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Original Scientific Paper

PRENATAL AND OBSTETRIC RISK FACTORS FOR DEVELOPMENT OF DISABILITIES IN CHILDHOOD

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SUMMARY – The main objective was to analyze prenatal and obstetric risk factors in relation to the development of disabilities. For that purpose, data on medication, i.e., use of benzodiazepines during pregnancy, gestational weeks, mode of delivery (vaginal or cesarean section), duration of delivery, and fetal presentation were retrieved from medical records and semi-structured interviews with mothers/legal guardians. Trained professionals clinically assessed the children's developmental status (N=107). Fisher exact test with post hoc analysis of standardized residuals showed that a statistically significant number of children with multiple disabilities were born by cesarean section ($z=3.7$, $p<0.001$), prematurely ($z=4.8$, $p<0.001$), and by mothers using benzodiazepines ($z=2.6$, $p<0.01$). Children with autism spectrum disorders were more often delivered post-term ($z=2.0$, $p<0.05$) by induced delivery ($z=2.9$, $p<0.01$). Children with developmental coordination disorder were more often born post-term ($z=2.2$, $p<0.05$). As for the duration of delivery and fetal presentation, there was no statistically significant correlation with developmental disabilities. There is a cumulative risk of developmental disabilities rather than just a single risk factor. More interdisciplinary and longitudinal research on developmental disabilities, including children's educational outcomes should be conducted.

Keywords: *Causality; Developmental disabilities; Parturition; Pregnancy; Risk factors*

Introduction

Several prenatal and obstetric factors are often mentioned as the main causes of adverse developmental outcomes in children. There are reports on the possible association between acetaminophen intake in the first and second trimester of pregnancy and behavior problems of the child in early childhood[1], and attention deficit hyperactivity disorder (ADHD)[2]. Strong connections are found between disability and benzodiazepines (BDZ) which are considered to have a teratogenic effect on fetal development[3-8]. Strong correlates are found between the use of BDZ in the first trimester and throughout pregnancy, and neurological impairment. A higher risk of BDZ use during pregnancy has been identified in relation to neural tube defect and neurological malformations, limb malformations, and congenital cardiovascular abnormalities in children[6,8], and recently with ADHD and autism spectrum disorder (ASD)[8]. Despite these findings, there is a continuous, even increased usage of BDZ in

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western societies due to the rise of psychological issues in overall population, such as anxiety and post-traumatic stress disorder[6]. Besides BDZ, researchers found a connection between several obstetric factors and potential adverse developmental outcomes. These factors are gestational weeks, mode of delivery, e.g., cesarean section and augmented/inducted delivery, fetal presentation, and duration of delivery. Gestational weeks are more likely to be connected with disabilities in preterm delivery, especially if accompanied with low birth weight and extremely low birth weight. In that case, it is mostly connected with intellectual disabilities, learning disabilities, and multiple disabilities[9-11]. Low birth weight is often the result of premature delivery and/or fetal growth retardation[10,12], which suggests that birth weight as a risk factor should be questioned continuously, not just by the weight at birth but rather as tempo of fetal weight increase throughout pregnancy. Preterm delivery is often connected with motor development, ranging from cerebral palsy to developmental coordination disorder (DCD)[13]. During the last few years, post-term delivery and associated risk factors are also capturing interest of researchers. Post-term delivery is considered to be a risk factor for cerebral palsy[13], intellectual disability[14], brain injury[15], and ASD[16-18]. This suggests a possible interactive effect of oxytocin that plays a role in social behavior, on ASD, yet some authors suggest the presence of mediating factors such as child's genetic sensitivity to oxytocin[19], and placental insufficiency[20-24]. Authors from the emerging field of neuroplacentology estimate that more than 10% of all pregnancies are affected by placental dysfunction, which is closely connected with ADHD, ASD, and learning disabilities[22-24]. Findings on post-term delivery, along with the mode of delivery, should be combined with biochemical findings in the placenta as a prerequisite for obtaining more objective data on their connection with adverse fetal outcomes, especially ASD. Reports on the duration of delivery and connection with adverse outcomes in childhood are quite rare, mostly connected to the cumulative intrapartum risks such as women's fear of childbirth, presence of augmentation, and instrumental mode of vaginal delivery[25], suggesting that prolonged delivery without additional risks has no negative impact on the child's outcome. As far as fetal presentation is concerned, research has indicated that non-cephalic presentation and adverse outcomes in children are potentially interconnected with the gestational age and mode of delivery. Non-cephalic presentation is closely connected to cesarean section[26-28] and preterm delivery[28,29], suggesting that these two factors are closely connected, often coming in pairs. Since the fetuses with breech presentation are at risk of less accurate estimation of fetal weight, especially in late pregnancies[30], this presentation elevates the risk of trauma and asphyxia[31], and is accompanied by several other risk factors such as preterm delivery and cesarean section[26]. According to the research available, non-cephalic presentation is considered a strong risk factor for adverse developmental outcomes; however, fewer papers connect the maternal/obstetric abnormalities with non-cephalic ones. For instance, Vranješ and Habek[32] studied several brow-presented deliveries with some obstetric anomalies such as polyhydramnios and myomatous uterus, and found that delivery management of non-cephalic presentation in non-operative matter (i.e., manual repositioning) had both short-term and long-term benefits for the mother and the child. To achieve benefits in the case of non-cephalic presentation, appropriate prenatal and intrapartum monitoring should be conducted, as well as appropriate training of obstetricians[31-34], with critical approach to cesarean section as a delivery option. This mode of delivery is rapidly increasing worldwide[27], although vaginal delivery is proven to be the best option even when other risks are present[27,34]. A meta-analysis of the clinical trials and research on cesarean section and child's developmental outcome revealed that cesarean section was connected with an increased risk of ADHD and ASD[35,36]. The main problem in the research of developmental outcomes and pre- and perinatal factors is the lack of reliable diagnostic procedures in early childhood, research studies based on parental reports, and lack of data on child's outcome regarding the pre- and perinatal factors[2,35,37]. Therefore, developmental outcomes should be researched through cooperation of scientists from various fields such as medicine, psychology, rehabilitation, education, etc.

Subjects and Methods

The study was performed over a one-year period (2018-2019) during the research project entitled Causal Induction in the Context of the Macro Paradigm of Developmental Psychopathology and Developmental Disabilities: Identification of Prenatal Factors for Adverse Developmental Outcomes in Children, conducted at the Osijek Faculty of Education. Project partners were Sveti Duh University Hospital and Catholic University of Croatia, Zagreb, Croatia. This project encompassed children and families living in seven Croatian counties (Osijek-Baranja County, Vukovar-Srijem County, Virovitica-Podravina County, Brod-Posavina County, Bjelovar-Bilogora County, Varaždin County, and Split-Dalmatia County). An independent Ethics Committee of the Osijek Faculty of Education approved the research project and it was conducted in accordance with ethical guidelines for research with children in Croatia. Participants, mothers/legal guardians and their children, were recruited through public annotation and participated on a voluntary basis, i.e., they did not receive any fee for their participation. Data were collected during clinical assessment of children; semi-structured interviews were conducted with mothers/legal guardians, whereas professionals trained in this field clinically assessed the children. Mothers/legal guardians provided medical documentation of pregnancy and delivery, as well as other medical records regarding pregnancy and neonatal period. All participants (mothers/legal guardians) gave their written consent for participating in the research.

Participants

Participants were mothers/legal guardians and their children. Overall, 107 pairs of mothers/legal guardians and their children participated in the study. Mothers/legal guardians provided history data and medical records of pregnancy and delivery. The mothers/legal guardians reported no previous records of disabilities in the families. It is important to say that four children were adopted, and three were living with another family member at the time of clinical assessment, so history data regarding prenatal development in these cases were to some extent insufficient. In addition, these seven participants did not provide any medical records on pregnancy and delivery, so we had to rely on the participants' reports and descriptions. The sample represented a convenience sample. Mothers/legal guardians of children at risk of disabilities were recruited from the general population, after public announcement, and participated voluntarily in this research. The majority of mothers/legal guardians had a college degree or a higher level of education (56.4%), and most of them were employed at the time of clinical assessment of children (72.7%). All mothers/legal guardians were concerned about their child's development, and only four (3.73%) mothers were smoking during pregnancy. Mothers/legal guardians gave history data on the prenatal and perinatal period, including delivery, as well as basic symptomatology of their children. The youngest mother was 21 years old, and the oldest 45 years old at the time of delivery (min=21, max=45, M=28.6). The youngest child enrolled in clinical assessment was 2 years old, the oldest was 14 years old (M=5.7), 76.6% were boys and 23.4% were girls.

Out of 107 children enrolled in the study, 94 met the clinical criteria for disability (Table 1), so their data were used in further statistical analysis. The remaining 13 children were typically developed children, i.e., no developmental disabilities were diagnosed.

Table 1. Distribution of participants (children) by developmental status

Developmental status	Frequency	%
Typical development	13	12.14
Intellectual disabilities	15	14.01
Autism spectrum disorder	28	26.17
Developmental coordination disorder	12	11.21
Speech and language disabilities	17	15.89
Multiple disabilities	22	20.56
Total	107	99.98

Instruments

For clinical assessment of children, in addition to history data and the semi-structured interview for mothers/legal guardians, additionally trained professionals used the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2®), the Wechsler Intelligence Scale for Children 4th edition (WISC-IV®),

and Croatian Developmental test Čuturić-2 (RTČ-2®) for toddlers and preschool children. In addition, the DSM-V diagnostic manual was consulted during assessment of children. Professionals had successfully completed additional training for standardized test. History data were obtained from mothers/legal guardians and from medical records. This step included analysis of medical documentation presented by mothers or caregivers, and the semi-structured interview for mothers/legal guardians conducted before clinical assessment of children. The semi-structured interview contained data on gestational weeks and maternal use of any medication during pregnancy. Furthermore, mothers/legal guardians were asked about delivery, including fetal presentation.

Procedure

Mothers/legal guardians were asked about pregnancy and delivery, and their concerns regarding the child's behavior. For that purpose, semi-structured interview was applied, and available medical documentation presented by mothers/legal guardians was analyzed, followed by clinical assessment of children. During clinical assessment of children, standardized tests were applied (ADOS-2®, WISC-IV® RTČ-2®). The questions and answers in the semi-structured interview were coded and statistically analyzed by use of SPSS.24.0.

Ethics

The study protocol was approved by the Ethics Committee of the Osijek Faculty of Education and was performed in accordance with ethical guidelines for research with children in Croatia (approval number: 641-01/19-02/02). The study was conducted in line with ethical principles of the World Medical Association Declaration of Helsinki. Informed consent was obtained from all individuals included in this study.

Statistics

The main objective of the study was to examine the characteristics of pregnancy and delivery in relation to developmental disabilities in children. The following characteristics were examined in more detail:

- type of delivery (vaginal, cesarean section);
- term of delivery (on time, premature or post-term delivery);
- gestational weeks (before week 35, between week 36 and 39, and between week 40 and 42);
- beginning of delivery (spontaneous, induced, planned cesarean section or emergency cesarean section);
- duration of delivery (3-4 cm cervical dilatation and three uterine contractions *per* 10 minutes lasting for ≥1 minute until complete delivery);
- fetal presentation during expulsion phase (cephalic and non-cephalic); and
- medications (combination of BDZ and progesterone) during pregnancy contributed to the disability in children.

Table 2. Association between delivery characteristics and types of disabilities

Delivery characteristics	Fisher exact test	Cramer's V
Mode of delivery	25.68***	0.51***
Term	37.59***	0.48***
Gestational age	17.82*	0.42**
Start mode of delivery	22.25**	0.33**
Duration of delivery	6.64	-
Fetal presentation during delivery	9.17	-
Use of medications (BDZ) during pregnancy	11.41*	0.40*

*p<0.05; **p<0.01; ***p<0.001

On data analysis, Fisher exact test was used (Table 2). Fisher exact test is used for small size samples, and in this research, it was used to examine the significance of association between two variables. All data were categorical and the sample size was relatively small (N=107). For the measure of effect size, Cramer's V was used (Table 2), which is suitable for examining association between two variables having two or more levels, i.e., how strongly the two categorical variables are associated. Post hoc analysis using standard residual method was used to check differences in prenatal and obstetric characteristics between the types of disabilities. Mode of delivery describes the way the child is born, i.e., vaginal or operative (cesarean section) delivery. Term of delivery refers to three categories of due date, i.e., preterm, term and post-term delivery. Start mode of delivery refers to the presence

of augmentative or operative procedures in delivery (spontaneous delivery, induced delivery or cesarean section, both elective and emergency ones). Duration of delivery refers to overall length of delivery (e.g., 3-4 cm cervical dilatation and three uterine contractions *per* 10 minutes lasting for ≥1 minute until complete delivery) as reported/described by mothers.

Post hoc analysis of standardized residuals yielded differences in obstetric factors for children with different types of disabilities. When it comes to children with multiple disabilities, a statistically significant number of them were born by cesarean section ($z=3.7$, $p<0.001$). Furthermore, they were more often prematurely born ($z=4.8$, $p<0.001$), more often born in gestational week 35 or earlier ($z=4.8$, $p<0.001$). Delivery more often began by emergency cesarean section ($z=3.5$, $p<0.001$), and these mothers used medications (BDZ) in the first and second trimester of pregnancy ($z=2.6$, $p<0.01$). At the time of clinical assessment, children born from these pregnancies were 9 years old on average. Children with the diagnosis of ASD were statistically significantly more often delivered post-term ($z=2.0$, $p<0.05$) and their birth more often started with induction ($z=2.9$, $p<0.01$). Children diagnosed with DCD were statistically significantly more often born post-term ($z=2.2$, $p<0.05$) but without augmentation. As far se the fetal presentation is concerned, Fisher exact test showed no statistically significant association between fetal presentation and disability ($F=9.17$, $p>0.05$), or between the duration of delivery and disability ($F=6.64$, $p>0.05$).

Discussion

The results obtained showed that Croatia follows worldwide trends. Several prenatal risk factors were confirmed to have possible connection with disabilities, BDZ being one of them. The use of BDZ is closely connected with multiple disabilities following cesarean section in preterm delivery, indicating that the overall effects of BDZ are accompanied by other prenatal and obstetric risk factors. We found preterm delivery (starting at week 35 and earlier) and induction to be connected with disabilities as potential obstetric risk factors. Similar to other authors[16,17,20], we found ASD risk factors to be connected with induced post-term delivery. We also found DCD to be connected with post-term (vaginal) delivery, yet no induction was present in these cases. DCD often stays unnoticed if the child has no memory deficit or if DCD is mild. Yet, this research revealed DCD as one of the potentially adverse child outcomes, connected with post-term delivery, the same as ASD but without induction. We found the results on post-term delivery particularly interesting because of the possible placental role in the development of disabilities, especially ASD, which is statistically increasing worldwide. In further research, more attention should be paid to the potential role of the placenta in the mechanism of developing disabilities, as suggested by several authors who emphasized the importance of placenta for one's health status later in life, especially in the case of schizophrenia, anxiety, depression, etc.[22,23]. Health issues in adulthood, e.g., anxiety and depression, are rising worldwide, especially in western societies, capturing the interest of researchers, including gynecologists. Therefore, research on developmental outcomes should be interdisciplinary and longitudinal. Here it is important to say that different studies used different diagnostic criteria for autism, mostly relaying on ICD-10 or ICD-11 and clinical observation, and almost none of them used the ADOS-2® with differential diagnoses, as applied in this research design.

Several prenatal and obstetric factors emerged as the possible contributors to disabilities. For multiple disabilities, it was the use of BDZ, preterm birth (35 weeks of gestation and earlier), and cesarean section. For ASD, there was a connection with post-term delivery, followed by induction. The connection of post-term delivery and DCD also emerged but without induction. These findings indicate a possible cumulative risk of developmental disabilities, especially multiple disabilities and ASD, rather than just one risk having direct impact on the disability. More interdisciplinary and longitudinal research on developmental disabilities, including clinical assessment of children and long-term developmental and educational outcomes should be conducted. Further methodologies for researching prenatal, perinatal and postnatal risk factors with long-term developmental outcomes should be discussed and developed.

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Sažetak

PRENATALNI I OBSTETRIČKI ČIMBENICI RIZIKA ZA RAZVOJNE TEŠKOĆE U DJETINJSTVU

K. Romstein, D. Habek, T. Velki i *M. K. Petrović*

Glavni cilj istraživanja je bio analizirati prenatalne i obstetričke čimbenike rizika u odnosu na razvoj teškoća u djetinjstvu. U tu svrhu su metodom polu-strukturiranog intervjua majki/zakonskih skrbnika prikupljeni podatci o uporabi lijekova, točnije benzodiazepina tijekom trudnoće, trajanju trudnoće, tjednima gestacije, načinu dovršetka poroda (vaginalno ili carski rez), trajanju poroda i fetalnoj prezentaciji. Dodatno obučeni kliničari procijenili su razvojni status djece (N=107) čije su majke/zakonski skrbnici sudjelovali u intervjuiranju. Fisherov egzaktni test s *post hoc* analizom pokazuje kako je statistički značajan broj djece s višestrukim teškoćama u razvoju rođen carskim rezom ($z=3,7$, $p<0,001$), prije termina ($z=4,8$, $p<0,001$) i od majki koje su koristile benzodiazepine ($z=2,6$, $p<0,01$). Djeca s poremećajem iz spektra autizma češće su rođena poslije termina ($z=2,0$, $p<0,05$), induciranim porođajem ($z=2,9$, $p<0,01$). Djeca s razvojnim koordinacijskim poremećajem češće su rođena poslije termina ($z=2,2$, $p<0,05$). Nije pronađena statistički značajna povezanost trajanja poroda i fetalne prezentacije i teškoća u razvoju. Zaključno, postoji kumulativni rizik za teškoće u razvoju, a ne samo jedan čimbenik rizika. Potrebno je više interdisciplinarnih i longitudinalnih istraživanja o rizicima pojave teškoća u razvoju, uključujući istraživanja vezana uz odgojno-obrazovne ishode rizične djece.

Ključne riječi: *Kauzalnost; Teškoće u razvoju; Porođaj; Trudnoća; Čimbenici rizika*