Alterations in neurodevelopment and brain damage in neonates

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ABSTRACT

Background: During fetal and neonatal development, the fetus’s brain is in a critical growth development phase, making it susceptible to alterations that affect its correct functioning. These alterations occur more frequently in preterm neonates or in those whose mothers have presented a pathology during their gestation period or their age. Objective: Search for information about alterations in neurodevelopment and brain damage in neonates. Methodology: The research was conducted through a scientific bibliographic review answering the research question; databases such as Google Academic, Scielo, Dialnet, Scopus, and Pubmed were used to collect information. Results: 15 investigations were obtained as results, and after applying the different filters, only 3 met the information required for this investigation and were updated. Discussion: These alterations occur in the first instance due to prematurity, followed by the age of the mother and pathologies that can occur during pregnancy, being a problem for which neonates are referred to the intensive care unit. Conclusion: Early detection of alterations that may occur in neonates is of vital importance since when this does not happen in the neonate, it can cause disabilities throughout their life, such as cerebral palsy and even death.

Keywords: Neurodevelopmental alterations, neonates, brain damage, prematurity.

ARTICLE INFORMATION

Science-Metric Classification (Domain):
Health Sciences

Main topic:
Neurodevelopment in neonates

Main practical implications:
Early detection of neurodevelopmental alterations in neonates, particularly those born preterm or to mothers with pregnancy complications, is crucial to prevent long-term disabilities such as cerebral palsy. This article brings insights from the specialized literature that can guide policies and new studies related to neurodevelopment in neonates.

Originality/value:
The analytical synthesis presented addresses a very relevant and scarce topic in Latin American and developing country literature.

PALABRAS CLAVE
ALTERACIONES DE NEURODESENVOLVIMIENTO, NEONATOS, DANOS CEREBRALES, PREMATURIDAD.
INTRODUCTION

The brain of a child is a structure that is in formation, therefore, it goes through several phases where cells create neuronal connections and all structures from the embryonic period with the aim of achieving their function, as well as their differentiation. During this stage of fetal and neonatal development, the brain of the fetus is in a critical period of growth-development, where it is vulnerable to suffering alterations that can cause neurologically based disorders, affecting its proper functioning (Alonso, 2023).

These alterations occasionally show up in structural lesions, although there is a possibility that they also occur due to a deficiency in the maturation of fibers that alter connectivity and, as a result, inadequate integration in neuronal communication (Kim, 2022). The bases of neurodevelopment come from adequate care, early learning, nutritional status and the prevention of diseases. When these bases are not well founded, there are alterations in neurodevelopment that cause deviations in brain function, for this reason The gestation period and the first 5 years of a child's life are essential for the well-being of physical, emotional, cognitive, psychological and social development that will be reflected throughout their life. (Alonso, 2023; Kim, 2022).

There are prenatal and perinatal risk factors that are related to the mother's condition and are associated with the existence of neurodevelopmental disorders, among them we have: maternal age at the time of pregnancy (mother under 18 years of age and mother aged over 35 years), substance consumption, nutritional factors, presence of infectious and contagious pathologies and accidents during embryonic development (Kim, 2022; Lepe, 2023).

Prematurity is the main cause of perinatal morbidity, which causes alterations in neurodevelopment and brain damage in neonates. Each year, approximately 15 million premature babies are born in the world, which is why it is necessary for the personnel who work in the neonatal intensive care (NICU) has expertise in managing patients (Barra, 2021; Cubillos, 2022; López, 2022; Pérez, 2024). In Latin America, the pathologies that occur most frequently during pregnancy are hypertensive disorders 25%, gestational diabetes 16% leading to preterm births in 25-43% of cases. Intrauterine infections, prematurity and neonatal asphyxia in 23% are related to neonatal alterations, in addition, these alterations that occur before and during birth represent 20% and are related to preterm births and low birth weight, resulting in alterations. of neurodevelopment where 13-24% present neurological disorders and 6-13% intellectual deficit. (Lepe, 2023; Barra, 2021; Millar, 2018; Salmón, 2024)

Likewise, the development of a brain injury in the premature newborn can occur due to different factors, among which we find perinatal asphyxia, infection, inflammation, chronic hypoxia and exposure to treatments that include mechanical ventilation and corticosteroids. Treatment is currently limited, the use of magnesium sulfate reduces in a small but important way the risk of cerebral palsy and gross motor dysfunction during early childhood, but its result in a combination of death or disability has not been proven to be effective. (Yates, 2021; Bachnas, 2021; Keir, 2022; Shepherd, 2024) On the other hand, preclinical studies emphasize several competent neuroprotective treatments, such as therapeutic hypothermia, melatonin, umbilical cord blood and vitamin D supplements, which help to reduce brain damage in premature neonates. (Yates, 2021; Wang, 2023; Xie, 2023; Razak 2023; Segler 2021)

Among the brain lesions in premature infants we find lesions of the white matter (WS), generally associated with neuronal and axonal alterations in the cerebral cortex and other areas of gray matter. SB injury also includes periventricular leukomalacia, which is a type of brain injury that affects premature babies. This condition involves the death of small areas of brain tissue around fluid-filled areas, called ventricles, as a result of this. holes are generated in the brain due to the damage caused. (Vinces, 2022; Schneider, 2019)

The incidence of severe hemorrhage, together with periventricular leukomalacia, constitutes the most serious threats to the brain of premature babies, being associated with greater morbidity and mortality and an adverse neurological prognosis. We classify intraventricular hemorrhage according to a brain ultrasound, leading to a classification of different grades (Grade I, Grade II, Grade III) according to the percentage of hemorrhage present at the time of performing an ultrasound. (Vinces, 2022; Pascal, 2023) Periventricular leukomalacia (PVL) is a type of brain injury, where “leuco” refers to the white matter of the brain, and “periventricular” refers to the area around the ventricles. An important cause of this condition is changes in blood flow around the ventricles of the brain. This is a very fragile area, therefore, it is very prone to injury, especially before 32 weeks of gestation. (Vinces, 2022; Valer, 2023; Perrone 2023)

Furthermore, ischemic lesions and hemorrhages in premature newborns are frequent complications in NICUs, periventricular leukomalacia and germinal matrix hemorrhage are two conditions that occur more frequently in premature newborns, thus becoming the main risk factors. associated with the development of cerebral palsy. (Vinces, 2022; Valer, 2023) Among the different risk factors and their incidence in the main types of brain injuries in premature infants, there are:

Lack of maturation with corticosteroids: The lack of administration or the incorrect dose of corticosteroids to the
mother during pregnancy can cause a lack of maturation of the fetus.

Severe depression: A 5-minute Apgar score of less than 6 points, or the need for endotracheal intubation at birth, are usually signs of severe depression.

Neonatal Sepsis: A clinical neonatal infection, confirmed by a blood culture, performed at any time during the hospitalization of the premature newborn. (Zarate, 2023)

Pneumothorax: An intrapleural air leak, with or without underwater pleural drainage.

Apnea: Presents as a lack of respiratory stimulation for 20 seconds or more, with or without oxygen desaturation, and with or without the need to administer xanthines.

Also a common condition in premature infants is focal necrosis of the cerebral white matter, accompanied by a diffuse gliosis reaction and activation of microglia in the affected area, this produces alterations in the functions of their oligodendroglial progenitors and in myelination, which can cause neurocognitive dysfunction. Likewise, this event may reflect damage to the gray matter of the brain, particularly in the thalamus, globus pallidus, hippocampus and dentate nucleus of the brain. These results indicate the severity of the disease and the need for a better understanding of the processes involved in the development of new, more effective therapies. (Vinces, 2022; Cerisola, 2019).

**METHODOLOGY**

The approach to be used will be the Systematic Review (S.R.), a research method that follows a thorough and clear process to identify, evaluate and summarize the available evidence related to a specific research question on a given topic. This process will be carried out using the PRISMA method to collect and organize data in a way that guarantees obtaining high-quality information (Linares-Espinós et al., 2018).

The criteria applied to select the articles are described below:

**Inclusion criteria:**

- Documents that contain titles with the terms Neurodevelopmental disorders, neonates, brain damage, prematurity.
- Agree with the search equation "Neurodevelopmental alterations AND neonates AND brain damage".
- Free access articles.
- Articles in English and Spanish languages.
- Articles that have been published between 2020 and 2024.
- Research with a methodological process and criteria that guarantee its rigor.

**Exclusion criteria:**

- Documents that are in languages that are difficult to translate.
- Articles without academic relevance and scientific verification.
- Documents not related to the topic.
- Repeated investigations

**Search engines:**

- Academic google, Pubmed, Elsevier, Scielo

Keywords were used as the main search strategy, along with filters that limit the selection of articles according to their year of publication, prioritizing the most recent ones. The keywords used are specified below.

**Table 1. Literature search strategies.**

<table>
<thead>
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<th>Key terms</th>
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Note. Prepared by the authors
Likewise, searches were carried out using different variables or search equations related to the keywords used.

Table 2. Main variables and modifications operated.

<table>
<thead>
<tr>
<th>Main variables</th>
<th>Modification and implication of variables</th>
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<tbody>
<tr>
<td>Neurodevelopmental disorders</td>
<td>Congenital malformations in neonates</td>
</tr>
<tr>
<td>Brain damage</td>
<td>Brain alteration in neonates</td>
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The study selection process is based on the following criteria:

1. Initial reading of the research titles to determine their relevance to the objectives of the study.
2. Subsequently, the summaries of the documents are read, which allows us to delve deeper into the information of the articles and exclude those that are repeated or that do not meet the research inclusion criteria.
3. Finally, a complete and intensive reading of the articles selected for inclusion in the research is carried out. This step ensures a comprehensive understanding of the findings and contribution of each study to the body of knowledge in the area of interest.

After identifying the publications to be used, data were extracted, which were established through tables where the following indicators were proposed to classify the articles: title of the publication, author/s, year of publication/country, design of the study, results and analysis.

RESULTS AND DISCUSSION
Characteristics of prematurity and neurodevelopmental alterations
Lepe Gejda, IR, Paz Sacramento, E, A, Reina Rojas, BK & Staii Sermeya, ME

2023/Guatemala
Descriptive cross-sectional study with an analytical approach.

In this article it was shown that young first-time mothers between 18 years of age and older first-time mothers over 35 years of age have a high percentage of risk of prematurity birth, which could influence neurodevelopmental alterations in the child. Furthermore, if there is a greater degree of prematurity, the risk of neurodevelopmental disorders occurring is greater.

Perinatal risk factors and evolution of neurodevelopment until the first year of age
Almeu Diaz, J, Morilla Guzman, A, Parada Merin, Y, Tamayo Perez, C, Cabrera Bentes, E, and Rodriguez Cortina, D.

2021/Cuba
Descriptive, retrospective and longitudinal observational study.

In this article, perinatal risk factors for alterations in neurodevelopment were found where the male sex was predominant. 68.5% in alterations in metabolic disorders 11.5% and perinatal asphyxia 11.2% that were related to neurodevelopmental alterations and respiratory interventions.

Risk of brain damage in premature infants under 34 weeks exposed to histological chorioamnionitis, Lima, Peru
Guznán, N, Lemenza, C, Samaleidos, S, Vila J, Juarez, T, Canes, J, and Guzñín, Pinto, D.

2020/Pru
Retrospective and descriptive study.

In this article it was found that histological chorioamnionitis (CAH) is a risk factor for developing brain lesions in premature infants under 34 weeks.

Prematurity: epidemiology, causes and consequences, first place in mortality and disability.
Maitos, L, Reyes, K, López Navarrete, G, Reyes, M, Aguilar, E, Pérez, O, Reyes, U, López Cruz, G, Flores, B, Quero Hernández A, and Quero Estrada, A.

2020/Mexico
Descriptive and retrospective study.

In this article, it was found that prematurity is the first cause of mortality and is also responsible for a large number of disabilities and adverse events, including neurological, physiological, respiratory, metabolic, and immunological complications, among others.

Prevalence of alterations in motor neurodevelopment in premature children without a diagnosis of cerebral palsy.
Millar, PA, Navarro, J-J, Martella, D and Gallardo, OP

2018/Chile
Cross-sectional descriptive study or prevalence study.

In this study it was shown that 65.9% of children with a history of extreme prematurity or moderate prematurity had mild psychomotor developmental delay.

Prevalence of alterations in neonates in children from a rural population of Oaxaca evaluated using the Child Development Assessment test.
Alonso López, N, Hernández Valle, V, Piedraza Vargas, ME, & García Medina, NL.

2023/Mexico
Description, cross-sectional and prospective study.

In this study, a prevalence of alterations in neurodevelopment was found, predominately in the male sex, with language as the area of greatest alteration with 29% neurological conditions only occurred in 2% of the total participants, in addition, the factor of the sex that had the highest prevalence is urinary infections in mothers with 56%.

Neonatology: Brain injuries in premature babies.
Vincs Menéndez, C, Calderón, VOR, Alzueta, AR, and Moreno, MPV

2012/Ecuador
Systematic review and meta-analysis of controlled clinical trials.

Within this research it was found that brain lesions are one of the main adverse consequences of premature birth, among the lesions that are associated are white matter (WM) lesions, mainly periventricular leukomalacia (PVL) and intraventricular hemorrhages (IVH), whose risk factors are associated with the development of cerebral palsy.


2021/United States
Observational and retrospective study.

In this article, through the collection of umbilical blood, it was shown that 10.7% of the included neonates developed brain lesions.

Effect of perinatal asphyxia and body hypothermia on auditory evoked potentials and development in the first two years of life.
Soler Ulimin, KM, Romero Esquivel, A, Romero, Gutierrez, PV, Orteco A, Calderon, C, and Orozco, R.

2022/Mexico
Prospective, descriptive and longitudinal study.

With the use of body hypothermia therapy as a treatment in the first hour, it has been possible to improve the survival of neonates, as well as the neurodevelopmental results in children with moderate to severe hypoxic-ischemic Encephalopathy (HIE). PEATC values were similar to those observed in those children and were significantly correlated with development at both ages.

Safety and effectiveness of therapeutic hypothermia in neonates with mild hypoxic-ischemic encephalopathy.

2023/China
Retrospective study.

In this article it was shown that therapeutic hypothermia reduced the incidence of brain injuries in neonates with mild hypoxic-ischemic encephalopathy.

Chorioamnionitis and risk of long-term neurodevelopmental disorders in offspring: a population-based cohort study.
Trumanstriy, E, Lisovskaya, S, Manaa, G, OrTzid, A.K, & Razac, N.

2022/Sweden
Retrospective population-based cohort study.

In this article it was found that 5700 offspring were exposed to chorioamnionitis during the pregnancy stage. During the follow-up time of the study, there were 0.21% cases of cerebral palsy in addition to 0.06% cases of epilepsy, continuing with 2.27% cases of autism and 5.12% cases of attention deficit hyperactivity disorder, after adjusting for potential confounders, exposure to chorioamnionitis increased the risk ratios for cerebral palsy.

Histological chorioamnionitis and neurodevelopment in premature children under 34 weeks, Lima, Peru
Vila, Judith, Guillén-Pinto, Daniel, Bellomo, bitcoin, and Guillian, Noelia.

2023/Pru
Retrospective study.

In this article, histological chorioamnionitis did not show influence on neurodevelopment in premature infants less than 34 weeks at 2 years of age, which means that it has no long-term effects.

Brain anatomopathological findings in neonates with congenital heart disease.

2022/Mexico
Retrospective and descriptive study.

In this article it was found that brain lesions in neonates with congenital heart disease are characterized by lesions of the white matter (WM), mainly periventricular leukomalacia (PVL) and intraventricular hemorrhages (ICH), whose risk factors are associated with the development of cerebral palsy.

Neurodevelopment in very low birth weight newborns born in Matanza during the period 2016-2018.
Rosaima Castellanos, Gerardo Ropaga, Rigoño Rodríguez, Solangel de la Caridad, & Hernandez Morales, Danara.

2022/Cuba
Prospective observational study.

This article showed that neurodevelopmental alterations in very low birth weight premature infants constitute up to 50% of childhood neurological abnormalities.

The research characterizes the risk factors in prematurity, as well as its possible alterations, so prematurity, perinatal and neonatal neurodevelopment and the gestational age of the child at birth is a significant factor in understanding the risk of developing neurodevelopmental disorders.

Note: Own elaboration with the research data (2023)
In the study carried out by Lepe, in relation to the factors that contribute to neurodevelopmental alterations in premature children and the incidence of the mother’s age, the result is that 55.6% of mothers under 18 years of age and elderly mothers are that is, those over 35 years of age are more likely to have a preterm birth, which as a consequence has a greater risk of neurodevelopmental alterations in the child. As well as, the pathologies that the mother presents during pregnancy are 85% risk factors for premature birth and those that are acquired during this stage with 15% are factors that influence the neurodevelopment of the premature child. (Lepe, 2023). Furthermore, in the study carried out by Abreu Díaz, perinatal risk factors for alterations in neurodevelopment were found where the male sex was predominant 68.4%, in addition to metabolic disorders 13.5% and perinatal asphyxia 11.2% that were related to alterations of the neurodevelopment. (Abreu, 2021)

Torres in his research indicates that there is a higher incidence of neurodevelopmental alterations in late preterm newborns at 6 months 18.8%, at 1 year 8.7% and at 2 years 7.7%, they also had a greater need for ventilation mechanics and the use of anticonvulsant drugs, predominate the male sex and birth by cesarean section to present these neurodevelopmental alterations, having a relationship with the research of Lepe and Abreu. (Torres, 2019). For his part, Alonso López, found a prevalence of alterations in neurodevelopment predominating in the male sex, with language being the area of greatest affection with 29%, neurological conditions only occurred in 2% of the total participants, in addition, the The risk factor that had the highest prevalence is urinary infections in mothers with 56%. (Alonso López, 2023). Guillén, in the results of his research, showed that histological chorioamnionitis (CAH) is a risk factor for developing brain lesions in premature babies under 34 weeks. (Guillén, 2020). On the other hand, Vila showed that CAH did not show influence on neurodevelopment at two years of age, which means that it does not have long-term effects. (Vila, 2023)

Vinces, in his research, found that brain lesions are one of the main adverse consequences of premature birth. Among the associated lesions are white matter (WM) lesions, mainly periventricular leukomalacia (PLV) and intracranial hemorrhages (HIC), whose risk factors are related to the development of cerebral palsy, agreeing with Carina’s study. (Vinces, 2022; Carina, 2022). Also, for his part, Segler, through the collection of umbilical blood, showed that 10.7% of the neonates included in his study developed brain lesions. (Segler, 2021).

In the study carried out by Matos, it was found that prematurity is the first cause of mortality and is also responsible for a large number of disabilities and adverse events, including neurodevelopmental, physiological, respiratory, metabolic, and immunological complications, among others. (Matos, 2020). In his research, Millar showed that 69.56% of children with a history of extreme prematurity or very premature children had mild psychomotor developmental delay. (Millar, 2018). Also, Robaina Castellanos in her research found that neurodevelopmental alterations in very low birth weight premature babies constitute up to 50% of the neurological abnormalities of childhood.

Soler and Wang, in their research, mention that with the use of body hypothermia therapy as a neuroprotector in the first 72 hours, it has been possible to improve the survival of neonates, as well as the results in neurodevelopment in cases with Hypoxic-Ischemic Encephalopathy (HIE) mild, moderate and severe. PEATC values were similar to those observed in healthy children and were significantly correlated with development at both ages. (Soler, 2022; Wang, 2023). Moreover, Tsamantioti, in his research with 5770 offspring who were exposed to chorioamnionitis during the pregnancy stage, during the follow-up time of the study, there were 0.21% cases of cerebral palsy in addition to 0.80% cases of epilepsy, continuing with 2.27% cases of autism and 5.12% cases. of attention deficit hyperactivity disorder, after adjusting for potential confounders, exposure to chorioamnionitis increased the risk ratios for cerebral palsy.

The literature consistently indicates that prematurity, maternal age, and maternal health conditions are significant contributors to neurodevelopmental alterations and brain damage in neonates. There is a clear emphasis on the importance of early detection and intervention to reduce the long-term impact of these conditions, with particular attention to the effectiveness of therapeutic strategies like body hypothermia in improving outcomes for affected neonates. The findings emphasize the complex interaction of prenatal and perinatal factors in shaping neonatal brain development and highlight the constant need for targeted research and clinical strategies to address these challenges.

CONCLUSIONS

There are prenatal and perinatal risk factors that are related to the mother’s condition and are linked to the existence of alterations in neurodevelopment, among them we have: prematurity, maternal age at the time of pregnancy, substance consumption, nutritional factors, presence of infectious and contagious pathologies, birth by cesarean section, evaluation of the low Apgar test at the fifth minute of birth, male sex, low birth weight, neonatal sepsis, systemic inflammatory response syndrome, hypocalcemia, hypoglycemia, neonatal asphyxia, seizures and accidents during embryonic development.

In addition, SB injury, including periventricular leukomalacia, affects premature babies, as it involves the death of fluid-filled ventricles, resulting in holes in the brain due to the damage caused. Thus we have that the neurodevelopmental
alterations that occur most in premature children are cognitive, linguistic, emotional and motor. Finally, based on all the arguments raised and supported in this article, it was determined that the early detection of alterations that may occur in neonates is of vital importance since when this does not happen in the neonate it can cause disabilities throughout life, your life such as cerebral palsy and even cause death.

**Limitations and future research**

Among the limitations of the study is that there is limited information about the topic of study in Ecuador, so the importance of expanding lines of research that help create protocols that support care in neonates with this pathology based on scientific evidence is emphasized. Future studies in Ecuador and other developing countries should focus on how socioeconomic factors, such as access to prenatal care and maternal education, influence the incidence and severity of neurodevelopmental alterations in neonates. Research also should explore the effectiveness of affordable, early intervention strategies for preventing neurodevelopmental damage in preterm neonates, particularly in under-resourced healthcare systems typical of developing nations.

**REFERENCES**


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**Contribution of each author to the manuscript:**

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There is no conflict of interest

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