Risk factors for cerebral palsy in Moldova

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Abstract

Background

This is the first study assessing risk factors for cerebral palsy (CP) among children born in Moldova.

Methods

We identified 351 children with CP born during 2009 and 2010 in state hospitals, maternity wards, orphanages and rehabilitation centres in Moldova. Detailed information on 417 children without CP (of the total number of 81,277 children) served as a reference group. Logistic regression analyses were applied to calculate crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) in addition to attributable risk (AR).

Results

Among children with CP (40.5% girls), 26% had unilateral, 54% bilateral, 13% dyskinetic, and 5% ataxic CP, with 2% unclassified. Almost three quarters of children with CP were from rural areas and 101 (29%) were prematurely born.

Significant risk factors for CP included low Apgar score at five minutes (OR 6.187, 95% CI 2.059–18.59), hyperbilirubinemia (OR 6.3, 95% CI 4.1–9.6), breech delivery (OR 3.5, 95% CI 2–6.01), assisted vaginal delivery (OR 47, 95% CI 11–194), birth out of maternity (OR 6.591, 95% CI 1.904–22.81), low education level (OR 3.889, 95% CI 2.8–5.248), alcohol consumption (OR 1.903, 95% CI 1.269–2.885) and hypertension (OR 2.264, 95% CI 1.5–5.417).

For singletons born at term, significant risk factors were low Apgar score (OR 2.115, 95% CI 1.22–3.808), hyperbilirubinemia (OR 5.854, 95% CI 3.648–9.393), breech delivery (OR 6.48, 95% CI 3.1–13.7), fundal pressure (OR 3.268, 95% CI 1.398–7.642), maternal hypertension (OR 2.248, 95% CI 1.55–3.997) and alcohol consumption (OR 2.105, 95% CI 1.315–3.369).

Hyperbilirubinemia, Apgar score (0–3), birth out of maternity and breech delivery had the highest AR for CP both in the total and term singleton groups. Chronic diseases among mothers also had a high AR for CP.

Conclusions

A combination of factors related to the child, the delivery and the mother were risk factors for CP among children born in Moldova, many of them possibly avoidable. The results may indicate a need for better maternal and perinatal childcare. A national CP register in Moldova is recommended as an opportunity to follow up these findings.

Background

This is the first study assessing the risk factors for cerebral palsy (CP) among children born in Moldova. CP is the most common physical disability of childhood, describing a group of permanent disorders of movement and posture attributed to non-progressive disturbances in the developing foetal or infant brain [1]. Potential risk factors have been studied in depth in many developed countries since the 1970s [2–4]. Preterm birth (<37 gestational weeks, GW), multiple birth, infection in pregnancy, and low birth weight are factors associated with an increased risk for CP [3–5].

In a systematic review conducted in 2016 by Pascal Van Liesholt et al. [5], included studies indicated that lower gestational age, maternal medical diagnoses, preeclampsia, low birth weight, and the combination of male gender with preterm birth or low birth weight were found to be positively associated with CP [6].

A 2013 systematic review of risk factors for CP among children born at term in developed countries found that 10 risk factors were statistically significant in each study: placental abnormalities, major and minor birth defects, low birth weight, meconium aspiration, instrumental or emergency Caesarean delivery, birth asphyxia, neonatal seizures, respiratory distress syndrome, hypoglycaemia and neonatal infections. Instrumental deliveries (compared with spontaneous vaginal or elective Caesarean deliveries) were associated with increased risk of CP, as was breech delivery. However, the study concluded that there is a need for more in-depth investigation of the associations [7].

A study from the Australian Collaborative Cerebral Palsy Research Group in 2011, including 587 individuals with CP and a large control group, concluded that preterm birth, intrauterine growth retardation, perinatal infections and multiple births were the largest risk factors for CP [8].

A study from Botswana in 2017 showed that significant risk factors for CP included serious neonatal infections, complications during delivery, and maternal human immunodeficiency virus (HIV). The study concluded that the major risk factors for CP in Botswana differ from those described in high-resource settings [9].

A 2017 study from China indicated 20 significant risk factors for CP, among which the most important were maternal age >30 years, maternal alcohol consumption during pregnancy, rural residence, paternal occupational exposure to harmful substances, and multiple births. This study concluded that maternal habits during pregnancy and rural residence had an important role and that the CP incidence could probably be further lowered if these factors were considered [10].

A population-based cohort study from 1999 to 2010, performed in 2014 in Sweden, concluded that vacuum-assisted delivery was associated with an increased risk of neonatal intracranial haemorrhages compared to Caesarean section [12].

In 2015, a study on the influence of high bilirubin levels in newborns showed that advances in the care of neonatal hyperbilirubinemia have decreased the incidence of kernicterus. However, neonatal exposure to high levels of bilirubin continues to cause CP. New categories of bilirubin-induced neurological

dysfunction, either independent or characterised by subtle bilirubin encephalopathy following moderate hyperbilirubinemia, have been implicated in long-term motor function [13].

A particular interest for us was to examine the existing literature regarding the consequences to the newborn of fundal pressure manoeuvres. Both the Kristeller manoeuvre and inflatable belts are still frequently used in obstetric practice in Moldova. A 2017 systematic review in the Cochrane Database [9] concluded that evidence from randomised controlled trials was insufficient to show whether manual fundal pressure or fundal pressure by inflatable belt have a severely harmful impact on the baby. However, some of the studies showed a decrease in the five-minute Apgar score. The findings being uncertain, the authors advised that “in the future studies should be of good quality, clearly describe how fundal pressure was applied, and focus on safety of the unborn baby” [11].

The present study aimed to identify and describe potential risk factors for CP among children born in Moldova. Data from the birth years 2009–2010 were linked with data from the National Agency for Public Health in Moldova to investigate risk factors for CP.

Methods

The recruitment area of the present study covered both rural and urban localities in Moldova. To perform this study, we first conducted a cohort study that allowed us to describe the characteristics of total births for two years (2009–2010): total number of births, neonatal mortality, gestational age, birth presentation and the total number of children diagnosed with CP versus those without CP.

Based on the findings, and because no detailed information on other variables was available, a second case-control study was performed, with two groups of children: one with a confirmed diagnosis of CP and one without.

A cohort of 417 children without CP born in Moldova between the 1st of January 2009 and 31st of December 2010, who survived the early neonatal period (first seven days of life), were included. This group was randomly selected by place of residence and place of birth (rural or urban), to have a reference group that was as representative as possible. The Institute of Mother and Child provides services to children from all over the country and University Clinics to children from the capital. The group number is comparatively small in both subgroups because the complete pre- and perinatal data were only available for these children. The second group comprised 351 children with a confirmed CP diagnosis born in the same period.

The CP diagnoses were ascertained by studying the medical records of all children born during the two birth years at the maternity wards, state hospitals for children, orphanages and rehabilitation centres across the country. Each ascertained diagnosis was tracked backwards from the age of seven years, when the diagnosis was confirmed, to the neonatal period, using the medical records from all the relevant departments of the hospitals, such as child neurology, neonatal intensive care units and maternity wards. In this way, we succeeded in covering approximately 95% of the population. In the first article on CP in

Moldova from 2018, we described a cohort based on 75% population coverage, with subtypes, severity and prevalence of CP diagnosed in children [14].

Data on maternal health, pregnancy, delivery and the early neonatal period were obtained from the National Agency of Public Health, Chisinau, Moldova. Detailed data on preconception, antenatal and intrapartum risk factors, as well as CP subtypes and the physical and intellectual development of children with CP born during the outlined period, were collected from hospital medical records. The clinical information on CP was collected between 1st of July 2016 and 20th of December 2017, when the children were at least seven years old, with the following inclusion criteria: children (1) born exclusively in Moldova, (2) meeting the criteria for CP defined by Surveillance of Cerebral Palsy in Europe (SCPE) [2] and (3) without a genetic diagnosis. Orphanages and habilitation centres in Moldova also provided summary and detailed perinatal and clinical data. SCPE criteria for the diagnosis of CP were applied based on detailed neurological descriptions in the medical records [2,14]. Only those children with CP with complete perinatal information were included in the present study.

Study population

The total number of births in 2009–2010 was 81,670, of which 393 children died during the neonatal period (0–7 days after birth). CP was diagnosed in 396 children. Twenty-seven children were abandoned at orphanages with no medical records, and thus perinatal data were missing. Eighteen children had a post-neonatal cause (i.e. traumatic brain damage took place more than 28 days after birth) and were excluded. Thus, the study population comprised 351 children). The reference group of 417 children with complete pre- and perinatal data was randomly selected from the total of 81,277 children using the medical records of the Institute of Mother and Child and the University Clinics, Chisinau, Moldova (Figure 1).

Variables

Exposure variables

Registration of obstetric and perinatal data at birth is compulsory in Moldova. Data recorded in the hospital medical records include gender, pre-labour rupture of membrane (any rupture of membranes persisting for more than 24 hours and occurring before the onset of labour), plurality (twins or triplets) and gestational age (GA) in weeks. GA was calculated from the first day of the last menstrual period and classified into term-born (37 weeks or more) or preterm-born (any birth before 37 completed weeks of gestation). Birth weight (BW) was recorded in grams, and being small for gestational age (SGA) was defined as BW below the 10th percentile for the GA. GA was also analysed as a continuous variable. Children with missing GA data were excluded. Birth presentation (vertex, breech or transverse) and mode of delivery were recorded as either vaginal birth (vertex or breech) or Caesarean section (but without specification of planned or emergency delivery).

Deliveries outside a maternity ward were considered home births. Home births also included deliveries at rural general practitioners' offices with no specialised medical assistance and/or ambulance available.

Maternal age at delivery was retrieved from the National Agency for Public Health and recorded in three age groups (a: 14–18 years; b: 19–34 years; and c: ≥ 35 years). Place of birth was recorded as urban or rural; maternal highest education was recorded as low (primary school), medium (high school) or high (university or college); and maternal employment was recorded as yes or no.

Assisted vaginal delivery (AVD) included instrumental implication (using forceps or vacuum extraction) and fundal pressure, defined as physical manipulation during the second stage of labour (Kristeller manoeuvre and/or inflatable belt).

All variables, for a better understanding, were classified into three categories:

1. Child-related variables: gender, birth year, GA, birth presentation, Apgar score at five minutes, multiple gestation, plurality, SGA, BW.
2. Delivery-related variables: breech delivery, fundal pressure (Kristeller manoeuvre and/or inflatable belt), Caesarean section, place of birth, birth out of maternity, AVD, premature rupture of membranes (PROM), meconium waters aspiration, and umbilical cord around neck.
3. Mother-related variables: maternal age categories, socioeconomic status, educational level, parity (number of previous births), alcohol consumption during pregnancy, and chronic diseases (hypertension, hepatitis, diabetes, intellectual disability, epilepsy and pyelonephritis) [15].

Outcome variables

According to the SCPE recommendations, all children diagnosed with CP were classified with spastic, dyskinetic, ataxic or not classified subtypes [16].

Ethics

The study was approved by the National Committee for Ethical Expertise of Clinical Trials (number 266), the Center of Early Intervention 'Voinicel' Ethical Committee (number 01/17) and the National Centre for Personal Data Protection. A statement of agreement of collaboration between the State Medical and Pharmacy University and the Institute of Mother and Child was signed, and permission to conduct the study was obtained from the Ministry of Health (12th of July, number 08/88), the Municipality Council of Social Protection, (13th of July 2016, number 070117/957) and the Ministry of Labour, Social Protection and Family of the Republic of Moldova.

Parents or primary caregivers of patients treated at all the hospitals sign an informed consent form stating that medical data collected as part of the admission process may be used for research purposes. The use of this regularly collected medical information in the present study was approved as described and did not require a new individual consent form to be completed.

Statistical analyses

Data analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA). A significance level of 0.05 was chosen.

Descriptive statistics with frequencies, proportions and Chi-square tests were used to compare the children with and without CP. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the risk for CP among children using the three categories of variables (child-, delivery- and mother-related). We calculated the attributable risk (AR) to identify the excess risk attributed to each of the exposure variables.

A variable was considered a confounder if it was associated both with exposure and outcome (CP). Thus, gender, plurality, GA, maternal age, birth out of maternity and SGA were assessed as possible confounders. Following the proposed hierarchical model of Victora et al. [17], several confounders were explored using logistic regression analyses. Singletons born at term were assessed separately for possible confounders to identify whether they had different risk factors for CP.

Results

Over the study period, there were 81,670 births and 81,277 (99.5%) children survived the neonatal period. Among those who survived, 3,770 (4.6%) were born preterm (22–36 GA) and 77,507 (95.4%) at term (≥ 37 GA; Figure 1).

Among the 81,277 children, 351 (4.3 per 1,000 live births) were diagnosed with CP, and we successfully identified complete information on the variables of interest in 417 children without CP, used as a reference group. Table 1 presents a comparison of the two groups regarding child-, delivery- and mother-related characteristics.

Of the 351 children diagnosed with CP, 209 (59.5%) were boys, 26% had unilateral, 54% bilateral, 13% dyskinetic, and 5% ataxic CP, with 2% unclassified. The proportion of preterm children (29%) was higher among those with CP than among those in the reference group (17%), giving an OR for CP among those born preterm of 1.162 and 95% CI 1.073–1.258. Low Apgar score (<4) at five minutes also showed an increased risk of CP, with OR 6.187 and 95% CI 2.059–18.59 (Table 2).

We also found an increased risk of CP among children born SGA, with OR 1.407 and 95% CI 1.01–1.962. Children with hyperbilirubinemia had an overall greater risk of CP, with OR 6.304 and 95% CI 4.112–9.671 (Table 2).

Hyperbilirubinemia and Apgar score at five minutes (0–3) had an 84% AR of CP, multiple gestation almost 75%, and BW $>1,500$ grams had a 58% excess risk of CP (Table 2).

When we examined potential risk factors during delivery, we found that children born in breech delivery had an increased risk of developing CP, with an OR of 3.48 and 95% CI 2.01–6.02 compared to the

reference group (Table 2).

Other factors that could lead to traumatic hypoxic events during delivery also increased the risk for CP: fundal pressure (OR 15.529, 95% CI 3.573–64.909), birth out of maternity (OR 6.591, 95% CI 1.904–22.81), umbilical cord around the neck (OR 2.751, 95% CI 1.293–3.936) and PROM (OR 0.197, 95% CI 0.088–0.438; Table 2). The AR was 87% for birth out of maternity, 80% for PROM and 67% for breech delivery (Table 2).

Mother-related variables showed that 251 children (72%) were born to mothers living in rural areas (Table 1), with an overall OR for CP of 1.961 and 95% CI 1.628–2.363 (Table 3). Other mother-related variables that showed an increased risk for CP were age above 35 years (OR 1.7, 95% CI 1.096–2.638), low education level (OR 3.889, 95% CI 2.8–5.248), alcohol consumption during pregnancy (OR 1.903, 95% CI 1.269–2.885), and chronic diseases such as hypertension (OR 2.264, 95% CI 1.5–5.417) and epilepsy (OR 1.133, 95% CI 1.075–1.194; Table 3). Other severe conditions among mothers, such as diabetes, intellectual disability and pyelonephritis, did not increase the risk for CP (Table 3). Epilepsy had an AR of 78%, hypertension 60% and parity 53% for CP (Table 3).

Multiple logistic regression analyses left only two child-related risk factors for CP: male gender and hyperbilirubinemia in the newborn (Table 4).

Among delivery-related variables, breech delivery showed an OR for CP of 2.982 and 95% CI 1.498–5.939, birth out of maternity an OR of 7.646 and 95% CI 1.868–31.303, and PROM an OR of 4.895 and 95% CI 1.956–12.249. Umbilical cord around the neck gave a 28% increased risk of developing CP (Table 4). Multiple regression analysis also showed that the AR for CP was 82% for hyperbilirubinemia, 87% for home births, 80% for PROM and 64% for the mother coming from a rural area (Table 4).

Analysis of mother-related variables showed that hypertension (OR 0.240, 95% CI 0.126–0.457) and age above 35 years (OR 1.995, 95% CI 1.254–3.174) remained statistically significant (Table 4). Mothers from rural areas had a 64% AR for CP, and those older than 35 years had a 50% AR (Table 4).

Table 5 shows that among the 217 singletons born at term with CP, 174 (70%) were from rural areas, a larger number in comparison to the 140 (41%) in the reference group. In the term singleton group, the number of boys with CP was 153 (61%), higher compared to the total group of children.

Among all singletons, 14 (6%) of those with CP had an extremely low Apgar score at five minutes compared to none in the reference group. Parity among mothers of children with CP was twice as high at 32 (13%) compared to 22 (6%) children in the reference group (OR 2.115, 95% CI 1.22–3.808). Singletons born SGA had an OR 3.941 and 95% CI 2.157–7.203 of developing CP (Table 6). The AR among all singletons for CP was 83% for hyperbilirubinemia, 33% for Apgar score (0–3) and 69% for fundal pressure (Table 6).

A higher risk of CP was also discovered among singletons born at term in breech presentation (OR 6.485, 95% CI 3.068–13.707) and among those born with the help of fundal pressure (OR 3.268, 95% CI 1.398–

7.642; Table 6). The AR for CP was 85% for breech presentation, 81% for home births, 78% for AVD and 69% for fundal pressure (Table 6).

Mother-related risk factors for CP among singletons born at term particularly included maternal chronic diseases, such as hypertension (OR 2.248, 95% CI 1.55–3.997) and epilepsy (OR 4.65, 95% CI 1.68–12.87), and maternal alcohol consumption during pregnancy (OR 2.105, 95% CI 1.315–3.369; Table 7). The hierarchical split of AR was epilepsy 78%, hypertension 60% and parity 53% (Table 7).

The multiple regression analysis, presented in Table 8, showed that the highest risk factors for CP among singletons born at term were home births, hyperbilirubinemia, umbilical cord around the neck, and birth presentation. The AR for CP was 79% for hyperbilirubinemia, 89% for umbilical cord around the neck and 82% for breech delivery (Table 8).

Discussion

In this first study on risk factors for CP in Moldova, we found that a combination of risk factors related to the child, delivery, and mother was significant and that the potential interdependency of variables should be the base for future in-depth studies.

We found that boys had a higher risk for CP, especially among singletons born at term, but the major risk for CP was found among children with hypoxic-traumatic events during delivery and hyperbilirubinemia during the neonatal period. Maternal residence in rural areas, low socioeconomic status, and alcohol consumption during pregnancy all increased the risk of CP. Chronic disease among mothers, an important public health issue in Moldova, was found to increase the risk of CP substantially. These risk factors were significant both in the total number of children with CP and among singletons born at term. The child- and delivery-related risks of hyperbilirubinemia, Apgar score (0–3) at five minutes, multiple gestation, birth out of maternity, and breech delivery all had high AR for CP, both in the total group and in term-born singletons. Assisted vaginal deliveries and fundal pressure manoeuvres, still performed in Moldova, had the highest AR for CP although not significant in multiple logistic regression analyses.

Strengths and limitations

A strength of the study is that in all 351 children with CP, the diagnosis was confirmed based on the medical records and physical examination of the children by the age of seven years. The CP diagnosis was classified in accordance with SCPE recommendations by the first author, based on detailed neurological descriptions from the children's medical records [2]. However, the cohort for the present study is small, only two birth years (2009–2010), in comparison with other, larger studies [6–8, 21–29]. Therefore, the results should be interpreted with caution. Detailed perinatal data were obtained from the National Agency of Public Health, and we were able to match 351 (89%) of 396 children diagnosed with CP, in addition to obtaining general perinatal data for all children with CP and all live births in Moldova in 2009–2010. Due to the general but not detailed information on child-, delivery- and mother-related factors

in all children born in 2009–2010, the reference group is small, and thus the results have to be interpreted with caution.

Comparison with other studies

Our first study from 2018, on the prevalence and severity of CP in Moldova in comparison to industrial developed countries in Europe, showed an almost two-fold increase in the number of children with severe forms of CP and associated impairments [14]. The present manuscript is a follow-up study to examine in depth the potential risk factors for CP from three presented groups of variables.

The present study showed a lower proportion of prematurely born children with CP compared to a Norwegian study, which could be explained by a different structure of risk factors for CP in Moldova, i.e. intra- and postnatal risk factors among children born at term constitute a large proportion of the CP population [18].

Another explanation of the low incidence of CP in Moldova among preterm children could be the high rate of neonatal deaths in Eastern Europe. According to a UNICEF report, over the last three decades (1990–2017), neonatal mortality has been decreasing in industrial developed countries in Europe. However, in Eastern Europe, neonatal mortality was three times higher than in western countries in 2019, at 153.240 versus 30.804, respectively [19]. In Moldova, in 2009–2010, the birth years of this study population, the neonatal mortality index was estimated to be 14.8, six times higher than the Norwegian neonatal mortality index (2.6) in the same period [19].

The largest proportion of total neonatal deaths is due to extremely premature babies, as shown in the results of a local study by Paladi et al. [20]. The study included 863 babies born with extremely low BW (500–1,000 grams) between the 22nd and 28th gestational weeks during 2008–2012. The authors determined a 3–4 times lower survival of these children compared to those in perinatal centres in developed countries. Due to Ministry of Health perinatology strategies implemented in recent years, neonatal mortality has decreased from 100.2‰ to 56.6‰ [20].

The proportion of children born prematurely or SGA among those who developed CP was significantly higher compared to the reference group. We also found that children born with a low or extremely low Apgar score at five minutes had a six-fold increased risk of developing CP, results in line with a registry-based Norwegian study [18] and a systematic review of risk factors for CP in developed countries [7].

An important finding related to the child was hyperbilirubinemia, which was found to be almost seven times higher among children with CP than in the reference group. This finding is in line with a study conducted in the USA on the total of children born at term from 1995–2011. The authors concluded that CP consistent with kernicterus occurred with an incidence of 0.57 per 100,000 births; all had high total serum bilirubin levels and at least two risk factors for neurotoxicity, such as prematurity, glucose-6-phosphate dehydrogenase deficiency or hypoxia-ischemia [21].

Hypoxic-traumatic events during labour were found to be important delivery-related risk factors for CP among children born in Moldova. We found that in Moldova, children born in breech delivery, after fundal pressure manoeuvres, or in AVD had a greatly increased risk of developing CP. These results are in line with a study performed in Sweden in 2006, where the authors concluded that several obstetric factors and low Apgar scores were associated with CP [22].

A Cochrane review on fundal pressure during the second stage of delivery showed that the existing publications did not prove the importance of these manoeuvres in shortening labour or reducing harmful impacts on the health status of the mother and child, such as foetal distress, failure to progress, and maternal exhaustion. Our study showed that the Kristeller manoeuvre is an important risk factor for developing CP. However, when we performed the multiple logistic regression analyses, both fundal pressure and AVD were not statistically significant [11].

We found that AVD among children born in Moldova also was a statistically significant risk factor for CP. However, the 95% CI is very wide, and thus a more in-depth study should be performed, using a larger group of children diagnosed with CP and a larger reference group. Vacuum extraction and forceps are frequently used in Moldova, so further population-based studies are crucial.

Our study identified that home births was an important risk factor associated with insufficient perinatal care for both mothers and newborns. These results are in line with a study from China where the authors concluded that home births were indicators of low socioeconomic status. Such deliveries are likely to have higher risks because they are mostly performed by untrained birth attendants. Rural residence and home births were found more commonly in the group with CP in our study. Low levels of births at hospitals have also been found to be related to CP in other studies from China and the USA [10,23].

We found that breech delivery was a significant risk factor for CP, particularly among singletons born at term (>37 GW). The same results were obtained in the 2009 Norwegian study by Andersen et al. and a study from Sweden [22,24]. However, in our study, breech delivery was not described in correlation with other variables because of insufficient available data. Thus, a more detailed study is required in Moldova.

The univariate analyses showed that PROM > 18 h was found to have a 20% increased risk for CP among singletons born at term born in Moldova. This finding may suggest a poor delivery protocol in these cases. A national registry cohort study in Norway on term-born singletons from 1999–2009 concluded that intervals of more than 24 hours between PROM and delivery were associated with CP, but not with neonatal mortality or death during delivery [25].

Regarding mother-related variables, our study showed that mothers above the age of 35 had a higher risk of a baby developing CP. This might be explained both by chronic diseases at older ages, including hypertension, hepatitis and pyelonephritis as described, and by higher parity. However, this effect can be prevented if women receive quality prenatal care and deliver in a healthcare facility well-equipped to care for high-risk pregnancies and neonates. We also found that this category of women had low socioeconomic status, which might indicate poor nutrition and low access to quality medical care. Other

studies have also concluded a higher risk of a child with CP among women over 30 years old [10]. However, some studies show that maternal age below 20 years is also associated with an increased risk of CP [26].

Multivariate analyses revealed that rural residence, alcohol consumption and chronic disease among mothers increased the risk of developing CP. Parturient women who had gestational hypertension and other diseases such as pyelonephritis, hepatitis and epilepsy also had an increased risk of children with CP, probably due to premature birth, low BW, foetal distress, SGA infants and other abnormal perinatal outcomes. These risk factors for CP were identified in a 2011 systematic review by Himmelmann et al. [27].

In Moldova, because particular attention is paid to non-communicable diseases (NCD), the largest causes of morbidity and mortality in the local population, these diseases are recorded in detail for parturient women. The Millennium Goals established by the World Health Organization for the end of 2020 in Moldova are to reduce the morbidity of NCD in the population. A more detailed, population-based study is required to identify potential harms to the foetus during the perinatal period [15].

The restricted analyses on singletons born at term in Moldova showed the same variables as causes for CP, with a higher risk among boys, children who had experienced hyperbilirubinemia, children born in breech delivery, and children born to mothers with chronic diseases. These results are comparable with several other international studies both from high- and low-income countries [18–27].

Conclusion And Policy Implications

In this study, we found that a combination of factors related to the child, the delivery process and the mother were risk factors for CP among children born in Moldova. Our findings suggest that improved perinatal care, following protocols in PROM and other potential hypoxic events, better follow-up during pregnancy, avoiding harmful habits and encouraging birth at maternity wards would potentially reduce the risk of CP. Further studies with larger numbers of participants are required in Moldova to be able to draw conclusions at the population level. Thus, we strongly recommend the creation of a national CP registry in Moldova, which should be linked to the National Agency for Public Health Data, to enable studies at a national level.

Abbreviations

AR: attributable risk, the effect of a risk factor on the exposed group

AVD: assisted vaginal delivery

BW: birth weight

CP: cerebral palsy

FP: fundal pressure

GA: gestational age

GMFCS: Gross Motor Function Classification System

BFMF: Bimanual Fine Motor Function

NNM: neonatal mortality

SCPE: Surveillance of Cerebral Palsy in Europe

SGA: small for gestational age

Declarations

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Ethics approval and consent to participate

The study was approved by the National Committee for Ethical Expertise in Clinical Trials (number 266) and the Centre of Early Intervention 'Voinicel' Ethical Committee (number 01/17). A statement of agreement of collaboration between the State Medical and Pharmacy University and the Institute of Mother and Child was signed. Finally, permission to conduct the study was obtained from the Ministry of Health (12th of July, number 08/88), the Municipality Council of Social Protection (13th of July 2016, number 070117/957) and the Ministry of Labour, Social Protection and Family of the Republic of Moldova.

Permission to access the children's data was obtained from the Republican Ethics Committee, the State Medical and Pharmacy Ethics Committee, the Ministry of Health, the Ministry of Labour and Social Protection, and the directors of the Institute of Mother and Child, the main hospital for children in the Republic of Moldova.

Consent for publication – not applicable.

Availability of data and materials section

The datasets generated and analysed in this study are not publicly available due to restrictions regarding the sharing of data with third parties. The Management Committee of the Institute of Mother and Child,

the hospital that provided the data, has specified that it is forbidden to share the data with third parties. Data are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

EGB designed the study, extracted and analysed the data, performed the statistical analyses and participated in drafting and improving the manuscript. RJ, LS and GA contributed to the design and conceptualisation of the study, provided critical input and oversight of fieldwork and reviewed the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Tables

Table 1. Comparison of child-, delivery-, and maternal characteristics in children with CP and the reference group.

	Children with CP N=351 (%)	Reference group N=417 (%)	P-Value
Child related factors			
Gender (male)	209 (59)	192 (46)	.000
GA<37 gestational weeks	101 (29)	72 (17)	.000
BW <1000g	12 (3)	9 (2)	
1000-1499g	27 (8)	16 (4)	
1500-2499g	71 (20)	53 (13)	
>2500g	241 (69)	339 (81)	.001
Apgar score at 5 min			
0-3	20 (6)	4 (1)	
4-6	79 (22)	77 (18)	
7-10	252 (72)	336 (81)	.000
Small for gestational age	96 (27)	88 (21)	.051
Multiple gestation	42 (12)	30 (7)	.016
Hyperbilirubinemia >1 week	118 (34)	31 (7)	.000
Delivery factors			
Breech delivery	50 (14)	19 (5)	.000
Csection	84 (24)	99 (23)	.509
Fundal Pressure*	24 (7)	9 (2)	.001
Assisted Vaginal Delivery*	65 (19)	18 (4)	.000
Home births	16 (5)	3 (1)	.001
Premature Rupture Membranes			
<12 hours	261 (74)	347 (83)	
12-18 hours	47 (13)	60 (14)	
>18 hours	43 (13)	10 (3)	.000

Meconium waters aspiration	121 (35)	120 (28)	.053
Umbilical Cord around neck	108 (31)	58 (14)	.000
Demographic characteristics			
Rural	251 (72)	184 (44)	.000
Low social-economic status	120 (34)	142 (34)	.969
Maternal Factors	45 (13)	15 (4)	.000
Parity			
Maternal age			
<18 years old	23 (7)	26 (6)	
19-34 years old	293 (83)	325 (78)	
>35 years old	35 (10)	66 (16)	.057
Mother low educational level	77 (22)	71 (17)	.052
Alcohol consumption	67 (19)	46 (11)	.000
Mother chronic diseases			
Hypertension	71 (20)	42 (10)	.000
Hepatitis	27 (8)	18 (4)	.034
Pyelonephritis	100 (29)	120 (28)	.497
Diabetes	40 (11)	35 (8)	.180
Intellectual disability	20 (6)	12 (3)	.069
Epilepsy	18 (5)	5 (1)	.001

*Fundal Pressure – Krissteller’s maneuver, belt

*Assisted Vaginal Delivery – vacuum, forceps

Table 2. Child and delivery related risk factors for CP

	Odds Ratio	95 % CI		P-value	AR* %
		Lower	Upper		
Child related factors					
Gender (male)	1.334	1.142	1.557	.000	25
GA<37 gestational weeks	1.162	1.073	1.258	.000	14
BW <1000g				.001	
1000-1499g	1.876	.778	4.521	.161	47
1500-2499g	2.374	1.252	4.502	.008	58
>2500g	1.884	1.273	2.789	.002	48
Apgar score at 5 min					
0-3	6.187	2.059	18.589	.002	84
4-6	1.318	.921	3.34	.059	24
7-10	1.342	.935	1.928	.111	25
Small for gestational age	1.407	1.01	1.962	.027	29
Multiple Gestation	3.941	2.157	7.203	.000	75
Hyperbilirubinemia	6.304	4.112	9.671	.000	84
Delivery factors					
Breech delivery	3.48	2.01	6.02	.000	71
C-section	1.01	.724	1.410	.036	1
Fundal Pressure*	15.529	3.573	64.909	.000	94
Assisted Vaginal Delivery*	47.149	11.455	194.15	.000	98
Home birthsy	6.591	1.904	22.810	.001	85
Premature Rupture of Membranes					
<12 hours				.000	
12-18 hours	.185	.090	.380	.000	<1
>18 hours	.197	.088	.438	.000	<1
Meconium waters aspiration	.835	.677	1.029	.053	<1

Umbilical Cord around neck	2.751	1.923	3.936	.000	64
*Fundal Pressure – Krissteller’s maneuver, belt					
*Assisted Vaginal Delivery – vacuum, forceps					
*AR – attributable risk, the effect of a risk factor on the exposed group %					

Table 3. Demographical and maternal related risk factors for CP

	Odds Ratio	95 % CI		P-value	AR* %
		Lower	Upper		
Demographic characteristics					
Rural	1.961	1.628	2.363	.000	49
Low Social-economic status	.994	.737	1.341	.514	<1
Maternal Factors					
Parity	.601	.385	.940	.016	<1
Maternal age					
>35 years old	1.7	1.096	2.638	.018	41
Mother educational level Low	3.889	2.8	5.248	.000	74
Alcohol consumption	1.903	1.269	2.855	.002	47
Mother chronic diseases					
-Hypertension	2.264	1.5	5.417	.000	56
-Hepatitis	1.847	1.0	3.414	.034	46
-Pyelonephritis	1.010	.807	1.264	.497	1
-Diabetes	1.404	.871	2.263	.163	<1
-Intellectual Disability	1.03	.999	1.062	.530	<1
-Epilepsy	1.133	1.075	1.194	.000	12
*AR – attributable risk, the effect of a risk factor on the exposed group %					

Table 4. Multivariate analyses of risk factors for CP

	Odds Ratio	95 % CI		P-value	AR* %
		Lower	Upper		
Child related factors					
Gender (male)	.691	.482	.992	.045	<1
Hyperbilirubinemia	5.406	3.121	9.363	.000	82
Delivery factors					
	2.982	1.498	5.939	.002	67
Breech deliveryHome births	7.646	1.868	31.303	.005	87
Premature Rupture of Membranes	4.895	1.956	12.249	.001	80
>18 hours	.278	.169	.458	.000	<1
Umbilical Cord around neck	2.795				
	1.995	1.914	4.082	.000	64
Maternal Factors					
Rural	.240	1.254	3.174	.004	50
>35 years old		.126	.457	.000	<1
Mother chronic diseases					
-Hypertension					

AR* – attributable risk, the effect of a risk factor on the exposed group %

Table 5. Characteristics of singletons at term with CP compared to the reference group

	Children with CP N=351 (%)	Reference Group N=417 (%)	P-value
Child related factors			
Gender (male)	153 (61)	153 (44)	.000
Apgar score at 5 min			
0-3	14 (6)	0 (0)	.000
4-6	36 (14)	36 (10)	
7-10	200 (80)	309 (90)	
Small for gestational age	33 (13)	55 (16)	.413
Hyperbilirubinemia >1 week	83 (33)	27 (8)	.000
Delivery factors			
Breech delivery	37 (15)	9 (3)	.000
C-section	61 (24)	70 (20)	.270
Fundal Pressure	18 (7)	8 (2)	.007
Assisted Vaginal Delivery	45 (18)	16 (5)	.000
Home births	11 (4)	3 (1)	.011
Premature Rupture of Membranes			
>18 hours	9 (13)	9 (3)	.000
Meconium waters	89 (36)	93 (27)	.025
Umbilical Cord around neck	81 (32)	47 (14)	.000
Demographic characteristics			
Rural			.000
Low Social-economic status	174 (70)	140 (41)	.860
Maternal Factors	84 (34)	113 (33)	
Parity			.009
<18 years old	32 (13)	22 (6)	.131
19-34 years old	16 (6)	22 (6)	.164

>35 years old	209 (84)	269 (78)	
Low educational level	25 (10)	54 (16)	.003
Alcohol consumption	53 (21)	57 (16)	
Mother chronic diseases	48 (19)	35 (10)	
-Hypertension			.000
-Hepatitis	52 (21)	33 (10)	.100
-Pyelonephritis	18 (7)	14 (4)	.578
-Diabetis	72 (29)	92 (27)	.134
-Intellectual Disability	32 (13)	31 (9)	.291
-Epilepsy	13 (5)	11 (3)	.002
	16 (6)	5 (1)	

Table 6. Child and delivery related risk factors for CP in singletons born at term

	Odds Ratio	95 % CI		P- value	AR* %
		Lower	Upper		
Child related factors					
Gender (male)	1.434	1.196	1.721	.000	30
Apgar score at 5 min (0-3)	1.494	.889	2.512	.130	33
Small for gestational age	3.941	2.157	7.203	.000	<1
Hyperbilirubinemia	5.854	3.648	9.393	.000	83
Delivery factors					
Breech delivery	6.485	3.068	13.707	.000	85
C-section	1.268	.858	1.873	.232	<1
Fundal pressure	3.268	1.398	7.642	.004	69
Assisted Vaginal Delivery	4.514	2.486	8.196	.000	78
Home births	5.247	1.448	19.008	.005	81
Premature Rupture of Membranes					
12-18 hours	.192	.088	.419	.000	<1
>18 hours	.196	.081	.472	.000	<1
Meconium waters aspiration	1.498	1.054	2.129	.024	33
Umbilical Cord around neck	3.039	2.025	4.560	.000	67

*AR – attributable risk, the effect of a risk factor on the exposed group %

Table 7. Maternal related risk factors for CP in singletons born at term

	Odds Ratio	95 % CI		P-value	AR* %
		Lower	Upper		
Demographic characteristics					
Rural	1.955	1.589	2.404	.000	48
Low Social-economic status	.963	.681	1.360	.829	<1
Maternal Factors					
Parity	2.115	1.220	3.808	.007	53
Maternal age					
>35 years old	1.650	.869	2.809	.065	40
Mother educational level Low	1.359	.897	2.060	.147	26
Alcohol consumption	2.105	1.315	3.369	.002	52
Mother chronic diseases					
-Hypertension	2.483	1.550	3.997	.000	60
-Hepatitis	1.834	.894	3.762	.094	<1
-Pyelonephritis	1.112	.774	1.559	.565	<1
-Diabetes	1.487	.881	2.509	.136	<1
-Intellectual Disability	1.666	.734	3.782	.218	<1
-Epilepsy	4.650	1.680	12.867	.001	78

*AR – attributable risk, the effect of a risk factor on the exposed group %

Table 8. Multivariate analysis of risk factors for CP in singletons born at term

	Odds Ratio	95 % CI		P-value	AR* %
		Lower	Upper		
Child related factors					
Gender (male)	2.210	1.384	3.530	.001	55
Hiperbilirubinemia	4.866	2.414	9.811	.000	79
Apgar at 5 min (0-3)	.471	.240	.925	.029	<1
Delivery factors					
Breech delivery	5.464	2.016	14.807	.001	82
Parity	.367	.172	.783	.010	<1
Meconium waters aspiration	.035	.004	.331	.003	<1
Premature Rupture of Membranes					
>18 hours	3.026	.965	9.485	.058	n/s
Umbilical Cord around neck	8.695	3.122	24.216	.000	89
Maternal Factors					
Rural	3.714	2.260	6.102	.000	73
>35 years old	.361	.160	.816	.014	<1
Mother chronic diseases					
-Hypertension	.252	.102	.624	.003	<1

*AR – attributable risk, the effect of a risk factor on the exposed group %

Figures

* NNM = neonatal mortality

Figure 1

Flowchart showing inclusion in the study population

Supplementary Files

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