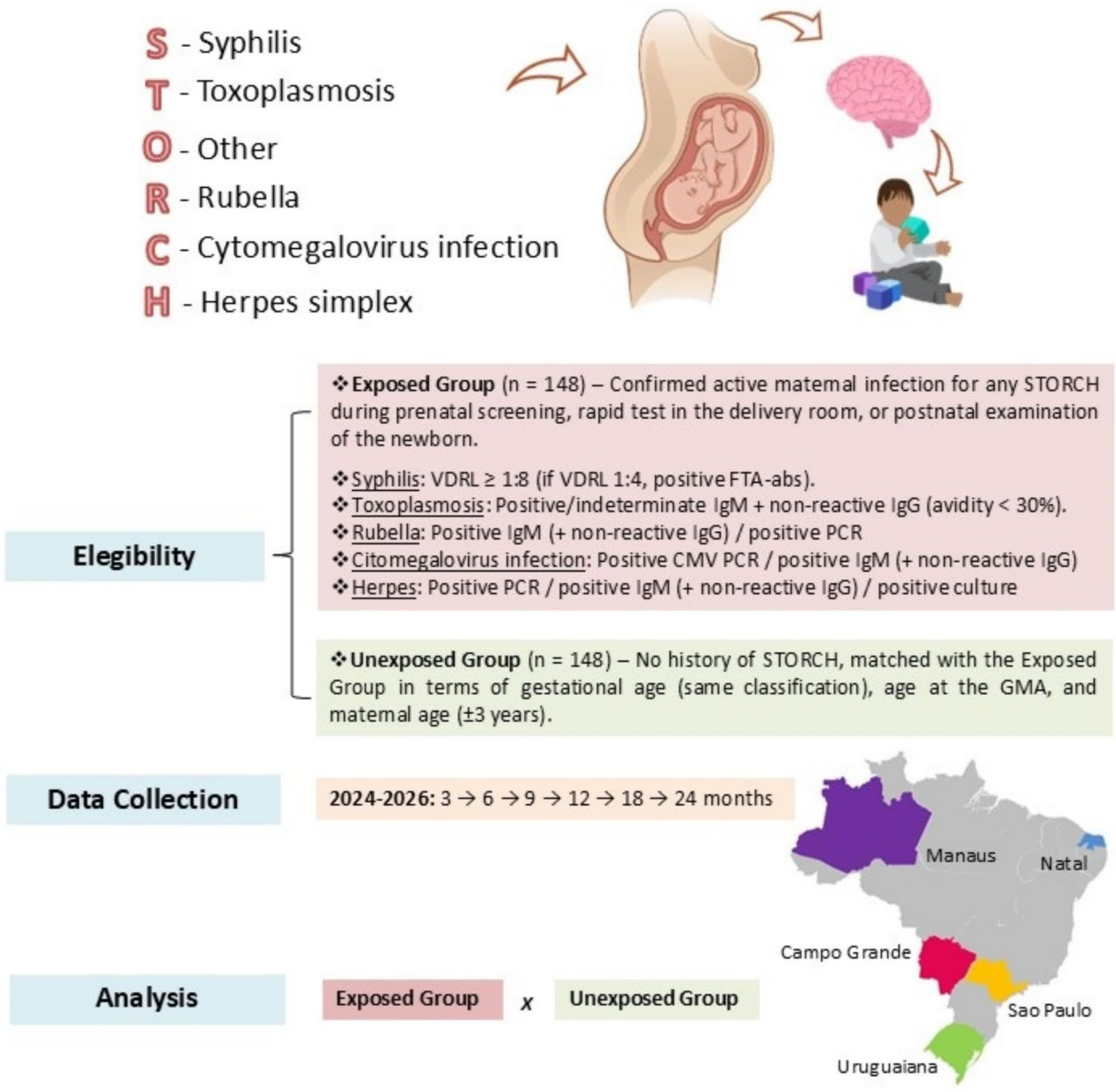

Fig. 1 Illustrated study design

Participants and eligibility

The study includes infants aged 3 to 24 months divided into *exposed group* and *unexposed group*.

For the exposed group, the study includes infants who are 3 months (12 to 15 weeks post-term) (corrected age for 40 weeks gestational age), of both sexes, clinically stable, with a diagnosis of any classic congenital STORCH (syphilis, toxoplasmosis, rubella, cytomegalovirus infection, and herpes), or whose mothers tested positive for any STORCH agent in serological screening during prenatal care or in the delivery room (reactive rapid test). This information is based on the Brazilian Ministry of Health and is obtained from the maternal health booklet, which is part of the Brazilian prenatal care for all pregnant women, and also based on the results of the serological tests available in the participants' medical records. In Brazil, screening and tests for STORCH during gestation, or in the delivery room when not done during prenatal care, are ensured by policies established by the Ministry of Health [9, 32].

The unexposed group will serve as the control group, based on the following inclusion criteria: infants who are 3 months (12–15 weeks post-term) (corrected age for 40 weeks gestational age), of both sexes, clinically stable,

whose mothers did not have an active STORCH infection during pregnancy, without congenital STORCH. Controls cannot present confounder conditions for neurodevelopmental problems, such as congenital malformations; genetic syndromes; progressive conditions; orthopedic problems; grade III and/or IV peri-intraventricular hemorrhage; hyperbilirubinemia; infections under treatment (change in blood count and positive blood culture); and fifth minute Apgar score < 7. They are matched with infants from the exposed group based on the gestational age classification (extreme preterm, very preterm, moderate preterm, full-term) and the assessment age (biological factors), as well as the maternal age (up to ± 3 years difference) (environmental factor).

Infants will be excluded if they are unable to participate in the assessments at the predetermined ages, and if they present any conditions that prevent the assessments, such as: sedation, use of central nervous system depressants, hemodynamic instability, poor general condition (fever, prostration, diarrhea, pain), infectious diseases, sequelae from fractures, joint dislocations, and surgical interventions on the days of assessments. Controls who present any of the exclusion criteria after inclusion in the study will be excluded, as well as infants whose parents request their withdrawal from the study.

For the selection of participants according to the eligibility criteria, medical records, maternal and newborn booklets, and discharge letters are taken as references.

Sample size

The sampling process started with at least one city selected by convenience based on the geographical locations of researchers who have infant neurodevelopmental follow-up as a line of research, from each geographical region of Brazil, as follows: Campo Grande (Central-West), Manaus (North), Natal (Northeast), Uruguaiana (South), and Sao Paulo (Southeast).

To determine the sample size, a longitudinal model with random slope was adopted, considering that infants tend to have greater variance within the groups (exposed and unexposed). Assessments are planned to be carried out at 3, 6, 9, 12, 18 and 24 months (6 repetitions). A power of 0.8 was adopted in a two-tailed test with significance equal to 0.05 and the smallest detectable effect size of 2 points on at least the General Movements Assessment (GMA) [18, 19]. It was assumed that the model has a random slope with variance equal to 20 and residual variance equal to 30. Sample size was adjusted for up to 10% losses.

The sample size calculation was performed in the software R [33] with the longpower library [34], using sample size formulas of Liu and Liang [35] for marginal models. It follows, therefore, with the parameters presented previously, that the study will require at least 148 individuals per group ($N = 296$).

Assessment tools

First, a form is used to collect data to characterize the sample regarding identification, clinical, and sociodemographic information, supplemented with information from the medical records, maternal and newborn booklets, and discharge letters. The maternal data will consist of the number of prenatal consultations, illnesses during pregnancy, use of drugs/alcohol/tobacco/medications during pregnancy, and other infections during pregnancy. Infant data will consist of anthropometric data at birth; Apgar scores; results of neonatal brain imaging; length of neonatal hospital stay; type of breastfeeding; and, for the exposed group, diagnosis of cerebral palsy and/or other neurodevelopmental problems, including ASD, diagnosed by health professionals at any point of the study. The sociodemographic characteristics include maternal age, marital status, maternal level of education, number of children, occupation, and family income per capita.

The standardized assessment tools compromise all ICF components, as summarized in Fig. 2 and detailed below.

Prechtl's general movements assessment (GMA)

The GMA [18, 19] is one of the gold standard tools used to identify early problems in brain function. It is based on the gestalt visual perception of the general movements (GMs), which are recognized as biomarkers for abnormal neurodevelopment [22]. GMs are a specific set of spontaneous motor patterns that engage the entire body through a varied sequence involving the upper and lower limbs, neck, and trunk from early fetal life to around 20 weeks post-term. They reflect the ongoing maturation of the infant's motor system and the brain's ability to integrate sensory and motor inputs [18, 19]. From 9 to around 20 weeks post-term, GMs are called fidgety movements (FMs). Their frequency increases after 9 weeks, and only fades out after 15–18 weeks, when intentional movements start dominating [18, 19]. Normal FMs are present and marked by low-intensity movements of the limbs, trunk, and head, occurring at a moderate speed. These movements exhibit varying acceleration and include small rotational actions of the hands and feet. Abnormal FMs can be classified as abnormal - appear similar to normal FMs but have increased amplitude, speed, and jerkiness; sporadic – present in only a few body parts and last no longer than 3s; or absent [36]. Sporadic and absent FMs are highly predictive of neurological impairment, particularly cerebral palsy [22, 24, 37, 38].

In addition to the qualitative assessment, a motor repertoire assessment form for infants aged 3 to 5 months is used to calculate the Motor Optimality Score-Revised

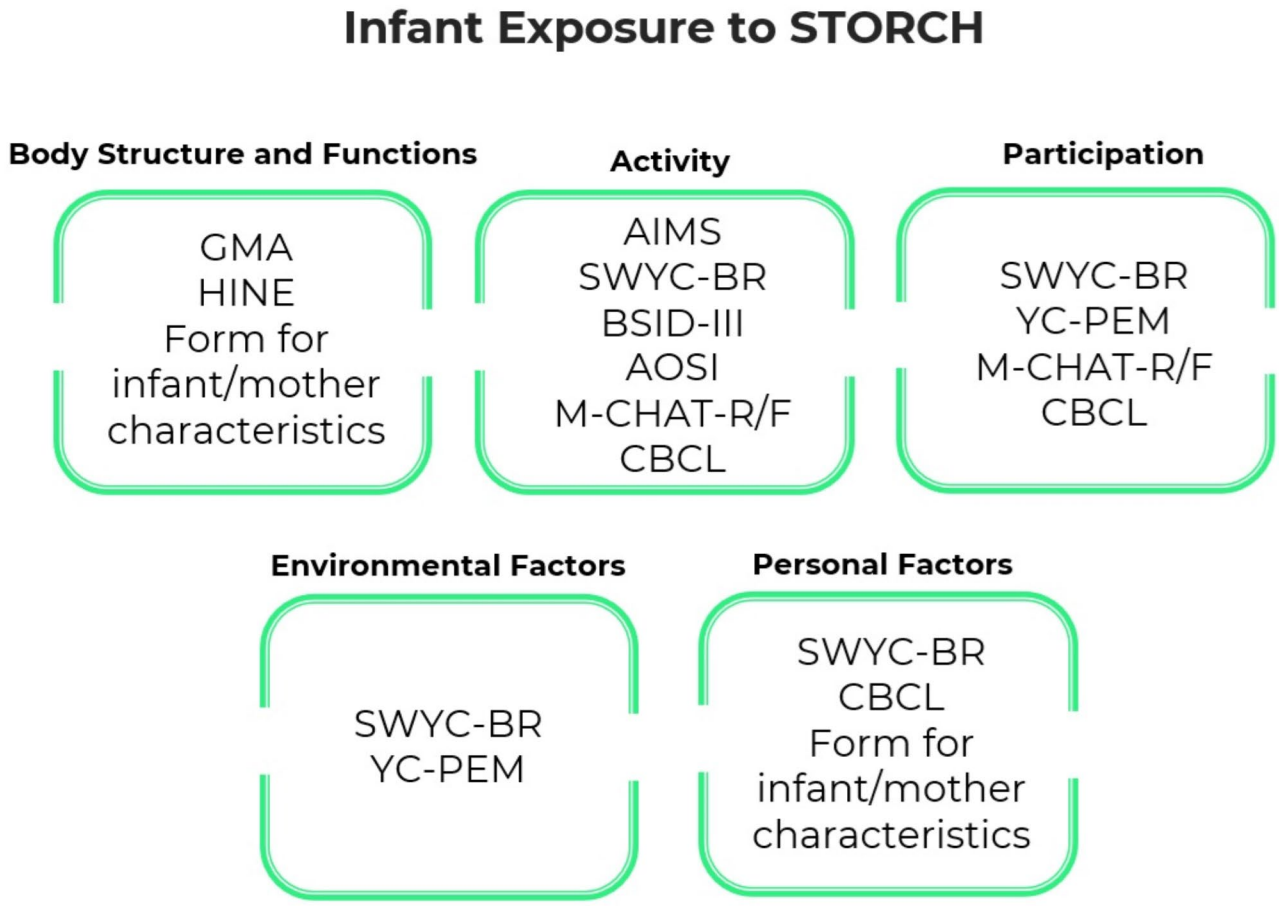

Fig. 2 Assessment tools considering the components of the ICF model

(MOS-R), which details postural and movement patterns and movement characteristics that coexist with FMs. The MOS-R is derived from the total of several subcategories: (1) fidgety movements, with scores of 12 points for normal, 4 points for abnormal, and 1 point for absent or sporadic; (2) observed movements patterns, with scoring as follows: 4 points if normal exceeds abnormal, 2 points if normal equals abnormal, and 1 point if normal is less than abnormal; (3) age-adequate movement repertoire, scored as 4 points for adequate, 2 points for reduced, and 1 point for absent; (4) observed postural patterns, assessed similarly to the previous category; and (5) movement character, with 4 points for smooth and fluent, 2 points for abnormal without cramped-synchronized movements, and 1 point for abnormal with cramped-synchronized movements. The maximum MOS-R is 28, while the minimum is 5 points. A MOS-R of 25 to 28 points is optimal; below 25 is considered reduced [39]; and below 20 and 9 are considered moderately and severely reduced, respectively [40]. Inter-rater reliability for the MOS ranges from 0.80 to 0.94 [41].

In this study, the FMs are filmed between 12 and 15 weeks post-term, for 5 min, following the Prechtl method´s instructions [18, 19]. The infants are supine on a mat, lightly dressed, on active alert, without stimuli, toys, or pacifiers. The assessments on the video will be carried out by at least two researchers certified by the GM Trust. In cases of disagreement, a senior GM Trust tutor will define the final classification and score.

Hammersmith infant neurological examination (HINE)

The HINE is employed to assess the infants' neurological responses from 3 to 24 months of age [20]. It has been widely used for the early detection of motor impairments, with various studies indicating its application in at-risk preterm and term infants. These studies demonstrate that the assessment can forecast sitting and walking capabilities, predict cerebral palsy, and offer more nuanced insights into the type and severity of motor issues [42]. The tool comprises 26 items categorized into the following subsections: cranial nerve function, posture, movements, tone, and reflexes and reactions. Each item is scored on a scale from 0 to 3, with the cumulative score yielding a maximum global score of 78 points [20].

Global scores are considered optimal if they are 73 or higher at 9 to 12 months, or 70 or higher at 6 months,

and 67 or higher at 3 months [20, 43]. Scores below these thresholds are classified as suboptimal and indicate a potential risk for motor impairment. Specific cut-off scores of ≤ 56 at 3 months and ≤ 65 at 12 months are highly predictive of cerebral palsy [21]. For the assessment, the infant must be in a diaper or in clothes that do not restrict their movements. The assessor positions the infant in different postures and conducts neurological tests. The assessment can be completed in 5 to 10 min. Good interrater reliability has been observed, even among inexperienced staff [20]. In this study we use the Brazilian version of the HINE [44].

Alberta infant motor scale (AIMS)

The AIMS is an observational tool used worldwide to assess gross motor skills in infants from birth to 18 months of age or independent walking. It systematically assesses the sequence of motor development and the control of antigravity muscles across four postures: prone, supine, sitting, and standing. The assessor records the infant's performance by assigning 1 point for each observed item and 0 points for non-observed items, yielding a maximum total score of 58 points. The maximum scores for each posture are as follows: 21 points for prone, 9 points for supine, 12 points for sitting, and 16 points for standing. The total score is calculated by summing these individual scores. The infant's percentile rank is determined by correlating the total score with an age-specific scoring chart provided in the scale. Interpretative criteria for the percentiles are as follows: normal motor performance is indicated by scores ≥ 25th percentile, suspicious motor performance is reflected by scores between the 5th and < 25th percentiles, and abnormal motor performance is indicated by scores < 5th percentile [45, 46]. The assessment lasts from 5 to 30 min [47]. Interrater reliability was set at 0.99 [48].

Bayley scales of infant and toddler development (BSID)

The BSID is internationally recognized as one of the most comprehensive tools for assessing child development. It is currently in its 4th edition [49], while the 3rd edition - BSID-III [50] has been adapted for Brazil [51] and is adopted in this study. Its purpose is to assess the global development of children aged from 16 days to 42 months and 15 days, covering five domains: cognitive, language, motor, socio-emotional, and adaptive. The first three domains are assessed through direct testing using the scale kit or through general observation of the infant or young child, involving activities and play that promote interaction between the child, the assessor, and/or objects. The language domain is subdivided into receptive communication and expressive communication. The motor domain is divided into fine motor skills and gross motor skills. The reliability coefficients for the BSID-III subtests range from 0.86 (fine motor), 0.87 (receptive communication), to 0.91 (cognitive, expressive communication, and gross motor) [52]. The socio-emotional and adaptive domains are assessed through an interview with the child's primary caregiver. The scale provides separate raw and scaled scores for each domain, as well as composite scores and percentile rankings for each scale. At the end of the process, the child's development is classified into one of seven levels (extremely low, borderline, low average, average, high average, superior, or very superior). The assessment takes approximately 30–90 min. Cutt-off scores of 85 will be adopted for considering developmental delay [53].

Modified checklist for autism in toddlers-revised with follow-up (M-CHAT-R/F)

The M-CHAT-R is a validated parent questionnaire used to screen for ASD in toddlers aged 16 to 30 months. Twenty yes/no questions can be completed and scored in less than two minutes. A total score of ≤ 2 indicates a low risk for ASD, and no additional Follow-up is necessary. If the total score falls between 3 and 7, the second-stage Follow-Up questions are administered to minimize false positives; if the score is ≥ 8, it is acceptable to skip the Follow-Up questions and refer the child directly for diagnostic evaluation. In this study, scores of ≥ 8 when skipping Follow-Up or scores of ≥ 2 with Follow-Up will be classified as indicating a positive risk (i.e., "At-Risk") for ASD [54]. Both continuous (raw) and categorical MCHAT-R/F risk scores will be used. The reliability index using Cronbach's alpha score test was $\alpha = 0.88$, suggesting an excellent reliability index [55]. In this study, we have used the Brazilian version of the M-CHAT-R/F [56].

Autism observational scale for infants (AOSI)

The AOSI [57] is a concise, semi-structured observational tool designed to assess early behaviors linked to ASD (referred to as autism) in infants aged 6 to 18 months. During the assessment, behaviors are recorded during interactive free-play sessions as well as in more structured activity interactions. The coding captures aspects such as visual attention tracking, developing social communication and responsiveness, and broader behavioral reactions, including temperamental reactivity and sensory/motor control and atypicality. The AOSI is typically scored in real-time, with 16 key items summed to produce a Total score (ranging from 0 to 38). Additionally, a Number of Markers (NoM) count is calculated based on the number of items that receive a non-zero score (ranging from 0 to 16) [58]. The reliability of the AOSI was assessed in high-risk infant siblings (those with older siblings diagnosed with ASD) at 6, 12, and 18 months. The inter-rater reliability for individual items and the total score was found to be good to excellent, especially at 12

months and older, while the test-retest reliability at 12 months was acceptable [57].

Child behavior checklist (CBCL)

The CBCL assesses behavioral and emotional issues in children aged 18 months to 5 years based on parents' reports. It consists of 99 items rated on a 3-point Likert scale, where 0 means "Not True," 1 means "Somewhat True," and 2 means "Very True/Often True." It assesses both internalizing problems (such as anxiety and depression) and externalizing problems (like aggressive and oppositional behaviors) through seven empirically derived subscales: Emotional Reactivity, Anxiety/Depression, Somatic Complaints, Withdrawal, Sleep Problems, Attention Problems, and Aggressive Behavior. Additionally, items are categorized into five subscales related to Affective Problems, Anxiety Problems, ASD, Attention-Deficit and Hyperactivity Disorder (ADHD), and Oppositional Defiant Disorder. Scores are interpreted using t-scores, with higher scores indicating more behavioral problems, and thresholds established for borderline and clinically significant behaviors [59]. The average test-retest reliabilities for the CBCL were 0.90 for empirically based syndromes and 0.88 for Diagnostic and Statistical Manual of Mental Disorders (DSM)-oriented scales. The competence scales also showed a reliability of 0.90. Internal consistencies, measured by Cronbach's alphas, ranged from 0.72 to 0.97 [60]. In this study, we will adopt the Brazilian version of the CBCL [61] to identify the risk for neurodevelopmental disorders such as ASD and ADHD.

Young children's participation and environment measure (YC-PEM)

The YC-PEM assesses the parents' perceptions of the involvement of their young infant (0–5 years old) in various activities across different settings: at home (e.g.: mealtime, indoor play and games), in daycare/preschool (e.g.: socializing with friends), and within the community (e.g.: dining out, community attractions). Caregivers also assess how various environmental factors (e.g.: physical layout, stimuli, social relationships, attitudes) and resources (including transportation, equipment and supplies, information, time, money) affect the infant's participation in each setting. Parents receive examples of each type of activity and environmental features and resources. The tool measures the frequency of the child's participation on an 8-point scale, from never (0) to once or more daily (7); the level of engagement in participation on a 5-point scale, ranging from not very involved (1) to very involved (5); and parents' satisfaction with their infant's current participation, along with the environmental supports and barriers considered significant at home, daycare/preschool, and in the community (with scores from zero to 100%). The instrument shows reliability ranging from moderate to excellent, with internal consistency between 0.68 and 0.96 and test-retest reliability between 0.31 and 0.93 [62]. In this study, we adopt the YC-PEM version translated into Brazilian Portuguese [63].

Survey of well-being of young children (SWYC-BR)

The SWYC is a screening tool designed as a structured interview consisting of 40 questions that assess various aspects of a child's well-being, including cognitive, language, and motor development; behavioral and emotional adjustment; ASD risk; and family stress. Each SWYC form is divided into four parts: (i) SWYC Milestones, which features a questionnaire with 10 questions tailored for each age group to assess developmental milestones in cognitive, motor, social, and language skills; (ii) the Baby Pediatric Symptom Checklist for children under 18 months or the Preschool Pediatric Symptom Checklist for those aged 18 to 65 months; (iii) a Family Questions section that includes 9 items related to child behavior and learning/development; and (iv) the Parent's Observation of Social Interaction, which assess risk for ASD for children aged 16 to 36 months. Each section has a specific score, allowing for classification at the end as "positive screening" or "negative screening." It is designed to be completed by parents and caregivers and takes around 10 min. In this study, we have used the adapted version of the tool for Brazil (SWYC-BR) [64]. The reliability of the SWYC-BR showed a convergent validity of 0.73 and an internal consistency of 0.97, indicating acceptable measurement qualities for the Brazilian version [65].

Assessment procedures

Infants are assessed longitudinally at the key ages of 3, 6, 9, 12, 18, and 24 months, with a tolerance of up to +20 days starting at 6 months. Assessments are age-specific according to each tool, as illustrated in Fig. 3.

The assessments can be conducted in a phased manner over up to 7 days. Assessments employing the GMA, AIMS, AOSI, and BSDI-III will be recorded.

Assessments are ideally scheduled between feeding intervals (1 to 1.5 h post-feeding) and cannot coincide with vaccination days. Except for questionnaire-based tools, which are completed by one of the parents, all assessments must occur while the infant is in an active alert state [66], in minimal clothing that does not restrict mobility or visibility of the upper and lower extremities. Assessments are performed with the infant on a mat. During developmental assessments, infants are provided a table and toys, such as rings, vehicles, dolls, and rattles, following the scales kits and guidelines. A cell phone on a tripod is used for recording purposes.

During the assessments, infants cannot be under the influence of medications, experiencing agitation,

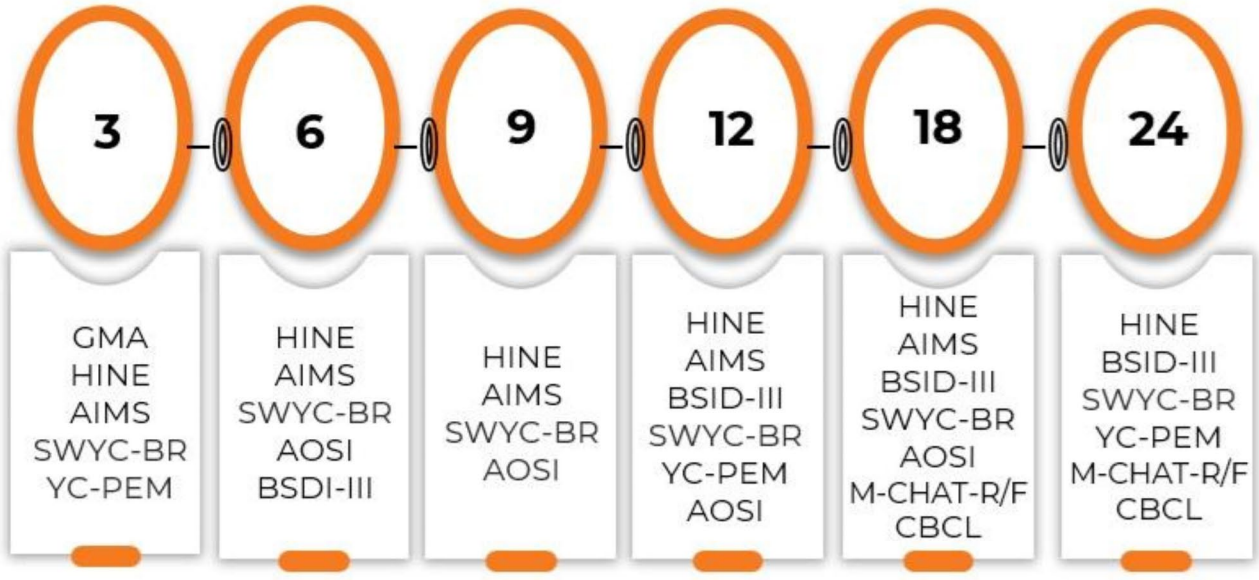

Fig. 3 Timeline, in months, of the assessment tools used in each age

irritability, inconsolable crying, or any clinical conditions that can adversely affect the execution of neuropsychomotor tasks. If infants cry or become fussy, the researcher and/or parents must try to soothe them. If the crying or fussy continues, an alternative date for the assessment must be scheduled by mutual agreement.

All participating centers conduct data collection following the same standards. On-line meetings have been performed to guarantee the maximum methodological alignment between centers.

Outcomes

The neurodevelopmental behaviors measured by GMA and HINE will be the primary outcome measures of this study. Motor performance, global development, risk of ASD, ADHD and other neurodevelopmental disorders, levels of participation, and the impact of the environment on participation, will be secondary outcome measures.

Diagnosis of cerebral palsy and other neurodevelopmental problems, including ASD and ADHD, will be response variables. The other clinical data, as well as the identification and sociodemographic data, will be independent variables.

Data analyses

The recordings of the assessments will be noted in the tools' forms. The data will then be inserted into a password-secured Excel spreadsheet in an online cloud. For statistical analysis, the support of software R (R Core Team, 2024) will be used. First, descriptive analysis will be conducted to characterize the sample and the study variables, using raw frequencies, percentages, means/standard deviations, and medians/interquartile ranges. The characteristics of the cohort will be described collectively and by location. Normality tests (Kolmogorov-Smirnov) and homogeneity tests (Levene) will be performed for the application of statistical tests. Parametric tests or non-parametric tests for repeated measures will be applied, depending on the initial analysis, to compare differences in the assessment tools outcomes across ages and between groups (exposed vs. unexposed).

Still with the aim of comparing differences in the assessment tools outcomes across ages, the model presented below will be estimated.

$$Y_{ij} = (\beta_{0E} + \beta_{0N}\ \text{Group}_{\ i}) + (\beta_{1E} + \beta_{1N}\ \text{Group}_{\ i} + b_{1i})\, x_{ij} + e_{ij},$$

where,

Y_{ij}= observed measurement of infant i in assessment (month) j;

Group_i = 1, if infant i belongs to the unexposed group (E if exposed group and N if unexposed group);

β_{0E}=intercept of the mean line of the exposed group;

$\beta_{0\,N}$=difference in the intercept of the mean line of the unexposed group in relation to the exposed group;

β_{1E}=slope of the mean line of the exposed group;

$\beta_{1\,N}$=difference in the slope of the mean line of the unexposed group in relation to the exposed group;

b_{1i}=random effect of slope;

x_{ij}= assessment j of infant i;

e_{ij}= random effect of infants.

To verify associations between the observed outcomes and the absence/presence of risk factors (exposure, unexposure), Pearson correlation tests (parametric) or

Spearman tests (non-parametric) will be applied. Relative risk or odds ratios will be calculated, along with their confidence intervals. Sensitivity analyses and regression models will be performed, taking into account missing data. A significance level of $\alpha = 5\%$ will be considered for all analyses.

Patient and public involvement

The public was involved in the design and plans for reporting and disseminating this research. Mothers provided input into priority research questions and the strategies for participants' enrolment and engagement. They also assist with recruiting potential participants by referring friends or relatives. Overall study findings are discussed with parents during study visits. Parents will be offered access to study summaries and materials resulting from the study findings and collaboration to improve language for knowledge translation. Parents will also help disseminating these summaries and materials to the community.

Discussion

The STORCH Brazil study is investigating the influence of STORCH exposure on the components of functioning in Brazilian infants throughout the first 2 years of life. Taking all its aims together, this study aligns with the ICF framework to provide a comprehensive view of how the exposition to maternal STORCH influences outcomes related to body structures and functioning, activity and participation, and contextual factors in infants, and how these components are connected in the exposed population. This will allow the understanding of the characteristics and needs of STORCH-exposed infants and will help therapists gain a deeper understanding of key factors that affect their clinical choices. We also expect that the findings of this study will help us to describe the neurodevelopmental trajectories of STORCH-exposed infants and understand their differences from typical, unexposed, neurodevelopment. Additionally, we expect to find that early neurodevelopmental assessment can predict later adverse outcomes in exposed infants. This would provide scientifically validated data to guide public policies on the early detection of neurodevelopmental problems in this population, allowing timely and tailored intervention. This is of widespread interest because the incidence of gestational STORCH has become problematic not only in Brazil but also in several other countries [8, 17].

Another potentiality of this study is to provide a protocol of standardized assessments for routinely evaluating infants exposed to various other infectious agents during gestation, including other STORCH infectious and new ones. There has been an increasing emergence of infections with teratogenic potential or suspected to cause negative outcomes in the developing fetus, such as Erythrovirus B19, Chikungunya virus, and more recently, Oropouche virus [67–69]. Therefore, having a well-established protocol to follow-up the exposed infants can be very useful.

We acknowledge that there are often significant challenges to maintaining families participating over the months in longitudinal studies, which can impact the sample size and the study validity. To improve that, we provide the parents with an immediate verbal report concerning the infant's assessment result and explain the advantages of such specialized follow-up for infants even in the absence of symptoms or STORCH exposure. If the parents cannot come to the laboratories or the ambulatory healthcare services for data collection, we assess the infants at their homes whenever possible. Including different centers in Brazil also helps us to enroll more participants and increase external validity.

We plan to communicate the results of this study at national and international scientific meetings and via submission of papers to high-quality peer-reviewed journals. The main finds will be disseminated in social media channels and engage with the involved universities' media offices to ensure maximum publicity. At the end of the study, we plan to create a scientific animation to illustrate the main research insights and offer accessible and digestible information to families. All knowledge translation activities will be done in both Brazilian Portuguese and English.

Overall, we believe that the STORCH Brazil project will help to put in evidence the needs of STORCH-exposed infants and to stimulate evidence-based strategies to optimize directed, early, and time-sensitive healthcare for this population.

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Author contributions

DSM conceived the original study that originated the present one, wrote the original version of this protocol, prepared the figures, and coordinates the overall data collection and project management. AOA is in data collection on site and contributed to the writing of this manuscript. ASGBM, CDLA, EMSC, SAP, and RHH coordinate data collection and data management at their local sites and contributed to the elaboration of this work. ASGBM contributed to the writing of this manuscript. CCW participated in the elaboration of this protocol. RHH participated in the development of the idea of this protocol. EFO and MJM collaborated in the methods design and contributed to the writing of this manuscript. MJM performed the sample size calculation and planned the statistical analyses. All authors read, revised, and approved the final version of this manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained before the start of the project by the Ethical Committee on Human Research of the Federal University of Mato Grosso do Sul (CAAE: 81691424.8.0000.0320). A written, informed legal consent form is signed by the parents before the infant is included in the study.

Consent for publication
Not applied at this moment.

Competing interests
The authors declare no competing interests.

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