DOI: 10.7860/JCDR/2023/56550.17671

Review Article

Physiotherapy Section

Narrative Review on Prenatal, Intrapartum and Neonatal Risk Factors for Cerebral Palsy in Children

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ABSTRACT

Cerebral Palsy (CP) is not a disease, however a syndrome advanced characterised by associate aberrant management of movement or posture, that seems early in life and ends up in long motor incapacity. The underlying causes of CP are still poorly understood. Many individual risk factors of CP are known, however less is understood concerning their interaction and the way they could relate to completely different pathophysiological pathways. The risk factors may be prenatal, intrapartum, neonatal or combined. Articles were searched to identify risk factors for CP, published from 2001 to 2021. A total of 43 relevant articles including randomised and non randomised controlled trials, systematic reviews and comparative studies were included in this review. From selected analysis reports, most of the studies enclosed within the review showed sturdy strength of association as a causative factor responsible for CP. From this review, it had been ended that multiple risk factors overcome the defence mechanisms and lead to CP. Although any one factor, if severe, may be sufficient to cause CP so preventive strategies and early intervention for high-risk infants are needed.

Keywords: Cognitive function, Early intervention, Motor disability

INTRODUCTION

Cerebral Palsy (CP) may be a non progressive condition affecting approximately 3 in 1000 newborns and it is characterised by acquired brain damage which affects motor and cognitive functions [1-3]. CP is the most common cause of physical disability in childhood, with limitations that persist throughout life [4-6]. CP is not an illness but a syndrome complex, characterised by an aberrant control of movement or posture, that seems early in life and results to lifelong motor disability. CP is defined as "a cluster of permanent disorders of the event of movement and posture inflicting activity limitation(s) that are attributed to non progressive disturbances that occurred in the developing foetal or infant brain".

The motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication and/or behaviour, epilepsy and musculoskeletal problems [7,8]. Incidence of perinatal and neonatal mortality has decreased, also maternal and neonatal care have undergone major changes, but the overall prevalence of CP has remained stable over the years, at between 1-3 per 1000 live births [9-11]. If a neuronic loss because of brain injuries, the cortical (pyramidal) region will have spasticity, the basal ganglia (extrapyramidal) region will experience dyskinetic movements, and the cerebellum will experience hypotonia and mixed CP. Spastic CP, which accounts for 75% of cases, is the most prevalent kind. A lesser percentage of children with CP exhibit dyskinetic behaviour [12].

The underlying causes of CP are still poorly understood. Many individual risk factors of CP are known. However, less is understood regarding their interaction and the way they could relate to completely different pathophysiological pathways. The risk factors that will be antenatal, perinatal or neonatal, or postneonatal are represented in [Table/Fig-1] [13]. Different areas of research are of interest over the years to spot causes of CP, and it is modified due to the development of maternal and neonatal care: as an example, the occurrence of cerebral damage due to hyperbilirubinemia has decreased dramatically in higher resource countries [14].

The purpose of this study was to review the current research on risk factors of CP for children and how the new findings can affect the content of the CP registers across the world. The research question for this study was 'What risk factors for CP have been identified in the literature for infants?'

Prenatal	Intrapartum and neonatal
Hypoxia	Asphyxia
Metabolic disorder of mother, Hypoxic-ischaemic Encephalopathy (HIE)	Premature birth <32 weeks or weight <2500 g
Multiple gestations	Infection
Intrauterine infection	Blood incompatibility
Chorioamnionitis	Abnormal foetal presentation
Maternal fever	Placental abruption
Exposures to toxins like lead, mercury, manganese, fluoride, tetrachloroethylene (organic solvent), Dichlorodiphenyltrichloroethane (DDT) and chlorpyrifos pesticide among others	Instrument delivery
Abdominal trauma	

[Table/Fig-1]: Known risk factors associated with cerebral palsy [13].

LITERATURE SEARCH

All the peer-reviewed full-text articles published in the English language, between 2001 to 2021, with the primary aim of identification of risk factors for CP in all birth types, were searched from various online databases including Google scholar, PubMed, Elton B. Stephens Company (EBSCO), Medline, ScienceDirect, Cumulated Index to Nursing and Allied Health Literature (CINAHL) and 182 articles were found. A 136 relevant articles were found out of 182, out of which 93 articles were excluded (i.e., three were published in languages other than English, 1-a case report, 38-included risk factors not specific to CP, 29 were articles dedicated entirely to genetic risk factors, 14 were published before 2001 and 8 were only abstracts). As a result, 43 full-text articles were identified and reviewed in this manuscript. A narrative review of all 43 articles was conducted to identify risk factors for CP.

There are several heterogeneous risk factors at focus in current research regarding CP. Studies regarding one or a few prenatal risk factors are listed in [Table/Fig-2] [15-36]. Those regarding perinatal and neonatal risk factors are listed in [Table/Fig-3] [36-49] and similar review articles are described in [Table/Fig-4] [50-56]. Preventive

S. No.	Author name and year	Place of the study	Study	Risk factor	Conclusion
1	Walstab J et al., (2002) [15]	Australia	Antenatal and intrapartum antecedents of Cerebral Palsy (CP): a case-control study	Cigarette smoking, antenatal Cardiotocograph	Protective effects of mother's negative Rhesus status, cigarette smoking at the primary visit, and an increased risk of CP related to an abnormal antenatal cardiotocograph.
2	Wu YW et al., (2003) [16]	California, San Francisco, United States of America (USA)	Chorioamnionitis and CP in term and near-term infants	Chorioamnionitis, intrauterine growth restriction, maternal black ethnicity; maternal age older than 25 years and nulliparity	Risk factors known in their study enclosed chorioamnionitis, intrauterine growth restriction, maternal black ethnicity; maternal age older than twenty five years and nulliparity.
3	Jacobsson B and Hagberg G (2004) [17]	Sweden	Antenatal risk factors for CP	Low Gestational Age (GA) asphyxia, congenital infections	They identified low GA is the most important risk factor for CP, asphyxia during delivery congenital malformations, specific brain malformation, are more often seen in children with CP, perinatal infections-bacterial, viral, and protozoal-can be cause for CP.
4	Neufeld MD et al., (2005) [18]		Maternal infection and risk of CP in term and preterm infants	Maternal infection	Maternal infection is a risk factor for CP in infants.
5	Greenwood C et al., (2005) [19]	Oxfordshire health authority, United Kingdom (UK)	Why is there a modifying effect of GA on risk factors for CP?	Pre-eclampsia, very preterm infants, GA	There is increase in the risk of CP associated with pre-eclampsia in term infants as very preterm cause itself abnormal event.
6	Bonelli SR et al., (2005) [20]	Scotland, UK	Comparison of risk factors for CP in twins and singletons	Multiple pregnancies, GA, birth weight	CP prevalence is predicted by birth weight, GA, and sex of the infant for both single and twin births.
7	Nielsen LF et al., (2008) [21]	Aarhus, Denmark	Asphyxia-related risk factors and their timing in spastic CP	Cord around the neck, abnormal foetal growth Small for Gestational Age (SGA)	According to their findings, placental infarction was associated with a fourfold higher risk of spastic quadriplegia and cord around the neck was associated with a threefold higher risk. There is a strong association between placental infarction and spastic quadriplegia, and cord around the neck with a threefold greater risk of spastic quadriplegia.
8	Kurjak A et al., (2010) [22]	Zagreb, Croatia	Intrauterine growth restriction and CP	Intrauterine Growth Retardation (IUGR)	Specific high-risk pregnancies complicated with IUGR and at risk for neurological complications can be diagnosed with the US.
9	Glinianaia SV et al., (2011) [23]	Newcastle, UK	CP rates by birth weight, gestation, and severity.	IUGR	It is still unclear how CP is related to intrauterine growth, according to them.
10	Himmelmann K et al., (2011) [24]	Gothenburg, Sweden	Risk factors for CP in children born at term	Infection, multiple gestations	As a result of their study, they concluded that malformation, infection, and multiple genders all contributed to CP risk.
11	Day SM (2014) [25]	Newport Beach, USA	Birth size and the risk of CP in term births	Birth size-IUGR	Degrees of associations of CP and the various anthropomorphic measures vary According to the CP subtype.
12	Wu CS et al., (2013) [26]	Denmark	Risk of CP and childhood epilepsy related to infections before or during pregnancy	Epilepsy and infection	These findings indicate that the maternal immune system, maternal infections before pregnancy may affect the development of cerebral diseases in the offspring.
13	Strand KM et al., (2013) [27]	Trondheim, Norway	Mediators of the association between pre-eclampsia and CP: A population-based cohort study	Pre-eclampsia	There was an increased risk of CP associated with pre-eclampsia, which was mediated by preterm birth, small gestational age, or both. CP is only associated with pre-eclampsia among children born at term.
14	Meeraus WH et al., (2015) [28]	United Kingdom	Association between antibiotic prescribing in pregnancy and CP or epilepsy in children born at term: A cohort study using the health improvement network	Antibiotic prescribed during pregnancy	They found that there is no overall association between antibiotic prescribing in pregnancy and CP and epilepsy in childhood.
15	Minocha P et al., (2017) [29]	Rajasthan, India	Clinical spectrum, co-morbidities, and risk factor profile of CP children: A prospective study	Primigravida, anaemia and Asphyxia	Asphyxia is the most common risk factor, and spastic quadriplegia is the most common type of CP. CP development can be prevented to some extent if people are aware of common risk factors that contribute to the development of CP.
16	Mor O et al., (2016) [30]	Beersheva, Israel	Early onset pre-eclampsia and CP: A double hit model?	Pre-eclampsia	In assessment with regular pregnant women, the charge of CP is double amongst sufferers with pre-eclampsia, specifically people with early-onset disease.
17	MacLennan AH et al., (2015) [31]	Adelaide, Australia	CP: Causes, pathways, and the role of genetic variants	Genetic	Different pathogenic genetic variations contributing to the CP spectrum are very likely to develop over the following decade, and have to open a new direction into the causes of CP.
18	Forthun I et al., (2016) [32]	Bergan, Norway	Maternal prepregnancy Body Mass Index (BMI) and risk of CP in offspring	Maternal BMI	Higher prepregnancy maternal BMI was associated with an increased risk of CP in offspring.
19	Schneider RE et al., (2018) [33]	Quebec, Canada	The association between maternal age and CP risk factors	Maternal age	The risk factor profiles of children with CP vary by maternal age. They came to the conclusion that when maternal age rises, CP prevalence does as well.

20	Smith DD et al., (2020) [34]	New York, USA	Risk of CP by GA among pregnancies at-risk for preterm birth	GA	With growing GA, the risk of CP populations reduces. Even though the majority of CP occurrences were in children born before 34 weeks, residual risk persisted thereafter.
21	Sternal M et al., (2020) [35]	Warsaw, Poland	Paternal age and the risk of CP	Paternal age	They came to the conclusion that neglecting paternal age while taking into account mother age and other risk factors may cause bias in estimates of the probability of CP.
22	Hemachithra C et al., (2020) [36]	Tamil Nadu, India	Association of risk factors of CP- a matched case-control study	Preterm male is more affected than female, low birth weight, birth asphyxia, neonatal seizures	Preterm birth, low birth weight, birth asphyxia, and newborn seizures are perinatal risk factors that are significantly associated with the development of CP in rural settings.

[Table/Fig-2]: Articles reviewed for prenatal risk factors [15-36].

S. No.	Author name and year	Place of the study	Study title	Risk factor	Conclusion
1	Collins MP et al., (2001) [37]	East Lansing, Michigan	Hypocapnia and other ventilation-related risk factors for CP in low birth weight infants	Hypocapnia, hyperoxaemia, and duration of ventilation support	From their research, they have drawn the conclusion that newborns should receive adequate ventilator support because of hypocapnia, hyperoxaemia and prolonged breathing.
2	Staneva KN et al., (2002) [38]	Rostock, Germany	Neonatal ultrasonographic cerebral findings: association with a risk factor for CP	Encephalitis, meningitis, cerebral haemorrhage.	Factors associated with CP can be Periventricular Leuckomalacia (PVL), cerebral atrophy, foetal hypoxia, abruption placenta, abnormal neurologic behaviour at term encephalitis, meningitis and cerebral haemorrhage.
3	Gurbuz A et al., (2006) [39]	Istanbul, Turkey	The role of perinatal and intrapartum risk factors in the aetiology of CP in term deliveries in a Turkish population	Extreme low birth weight, low Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score, and NICU admission	According to the study's findings, the need for NICU hospitalisation, an APGAR score of 7 at 1 and 5 minutes, a neonatal weight of less than 2500 g, and decreased electronic foetal monitoring were all perinatal risk factors.
4	Thorngren-Jerneck K and Herbst A (2006) [40]	Lund, Sweden	Perinatal factors associated with CP in children born in Sweden	Small or large for GA, abruption placental diabetes mellitus type 1, maternal age, pre-eclampsia, instrumental delivery, smoking, c-section, primiparity, breech presentation at vaginal birth	The study concluded that smoking, low APGAR scores, placental abruption, insulin-dependent diabetes mellitus type 1, pre-eclampsia, maternal age greater than 40 years, instrumental delivery, and emergency caesarean delivery primiparity were all risk factors for CP. Breech delivery by vaginal birth.
5	Drougia A et al., (2007) [41]	Greece	Incidence and risk factors for CP in infants with perinatal problems: A 15-year review	GA, PVL, PDA, SGA, neonatal transfer and sepsis/ meningitis	They came to the conclusion from their analysis that PVL and PDA were the most effective independent predictors of CP in children whose GA was less than 34 weeks and of SGA, neonatal transfer, and sepsis/meningitis in children whose GA was greater than 34 weeks.
6	Andersen GL et al., (2009) [42]	Trondheim, Norway	Is breech presentation a risk factor for CP? A Norwegian birth cohort study	Breech presentation	In their study, they found that breech presentation is a significant risk factor for CP the most striking finding was a fourfold increased risk for CP in singletons in breech born vaginally at term.
7	Menticoglou SM (2008) [43]	Winnipeg, Canada	How often do perinatal events at full term cause CP?	Perinatal event	In their study, they concluded that in their hospital, perinatal events are an important cause of CP in children born at full term, but few cases are potentially preventable.
8	Ahlin K et al., (2013) [44]	Norway	CP and perinatal infection in children born at term	Infection, Urinary Tract Infection (UTI)	Infection-related risk factors were shown to be independent risk factors for spastic CP especially pronounced in the subgroup with spastic hemiplegia in children with CP born at term.
9	Soleimani F et al., (2013) [45]	Tehran, Iran	Antenatal and intrapartum risk factors for CP in term and near-term newborns	Perinatal asphyxia, mother's age, high-risk pregnancy	This study shows that perinatal asphyxia, mother's age, and any pathology during pregnancy are independent factors associated with CP in term newborns. Previous studies have suggested that improving maternal care improves neonatal outcomes.
10	Sellier E et al., (2012) [46]	France	Epilepsy and CP: Characteristics and trends in children born from 1976 to 1998	Epilepsy	The prevalence of CP with epilepsy follows the quadratic trend however it requires longitudinal studies to be better understood.
11	Ellenberg JH and Nelson KB (2013) [47]	Philadelphia, USA	The association of CP with birth asphyxia: A definitional-Quagmire	Birth asphyxia	They have concluded that the asphyxial aetiology of CP would be that an intervention designed to improve the oxygenation of the fetus during the birth result in a decrease in CP.
12	Hafstrom M et al., (2018) [48]	Gothenburg, Sweden	CP in extremely preterm infants	Extremely preterm	Children born extremely preterm with CP have various co-morbidities and often overall severe disability.
13	Joud A et al., (2020) [49]	Lund, Sweden	Associations between antenatal and perinatal risk factors and CP: A Swedish cohort study	Preterm, low birth weight, birth asphyxia	They identified antenatal and postnatal factors associated with CP in one population-based study.

14	Hemachithra C et al., (2020) [36]	Annamalai, Tamil Nadu, India	Association of risk factors of CP-A matched case-control study	Perinatal events such as preterm, low birth weight, birth asphyxia, and neonatal seizures	The perinatal risk factors such as preterm, low birth weight, birth asphyxia, and neonatal seizures had a significant association with the development of CP.

[Table/Fig-3]: Articles reviewed for intrapartum and neonatal risk factors [36-49].

S. No.	Author name and year	Place of the study	Study title	Risk factor	Conclusion
1	Reddihough DS and Collins KJ, (2003) [50]	Melbourne, Australia	The epidemiology and causes of CP	Prenatal, perinatal, neonatal and postnatal	In their study, they concluded the review of all antenatal, perinatal, neonatal, and postnatal risk factors before pregnancy, during labour, risk factors at birth, and during the newborn period.
2	Belonwu RO et al., (2009) [51]	Nigeria	CP in Kano, Nigeria-a review.	Birth asphyxia, neonatal jaundice, encephalitis, meningitis, seizure disorder	Their study reveals that severe birth asphyxia is an important predisposing factor for CP. Acquired causes of CP such as meningoencephalitis, seizure disorder, and neonatal jaundice constitute a significant proportion of CP cases.
3	O'Callaghan ME et al., (2011) [52]	Australia	Epidemiologic associations with CP	Preterm birth, intrauterine growth restriction, perinatal infection, and multiple births	In their study, they have concluded that preterm birth, intrauterine growth restriction, perinatal infection, and multiple births present the largest risks for a CP outcome.
4	McIntyre S et al., (2013) [53]	Australia	A systematic review of risk factors for CP in children born at term in developed countries	Placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, instrumental/ emergency Caesarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia, and neonatal infections	With a low risk of bias, they have identified Ten risk factors for term-born infants that were statistically significant in each study: placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, instrumental/emergency caesarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia, and neonatal infections.
5	Abd Elmagid DS and Magdy H (2021) [54]	Egypt	Evaluation of risk factors for CP	Antenatal, natal, and postnatal, maternal DM, prolonged rupture of membrane, maternal haemorrhage, and pre-eclampsia. Natal and postnatal as hypoxic-ischaemic encephalopathy, infection, hyperbilirubinemia, meconium aspiration, and intracranial haemorrhage. Postneonatal as CNS infection, cerebrovascular accidents, sepsis, and intracranial haemorrhage	They have concluded that CP has different aetiologies and risk factors. Further studies are necessary to determine optimal preventative strategies in these patients.
6	Zhao M et al., (2016) [55]	China	SGA as a risk factor for cerebral palsy in moderate to late preterm infants: a system review and meta-analysis	SGA	Infants born in the 32-36 week GA with SGA showed up to 4 fold increase in the risk for CP as compared to infants with appropriate GA.
7	Stavsky M et al., (2017) [56]	Israel	CP- trends in epidemiology and recent development in prenatal mechanisms of disease, treatment, and prevention	SGA, Preterm	The risk for CP is GA dependent, and it is much more prevalent among preterm neonates, especially those who were extremely premature.
8	Present article (2023)	India	Risk factors for CP in children- a narrative review	Chorioamnionitis, pre-eclampsia, SGA, fetoplacental infection	The presence of multiple risk factors that overcome the defense mechanisms leads to CP. Although any one factor, if severe, may be sufficient to cause CP, so preventive strategies and early intervention for high-risk infants are required.

[Table/Fig-4]: Description of review articles related to the identification of risk factors for CP [50-56].
Note: The abbreviations of terms used in the table were provided below

strategies for CP in high-risk infants by identifying risk factors for CP are necessary. For an individual infant, it is essential to establish a diagnosis of CP or motor development as early as possible to optimise the effectiveness of rehabilitative intervention.

PRENATAL RISK FACTORS

Foetoplacental and uterine infection or inflammation will cause the initiation of preterm labour, which might cause Central Nervous System (CNS) injury and CP. Underdeveloped foetal brains are more prone to inflammation and inflammatory cytokines. These cytokines are hypothesised to be accountable for the event of Periventricular Leuckomalacia (PVL) [26,45].

Chorioamnionitis is an infection of the chorion and amnion, the two membranes encompassing the developing foetus. It's the foremost frequently related to maternal infection in CP. Wu YW et al., concluded that chorioamnionitis will be thought about a reason for CP. In their study, they found that chorioamnionitis is severally related to a 4-fold exaggerated risk of CP in infants [16]. Chorioamnionitis could cause CP by depriving the foetus of oxygen for a while which can cause brain injury. Researches show that maternal infection and Urinary Tract Infection (UTI) is one of the causes of CP [18,24,26,45]. The main finding of this study was that maternal infection was related to more or less two-fold exaggerated risk of CP in each term and preterm infants. The effect of maternal infection on CP risk appears to be greater in preterm than in term infants.

Few studies showed that GA and pre-eclampsia are the reason for CP. GA appears to modify the impact of risk factors for CP, significantly pre-eclampsia, and small for GA [17,19-21]; these seems protective before 33 weeks gestation, however it is associated with an exaggerated risk of CP in term babies. Many explanations have previously been put forward to explain this counterintuitive phenomenon. Firstly, babies with cerebral damage delivered preterm

to mothers with pre-eclampsia are more vulnerable to mortality. With current management, however, most babies delivered preterm attributable to severe pre-eclampsia survive. Secondly, magnesium sulfate, used in many centers for the prevention or treatment of seizures is also neuroprotective [14]. Maternal age, the exaggerated risk of CP among offspring of women over the age of 35 years in one study was vital compared with offspring of women aged from 18 years to 35 years. The exaggerated risk of CP in this group might be associated with changes in uterine function seen with advancing age and the state of high-risk pregnancy and its multiple co-variates [33]. In the present study, one of the articles showed that multiple pregnancies, low birth weight, and GA are causes of CP [34]. Meeraus WH et al., in their study, found no association between antibiotic prescribing in pregnancy and CP [28]. The distribution of cases differs substantially between twins and singletons, and the higher rate of CP in twins cannot be exclusively attributed to their low birth weight and GA [20].

INTRAPARTUM AND NEONATAL RISK FACTORS

Intrapartum risk factors as well as asphyxia and intrapartum stroke, had attracted the more range of publications, followed by genetic studies [57-62]. In general, CP is associated with complicated perinatal events, but most cases may require delivery care as well. Toxoplasmosis, other infections (varicella zoster, adenovirus, enterovirus), rubella, cytomegalovirus, herpes simplex virus, and syphilis are associated with Toxoplasmosis, Others (syphilis, hepatitis B), Rubella, Cytomegalovirus, Herpes simplex (TORCH) [63,64]. About 5% of CP cases are caused by TORCH infections [62]. There has been some evidence that birth asphyxia contributes to CP [27,47,36,51,53]. Between 4 and 9 million infants in developing countries suffer from birth asphyxia annually [65]. Neonatal asphyxia accounts for 20%-40% of all neonatal deaths every year [15]. There was also a strong association between birth asphyxia and CP, which is supported by recent reports identifying birth asphyxia in clinical chorioamnionitis [16].

Although CP is associated with preterm deliveries, the majority of infants with CP (75%) are born after 36 weeks. It is hypothesised that delivering a foetus with cerebral abnormalities is also associated with physiological changes that trigger labour as foetuses with cerebral abnormalities tend to be delivered either preterm or post-term [66]. Gurbuz A et al., in their study concluded that low birth weight is one in every common causes of CP. The only significant perinatal risk factor was the neonatal weight of <2500 grams [39].

Few articles showed that low APGAR score, placental abruption, and vaginal breech delivery can be one of the causes of CP [15,19]. Low APGAR scores were highly associated with CP, and although low scores may reflect a compromise of different origins [15,19]. Five-minute APGAR scores below 4 at term in no malformed neonates are often associated with acidemia at birth, indicating intrapartum hypoxia, and with neonatal encephalopathy [19]. Instrumental delivery and emergency caesarean delivery were both associated with CP [40].

A few causes supported by different articles are Meningitis, PDA, and PVL, IUGR; which is one of the causes of CP. PVL is considered the result of different causal pathways leading to CP in preterm neonates and is better interpreted as a proxy measure of CP rather than a risk factor, although a minority of children with PVL do not develop CP [41]. The most common cause of CP in preterm newborns is PVL, a disorder in which the white matter around the ventricles of the brain is undeveloped. Intraventricular Haemorrhage (IVH), which is mostly linked to prematurity, is brought on by the infant's developing blood vessels' susceptibility to rupture. Other areas of the brain may experience ischaemia or PVL due to IVH [67]. One study demonstrates that hypoxia and the neck cord are two causes of CP. Most cases of suffocation were caused by cord and placental problems. In one study, the chord around the neck was significantly associated with an increased risk of spastic CP, while placental infarction was more strongly connected with an increased risk of spastic quadriplegia [42].

Collins MP et al., showed that there was a strong relationship between exposure to a modest degree of hypocapnia and the risk of developing CP [37]. One study showed that meningitis and encephalitis are also the cause of CP and they also found that mature babies had prenatal brain atrophy or hypoxic-ischaemic cerebral lesions. Immature babies ≥33 week showed prenatal porencephaly or encephalomalacia after asphyxia. Premature babies ≤32 week had cystic periventricular leucomalacia or cerebral haemorrhage [38].

A sizable number of CP cases are due to acquired factors such meningoencephalitis, seizure disorders, and newborn jaundice [51]. One of the risk factors for CP is also epilepsy. A dyskinetic or bilateral spastic kind of CP, as well as other associated deficits, was more common in children with epilepsy, according to one of the studies, the author discovered [47].

All studies that have examined these risk factors for babies have found them to exist, and targeted prevention efforts should be made to address them; limiting the number of IVF embryo transfers, quitting smoking while pregnant, screening for and treating asymptomatic bacteriuria during pregnancy, and antiplatelet medications to prevent pre-eclampsia are some specific methods to lower the likelihood of premature birth [68].

Reducing the risk of premature delivery and other preventative measures by being aware of the risk factors are interventions that show promise for lowering the prevalence of CP. Since infancy and early childhood are times of maximum neuronal plasticity and when therapeutic interventions have the best chance of long-term effectiveness, it is important to diagnose CP or developmental delay in infants as early as possible to optimise the effect of the intervention. Therefore, the earlier we begin the intervention, the greater the impact on motor and cognitive outcomes [69-72].

CONCLUSION(S)

Preventive measures and early intervention for infants who are at high risk for CP are necessary because the condition includes a variety of aetiologies and risk factors, including prenatal, perinatal, and neonatal causes. Although the existence of many risk factors that override the body's defence mechanisms may exacerbate CP, although any one risk factor, if significant, may be sufficient to cause CP. Patients with brain malformations are a unique population that requires additional research to determine the risk factors that may contribute to it, including environmental variables, genetic predisposition, and other prenatal or perinatal events. To discover the best preventative measures to use with these patients, more research is required.

Acknowledgement

Author, Dr. Pranali Saurabh Thakkar expresses immense pleasure and satisfaction in presenting this review. Author would like to express sincere gratitude to the advisor, Dr. Madhavan Iyengar for the guidance during the review. Author would wish to avail herself of this opportunity and, express a sense of gratitude and to author's husband, parents and family for providing with all kinds of support. Author expresses heartily thanks to all the colleagues and friends.

REFERENCES

[1] Nelson KB. Can we prevent cerebral palsy? N Engl J Med. 2003;349:1765-69.
[2] Volpe JJ. Hypoxic-ischemic encephalopathy. In: Volpe JJ, ed. Neurology of the Newborn. 4th ed. Philadelphia: WB Saunders; 2001: 296-330.
[3] Kadhim H, Evrard P, Kahn A. Insights into etiopathogenic mechanisms involved in perinatal cerebral injury: Implications for neuroprotection. Focus on Cerebral Palsy Research. 2005:01-27.
[4] Mesterman R, Leitner Y, Yifat R, Gilutz G, Levi-Hakeini O, Bitchonsky O, et al. Cerebral palsy—long-term medical, functional, educational, and psychosocial outcomes. J Child Neurol. 2010;25(1):36-42.

[5] Krägeloh-Mann I, Cans C. Cerebral palsy update. Brain and development. 2009;31(7):537-44.
[6] Pakula AT, Braun KV, Yeargin-Allsopp M. Cerebral palsy: Classification and epidemiology. Phys Med and Rehabil Clin N. 2009;20(3):425-52.
[7] Anamarija Kavcic MD, Vodusek DB. 'The definition of cerebral palsy, April 2006'. Dev Med Child Neurol Suppl. 2008;50(3):240.
[8] Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, et al. A report: The definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109(suppl 109):08-14.
[9] Europe S. A collabouration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol. 2000;42:816-24.
[10] Himmelmann K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995-1998. Acta Paediatr Int J Paediatr. 2005;94(3):287-94.
[11] Blair E, Watson L. Epidemiology of cerebral palsy. In Semin fetal neonatal med. 2006;11(2):117-25). WB Saunders.
[12] Jan MM. Cerebral palsy: Comprehensive review and update. Ann Saudi med. 2006;26(2):123-32.
[13] Jones MW, Morgan E, Shelton JE, Thorogood C. Cerebral palsy: Introduction and diagnosis (part I). J Pediatr Health Care. 2007;21(3):146-52.
[14] Hankins GD, MacLennan AH, Speer ME, Strunk A, Nelson K. Obstetric litigation is asphyxiating our maternity services. Obstet Gynecol. 2006;107(6):1382-85.
[15] Walstab J, Bell R, Reddihough D, Brennecke S, Bessell C, Beischer N. Antenatal and intrapartum antecedents of cerebral palsy: A case-control study. Aust N Z Obstet and Gynecol. 2002;42(2):138-46.
[16] Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. JAMA. 2003;290(20):2677-84.
[17] Jacobsson B, Hagberg G. Antenatal risk factors for cerebral palsy. Best Pract Res Clin Obstet Gynecol. 2004;18(3):425-36.
[18] Neufeld MD, Frigon C, Graham AS, Mueller BA. Maternal infection and risk of cerebral palsy in term and preterm infants. J Perinatal. 2005;25(2):108-13.
[19] Greenwood C, Yudkin P, Sellers S, Impey L, Doyle P. Why is there a modifying effect of gestational age on risk factors for cerebral palsy? Arch Dis Child Fetal and Neonatal Ed. 2005;90(2):F141-46.
[20] Bonelli SR, Currie D, Chalmers J. Comparison of risk factors for cerebral palsy in twins and singletons. Dev Med Child Neurol. 2005;47(9):587-91.
[21] Nielsen LF, Schendel D, Grove J, Hvidtjørn D, Jacobsson B, Josiassen T, et al. Asphyxia-related risk factors and their timing in spastic cerebral palsy. BJOG: Int J of Gynaecol Obstet. 2008;115(12):1518-28.
[22] Kurjak A, Predojevic M, Stanojevic M, Salihagic-Kadic A, Miskovic B, Badreldeen A, et al. Intrauterine growth restriction and cerebral palsy. Acta Inform Med. 2010;18(2):64.
[23] Glinianaia SV, Rankin J, Colver A, North of England Collabourative Cerebral Palsy Survey. Cerebral palsy rates by birth weight, gestation, and severity in North of England, 1991-2000 singleton births. Arch Dis Child. 2011;96(2):180-85.
[24] Himmelmann K, Ahlin K, Jacobsson BO, Cans C, Thorsen P. Risk factors for cerebral palsy in children born at term. Acta Obstet Gynecol Scand. 2011;90(10):1070-81.
[25] Day SM. Birth size and the risk of cerebral palsy in term births. Dev Med Child Neurol. 2014;56(1):06-06.
[26] Wu CS, Pedersen LH, Miller JE, Sun Y, Streja E, Uldall P, et al. Risk of cerebral palsy and childhood epilepsy related to infections before or during pregnancy. PloS One. 2013;8(2):e57552.
[27] Strand KM, Heimstad R, Iversen AC, Austgulen R, Lydersen S, Andersen GL, et al. Mediators of the association between preeclampsia and cerebral palsy: Population based cohort study. Brit Med J. 2013;347:f4089.
[28] Meeraus WH, Petersen I, Gilbert R. Association between antibiotic prescribing in pregnancy and cerebral palsy or epilepsy in children born at term: A cohort study using the health improvement network. PloS One. 2015;10(3):e0122034.
[29] Minocha P, Sitaraman S, Sachdeva P. Clinical spectrum, comorbidities, and risk factor profile of cerebral palsy children: A prospective study. J Pediatr Neurosci. 2017;12(1):15.
[30] Mor O, Stavsky M, Yitshak-Sade M, Mastrolia SA, Beer-Weisel R, Rafaeli-Yehudai T, et al. Early onset preeclampsia and cerebral palsy: A double hit model? Am J Obstet Gynecol. 2016;214(1):105-e1.
[31] MacLennan AH, Thompson SC, Getz J. Cerebral palsy: Causes, pathways, and the role of genetic variants. Am J Obstet Gynecol. 2015;213(6):779-88.
[32] Forthun I, Wilcox AJ, Strandberg-Larsen K, Moster D, Nohr EA, Lie RT, et al. Maternal prepregnancy BMI and risk of cerebral palsy in offspring. Pediatrics. 2016;138(4):e20160874.
[33] Schneider RE, Ng P, Zhang X, Andersen J, Buckley D, Fehlings D, et al. The association between maternal age and cerebral palsy risk factors. Pediatr Neurol. 2018;82:25-28.
[34] Smith DD, Sagaram D, Miller R, Gyamfi-Bannerman C. Risk of cerebral palsy by gestational age among pregnancies at risk for preterm birth. J Matern Fetal Neonatal Med. 2020;33(12):2059-63.
[35] Sternal M, Kwiatkowska B, Borysławski K, Tomaszewska A. Paternal age and the risk of cerebral palsy. Anthropol Rev. 2020;83(1):31-41.
[36] Hemachithra C, Meena N, Ramanathan R, Felix AJ. Association of risk factors of cerebral palsy-a matched case-control study. Index Medicus for South-East Asia Region (IMSEAR). 2020.
[37] Collins MP, Lorenz JM, Jetton JR, Paneth N. Hypocapnia and other ventilation-related risk factors for cerebral palsy in low birth weight infants. Pediatr Res. 2001;50(6):712-19.
[38] Staneva KN, Hartmann S, Uhlemann M, Dietze H, Reschke E, Koepcke E, et al. Neonatal ultrasonographic cerebral findings: Association with a risk factor for cerebral palsy. Z fur Geburtshilfe Neonatol. 2002;206(4):142-50.
[39] Gurbuz A, Karateke A, Yilmaz U, Kabaca C. The role of perinatal and intrapartum risk factors in the etiology of cerebral palsy in term deliveries in a Turkish population. J Matern Fetal Neonatal Med. 2006;19(3):147-55.
[40] Thorngren-Jerneck K, Herbst A. Perinatal factors associated with cerebral palsy in children born in Sweden. Obstet Gynecol. 2006;108(6):1499-505.
[41] Drougia A, Giapros V, Krallis N, Theocharis P, Nikaki A, Tzoufi M, et al. Incidence and risk factors for cerebral palsy in infants with perinatal problems: A 15-year review. Early Hum Dev. 2007;83(8):541-47.
[42] Andersen GL, Irgens LM, Skranes J, Salvesen KÅ, Meberg A, Vik T. Is breech presentation a risk factor for cerebral palsy? A Norwegian birth cohort study. Dev Med Child Neurol. 2009;51(11):860-65.
[43] Menticoglou SM. How often do perinatal events at full term cause cerebral palsy? J Obstet and Gynaecol Can. 2008;30(5):396-403.
[44] Ahlin K, Himmelmann K, Hagberg G, Kacerovsky M, Cobo T, Wennerholm UB, et al. Cerebral palsy and perinatal infection in children born at term. Obstet & Gynecol. 2013;122(1):41-49.
[45] Soleimani F, Vameghi R, Biglarian A. Antenatal and intrapartum risk factors for cerebral palsy in term and near-term newborns. Arch Iran Med. 2013;16(4):0-0.
[46] Sellier E, Uldall P, Calado E, Sigurdardottir S, Torrioli MG, Platt MJ, et al. Epilepsy and cerebral palsy: Characteristics and trends in children born in 1976-1998. Euro J of Paediatr Neurol. 2012;16(1):48-55.
[47] Ellenberg JH, Nelson KB. The association of cerebral palsy with birth asphyxia: A definitional quagmire. Dev Med Child Neurol. 2013;55(3):210-16.
[48] Hafström M, Källén K, Serenius F, Maršál K, Rehn E, Drake H, et al. Cerebral palsy in extremely preterm infants. Pediatr. 2018;141(1):e20171433.
[49] Jöud A, Sehlstedt A, Källén K, Westbom L, Rylander L. Associations between antenatal and perinatal risk factors and cerebral palsy: A Swedish cohort study. BMJ Brit Med J open. 2020;10(8):e038453.
[50] Reddihough DS, Collins KJ. The epidemiology and causes of cerebral palsy. Aust J Physiother. 2003;49(1):07-12.
[51] Belonwu RO, Gwarzo GD, Adeleke SI. Cerebral palsy in Kano, Nigeria--a review. Niger J Med: Journal of the National Association of Resident Doctors of Nigeria. 2009;18(2):186-89.
[52] O'Callaghan ME, MacLennan AH, Gibson CS, McMichael GL, Haan EA, Broadbent JL, et al; Australian Collabourative Cerebral Palsy Research Group. Epidemiologic associations with cerebral palsy. Obstet & Gynecol. 2011;118(3):576-82.
[53] McIntyre S, Taitz D, Keogh J, Goldsmith S, Badawi N, Blair EV. A systematic review of risk factors for cerebral palsy in children born at term in developed countries. Dev Med Child Neurol. 2013;55(6):499-508.
[54] Abd Elmagid DS, Magdy H. Evaluation of risk factors for cerebral palsy. Egypt J Neurol Psychiatr Neurosurg. 2021;57(1):01-09.
[55] Zhao M, Dai H, Deng Y, Zhao L. SGA as a risk factor for cerebral palsy in moderate to late preterm infants: A systematic review and meta-analysis. Sci Rep. 2016;6(1):01-07.
[56] Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O. Cerebral palsy—trends in epidemiology and recent development in prenatal mechanisms of disease, treatment, and prevention. Front Pediatr. 2017;5:21.
[57] Dolk H, Pattenden S, Johnson A. Cerebral palsy, low birth weight and socioeconomic deprivation: Inequalities in a major cause of childhood disability. Paediatr Perinat Epidemiol. 2001;15:359-63.
[58] Sundrum R, Logan S, Wallace A, Spencer N. Cerebral palsy and socioeconomic status: A retrospective cohort study. Arch Dis Child. 2005;90:15-18.
[59] Hjern A, Thorngren-Jerneck K. Perinatal complications and socio-economic differences in cerebral palsy in Sweden- a national cohort study. BMC Pediatr. 2008;8:49.
[60] Reid S, Halliday J, Ditchfield M, Ekert H, Byron K, Glynn A, et al. Factor V Leiden mutation: A contributory factor for cerebral palsy? Dev Med Child Neurol. 2006;48:14-19.
[61] Senbil N, Yüksel D, Yilmaz D, Gürer YK. Prothrombotic risk factors in children with hemiplegic cerebral palsy. Pediatr Int. 2007;49:600-02.
[62] Nelson KB. Causative factors in cerebral palsy. Clin Obstet Gynecol. 2008;51(4):749-62.
[63] Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, Giannone PJ. Maternal preeclampsia and neonatal outcomes. J Pregnancy. 2011;2011:214365.
[64] Perlman JM. Intrapartum asphyxia and cerebral palsy: Is there a link? Clin Perinatol. 2006;33(2):335-53.
[65] Agarwal A, Verma I. Cerebral palsy in children: An overview. J Clin Orthop Trauma. 2012;3(2):77-81.
[66] Antsaklis A, Antsaklis P. The assessment of fetal neurobehaviour with four-dimensional ultrasound: The Kurjak antenatal neurodevelopmental test. Donald School Ultrasound Obstet Gynecol. 2012;6:362-75.
[67] Wong E. Pathogenesis of cerebral white matter injury of prematurity Arch Dis Child Fetal Neonatal Ed. 2008;93(2):F153-61.
[68] Iams JD, Romero R, Culhane JF, Goldenberg RL. Preterm birth 2- Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet. 2008;371(9607):164-75.
[69] Johnston MV, Ishida A, Ishida WN, Matsushita HB, Nishimura A, Tsuji M. Plasticity and injury in the developing brain. Brain Dev. 2009;31(1):01-10.
[70] Nudo RJ. Adaptive plasticity in motor cortex: Implications for rehabilitation after brain injury. J Rehabil Med. 2003(41 Suppl.):07-10.

[71] Stein DG, Hoffman SW. Concepts of CNS plasticity in the context of brain damage and repair. J Head Trauma Rehabil. 2003;18(4):317-41.

[72] Gordon AL, di Maggio A. Rehabilitation for children after acquired brain injury: Current and emerging approaches. Pediatr Neurol. 2012;46(6):339-44.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 02, 2022
- Manual Googling: Sep 23, 2022
- iThenticate Software: Oct 18, 2022 (22%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Mar 24, 2022**
Date of Peer Review: **Jun 18, 2022**
Date of Acceptance: **Oct 20, 2022**
Date of Publishing: **Mar 01, 2023**