Original articles

Pre and postnatal characteristics of children and adolescents with intellectual disability

Antônio Augusto Schäfer[1]
https://orcid.org/0000-0002-8834-0434

Lisiane Tuon Generoso Bitencourt[1]
https://orcid.org/0000-0002-0809-0712

Bettina Stopazzolli Cassetari[2]
https://orcid.org/0000-0002-4397-9250

Emily dos Santos Uggioni[2]
https://orcid.org/0000-0002-7648-0149

Fernanda de Oliveira Meller[1]
https://orcid.org/0000-0002-1174-4721

[1] Universidade do Extremo Sul Catarinense, Programa de Pós-graduação em Saúde Coletiva, Criciúma, Santa Catarina, Brasil.

[2] Universidade do Extremo Sul Catarinense, Curso de Psicologia, Criciúma, Santa Catarina, Brasil.

Conflict of interests: Nonexistent

ABSTRACT

Purpose: to describe pre and postnatal characteristics of children and adolescents with intellectual disability.

Methods: study performed with all individuals who received healthcare between August 2016 and February 2018 at a reference Rehabilitation Center which serves 27 towns and cities in the South of Santa Catarina State, Brazil. A questionnaire focusing on demographic, socioeconomic, pre and postnatal variables was administered to parents or guardians of children and adolescents by trained interviewers. Descriptive analyses were performed using absolute and relative frequencies of categorical variables and central tendency and dispersion measures of numerical variables.

Results: 42 individuals in the mean age of 11 years ($\pm$ 3.0) were studied. Most mothers reported having unintended pregnancy and more than a half reported having had a cesarean section. In addition, about one-fifth of the subjects had low birth weight and most of them received exclusive breastfeeding up to six months of age.

Conclusion: these findings are crucial for the organization and improvement of health care services, since they provide evidence for health professionals to improve and/or focus their health care initiatives on these individuals.

Keywords: Child; Adolescent; Intellectual Disabilities; Prenatal Care; Postnatal Care

INTRODUCTION

Intellectual disability (ID) is a neuropsychiatric disorder diagnosed during the developmental period, i.e., until 18 years of age. It is characterized by limitations in intellectual functioning, such as reasoning, organization, problem-solving and learning, as well as in adaptive functioning, e.g., communication, personal independence and social responsibility[1,2].

In Brazil, approximately 1.4% of the population has ID[3], and in approximately 30% of cases, the causes are unknown[4]. However, there are some known factors that may occur in prenatal and neonatal periods. Factors may be biomedical, e.g., chromosome disorders; behavioral, such as drug and alcohol abuse by mothers during pregnancy; social, such as lack of access to prenatal care and health care during and after birth, and also educational, for example, educational disadvantageand lack of family support[5-7].

In a recent systematic review and meta-analysis which examined the influence of these variables on development of ID, it was found that maternal characteristics, such as low education, alcohol abuse and smoking during pregnancy, diabetes and hypertension, were associated with this disorder, because they affect children's cognitive and behavioral development[6]. In addition, advanced maternal age, premature birth, prelabor rupture of membranes, cesarean delivery and low birth weight are also factors that influence the development of ID[5,8-10].

Postnatal factors include traumatic brain injury, infections, convulsive diseases and exposure to neurotoxins, such as lead and mercury[2]. According to previous studies, another variable that is associated with ID is sex; boys have a higher prevalence of ID when compared togirls[5,10,11]. This is due to increased occurrence of X chromosomal mutations12.

In the face of several factors that may be related to ID, it is crucial to understand the characteristics of individuals with the disease, in order to implement specific prevention measures through qualified and accessible public policies. Thus, the objective of the present study was to describe pre and postnatal characteristics of children and adolescents with ID, treated in a reference rehabilitation center, in the South of Santa Catarina, in Brazil.

METHODS

The present study was approved by the Research Ethics Committee of the Universidade do Extremo Sul Catarinense - Unesc under protocol 57366316.6.0000.0119. All individuals who agreed to participate in the research signed an Informed Consent Form.

This is a descriptive study conducted between August 2016 and February 2018 with parents/guardians of children and adolescents with ID who received health care in a rehabilitation center (CER II) in the city of Criciúma, SC. CER II is located in the clinics of the institution of origin and serves the entire region of the Association of Municipalities of the Coal Industry Region (AMREC) and the Association of Municipalities of the Far South of Santa Catarina State (AMESC), in a total of 27 towns and cities.

ID was diagnosed by means of psychological evaluation, WISC IV tests[13] and/or the Columbia Mental Maturity Scale[14], multidisciplinary assessment by structured teams according to the individual demands of each case, including a speech pathologist, an occupational therapist, a psychopedagogist and a physiotherapist. Finally, a neurologist concluded the diagnoses.

For data collection, the parents/guardians of the children and adolescents answered a questionnaire applied by trained interviewers. This questionnaire contained the following demographic and socioeconomic information: sex ofchild/adolescent (male/female), age of child/adolescent (in full years), maternal age at birth (in full years), paternal and maternal education (elementary school, completed; elementary school, not completed; high school, completed; high school, not completed; higher education, completed; higher education, not completed) and maternal skin color (white/black/other). In addition, the following prenatal variables were analyzed: maternal age at birth (≤19 years/20-34 years/≥35 years) intendedpregnancy (yes/no), smoking (yes/no) and alcohol abuse during pregnancy (yes/no), provision of prenatal care (yes/no), location of prenatal care services (public/private facilities), trimester when prenatal care started (first/second/third) and number of prenatal visits (≤5 visits /≥6 visits). The following neonatal characteristics were also studied: type of delivery (vaginal delivery/cesarean section), gestational age (<37 weeks/≥37 weeks), breastfeeding (yes/no), exclusive breastfeeding (yes/no), infant's age at the end of exclusive breastfeeding

(<6 months/≥6 months), birth weight (<2,500g/2,500-2,999g/3,000-3,499g/≥3,500g), birth length (cm) and head circumference (cm).

Descriptive analyses were made of the study variables using absolute frequency (n) and relative frequency (%) of the categorical variables and measure of central tendency (mean) and dispersion (standard deviation) of the numerical variables. The software Stata version 12.1. was used for analysis of data.

RESULTS

All 42 children and adolescents with ID who received health care within the established period participated in the study. Table 1 shows the demographic characteristics of the participants and their mothers. Half of the subjects were male (50.0%), and mean age was 11.1 (±3.0) years. Approximately half of the mothers had non-white skin color (47.6%) and one fifth of them had completed secondary education (20.5%).

Table 1. Participants' sociodemographic characteristics. Criciúma, SC, Brazil, 2018 (n=42)

Variables	n	%
Sex		
Males	21	50.0
Females	21	50.0
Age		
Mean	11.1	
SD	3.0	
Maternal skin color		
White	22	52.4
Black	8	19.0
Other	12	28.6
Maternal education		
Elementary school, incomplete	24	61.6
Elementary school, complete	5	12.8
High school, incomplete	2	5.1
High school, complete	8	20.5

SD: standard deviation
Maximum percentage of unknown comments for the variable maternal education: 7.1% (n=3).

Table 2 shows the prenatal variables of the subjects. The vast majority of mothers were aged between 20 and 34 years at the birth of their child (75.0%) and said that their pregnancy was unintended (75.0%). Smoking and alcohol abuse during pregnancy were reported by a minority of mothers (14.6% and 7.3%, respectively). In addition, almost all of them used prenatal care services at a public health center (97.4%), started prenatal care in the first trimester of pregnancy (81.8%) and had at least 6 visits (73.5%).

Table 2. Participants' prenatal characteristics. Criciúma, SC, Brazil, 2018 (n=42)

Variables	n	%
Maternal age at the birth of her child		
≤19 years	4	10.0
20 to 34 years	30	75.0
≥35 years	6	15.0
Intended pregnancy		
No	30	75.0
Yes	10	25.0
Smoking during pregnancy		
No	35	85.4
Yes	6	14.6
Alcohol abuse during pregnancy		
No	38	92.7
Yes	3	7.3
Provision of prenatal care		
No	1	2.6
Yes	38	97.4
Location of prenatal services		
Public facilities	37	97.4
Private facilities	1	2.6
Trimester when prenatal care started		
First	27	81.8
Second	4	12.1
Third	2	6.1
Number of prenatal visits		
Up to 5	9	26.5
6 or more	25	73.5

Maximum percentage of unknown comments for the variable trimester when prenatal care started: 19.0% (n=8).

Table 3 shows the participants' postnatal characteristics. Clearly, more than half of the mothers had cesarean section (55.0%). As far as anthropometric variables are concerned, approximately one-fifth of the subjects were born with low birth weight (16.7%), and mean birth length was 47.9 cm (±3.1). The vast majority of them received exclusive breastfeeding (90.3%) and were breastfed until 6 months of age (82.8%).

Table 3. Participants' postnatal characteristics. Criciúma, SC, Brazil, 2018 (n=42)

Variables	n	%
Type of birth		
Natural	18	45.0
Cesarian	22	55.0
Gestational age		
<37 weeks	5	27.8
≥37 weeks	13	72.2
Birth weight		
<2,500g	5	16.7
2,500 to 2,999g	10	33.3
3,000 to 3,499g	10	33.3
≥3,500g	5	16.7
Breastfeeding		
No	9	22.0
Yes	32	78.0
Exclusive breastfeeding		
No	3	9.7
Yes	28	90.3
Infant's age at the end of exclusive breastfeeding		
≤6 months	14	82.8
>6 months	15	17.2
Length at birth (cm)		
Mean	47.9	
SD	3.1	
Head circumference at birth (cm)		
Mean	33.5	
SD	1.9	

SD: standard deviation
Maximum percentage of comments unknown as to the variable gestational age: 57.1% (n=24).

DISCUSSION

The analysis of the sociodemographic variables showed that few mothers of children and adolescents with ID had completed secondary education. In agreement with previous studies, low maternal education is pointed out as a factor associated with ID[5,6,15]. A recent systematic review and meta-analysis found 100% higher risk of ID among children and adolescents whose mothers had low education levels[5]. According to the authors, when parents have a low education level, they may often feel uninterested in their children's education or may fail to recognize that education has an important role in upward mobility[5]. This may explain why the children in the study were diagnosed with ID at an advanced age (mean 11 years). On the other hand, a study conducted in India with older children showed no association between these variables[16].

A cohort study conducted in Finland with a view to examining the impact of sociodemographic factors over 20 years, monitored children with ID whose mean age was 11.5 years[15]. When analyzing the specific group of children who had moderate ID, the researchers found that low socioeconomic level is a very common situation in those families. As to maternal variables, it was evidenced that, after a 20-year follow-up, low socioeconomic status, low education level and multiparity were the most relevant determinants for an increase in the cases of ID[15]. A possible explanation for these findings is that low education level and low socioeconomic level can impact both education and development of children[17]. Importantly, these sociodemographic factors are modifiable, which enables the implementation of primary healthcare prevention actions to reduce the number of children with ID.

Huang et al.[5] showed that maternal age above 35 years is an important risk factor for ID: women in this age group were 54% more likely to have children with ID. In the study, no association was found between early age (<20 years) and ID. Conversely, some authors showed that the majority of the mothers in their studies were aged up to 35[8,18], which corroborates the findings of the present study.

Another demographic variables studied were skin color and sex. Although there was no difference in prevalence of boys and girls in the present study, other authors have evidenced a higher occurrence of DI between males 8.11. Huang et al.[5] found that boys have 84% higher risk of developing ID when compared to girls. According to Werling and Geschwind[12], sex chromosome genes have a key role in molecular mechanisms that protect women against some deficiencies caused by specific risk loci and/or by genome mutation load, since they are protected from the deleterious effects of X chromosomal mutations through compensatory transcription from an intact, second X chromosome.

In their review and meta-analysis study, Huang et al.[5] found that child and adolescent offspring of black mothers had a 70% higher risk of having ID. This result corroborates the data collected in the present study, i.e., approximately half of the mothers declared not having white skin color. A possible explanation for this finding is that black skin color is related to low income and low education, which, as discussed above, are directly associated with ID[5,15].

Another finding of this study is that the vast majority of mothers reported unintended pregnancy; however, they started prenatal care in the first trimester of pregnancy and had the minimum number of visits as recommended by the Ministry of Health[19]. Similarly, the cohort study carried out in Pelotas (RS) showed that more than half of the pregnant women had the first prenatal visit in the first trimester of pregnancy, and most of them had at least seven visits throughout the gestation period[6].

According to the World Health Organization, in addition to clinical follow-up for detection and prevention of diseases, prenatal care includes advice about healthy life style and family planning, advice on smoking, alcohol abuse and use of other substances that may harm the fetus. Therefore, prenatal care is essential during pregnancy[20].

Among substances of abuse, alcohol is the one that produces the most serious neurobehavioral disorders in the fetus. As it is a teratogenic substance, its use is contraindicated in pregnancy[21]. According to Huang et al.[5], the fetus is highly susceptible to maternal condition; therefore, risk factors, such as exposure to toxic substances ingested by mothers and metabolic disorders, can significantly affect the genetically programmed brain development of the fetus. Children whose mothers reported alcohol abuse have 54% higher risk of developing ID than those whose mothers did not consume alcohol during pregnancy.

It should also be noted that smoking can affect the development of ID[7,22]. The risk of children having ID is 10% higher when their mother smoked during pregnancy compared to children whose mothers did not smoke[5]. According to the authors who found such result, the fetus is highly susceptible to maternal conditions, i.e., exposure to toxic substances ingested by mothers and metabolic disorders can significantly affect the genetically programmed brain development of the fetus[5,7].

In addition, in the present study, it was found that more than half of the mothers reported having had a cesarean section and that around 1/3 of children were born before 37 weeks. Moreover, approximately 20% of children had low birth weight. Similar results were found in other studies[5,8-10,23]. It was found that cesarean section, low birth weight and prematurity were associated with ID in children[5,8,10]. A previous study, conducted in Kenya with children and adolescents diagnosed with ID but without an associated genetic syndrome, pointed a significant a significant increase in the prevalence of severe intellectual disability in children born through cesarean section (50%) compared to those born through vaginal delivery (17.7%)[9]. A possible explanation for the influence of cesarean sections on psychological development is that they are usually scheduled between the 37th and 39th weeks of pregnancy, which may impair a baby's full development[8].

A cohort study conducted in Sweden to examine the relationship between prematurity and intellectual disabilities, found that 5.6% of babies born before 37 weeks of pregnancy had ID, while only 0.9% of babies born at full term had the disease[24]. Similarly, showed that premature infants with low birth weight had 3 times as much risk of Attention Deficit Disorder and Hyperactivity Disorder (ADHD)when compared to their peers[25].

Previous studies have shown that prematurity is a major perinatal risk factor for ID[8,10,26]. Palumbi et al.[18]

found the presence of different neural development disorders among late preterm infants. The end of pregnancy is a crucial period for brain development, since brain volume is 65% until the 34th gestational week. In addition, although the process of myelination is five times higher between the 35th and the 41th weeks of pregnancy, brain development continues until the 40th week of pregnancy. Thus, the brain of premature infants is not fully mature and functional; moreover, it is very vulnerable and susceptible to adverse environmental factors[8,27].

Other authors have suggested that premature children with ADHD have phenotypic characteristics, such as symptoms of inattention, which differ from those of children who have the disorder, but were not born at term[28]. According to Franz et al.[25], the reasons for premature children with low birth weight to be more likely to have ADHD and psychiatric problems are not yet clear. However, some hypotheses include prenatal and postnatal issues; for example, environmental and biological problems (dysregulation of the hypothalamic-pituitary-adrenal axis and perinatal systemic inflammatory response), which could lead to structural and functional brain disorders.

Importantly, breastfeeding is a protective factor for ID. Breastfed babies showed better results in measures of intelligence quotient, and had improved performance and cognitive development[29,30]. According to Doom et al.[31], iron deficiency in infants is associated with lower intelligence quotient rates, and it increases the chances of memory losses. A systematic review found that even after measurement of home environment characteristics or intellectual stimulation, breastfed infants have better performance in cognitive tests[32], which suggests that breast milk has a programming effect on intelligence[29]. Most of the children who participated in the present study were exclusively breastfed until 6 months of age.

In a systematic review and meta-analysis, Huang et al.[5] found that several non-genetic factors may be associated with ID, and they are classified as prenatal, perinatal and postnatal, depending on the time when they occur. Major prenatal factors for incidence of ID are advanced maternal age, maternal black skin color, low maternal education, three or more deliveries, alcohol abuse during pregnancy, smoking during pregnancy, and the mother's diabetes, high blood pressure, epilepsy and asthma. Only preterm birth was a relevant perinatal variable. Among postnatal factors, the most relevant ID-related variables are being a male and having low birth weight[5].

Also, taking into consideration that ID is a multifactorial disease, some authors have identified families that may be characterized as multi-risk families[33]. According to Landy and Menna[33], if families have at least four of these factors - moderate to severe level of stress during prenatal care, poverty, low level of maternal education, family discord/divorce, parents' alcohol abuse and parents' mental disorders - they can be classified as having multiple risks for development of ID. Since not all factors could be evaluated in the present study, the findings could not be compared.

It should be noted that the design of the present study is observational and descriptive, i.e., there was no comparison group; only children and adolescents with ID were participants. Thus, based on the results, no relationship can be inferred between the study variables and prevalenceof ID. Descriptive studies are often used to generate hypotheses, thereby encouraging further epidemiological studies focused on determinants of ID in children and adolescents.

Importantly, this is a pioneering study on the theme, since there are no studies to date on ID of children belonging to the 27 towns and cities in the Southern region of Santa Catarina State.

CONCLUSIONS

In this study, the profile of individuals with ID was identified. Most of them were born through C-section, with 37 weeks or more, and they were breastfed exclusively for the first 6 months of life. Most mothers had low schooling and their pregnancy was unintended. However, they started having prenatal care in the first trimester of pregnancy and had the number of visits recommended by the Ministry of Health.

These results are of paramount importance for the organization, and they offer useful insights to health care services, because they provide evidence for health professionals to improve and/or focus their health care initiatives on these individuals.

Moreover, further research is needed with other epidemiological designs to evaluate risk factors and/or protection factors for ID and, consequently, to develop preventive actions aimed at this target public, with a view to reducing the prevalence of ID in the population.

ACKNOWLEDGMENTS

REFERENCES

1. American Association on Intellectual and Developmental Disabilities. Definition of Intellectual Disability [acesso em 05 set 2018]. Disponível em: http://aaidd.org

2. American Psychiatric Association. DSM-5: Manual Diagnóstico e Estatístico de Transtornos Mentais. 5ª ed. Porto Alegre: Artmed; 2014.

3. Brasil. Instituto Brasileiro de Geografia e Estatística [homepage na internet]. Censo Demográfico 2010 [acesso em 04 set 2018]. Disponível em: http://www.ibge.gov.br/home/estatistica/populacao/censo2010/default.shtm

4. Gonzales G, Raggio V, Boidi M, Tapié A, Roche L. Avances en la identificación etiológica del retraso mental. Rev Neurol. 2013;57(1):75-83.

5. Huang J, Zhu T, Qu Y, Mu D. Prenatal, perinatal and neonatal risk factors for intellectual disability: a systemic review and meta-analysis. PLoSONE. 2016;11(4):e0153655.

6. Karam SM, Barros AJD, Matijasevich A, Dos Santos IS, Anselmi L, Barros F et al. Intellectual disability in a birth cohort: prevalence, etiology, and determinants at the age of 4 years. Public Health Genomics. 2016;19(5):290-7.

7. Ekblad M, Korkeila J, Lehtonen L. Smoking during pregnancy affects foetal brain development. Acta paediatrica. 2015;104(1):12-8.

8. Schieve LA, Clayton HB, Durkin MS, Wingate MS, Drews-Botsch C. Comparison of perinatal risk factors associated with Autism Spectrum Disorder (ASD), Intellectual Disability (ID), and Co-occurring ASD and ID. J Autism Dev Disord. 2015; 45(8):2361-72.

9. Nemerimana M, Chege MN, Odhiambo EA. Risk factors associated with severity of nongenetic intellectual disability (mental retardation) among children aged 2-18 years attending Kenyatta National Hospital. Neurol Res Int. 2018;18:1-11.

10. Schieve LA, Tian LH, Rankin K, Kogan MD, Yeargin-Allsopp M, Visser S et al. Population impact of preterm birth and low birth weight on developmental disabilities in US children. Ann Epidemiol. 2016; 26(4):267-74.

11. Vilaseca R, Rivero M, Bersabé RM, Cantero MJ, Navarro-Pardo E, Valls-Vidal C et al. Demographic and parental factors associated with developmental outcomes in children with intellectual disabilities. Front Psychol. 2019;10:872-86.

12. Werling DM, Geschwind DH. Sex differences in autism spectrum disorders. Curr Opin Neurol. 2013;26(2):146-53.

13. Wechsler D. Escala Weschsler de inteligência para crianças: WISC-IV. Manual Técnico. 4ª ed. São Paulo: Casa do Psicólogo; 2013.

14. Alves ICB, Duarte JLM. Padronização brasileira da Escala de Maturidade Mental Colúmbia. In: Burgmeister BB, Blum LH, Lorge I (eds). Escala de Maturidade Mental Colúmbia. 3 ed. Manual para aplicação e interpretação. São Paulo: Casa do Psicólogo; 1993. p. 25-35.

15. Heikura U, Taanila A, Hartikainen AL, Olsen P, Linna SL, Von Wendt L et al. Variations in prenatal sociodemographic factors associated with intellectual disability: a study of the 20-year interval between two birth cohorts in northern Finland. Am J Epidemiol. 2008;167(2):169-77.

16. Naskar S, Nath K. A clinical study on intellectual disability in northeastern India: insight into the sociodemographic risk factors of a developing country. Int J Med Sci Public Health. 2016;5(9):1789-97.

17. Engle PL, Black MM. The effect of poverty on child development and educational outcomes. Ann NY Acad Sci. 2008;1136:243-56.

18. Palumbi R, Peschechera A, Margari M, Craig F, Cristella A, Petruzzelli MG et al. Neurodevelopmental and emotionalbehavioral outcomes in late-preterm infants: an observational descriptive case study. BMC Pediatric. 2018;18:318-23.

19. Brasil. Ministério da Saúde. Cadernos de Atenção Básica nº 32. Atenção ao pré-natal de baixo risco. Brasília, DF; 2012.

20. Organização Mundial da Saúde. OMS publica novas orientações sobre pré-natal para reduzir mortes de mães e bebês. [Acesso em 11 jun 2019]. Disponível em: https://nacoesunidas.org/oms-publica-novas-orientacoes-sobre-pre-natal-para-reduzir-mortes-de-maes-e-bebes/

21. Stratton K, Howe C, Battaglia F. Fetal alcohol syndrome: diagnosis, epidemiology, prevention and treatment. Washington: National Academy Press; 1996.

22. Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. Pediatrics. 2014;133(1):e14-22.

23. Schieve LA, Tian LH, Baio J, Rankin K, Rosenberg D, Wiggins L et al. Population attributable fractions for three perinatal risk factors for autism spectrum disorders, 2002 and 2008 autism and developmental disabilities monitoring network. Ann Epidemiol. 2014;24(4):260-6.

24. Heuvelman H, Abel K, Wicks S, Gardner R, Johnstone E, Lee B. Gestational age at birth and risk of intellectual disability without a common genetic cause. Eur J Epidemiol. 2018;33(7):667-79.

25. Franz AP, Bolat GU, Bolat H, Matijasevich A, Santos IS, Silveira RC et al. Attention-Deficit/Hyperactivity Disorder and very preterm/very low birth weight: a meta-analysis. Pediatrics. 2018;141(1):e20171645.

26. Onicescu G, Lawson AB, Mcdermott S, Aelion CM, Cai B. Bayesian importance parameter modeling of misaligned predictors: soil metal measures related to residential history and intellectual disability in children. Environ Sci Pollut Res Int. 2014;21(18):10775-86.

27. Walsh JM, Doyle LW, Anderson PJ, Lee KJ, Cheong JL. Moderate and late preterm birth: effect on brain size and maturation at term-equivalent age. Radiology. 2014;273(1):232-40.

28. Johnson S, Kochhar P, Hennessy E, Marlow N, Wolke D, Hollis C. Antecedents of attention-deficit/hyperactivity disorder symptoms in children born extremely preterm. J Dev Behav Pediatr. 2016;37(4):285-97.

29. Victora CG, Horta BL, Loret de Mola C, Quevedo L, Pinheiro RT, Gigante DP et al. Association between breastfeeding and intelligence, educational attainment, and income at 30 years of age: a prospective birth cohort study from Brazil. Breastfeeding and intelligence: a systematic review and meta-analysis. Lancet Glob Health. 2015;3(4):e199-205.

30. Horta BL, Loret de Mola C, Victora CG. Breastfeeding and intelligence: a systematic review and meta-analysis. Acta Paediatr. 2015;104(467):14-9.

31. Doom JR, Gunnar MR, Georgieff MK, Kroupina MG, Frenn K, Fuglestad AJ et al. 2014. Beyond stimulus deprivation: iron deficiency and cognitive deficits in postinstitutionalized children. Child dev. 2014;85(5):1805-12.

32. Horta BL, Victora CG. Long-term effects of breastfeeding: a systematic review. World Health Organization; Geneva: 2013.

33. Landy S, Menna R. Characteristics of multi-risk families. In: Landy S, Menna R (eds). Early intervention with multi-risk families: an integrative approach. New York: Paul Brookes Publishing; 2006. p. 3-54.